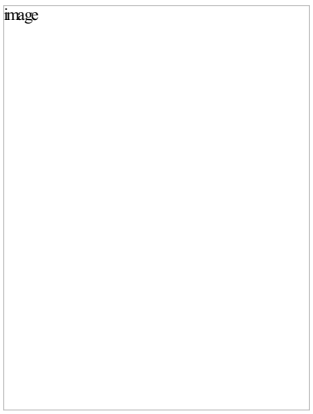
CORA Cork Open Research Archive
Cartlann Taighde Oscailte Chorcaí

Title	It's all about the brain - neuromonitoring during newborn transition
Authors	Dempsey, Eugene M.;Kooi, Elisabeth M. W.;Boylan, Geraldine B.
Publication date	2018-05-11
Original Citation	Dempsey, E. M., Kooi, E. M. W. and Boylan, Geraldine B. (2018) 'It's all about the brain - neuromonitoring during newborn transition', Seminars in Pediatric Neurology. doi:10.1016/j.spen.2018.05.006
Type of publication	Article (peer-reviewed)
Link to publisher's version	10.1016/j.spen.2018.05.006
Rights	© 2018, Elsevier Inc. All rights reserved. This manuscript version is made available under the CC-BY-NC-ND 4.0 license. - https://creativecommons.org/licenses/by-nc-nd/4.0/
Download date	2026-11-05 17:30:13
Item downloaded from	https://hdl.handle.net/10468/6148



UCC
University College Cork, Ireland
Coláiste na hOllscoile Corcaigh

Author's Accepted Manuscript



It's all about the brain - Neuromonitoring during newborn transition

E.M. Dempsey, E. Kooi, G.B. Boylan

www.elsevier.com/locate/bios

PII: S1071-9091(18)30035-4
DOI: https://doi.org/10.1016/j.spen.2018.05.006
Reference: YSPEN727

To appear in: *Seminars in Pediatric Neurology*

Cite this article as: E.M. Dempsey, E. Kooi and G.B. Boylan, It's all about the brain - Neuromonitoring during newborn transition, *Seminars in Pediatric Neurology,* doi:10.1016/j.spen.2018.05.006

This is a PDF file of an unedited manuscript that has been accepted for publication. As a service to our customers we are providing this early version of the manuscript. The manuscript will undergo copyediting, typesetting, and review of the resulting galley proof before it is published in its final citable form. Please note that during the production process errors may be discovered which could affect the content, and all legal disclaimers that apply to the journal pertain.

ACCEPTED MANUSCRIPT

It's all about the brain - Neuromonitoring during newborn transition.

[1,2] Dempsey EM, [1,3]Kooi E, [1,2]Boylan GB

[1]Department of Paediatrics and Child Health, Neonatal Intensive Care Unit, University College Cork, Ireland

[2]INFANT, Irish Centre for Fetal and Neonatal Translational research, University College Cork, Ireland

[3]University of Groningen, University Medical Center Groningen, Beatrix Children's Hospital, Division of Neonatology, Groningen, the Netherlands

Please address Correspondence to:

Professor Geraldine Boylan,

Department of Paediatrics and Child Health, Neonatal Intensive Care Unit, Wilton, Cork, Ireland.

Telephone: 00353214205040

Email: g.boylan@ucc.ie

Word Count: 4959

Funding: This work was supported by a Science Foundation Ireland Research Centre Award (INFANT-12/RC/2272)

Acknowledgments: None

Conflict of Interest: None

Keywords: cerebral oxygenation, brain injury, cerebral autoregulation, transcranial Doppler, Near infrared spectroscopy, electroencephalography

Accepted manuscript

ACCEPTED MANUSCRIPT

Introduction

"*.... the matter of being born is such a physiologic adventure and the hazards to the brain so obvious that one would expect to find evidence of cortical electrical abnormality in those newcomers who have not survived too well the physical and chemical stresses incident to labour and delivery" Hughes et al. 1948 Am J Dis Child. 76(5):503-12)*

The primary focus on foetal to neonatal transition has been defining the significant cardiorespiratory changes that occur over the first postnatal minutes and subsequent hours. Our understanding of this complex process continues to evolve, providing opportunities to enhance adaptation and initiate interventions when physiology may be compromised. More recently animal models have focussed on the role of ventilation in the setting of immediate and delayed cord clamping (1). This has provided insights into the importance adequate ventilation plays in reducing pulmonary vascular resistance and enhancing pulmonary blood flow, thus facilitating adaptation. However, studying the complex mechanisms of cardiorespiratory adaptation in the newborn infant remains somewhat challenging. Assessing real time changes in pulmonary compliance, pulmonary blood flow, systemic vascular resistance and cardiac output are all readily achievable in an instrumented animal model, but are more difficult in the newborn infant, particularly in the delivery room.

Assessment of newborn neurological adaptation has changed little over the last 30 years. The newborn brain is at a critical stage of development around the time of birth and is vulnerable to brain injury particularly in early prematurity or as a result of hypoxia-ischaemia, infection and haemorrhage (2, 3). Immediate objective information about the function of the newborn brain is needed but is rarely available. As a result, many caregivers are operating without valuable information about neurological function. Animal models, predominantly fetal sheep, have provided insights into the complications of labour such as acute (e.g., cord occlusion) and chronic intrauterine hypoxia. However, neurological assessment of the newborn has remained predominantly subjective, as timely objective monitoring methods to date have been limited. A general assessment of tone, level of activity and primitive reflexes provides a crude

Accepted manuscript

ACCEPTED MANUSCRIPT

overall assessment of neurological status but this method of assessment remains subjective. The early neurological examination may be less useful than later examinations, particularly in neonatal encephalopathy when a neurological examination at discharge is often the most predictive of later neurodevelopmental outcome (4).

However, we would contend that it is relatively easy to objectively determine neurological wellbeing in the delivery room. Whilst we have very little objective information on neurological adaptation to date, and more importantly on how to determine when neurological adaptation may be compromised, this is an important area of newborn care that has garnered very little attention. One prime area where this is relevant is in relation to term newborn encephalopathy and the ever-increasing move towards commencing therapeutic hypothermia in babies with mild encephalopathy. The limitations of our current ability to objectively determine this needs to be acknowledged and efforts made to ensure the appropriate therapy is commenced early, but in the appropriate group of infants.

In this review we present details on neurological assessment of newborn infants in the delivery room and over the first hours of life, discussing the potential benefits and limitations of these assessment methods and providing an insight into potential future monitoring modalities in the early transitional period. This is not an attempt to prioritise one area of assessment over another; it is merely an attempt to highlight the current lack of objective neurological evaluation.

Accepted manuscript

Subjective Assessment of Neurological Wellbeing

The Apgar score is the most commonly utilised score to assess adaptation at birth. With the exception of heart rate the remaining variables included in the Apgar score are based on visual inspection of the infant. This raises concerns about subjectivity, and a number of studies have highlighted issues around inter-rater variability (5-7). The Apgar score continues to be utilised as a method of assessing general well-being at birth, with two relatively poorly defined subjective criteria assessing neurological wellbeing, namely tone and the response to suctioning. Whilst these have not been individually evaluated in terms of variability, it is easy to appreciate how these two criteria are prone to significant variability in assessment. The Apgar

ACCEPTED MANUSCRIPT

score remains one of the main criteria included in determining the need for therapeutic hypothermia and thus highlights the need for more objective assessment criteria.

Objective Assessment of Neurological Wellbeing

Transcranial Doppler (TCD)

Studies that sought to introduce neurological monitoring into the delivery room (DR) initially focused on cerebral blood flow assessments incorporating Doppler measurements of cerebral or carotid arteries (8-13). Monitoring was found to be technically difficult and did not provide continuous data (14). Furthermore, there is conflicting evidence on the role of cerebral Doppler in identifying impaired cerebral autoregulation in infants and resultant abnormal cranial ultrasound findings (15, 16). Boylan et al. measured the gradient of the cerebral blood flow velocity (CBFV) response with TCD following spontaneous blood pressure (BP) peaks to assess dynamic autoregulation in infants undergoing intensive care(16). Term and preterm infants at high risk of neurologic injury were compared with a control group. Measurements were obtained intermittently during a study period of at least 2 h. Intact cerebral autoregulation consisted of a brief period when CBFV follows arterial blood pressure but quickly returns to baseline value. The authors found that autoregulation was absent in high-risk term and preterm infants, but also absent in preterm control infants. Term neurologically healthy infants undergoing intensive care were found to have an intact autoregulatory response. Numerous studies since have focused on measures of cerebral blood flow as determined by Doppler (17-22). Recently, Forster and colleagues measured the CBFVs, resistive index (RI) and pulsatility index (PI) in the anterior and middle cerebral arteries (ACA and MCA) of 38 normal neonates (22). All CBFVs in the ACA correlated with gestation. The RI in the ACA (0.67 +/- 0.06) and MCA (0.68 +/- 0.07) were correlated ($r = 0.72$, $P < 0.001$) (22). Resistive index, pulsatility index and cerebral blood flow velocities of middle cerebral artery (MCA) were measured at 24 to 48h of life in two hundred newborns (>36wk) randomized to either umbilical cord milking (UCM) or delayed cord clamping (DCC) at delivery. No differences were identified between the two groups (23). Kaiser et al have investigated the critical closing pressure (CrCP) in preterm infants at risk of brain injury

Accepted manuscript

ACCEPTED MANUSCRIPT

in the first days of life. One hundred eighty-six premature infants with a GA range of 23-33 weeks were monitored with umbilical artery catheters and TCD insonation of middle cerebral artery flow velocity for 1-h sessions. The CrCP increased significantly with GA ($r = 0.47$; slope = 1.4 mmHg/week gestation), an association that persisted with multivariate analysis ($p < 0.001$). Higher diastolic ABP and higher GA were associated with increased CrCP ($p < 0.001$ for both). The authors concluded that low CrCP observed in premature infants might explain their ability to tolerate low ABP without global cerebral infarct or hemorrhage. Doppler thus has an important potential role to play in assessing neurological well-being in the term and preterm infant but its limitations remain, predominantly the lack of continuous reliable data for newborn infants.

