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Quick and accurate quantification of the premature brain

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The immature brain is selectively vulnerable to injury (Volpe, 2009; Bonifacio et al., 2015) and premature birth places children at increased risk of chronic neurological morbidities including epilepsy, motor impairment, and cognitive delay (Back et al., 2007; Nardou et al., 2013). In spite of the increased risks, acute brain damage can be particularly difficult to identify in premature neonates. Neurological evaluations remain limited because the underdeveloped brain lacks the sophisticated functions that can be easily tested at the bedside and thus provides little prognostic information on cortical development (Yang, 2004). To complement the clinical exam, neuromonitoring with electroencephalogram (EEG) is a non-invasive tool that offers continuous measurement of subclinical brain cortical activity and has become increasingly utilized in neonatal intensive care units (Abend et al., 2013). Continuous EEG monitoring provides increased diagnostic and prognostic information and has been formally recommended for use in all neonates at risk of brain injury by the American Clinical Neurophysiology Society (Shellhaas et al., 2011). Given the unique vulnerabilities of the immature brain and the additional limitations of the clinical examination, growing evidence suggests that premature neonates stand to benefit even further from continuous EEG monitoring (Glass et al., 2016; Kahle and Staley, 2012).

Although much recent work has focused on detection of electrographic seizures in the immature brain using EEG (Nardou et al., 2013; Uria-Avellanal et al., 2013; Abend et al., 2013), abnormal EEG background activity even in the absence of seizures also provides useful prognostic information (Holmes and Lombroso, 1993). Longstanding observations note that mild, moderate and severe EEG abnormalities closely parallel the well-established Sarnat criteria for neonatal encephalopathy (Sarnat and Sarnat, 1976). Several studies have also demonstrated that abnormal backgrounds in the neonatal EEG correlate with long term prognosis (Monod et al., 1972; Tharp et al., 1981; Bjerre et al., 1983; Hellstrom-Westas and Rosen, 2006; Holmes et al., 1982; Biagioni et al., 2001; Hellstrom-Westas et al., 1995; Toet et al., 1999). Indeed, the return of normal EEG background features is currently the best available biomarker for neurological prognosis in neonatal encephalopathy (Bonifacio et al., 2011).

The normal EEG background in a premature infant however is not static. The expected EEG patterns that comprise a healthy brain physiology vary dramatically and rapidly over the first several months of perinatal development (Parmelee et al., 1968). Several well characterized

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features progress along a stereotyped sequence including dynamic changes in background continuity, amplitude, frequency content, interhemispheric synchrony, inter-burst interval duration, sleep states and the presence, location, and morphology of sharp transients (Tsuchida et al., 2013). On visual analysis of the EEG, an experienced neonatal encephalographer can evaluate the presence or absence of these features to estimate the age of a premature infant within two weeks (Shellhaas et al., 2011). The absence of expected EEG features at a stated gestational age suggests delayed brain maturation, termed dysmaturity, and correlates with increased risk of abnormal neurological outcome (Biagioni et al., 1996; Holmes and Lombroso, 1993).

In spite of the known utility of the EEG background in prognostication for premature neonates, there are many practical barriers that currently limit our ability to optimize the information available for these children. Because of the dynamic nature of the normal background, neonatal EEGs are difficult to interpret, requiring additional time and expertise to identify subtle background abnormalities. In addition, the volumes of data collected through continuous EEG monitoring is time-consuming and laborious to review such that an interpretation of the continuous data is typically only provided by clinical experts every 12–24 h (Shellhaas et al., 2011). A reliable automated detector of important features would enable more available and consistent estimation of background activity. In addition, more consistent attention to background features would provide increased understanding of their clinical significance as a biomarker for outcome.

In this issue of Clinical Neurophysiology, O'Toole et al. utilize automated analysis of EEG recordings to estimate gestational age in a cohort of 49 preterm neonates ranging from 23 to 32 weeks gestational age (O'Toole et al., 2016). Rather than pursuing an unassisted approach, the authors quantify clinically described features in the EEG of premature neonates. They first categorize the EEG into high or low activity states representing active sleep versus quiet sleep. The authors then focus on three classes of features: amplitude, spatial organization, and temporal organization. The resultant classification was then tested against a gold standard database of EEGs determined to be appropriate for maturational age by an experienced neurophysiologist. This groups' automated approach was able to estimate maturational age with a correlation of 0.889 with known gestational age and correctly aged 87% of premature infants within 2 weeks. Among the 49 premature neonates, two were not able to be accurately classified. Overall, the estimator performed with an improved standard deviation of error of approximately 4 days compared to expert visual analysis.

This study was limited by a small sample size and validation that was only tested against hand-picked EEGs selected by a single neurophysiologist. As this same group has noted that inter-rater agreement varies among neonatal neurophysiologists (Stevenson et al., 2015), this algorithm remains to be tested against other readers. Furthermore, the clinical utility of this automated estimator relies on its ability to perform on clinically ill children and remains to be tested on a representative clinical population including premature neonates with abnormal EEGs. Nonetheless, this study provides an important step to reliably categorize the dynamic cortical physiology present during early cortical maturation and contributes to an exciting growing literature that careful quantification of clinically recognized EEG features can provide reliable and improved EEG classification in this age group (Iyer et al., 2015).

Successful characterization of the complex age-specific baseline present in early development paves the road for future work to unmask the subtle abnormalities that may present on top of this background and further accelerate our discovery of novel physiological biomarkers of cortical development and disease.

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