Near Infrared Spectroscopy (NIRS)

Cerebral oxygenation and blood flow during early transition

Cerebral oxygenation after birth and during transition depends on three factors. The first is arterial oxygen saturation (SpO2), which mainly reflects pulmonary function and the amount of oxygen administered to the newborn. Second, haemoglobin (Hb) levels which reflect both Hb levels during fetal life and management of the umbilical cord after birth. Finally, the infant's capacity to self-regulate its cerebral blood flow irrespective of changes in blood pressure or carbon dioxide levels, by cerebrovascular autoregulation or vascular reactivity. Cerebral oxygen saturation during transition can easily be assessed using near-infrared spectroscopy (NIRS). Several studies have measured cerebral oxygen saturation during transition and during the first days of life, in both term and preterm infants. The focus of previously performed studies has been on obtaining reference values for cerebral oxygenation after birth, determining factors that may affect this, and also measuring potential effects of several antepartum or peripartum interventions.

Normal cerebral oxygen saturation in term and preterm infants during transition

Normal values of cerebral oxygen saturation and fractional tissue extraction (FTOE) in the first minutes after birth have been determined, predominantly from the group of investigators at Graz University. First,

Accepted manuscript

ACCEPTED MANUSCRIPT

an increase in cerebral oxygenation was observed in a small group of healthy term infants from three minutes after birth onwards, starting at around 44%, rising to 76% by seven minutes of age (24). Later this was confirmed in a larger group of 381 healthy non-ventilated term infants, with a gradual increase of cerebral oxygen saturation from two minutes after birth (41%) to 15 minutes after birth (77%). FTOE gradually reduced from 33% at two minutes, to 18% at 15 minutes of age. Reference ranges were obtained using the INVOS NIRS device (Medtronic, USA) (25). The same group subsequently presented data obtained from the NIRO NIRS device (Hamamatsu) in 140 term healthy infants(26). This has shown some differences compared with the INVOS device, highlighting the importance of using the appropriate reference values for each specific device. This was confirmed by a study that directly compared two different devices during transition showing different sensitivities to changes in cerebral oxygenation between two NIRS devices (27). In another study aiming to assess the course of cerebral and peripheral (renal and mesenteric) tissue oxygen saturation in the first hours after birth, a similar increase in mainly cerebral oxygen saturation during the first minutes after birth was observed. Peripheral values were lower compared to cerebral values, possibly suggesting preferential arterial blood flow to the brain in healthy term infants.

Reference values have been presented for cerebral oxygen saturation and extraction during the first minutes of life in preterm infants (28, 29). We recently evaluated transitional cerebral oxygenation in preterm infants less than 32 weeks and noted that infants requiring higher concentrations of oxygen had a significantly higher degree of cerebral hypoxia over the first 15 minutes of age when compared with those infants requiring lower amounts of oxygen (30) (Figure 1). The area below 55% quantifies both the duration and the extent of rcSO2 below the established lower limit of 55% to represent hypoxia (<55%) .The area was calculated using the trapezoidal method, a numerical approximation of integration. The area measures were normalized to total duration and lower limit of the INVOS recording (15%).

Accepted manuscript

ACCEPTED MANUSCRIPT

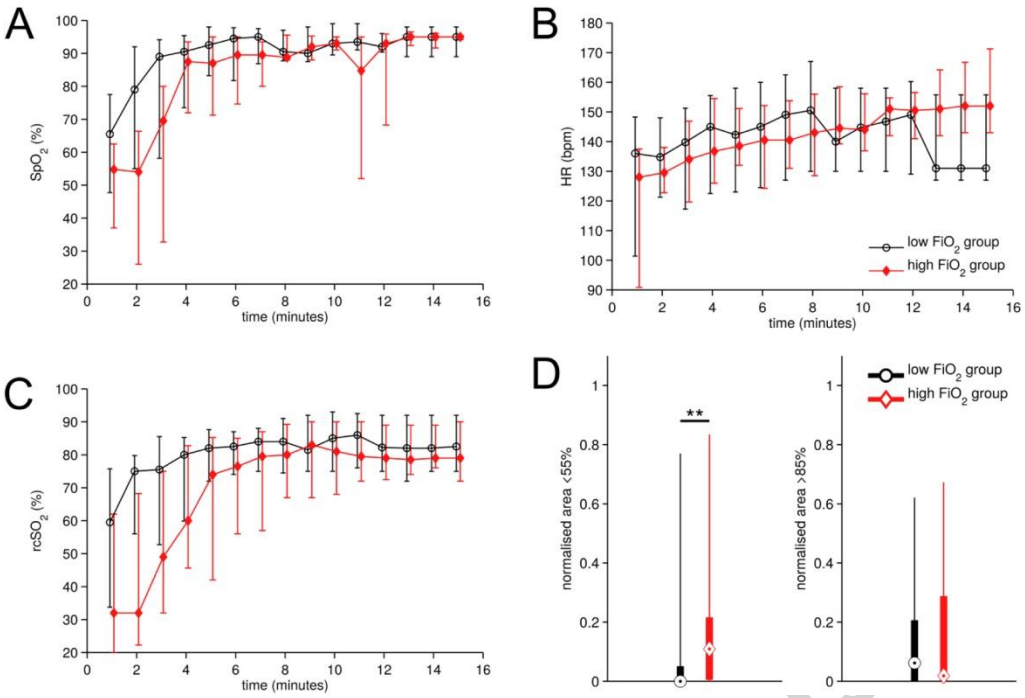


*Figure 1. Data for oxygen saturation (SpO2), HR, and cerebral oxygen saturation (rcSO2) recorded in the delivery suite for the first15 minutes of life. A, SpO2, B, HR, and C, rcSO2. D, represents features of rcSO2 comparing low (FiO2 <0.3) and high (FiO2 >0.3). Circles and diamonds represent median values; bars represent IQR for A, B, and C. D, Thick bars represent IQR and thin bars represent 95 percentiles. Lines plotted along circles represents the low FiO2 group, and one plotted along diamond shapes represent high FiO2 groups during resuscitation in the delivery suite. ** Statistical significance, with P < .01. Data from: Kenosi M, O'Toole JM, Livingston V, Hawkes GA, Boylan GB, O'Halloran KD, et al. Effects of Fractional Inspired Oxygen on Cerebral Oxygenation in Preterm Infants following Delivery. J Pediatr. 2015;167(5):1007-12 e1. Used with permission from Elsevier.*

Pichler et al recently reported the results of a pilot RCT utilising continuous NIRS (cNIRS) monitoring (COSGOD trial) in the delivery room (31). This study assessed the role of cNIRS as an adjunct to newborn stabilisation in babies less than 34 weeks. The primary endpoint was the % mins that cerebral oxygenation was below the 10th percentile and above the 90th percentile over the first 15 mins of age. In the NIRS-visible group, NIRS monitoring in addition to pulse oximetry was used to guide respiratory and supplemental oxygen support whereas in the NIRS-not-visible group, pulse oximetry alone was used as is standard of care. The authors noted a significant relative reduction in cerebral hypoxia in the NIRS visible

ACCEPTED MANUSCRIPT

group of 55.4% (95% CI 37.6-73.2%; P = .028). Beyond the delivery room, Alderlistein and colleagues presented values on almost 1000 preterm infants over the first 3 days of life. The values show a parabolic curve, with an initial increase of cerebral oxygen saturation, followed by a slow decrease after 40 hours of age (32). What is clear during transition is that the values mainly depend on gestational and postnatal age, gender and birthweight (Figure 2).

Figure 2

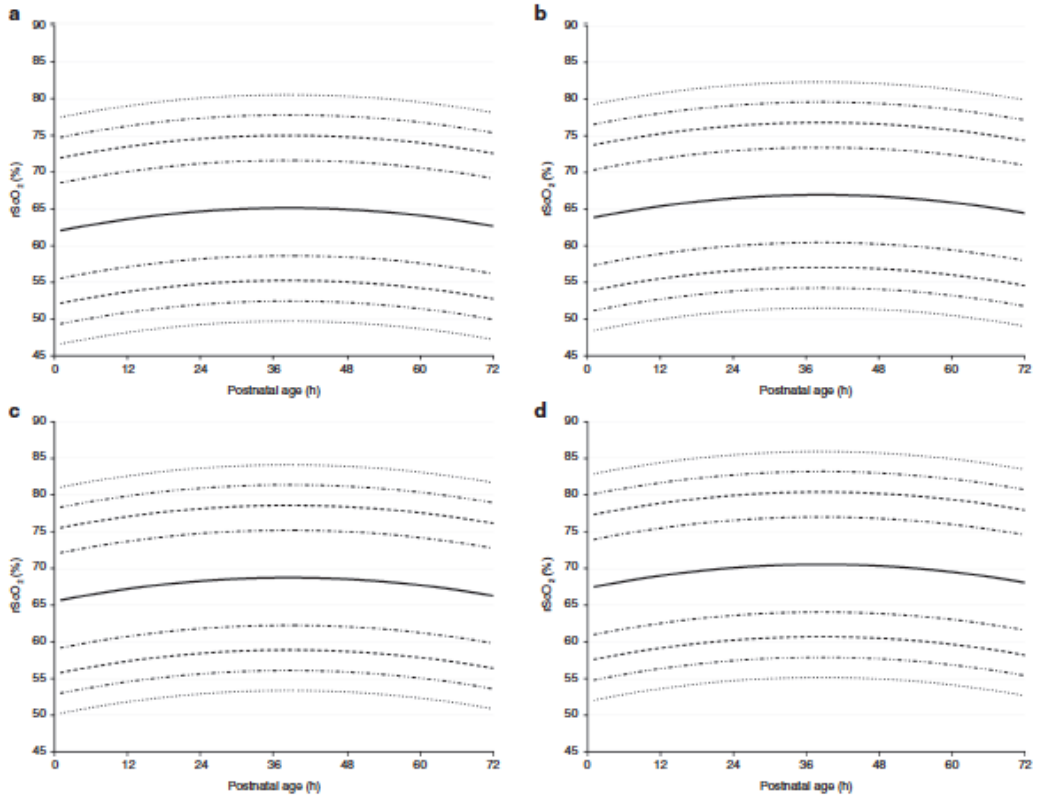


Figure 2. rScO2 reference value curves for neonates of (a) 24–25 wk GA, (b) 26–27 wk GA, (c) 28–29 wk GA, and (d) 30–31 wk GA. The line patterns depict different percentiles: dotted lines indicate p2.3 and p97.7, dash dot dot dash lines indicate p5 and p95, dashed lines indicate p10 and p90, dash dot dash lines indicate p20 and p80, and solid lines indicate p50. GA, gestational age. Data reproduced from Alderliesten T et al Reference values of regional cerebral oxygen saturation during the first 3 days of life in preterm neonates. Pediatr Res. 2016;79(1-1):55-64.

ACCEPTED MANUSCRIPT

The effects of carbon dioxide on cerebral saturation

One of the first to show the relationship between $PaCO_2$ and cerebral blood flow were Pryds and Greisen, highlighting an intra-individual variation of CBF to be positively related to changes in PaCO2 and inversely related to changes in Hb in preterm infants (33). This relation between CO_2 and cerebral oxygen saturation has been seen subsequently, and recently described again, when a decrease in $etCO_2$ not only resulted in decreased cerebral oxygenation, but also reduced brain activity in preterm infants over the first 72 hours after birth(34). Little is known about early transitional CO_2 cerebral vascular reactivity in both term and preterm infants. If early transitional cerebral oxygenation relates to outcome then an understanding of partial pressure of arterial carbon dioxide levels and their effect on cerebral oxygenation might be crucial.

Cord clamping practice

Deferring cord clamping (DCC) for at least 1 minute after birth in preterm infants might result in higher cerebral perfusion and improved oxygenation during transition. A small RCT randomizing 39 preterm infants in an early versus delayed cord clamping (60-90 sec) trial , resulted in a higher mean regional tissue oxygenation in the DCC group at the ages of 4 hours (69.9% vs 65.5%) and of 24 hours (71.3% vs 68.1%), with similar measures of cerebral blood volume in both groups(35). This suggests a better capacity for oxygen transport to the brain, potentially through a higher haematocrit. However, a more recent trial compared milking versus delayed cord clamping in preterm infants less than 32 weeks found no difference in cardiac output, peripheral saturation and cerebral oxygenation between both groups (36). The PREMOD2 (NCT03145142) study has recently commenced, aiming to recruit 400 infants (<28 weeks of gestation) into an RCT comparing cord milking versus DCC, and will assess cerebral oxygenation over the first minutes of life in both groups.

Accepted manuscript

ACCEPTED MANUSCRIPT

Cerebrovascular autoregulation

Little is known about autoregulatory capacity during immediate transition in both term and preterm infants. Given that NIRS can be used as a surrogate for cerebral blood flow, and combined with blood pressure (invasive or noninvasive), as a surrogate for cerebral perfusion pressure, it is reasonable to assume that it might provide an indication of autoregulatory capacity in the newborn. However, most studies on this subject focussed on validity issues and were performed after NICU admission (37), possibly because of the fact that arterial lines, needed for continuous BP readings, are mostly only inserted then. Several observational studies have shown a relation between probable impaired cerebrovascular autoregulation after birth and the development of IVH in preterm infants (38) (39). Being able to measure cerebrovascular autoregulation during transition could possibly provide a better understanding of cerebral oxygenation, and possibly guide our therapeutic approach towards hemodynamic changes immediately after birth.

Predicting outcome and intervention

In a case control study of 12 preterm infants with IVH and 12 infants without IVH, early transitional cerebral oxygenation over the first 15 minutes after birth was associated with brain injury. Both the duration and magnitude of centiles-deviation of cerebral oxygen saturation was more pronounced in infants with IVH compared with non-IVH infants, while no differences were found in heart rate and SpO2 in this group of (26). Noori et al found lower systemic perfusion, CBF and cerebral oxygenation over the first 12 hours after birth preceding the development of IVH (40). Cerbo et al found that both rSO2 ≤40% and superior vena cava flow <40 ml/kg/min in the first 48 hours after birth independently increased the risk of death (41). Recently it was observed that an increased burden of cerebral hypoxia during immediate transition and resuscitation was associated with impaired general movement scores at term equivalent age, suggesting that cerebral oxygenation in the first minutes of life may be an important predictor of short term problems (42).

Accepted manuscript

ACCEPTED MANUSCRIPT

A key question remains: is cerebral oxygen saturation during transition predictive of longer-term outcome and does intervention result in improved outcome? The Safeboosc II study was designed as a phase 2 study to address this question, by first investigating whether it was possible to use NIRS to guide cerebral oxygenation and keep it within certain limits in the first 72 hours of birth in very preterm born infants (43). Indeed, the burden of cerebral hypoxia was reduced (44) in the intervention group but there was no significant reduction in brain injury overall(45). However, looking at the entire group of infants regardless of their allocation assignment, infants with a cerebral burden of hypoxia (time with cerebral haemoglobin saturation <55%) within the fourth quartile were more often diagnosed with severe IVH, had low burst rate on EEG or an increased mortality risk, compared to infants in the first three quartiles (46).

In term born infants with hypoxic ischaemic encephalopathy (HIE), significantly elevated cerebral oxygenation values and reduced cerebral fractionated oxygen extraction values have been identified in the first 24 hours and found to correlate with poor neurodevelopmental outcomes at 2 years of age (47-49). The rise in cerebral oxygenation most likely reflects increased cerebral perfusion, decreased oxygen utilization and impaired cerebral autoregulation (50, 51). The possibility of using cerebral NIRS as a tool to assess cerebrovascular autoregulation and maintain cerebral blood flow in a range that results in optimal cerebral oxygenation might improve neurodevelopmental outcome in HIE infants and is a key priority for future research. It is important to note that rSO2 values are dependent on cerebral metabolic rate, which may be influenced by interventions such as therapeutic hypothermia and medication administration. A number of recent studies have highlighted long-term adverse outcome in the setting of mild encephalopathy (52, 53) and there is now an increasing trend towards cooling infants with mild encephalopathy. This is where cerebral oxygenation monitoring in combination with other biomarkers of brain injury may help individualise the approach to therapeutic hypothermia in infants with mild encephalopathy. However, further studies are certainly warranted in this area of care.

In summary cerebral oxygen saturation in both term and preterm neonates is easy to perform during early transition using NIRS and might help predict short term and possibly even longer term outcome.

Accepted manuscript

ACCEPTED MANUSCRIPT

Reference values have been presented for various devices, but it is still not known if intervening for low or high values, and in what way, improves short and long-term outcome.

Electroencephalography (EEG)

In contrast to cerebral blood flow and NIRS, EEG monitoring has become an essential tool for the objective assessment of neurological function in infants with neonatal encephalopathy (54) (55) (56) (47 , 57-59)(43, 53-56) seizures (60-64) and more recently in the care of premature infants (65-67). However, it is rarely used in the immediate minutes and hours after birth to assess neurological function, despite limitations of the early clinical examination.

The signals measured by EEG are of the order of microvolts and represent postsynaptic neuronal activity in the cerebral cortex. The EEG is easy to acquire using electrodes placed on the surface of the scalp in predetermined regions and modern flat disposable electrodes can record for days undisturbed in neonates in the NICU, even in extremely preterm neonates (68). EEG has a temporal resolution that is much higher than functional MRI and activity is represented on a millisecond scale. EEG exhibits a rich variety of frequencies, amplitudes and waveform morphologies from all monitored brain regions and features such as synchrony and symmetry across cerebral hemispheres are very easily assessed (Figure 3). A knowledge of the gestational age of the infant is essential as the EEG varies quite dramatically with maturity (65).

Accepted manuscript

ACCEPTED MANUSCRIPT

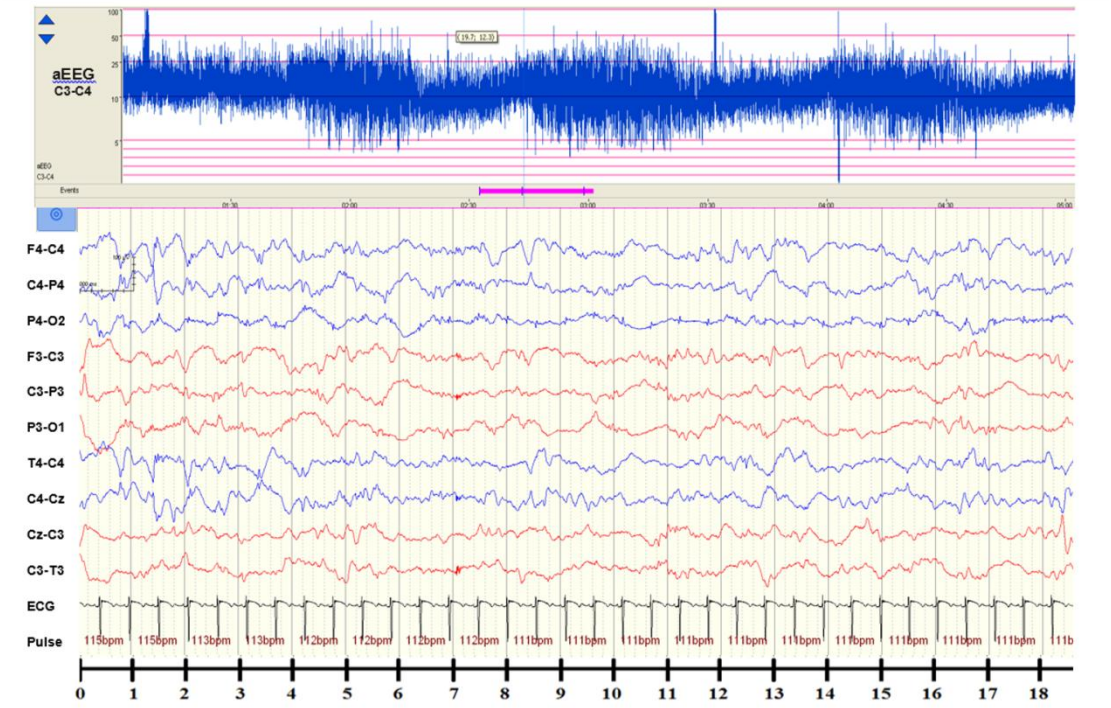


Figure 3: Normal Term aEEG & multichannel EEG showing moderate voltage continuous mixed frequency activity over a six hour period within the first 12 hours of age. Sleep cycles are evident on the aEEG tracing.

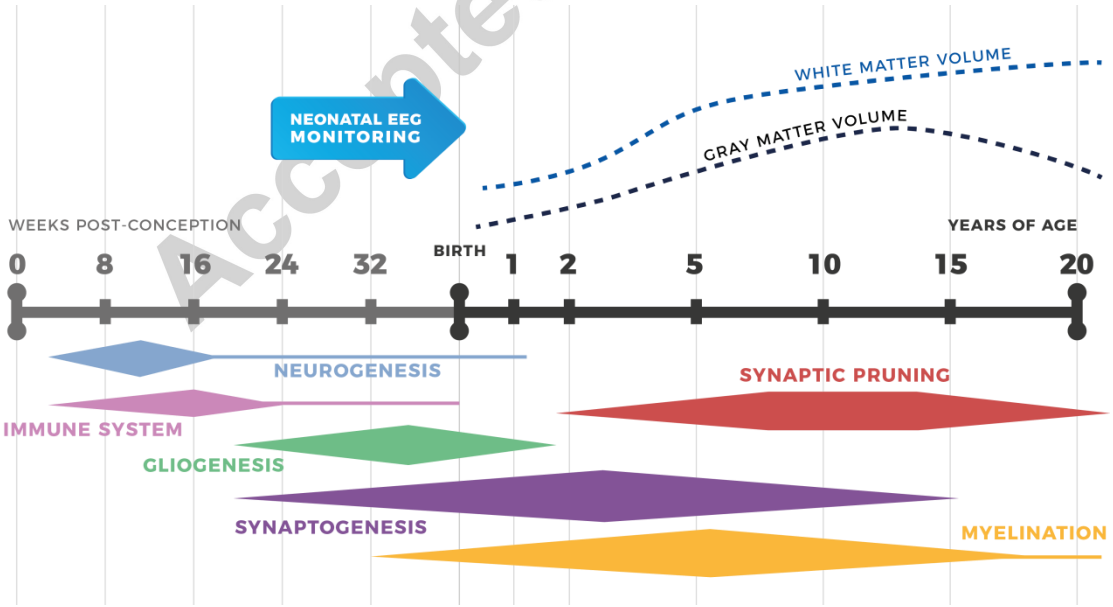


Figure 4: Time course of key neurodevelopmental milestones showing the critical period when EEG monitoring takes place in preterm and full term newborns i.e. 23-44 weeks gestational age, adapted from Semple et al. 2013 (70)

ACCEPTED MANUSCRIPT

It is well known that cerebral electrical activity is essential to drive gene expression in the brain and morphological neuronal development (69). During development, up to a trillion cortical neurons establish specific synaptic connections so that highly organized cortical networks are formed (70) (71) (Figure 2). Any interruptions in neuronal activity will disrupt connectivity and cortical excitation/inhibition balance which will be reflected as abnormal patterning on the neonatal EEG (72). Studies in newborn rodents have shown that transient changes in electrical activity are associated with changes in activity regulated protein expression, neuronal morphology and cortical plasticity (73). If an infant is exposed to hypoxia and/or ischaemia, neuronal firing ceases very quickly (an adaptive shut down response to preserve energy), as shown in both human neonates and animal models ref (73, 74). After restoration of oxygenation, activity can return rapidly if the period of hypoxia is short (75). However, if the period of hypoxia is long, it may take some time for neuronal firing to recommence. In addition, the initial EEG patterns that emerge may be disrupted and may take some time to recover (Figures 5-8) (55). The evolving patterns of EEG recovery commonly seen post moderate and severe hypoxic ischaemic encephalopathy (HIE) are prognostic for later neurodevelopment (52, 76). In addition, serial EEGs starting soon after birth have been shown to be of use in determining the timing and severity of brain injury (77). Therefore, the EEG is critical for diagnosis, treatment and prognosis in the newborn period.

Seizures occur most frequently during newborn transition and in neonates with moderate and severe hypoxic ischaemic encephalopathy seizures peak around 18-24 hours of age (78). Multichannel EEG is the gold standard tool for the accurate diagnosis and monitoring of all neonatal seizures.

In preterm infants, the EEG develops from the most immature neonates of approximately 23 weeks' gestational age (GA) through to full term age with 3 major trends; increasing continuity, with defined periods of normal EEG quiescence for specific GAs; appearance of several normal transient waveforms of prematurity; and the appearance of sleep cycling (67) (79). Assessment of an infant's EEG against these parameters can indicate whether the maturity of the brain is appropriate for GA (Figure 9).

Accepted manuscript

ACCEPTED MANUSCRIPT

Despite the obvious benefits of EEG monitoring, it has long been considered too difficult to deploy within the first minutes and hours after birth. However, in the 1970s and early 1980s huge efforts were made to record the EEG during labour and many of these were successful. The Pioneering work of Rosen and colleagues clearly demonstrated that the fetal EEG recorded during an uncomplicated labour in the term fetus is very similar to the EEG recorded within 30 minutes and 3 days of birth in the same infants (80). This is an important observation and demonstrates that continuous mixed frequency activity is anticipated in the term fetus immediately after birth and throughout transition.

Recently there has been a renewed interest in monitoring the fetal brain during labour using EEG and this is an exciting development. Using animal models, a new algorithm for fetal EEG as a predictor of academia has been developed and abnormal EEG changes were seen to emerge at a pH $\leq$ 7.20 (81). A clinical study using this algorithm and a bespoke fetal EEG electrode is now underway (NCT03013569).

Fetal EEG monitoring is now evolving rapidly but is still very much in the research phase. Therefore, EEG monitoring in the immediate transition period should be easier. However, a number of perceived barriers still exist such as determining the most appropriate EEG electrodes and application method; the best EEG recording system and how to interpret the EEG signals.

In order to assess the baseline activity of the newborn brain, only a few electrodes are needed. Multiple sensors are needed for seizure detection but this is not the goal of early EEG monitoring. The goal is to establish if the newborn has continuous (term) or semi-continuous EEG activity (preterm). Therefore, only a small number of electrodes are needed to provide 1 or ideally 2 channels of EEG. A full-term infant with continuous activity in the first minutes after birth has not been exposed to hypoxic ischaemia. Korotchikova et al. demonstrated that healthy term newborns who had EEG monitoring within 6 hours of birth had continuous mixed frequency patterns with well-developed sleep cycling (82). Two recent studies have shown that single channel amplitude integrated EEG (aEEG) monitoring is feasible in the immediate newborn period.(25, 83, 84). However, the aEEG does have limitations as it displays a very processed EEG signal, which has been filtered, rectified and compressed, and artefacts can be difficult to recognise (85-87).

Accepted manuscript

ACCEPTED MANUSCRIPT

We recently performed a pilot study on the feasibility of conventional EEG monitoring in the delivery room in healthy full term infants following elective CS. Six sterile disposable flat surfaced EEG electrodes were attached to the infants' scalp over frontal and central regions (F4, C4, F3, C3, ground, and reference) bilaterally. We recorded the EEG within 10 minutes of birth in 49 infants. Good quality EEG, with continuous mixed frequency activity in the range of 25-50μV, was observed in all infants (88).

Another barrier to early adoption of early neonatal EEG has been the lack of appropriate EEG technology for the acute environment. Traditional paper based EEG machines were very large, cumbersome, and non-digital, making them difficult to use in an acute setting. However, technology has evolved dramatically in the last decade and EEG machines capable of continuous multi-channel video EEG monitoring can now be laptop based and unobtrusive. In addition, new EEG amplifiers have excellent common mode rejection and can work very well in electrically noisy environments even when surrounded by other monitoring equipment. This has certainly helped to advance the adoption of conventional EEG in the NICU in recent years (89).

EEG interpretation, particularly neonatal EEG, has always posed difficulties for non-neurophysiologists and neurologists. This area is advancing rapidly due to huge leaps in machine learning and artificial intelligence techniques which will soon be able to provide non EEG experts with the help needed to assist in the interpretation of EEG patterns on a 24/7 basis. Indeed the first ever clinical investigation of an algorithm for neonatal seizure detection, developed using machine learning, has recently completed recruitment in a multicentre study across Europe (The ANSeR study - NCT02431780). Algorithms for automated baseline neonatal EEG interpretation in term and preterm neonates are advancing at a rapid pace and it is likely that a version ready for clinical deployment will soon be available (90-96).

It is clear that EEG provides objective information about newborn brain function and technological barriers that previously made it difficult to deploy in the minutes and hours after birth are no longer a concern. The time is now right to advance our understanding the neurological function in the immediate newborn period and urgent research is clearly warranted. More EEG studies from healthy term and preterm newborns in the immediate postnatal period are required to establish normative reference ranges.

Accepted manuscript

ACCEPTED MANUSCRIPT

Advances in machine learning will provide the much need support to interpret these signals in the acute setting and we look forward to further studies in this area.

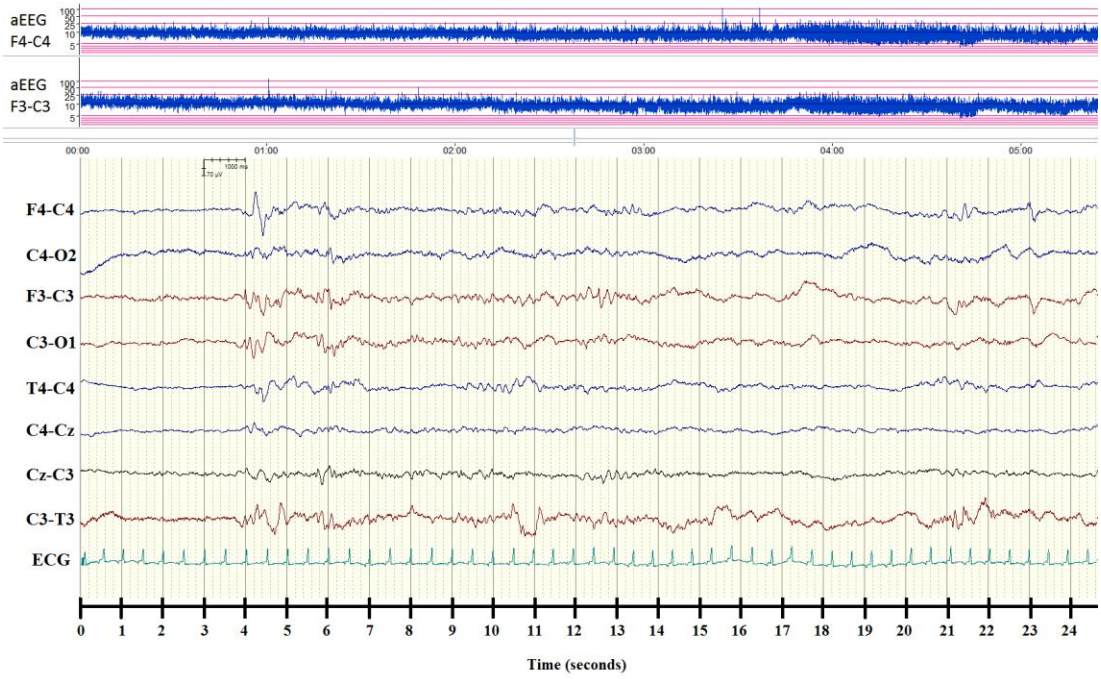


Figure 51: aEEG and multichannel EEG in a full term infant with mild encephalopathy during the first 12 hours of age. Some short duration suppressed periods are evident with disrupted sleep cycling.

Accepted

ACCEPTED MANUSCRIPT

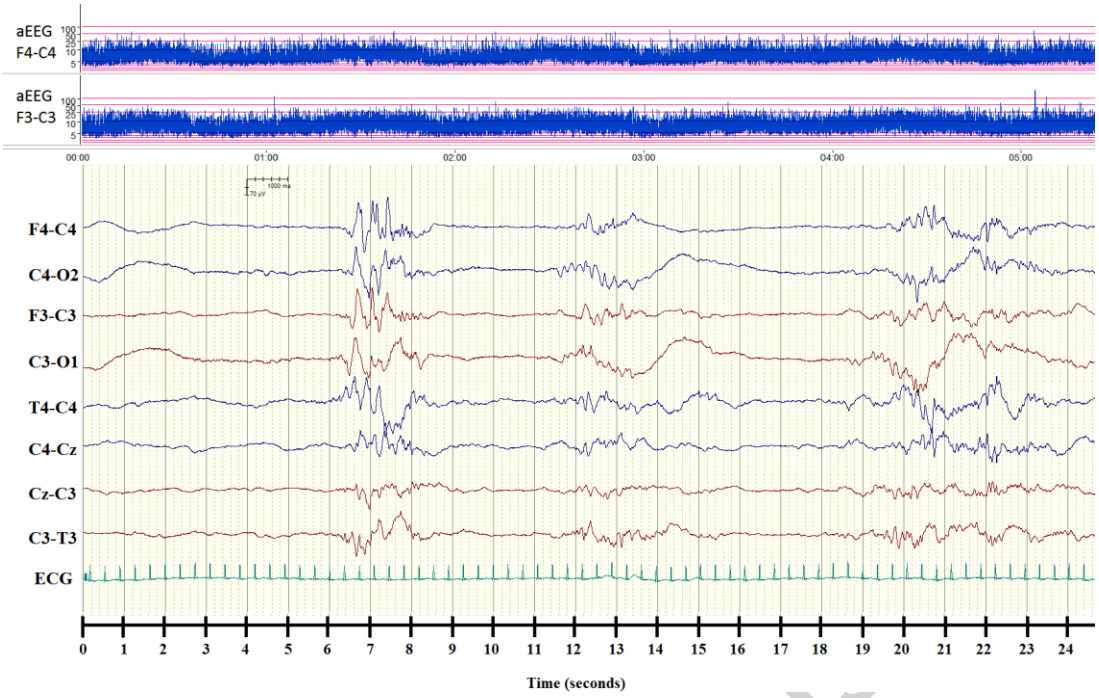


Figure 62: aEEG and multichannel EEG in a full term infant with moderate encephalopathy during the first 12 hours of age. EEG shows general discontinuity and no sleep cycling.

Accepted manuscript

ACCEPTED MANUSCRIPT

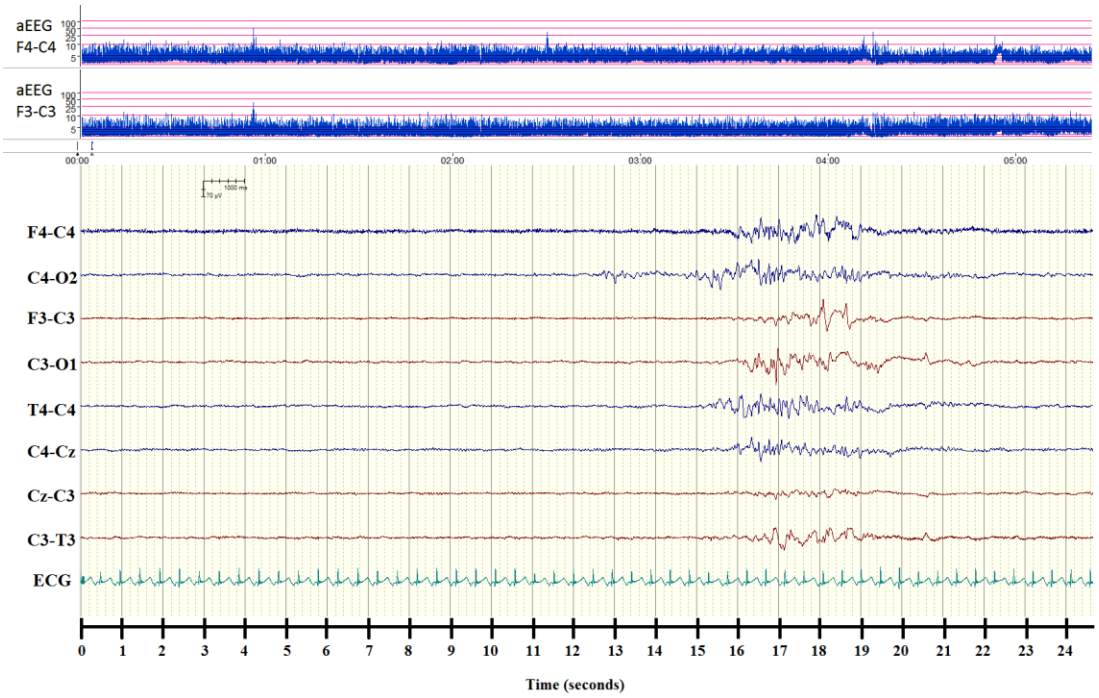


Figure 7: aEEG and multichannel EEG in a full term infant with severe encephalopathy during the first 12 hours of age. Overall suppressed amplitude but a burst suppression pattern and no evidence of variability or sleep cycling.

Accepted manuscript

ACCEPTED MANUSCRIPT

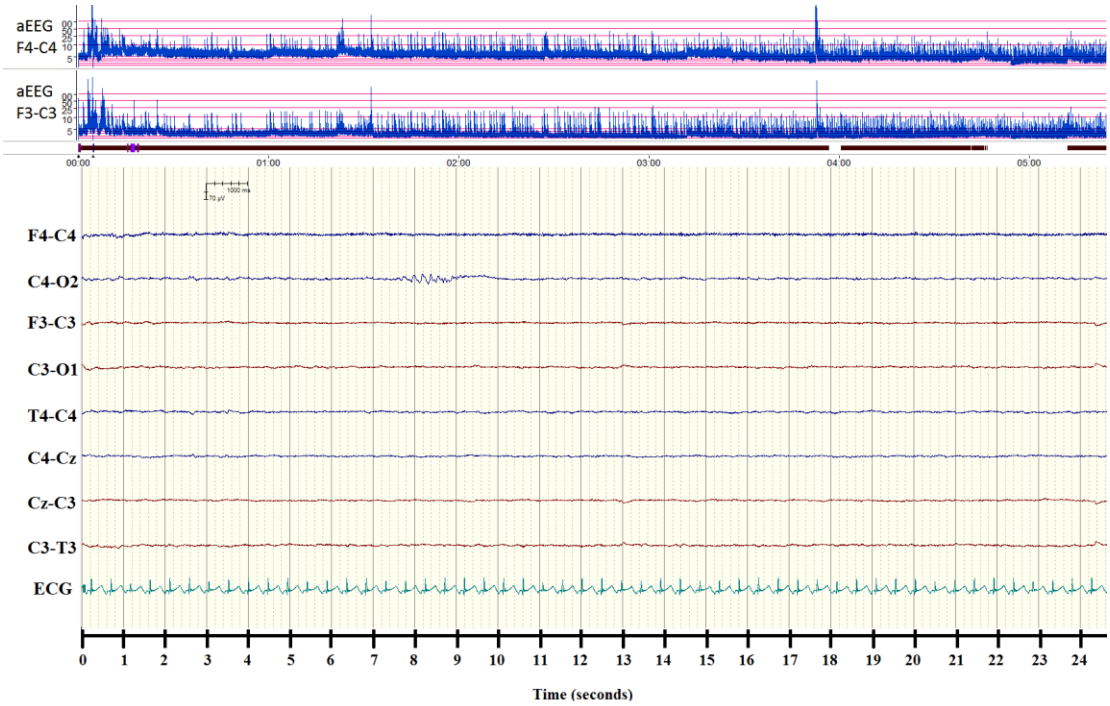


Figure 8: aEEG and multichannel EEG in a full term infant with severe encephalopathy during the first 12 hours of age. The EEG is the most severe form, showing complete suppression of all electrocortical activity (isoelectric).

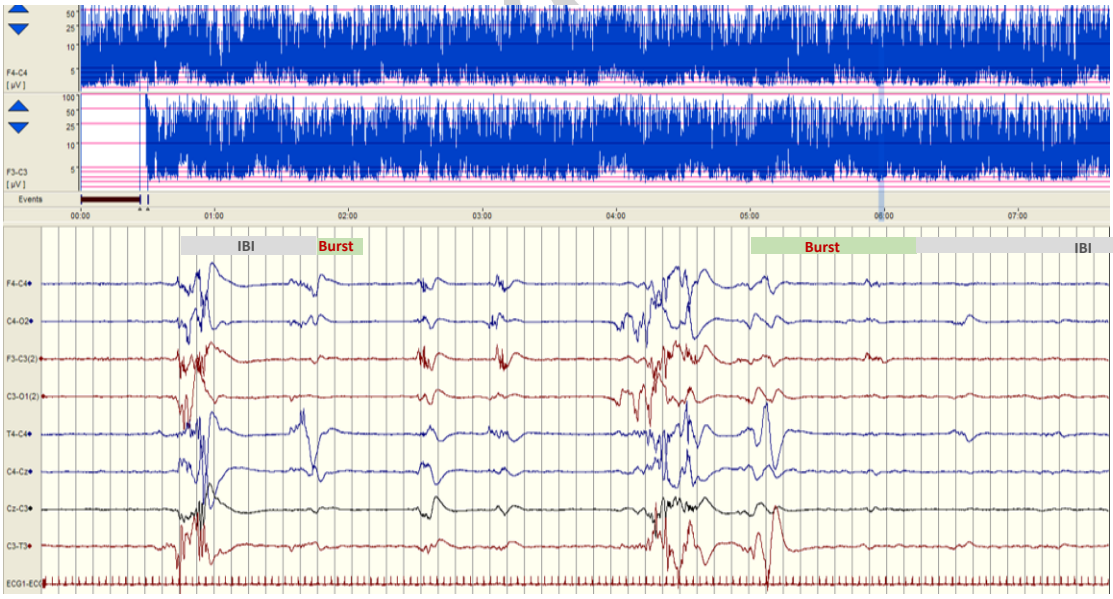


Figure 9: aEEG and multichannel EEG in a premature infant of 25 weeks gestation during the first 12 hours of age. The EEGs shows a typical Trace Discontinu pattern with bursts of high amplitude activity interspersed with periods of quiescence (interburst intervals).

ACCEPTED MANUSCRIPT

Summary

In this review, we have presented the most recent advances in neonatal CBFV, NIRS and EEG for both term and preterm infants and have described their suitability for use in the early transitional period. An accurate objective measure of neurological function is required as soon as possible after birth in order to initiate the most appropriate therapeutic interventions. This is particularly the case for infants with HIE where rapid identification of those infants who will benefit most from therapeutic hypothermia is imperative. Rapid advances in technology and machine learning have now made the information obtained using neuromonitoring devices more accessible and this may prove very useful for simultaneous multimodality neuromonitoring using combinations of CBFV, NIRS and EEG. Clearly, this rapidly developing field of research is urgently needed in order to increase our understanding of transitional neurology and improve longer term outcomes.

Accepted manuscript

1. Hooper SB, Polglase GR, te Pas AB. A physiological approach to the timing of umbilical cord clamping at birth. Arch Dis Child Fetal Neonatal Ed. 2015;100(4):F355-60.

2. Blencowe H, Lee AC, Cousens S, Bahalim A, Narwal R, Zhong N, et al. Preterm birth-associated neurodevelopmental impairment estimates at regional and global levels for 2010. Pediatr Res. 2013;74 Suppl 1:17-34.

3. Lee ACC, Kozuki N, Blencowe H, Vos T, Bahalim A, Darmstadt GL, et al. Intrapartum-related neonatal encephalopathy incidence and impairment at regional and global levels for 2010 with trends from 1990. Pediatric research. 2013;74 Suppl 1(December):50-72.

4. Murray DM, Bala P, O'Connor CM, Ryan CA, Connolly S, Boylan GB. The predictive value of early neurological examination in neonatal hypoxic-ischaemic encephalopathy and neurodevelopmental outcome at 24 months. Developmental medicine and child neurology. 2010;52(2):e55-9.

5. O'Donnell CP, Kamlin CO, Davis PG, Carlin JB, Morley CJ. Interobserver variability of the 5-minute Apgar score. The Journal of pediatrics. 2006;149(4):486-9.

ACCEPTED MANUSCRIPT

6. Gupta S, Natarajan G, Gupta D, Karnati S, Dwaihy M, Wang B, et al. Variability in Apgar Score Assignment among Clinicians: Role of a Simple Clarification. Am J Perinatol. 2017;34(1):8-13.

7. Bashambu MT, Whitehead H, Hibbs AM, Martin RJ, Bhola M. Evaluation of interobserver agreement of apgar scoring in preterm infants. Pediatrics. 2012;130(4):e982-7.

8. Sonesson SE, Winberg P, Lundell BP. Early postnatal changes in intracranial arterial blood flow velocities in term infants. Pediatr Res. 1987;22(4):461-4.

9. Maesel A, Sladkevicius P, Gudmundsson S, Mars al K. Mode of delivery and perinatal cerebral blood flow. Early Hum Dev. 1996;44(3):179-85.

10. Maesel A, Sladkevicius P, Valentin L, Marsal K. Fetal cerebral blood flow velocity during labor and the early neonatal period. Ultrasound Obstet Gynecol. 1994;4(5):372-6.

11. Ipsiroglu OS, Stockler S, Hausler MC, Kainer F, Rosegger H, Weiss PA, et al. Cerebral blood flow velocities in the first minutes of life. Eur J Pediatr. 1993;152(3):269-70.

12. Noori S, Wlodaver A, Gottipati V, McCoy M, Schultz D, Escobedo M. Transitional changes in cardiac and cerebral hemodynamics in term neonates at birth. J Pediatr. 2012;160(6):943-8.

13. Jorch G, Rabe H, Michel E, Engels M, Schulz V, Hentschel R, et al. Resuscitation of the very immature infant: cerebral Doppler flow velocities in the first 20 minutes of life. Biol Neonate. 1993;64(4):215-20.

14. Pichler G, Cheung PY, Aziz K, Urlesberger B, Schmolzer GM. How to monitor the brain during immediate neonatal transition and resuscitation? A systematic qualitative review of the literature. Neonatology. 2014;105(3):205-10.

15. Rennie JM, Coughtrey H, Morley R, Evans DH. Comparison of cerebral blood flow velocity estimation with cranial ultrasound imaging for early prediction of outcome in preterm infants. J Clin Ultrasound. 1995;23(1):27-31.

16. Boylan GB, Young K, Panerai RB, Rennie JM, Evans DH. Dynamic cerebral autoregulation in sick newborn infants. Pediatr Res. 2000;48(1):12-7.

Accepted manuscript

ACCEPTED MANUSCRIPT

17. Pezzati M, Dani C, Biadaioli R, Filippi L, Biagiotti R, Giani T, et al. Early postnatal doppler assessment of cerebral blood flow velocity in healthy preterm and term infants. Dev Med Child Neurol. 2002;44(11):745-52.

18. Gergont A, Nowak A, Kroczka S. [Assessment of the Doppler cerebral blood flow measurement in infants with perinatal trauma]. Przegl Lek. 2007;64(11):929-33.

19. Basu S, Dewangan S, Shukla RC, Anupurva S, Kumar A. Cerebral blood flow velocity in early-onset neonatal sepsis and its clinical significance. Eur J Pediatr. 2012;171(6):901-9.

20. Chock VY, Ramamoorthy C, Van Meurs KP. Cerebral autoregulation in neonates with a hemodynamically significant patent ductus arteriosus. J Pediatr. 2012;160(6):936-42.

21. Rhee CJ, Fraser CD, Kibler K, Easley RB, Andropoulos DB, Czosnyka M, et al. The Ontogeny of Cerebrovascular Pressure Autoregulation in Premature Infants. Acta Neurochir Suppl. 2016;122:151-5.

22. Forster DE, Koumoundouros E, Saxton V, Fedai G, Holberton J. Cerebral blood flow velocities and cerebrovascular resistance in normal-term neonates in the first 72 hours. J Paediatr Child Health. 2017.

23. Jaiswal P, Upadhyay A, Gothwal S, Chaudhary H, Tandon A. Comparison of Umbilical Cord Milking and Delayed Cord Clamping on Cerebral Blood Flow in Term Neonates. Indian J Pediatr. 2015;82(10):890-5.

24. Urlesberger B, Grossauer K, Pocivalnik M, Avian A, Muller W, Pichler G. Regional oxygen saturation of the brain and peripheral tissue during birth transition of term infants. J Pediatr. 2010;157(5):740-4.

25. Pichler G, Binder C, Avian A, Beckenbach E, Schmolzer GM, Urlesberger B. Reference ranges for regional cerebral tissue oxygen saturation and fractional oxygen extraction in neonates during immediate transition after birth. J Pediatr. 2013;163(6):1558-63.

26. Baik N, Urlesberger B, Schwaberger B, Schmolzer GM, Mileder L, Avian A, et al. Reference Ranges for Cerebral Tissue Oxygen Saturation Index in Term Neonates during Immediate Neonatal Transition after Birth. Neonatology. 2015;108(4):283-6.

Accepted manuscript

ACCEPTED MANUSCRIPT

27. Hessel TW, Hyttel-Sorensen S, Greisen G. Cerebral oxygenation after birth - a comparison of INVOS((R)) and FORE-SIGHT near-infrared spectroscopy oximeters. Acta Paediatr. 2014;103(5):488-93.

28. Fuchs H, Lindner W, Buschko A, Almazam M, Hummler HD, Schmid MB. Brain oxygenation monitoring during neonatal resuscitation of very low birth weight infants. J Perinatol. 2012;32(5):356-62.

29. Binder C, Urlesberger B, Avian A, Pocivalnik M, Muller W, Pichler G. Cerebral and peripheral regional oxygen saturation during postnatal transition in preterm neonates. J Pediatr. 2013;163(2):394-9.

30. Sweet DG, Carnielli V, Greisen G, Hallman M, Ozek E, Plavka R, et al. European Consensus Guidelines on the Management of Respiratory Distress Syndrome - 2016 Update. Neonatology. 2017;111(2):107-25.

31. Pichler G, Urlesberger B, Baik N, Schwaberger B, Binder-Heschl C, Avian A, et al. Cerebral Oxygen Saturation to Guide Oxygen Delivery in Preterm Neonates for the Immediate Transition after Birth: A 2-Center Randomized Controlled Pilot Feasibility Trial. J Pediatr. 2016;170:73-8 e1-4.

32. Alderliesten T, Dix L, Baerts W, Caicedo A, van Huffel S, Naulaers G, et al. Reference values of regional cerebral oxygen saturation during the first 3 days of life in preterm neonates. Pediatr Res. 2016;79(1-1):55-64.

33. Pryds O, Greisen G. Effect of PaCO2 and haemoglobin concentration on day to day variation of CBF in preterm neonates. Acta Paediatr Scand Suppl. 1989;360:33-6.

34. Dix LM, van Bel F, Lemmers PM. Monitoring Cerebral Oxygenation in Neonates: An Update. Front Pediatr. 2017;5:46.

35. Baenziger O, Stolkin F, Keel M, von Siebenthal K, Fauchere JC, Das Kundu S, et al. The influence of the timing of cord clamping on postnatal cerebral oxygenation in preterm neonates: a randomized, controlled trial. Pediatrics. 2007;119(3):455-9.

36. Katheria AC, Truong G, Cousins L, Oshiro B, Finer NN. Umbilical Cord Milking Versus Delayed Cord Clamping in Preterm Infants. Pediatrics. 2015;136(1):61-9.

Accepted manuscript

ACCEPTED MANUSCRIPT

37. Kooi EMW, Verhagen EA, Elting JWJ, Czosnyka M, Austin T, Wong FY, et al. Measuring cerebrovascular autoregulation in preterm infants using near-infrared spectroscopy: an overview of the literature. Expert Rev Neurother. 2017;17(8):801-18.

38. Alderliesten T, Lemmers PM, Smarius JJ, van de Vosse RE, Baerts W, van Bel F. Cerebral oxygenation, extraction, and autoregulation in very preterm infants who develop peri-intraventricular hemorrhage. The Journal of pediatrics. 2013;162(4):698-704 e2.

39. da Costa CS, Greisen G, Austin T. Is near-infrared spectroscopy clinically useful in the preterm infant? Arch Dis Child Fetal Neonatal Ed. 2015;100(6):F558-61.

40. Noori S, McCoy M, Anderson MP, Ramji F, Seri I. Changes in cardiac function and cerebral blood flow in relation to peri/intraventricular hemorrhage in extremely preterm infants. J Pediatr. 2014;164(2):264-70 e1-3.

41. Cerbo RM, Scudeller L, Maragliano R, Cabano R, Pozzi M, Tinelli C, et al. Cerebral Oxygenation, Superior Vena Cava Flow, Severe Intraventricular Hemorrhage and Mortality in 60 Very Low Birth Weight Infants. Neonatology. 2015;108(4):246-52.

42. Pansy J, Baik N, Schwaberger B, Scheuchenegger A, Pichler-Stachl E, Avian A, et al. Cerebral hypoxia during immediate transition after birth and short term neurological outcome. Early Hum Dev. 2017;110:13-5.

43. Hyttel-Sorensen S, Austin T, van Bel F, Benders M, Claris O, Dempsey E, et al. A phase II randomized clinical trial on cerebral near-infrared spectroscopy plus a treatment guideline versus treatment as usual for extremely preterm infants during the first three days of life (SafeBoosC): study protocol for a randomized controlled trial. Trials. 2013;14:120.

44. Hyttel-Sorensen S, Pellicer A, Alderliesten T, Austin T, van Bel F, Benders M, et al. Cerebral near infrared spectroscopy oximetry in extremely preterm infants: phase II randomised clinical trial. BMJ. 2015;350:g7635.

Accepted manuscript

ACCEPTED MANUSCRIPT

45. Plomgaard AM, van Oeveren W, Petersen TH, Alderliesten T, Austin T, van Bel F, et al. The SafeBoosC II randomized trial: treatment guided by near-infrared spectroscopy reduces cerebral hypoxia without changing early biomarkers of brain injury. Pediatr Res. 2016;79(4):528-35.

46. Plomgaard AM, Alderliesten T, Austin T, van Bel F, Benders M, Claris O, et al. Early biomarkers of brain injury and cerebral hypo- and hyperoxia in the SafeBoosC II trial. PLoS One. 2017;12(3):e0173440.

47. Toet MC, Lemmers PM, van Schelven LJ, van Bel F. Cerebral oxygenation and electrical activity after birth asphyxia: their relation to outcome. Pediatrics. 2006;117(2):333-9.

48. Lemmers PM, Zwanenburg RJ, Benders MJ, de Vries LS, Groenendaal F, van Bel F, et al. Cerebral oxygenation and brain activity after perinatal asphyxia: does hypothermia change their prognostic value? Pediatr Res. 2013;74(2):180-5.

49. Peng S, Boudes E, Tan X, Saint-Martin C, Shevell M, Wintermark P. Does near-infrared spectroscopy identify asphyxiated newborns at risk of developing brain injury during hypothermia treatment? Am J Perinatol. 2015;32(6):555-64.

50. Greisen G. Cerebral blood flow and oxygenation in infants after birth asphyxia. Clinically useful information? Early Hum Dev. 2014;90(10):703-5.

51. Howlett JA, Northington FJ, Gilmore MM, Tekes A, Huisman TA, Parkinson C, et al. Cerebrovascular autoregulation and neurologic injury in neonatal hypoxic-ischemic encephalopathy. Pediatr Res. 2013;74(5):525-35.

52. Murray DM, O'Connor CM, Ryan CA, Korotchikova I, Boylan GB. Early EEG Grade and Outcome at 5 Years After Mild Neonatal Hypoxic Ischemic Encephalopathy. Pediatrics. 2016;138(4).

53. Walsh BH, Neil J, Morey J, Yang E, Silvera MV, Inder TE, et al. The Frequency and Severity of Magnetic Resonance Imaging Abnormalities in Infants with Mild Neonatal Encephalopathy. J Pediatr. 2017;187:26-33 e1.

Accepted manuscript

ACCEPTED MANUSCRIPT

54. Jan S, Northington FJ, Parkinson CM, Stafstrom CE. EEG Monitoring Technique Influences the Management of Hypoxic-Ischemic Seizures in Neonates Undergoing Therapeutic Hypothermia. Developmental neuroscience. 2017;39(1-4):82-8.

55. Lamblin MD, Esquivel EW, Andre M. The electroencephalogram of the full-term newborn: Review of normal features and hypoxic-ischemic encephalopathy patterns. Neurophysiologie Clinique-Clinical Neurophysiology. 2013;43(5-6):267-87.

56. Skranes JH, Lohaugen G, Schumacher EM, Osredkar D, Server A, Cowan FM, et al. Amplitude-Integrated Electroencephalography Improves the Identification of Infants with Encephalopathy for Therapeutic Hypothermia and Predicts Neurodevelopmental Outcomes at 2 Years of Age. The Journal of pediatrics. 2017;187:34-42.

57. Hellstrom-Westas L, Rosen I. Continuous brain-function monitoring: state of the art in clinical practice. Semin Fetal Neonatal Med. 2006;11(6):503-11.

58. al Naqeeb N, Edwards AD, Cowan FM, Azzopardi D. Assessment of neonatal encephalopathy by amplitude-integrated electroencephalography. Pediatrics. 1999;103(6 Pt 1):1263-71.

59. Shany E, Goldstein E, Khvatskin S, Friger MD, Heiman N, Goldstein M, et al. Predictive value of amplitude-integrated electroencephalography pattern and voltage in asphyxiated term infants. Pediatr Neurol. 2006;35(5):335-42.

60. Lloyd RO, O'Toole JM, Pavlidis E, Filan PM, Boylan GB. Electrographic Seizures during the Early Postnatal Period in Preterm Infants. The Journal of pediatrics. 2017.

61. Murray DM, Boylan GB, Ali I, Ryan CA, Murphy BP, Connolly S. Defining the gap between electrographic seizure burden, clinical expression and staff recognition of neonatal seizures. Archives of disease in childhood Fetal and neonatal edition. 2008;93(3):F187-91.

62. Glass HC. Neonatal seizures: advances in mechanisms and management. Clin Perinatol. 2014;41(1):177-90.

Accepted manuscript

ACCEPTED MANUSCRIPT

63. Buraniqi E, Sansevere AJ, Kapur K, Bergin AM, Pearl PL, Loddenkemper T. Electrographic Seizures in Preterm Neonates in the Neonatal Intensive Care Unit. Journal of child neurology. 2017;32(10):880-5.

64. Glass HC, Shellhaas RA, Tsuchida TN, Chang T, Wusthoff CJ, Chu CJ, et al. Seizures in Preterm Neonates: A Multicenter Observational Cohort Study. Pediatric neurology. 2017;72:19-24.

65. Pavlidis E, Lloyd RO, Boylan GB. EEG - A Valuable Biomarker of Brain Injury in Preterm Infants. Developmental neuroscience. 2017.

66. Fogtmann EP, Plomgaard AM, Greisen G, Gluud C. Prognostic Accuracy of Electroencephalograms in Preterm Infants: A Systematic Review. Pediatrics. 2017;139(2).

67. Pavlidis E, Lloyd RO, Mathieson S, Boylan GB. A review of important electroencephalogram features for the assessment of brain maturation in premature infants. Acta paediatrica. 2017;106(9):1394-408.

68. Lloyd R, Goulding R, Filan P, Boylan G. Overcoming the practical challenges of electroencephalography for very preterm infants in the neonatal intensive care unit. Acta paediatrica. 2015;104(2):152-7.

69. West AE, Greenberg ME. Neuronal activity-regulated gene transcription in synapse development and cognitive function. Cold Spring Harb Perspect Biol. 2011;3(6).

70. Khazipov R, Luhmann HJ. Early patterns of electrical activity in the developing cerebral cortex of humans and rodents. Trends Neurosci. 2006;29(7):414-8.

71. Semple BD, Blomgren K, Gimlin K, Ferriero DM, Noble-Haeusslein LJ. Brain development in rodents and humans: Identifying benchmarks of maturation and vulnerability to injury across species. Progress in neurobiology. 2013;0:1-16.

72. Gatto CL, Broadie K. Genetic controls balancing excitatory and inhibitory synaptogenesis in neurodevelopmental disorder models. Front Synaptic Neurosci. 2010;2:4.

Accepted manuscript

ACCEPTED MANUSCRIPT

73. Ranasinghe S, Or G, Wang EY, Ievins A, McLean MA, Niell CM, et al. Reduced Cortical Activity Impairs Development and Plasticity after Neonatal Hypoxia Ischemia. The Journal of neuroscience : the official journal of the Society for Neuroscience. 2015;35(34):11946-59.

74. Gunn AJ, Parer JT, Mallard EC, Williams CE, Gluckman PD. Cerebral histologic and electrocorticographic changes after asphyxia in fetal sheep. Pediatric research. 1992;31(5):486-91.

75. Low E, Dempsey EM, Ryan CA, Rennie JM, Boylan GB. EEG suppression associated with apneic episodes in a neonate. Case reports in neurological medicine. 2012;2012:250801.

76. Murray DM, Boylan GB, Ryan CA, Connolly S. Early EEG findings in hypoxic-ischemic encephalopathy predict outcomes at 2 years. Pediatrics. 2009;124(3):e459-67.

77. Watanabe K, Hayakawa F, Okumura A. Neonatal EEG: a powerful tool in the assessment of brain damage in preterm infants. Brain Dev. 1999;21(6):361-72.

78. Lynch NE, Stevenson NJ, Livingstone V, Murphy BP, Rennie JM, Boylan GB. The temporal evolution of electrographic seizure burden in neonatal hypoxic ischemic encephalopathy. Epilepsia. 2012;53(3):549-57.

79. Le Bihannic A, Beauvais K, Busnel A, de Barace C, Furby A. Prognostic value of EEG in very premature newborns. Archives of disease in childhood Fetal and neonatal edition. 2012;97(2):F106-9.

80. Rosen MG, Scibetta JJ. The human fetal electroencephalogram. 2. Characterizing the EEG during labor. Neuropadiatrie. 1970;2(1):17-26.

81. Frasch MG, Durosier LD, Gold N, Cao M, Matushewski B, Keenliside L, et al. Adaptive shut-down of EEG activity predicts critical acidemia in the near-term ovine fetus. Physiological reports. 2015;3(7).

82. Korotchikova I, Stevenson NJ, Livingstone V, Ryan CA, Boylan GB. Sleep-wake cycle of the healthy term newborn infant in the immediate postnatal period. Clinical neurophysiology : official journal of the International Federation of Clinical Neurophysiology. 2016;127(4):2095-101.

Accepted manuscript

ACCEPTED MANUSCRIPT

83. Tamussino A, Urlesberger B, Baik N, Schwaberger B, Binder-Heschl C, Schmolzer GM, et al. Low cerebral activity and cerebral oxygenation during immediate transition in term neonates-A prospective observational study. Resuscitation. 2016;103:49-53.

84. Pichler G, Avian A, Binder C, Zotter H, Schmolzer GM, Morris N, et al. aEEG and NIRS during transition and resuscitation after birth: promising additional tools; an observational study. Resuscitation. 2013;84(7):974-8.

85. Rennie JM, Chorley G, Boylan GB, Pressler R, Nguyen Y, Hooper R. Non-expert use of the cerebral function monitor for neonatal seizure detection. Arch Dis Child Fetal Neonatal Ed. 2004;89(1):F37-40.

86. Shellhaas RA, Soaita AI, Clancy RR. Sensitivity of amplitude-integrated electroencephalography for neonatal seizure detection. Pediatrics. 2007;120(4):770-7.

87. Shah DK, Mackay MT, Lavery S, Watson S, Harvey AS, Zempel J, et al. Accuracy of bedside electroencephalographic monitoring in comparison with simultaneous continuous conventional electroencephalography for seizure detection in term infants. Pediatrics. 2008;121(6):1146-54.

88. Finn D, O'Toole J, Herlihy I, Dempsey E, Boylan G. Electroencephalography (EEG) in healthy term infants within 10 minutes of birth. European Journal of Pediatrics. 2017;175(11):1671-2.

89. Chang T, Tsuchida TN. Conventional (continuous) EEG monitoring in the NICU. Current pediatric reviews. 2014;10(1):2-10.

90. Murphy K, Stevenson NJ, Goulding RM, Lloyd RO, Korotchikova I, Livingstone V, et al. Automated analysis of multi-channel EEG in preterm infants. Clinical neurophysiology : official journal of the International Federation of Clinical Neurophysiology. 2015;126(9):1692-702.

91. Matic V, Cherian PJ, Koolen N, Ansari AH, Naulaers G, Govaert P, et al. Objective differentiation of neonatal EEG background grades using detrended fluctuation analysis. Frontiers in human neuroscience. 2015;9:189.

Accepted manuscript

ACCEPTED MANUSCRIPT

92. Koolen N, Oberdorfer L, Rona Z, Giordano V, Werther T, Klebermass-Schrehof K, et al. Automated classification of neonatal sleep states using EEG. Clinical neurophysiology : official journal of the International Federation of Clinical Neurophysiology. 2017.

93. Dunne JM, Wertheim D, Clarke P, Kapellou O, Chisholm P, Boardman JP, et al. Automated electroencephalographic discontinuity in cooled newborns predicts cerebral MRI and neurodevelopmental outcome. Archives of disease in childhood Fetal and neonatal edition. 2017;102(1):F58-F64.

94. O'Toole JM, Boylan GB, Vanhatalo S, Stevenson NJ. Estimating functional brain maturity in very and extremely preterm neonates using automated analysis of the electroencephalogram. Clinical neurophysiology : official journal of the International Federation of Clinical Neurophysiology. 2016;127(8):2910-8.

95. Ahmed R, Temko A, Marnane W, Lightbody G, Boylan G. Grading hypoxic-ischemic encephalopathy severity in neonatal EEG using GMM supervectors and the support vector machine. Clinical neurophysiology : official journal of the International Federation of Clinical Neurophysiology. 2016;127(1):297-309.

96. Stevenson NJ, Korotchikova I, Temko A, Lightbody G, Marnane WP, Boylan GB. An automated system for grading EEG abnormality in term neonates with hypoxic-ischaemic encephalopathy. Annals of biomedical engineering. 2013;41(4):775-85.

Accepted manuscript