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Review

Automated EEG-sleep analyses and neonatal neurointensive care

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Abstract

Clinical applications of neonatal EEG-sleep studies can improve neurointensive care for preterm and fullterm infants. Behavioral and physiologic assessments of neonatal sleep by nursing and physician personnel can result in more developmentally appropriate state regulation for infants, particularly for those who require medical care for many weeks to months in the intensive care unit. Secondly, prediction of altered expressions of EEG-sleep patterns for those children at higher risk for neurological sequelae can anticipate the need for aggressive interventional strategies. The application of digital analyses of specific cerebral and noncerebral physiologic measures for long-term monitoring periods can utilize efficient and novel strategies of automated EEG and sleep state identification which can also assist in daily medical care and prediction of neurodevelopmental outcome.

Keywords: Neonate; EEG-sleep; Automated analyses; Neurointensive care; Neuroplasticity

1. The modern *NICU*: progress and challenges

Newborn mortality rates for the United States have dramatically decreased from 12 per 1000 live births in the 1980s to less than 7 per 1000 live births by the end of the millennium [1]. This reduction in mortality has resulted in an increased percentage of survivors, many of whom are premature and have low birthweight (LBW). Advances in both prenatal and neonatal care account for this improved neonatal survival, specifically for the lowest birthweight groups. There has also been a reduction in specific neonatal neurological morbidities, exemplified by two principal cerebrovascular injuries of the newborn (i.e. severe intraventricular hemorrhage and periventricular leukomalacia). The occurrence of these vascular injuries have been reduced, particularly for LBW populations [2,3].

Paradoxically there also can be a negative impact of neonatal intensive care practices on the developing brain [4] which contribute to later morbidities. Severe neurosensory impairments, for example, occur in infants under 1000 gm, involving as high as 40% of survivors [2]. Unfortunately potential medical and environmental risk factors exist in modern neonatal intensive care units (NICU's) which adversely affect brain development, given prolonged hospitalizations for up to 3–4 months after birth, usually after a high-risk prenatal period [5]. Strategies to reduce neurobehavioral and cognitive deficits, particularly for LWB populations, therefore, remain a high priority for children treated in present day NICU's. A recent NIH report [6] challenges clinical scientists to translate the remarkable findings achieved by basic neuroscience research regarding neuroplasticity of the developing brain into useful therapies. Better surrogate markers of brain maturation and organization are therefore needed to document neurodevelopmental progress, determine therapeutic effectiveness of interventional strategies, enhance the efficiency of clinical trials using pharmacologic and nonpharmacologic protocols, and improve environmental conditions in the NICU.

2. Neurophysiologic assessment of high risk neonates

Electroencephalographic and polysomnographic studies of the newborn have assisted in bedside assessment of functional brain maturation and the detection of brain disorders for over half a century [7–15]. Serial neonatal neurophysiologic assessments offer the clinician important

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neurodevelopmental information concerning the severity and persistence of brain disorders in the context of expected functional brain maturation [16]. Recognition of EEG abnormalities readily identify severe brain abnormalities [17], such as suppression-burst (Fig. 1) low voltage invariant and multifocal seizure patterns. However, severe EEG pattern abnormalities reflect significant brain disorders for only a minority of patients (i.e. 10–15% of NICU patients) [18,19]. Less severe encephalopathies are expressed for the majority of neonates (i.e. 85–90%), as documented by serial EEG studies [18,19]. Even the most severely encephalopathic EEG records shortly after birth will generally convert over days or weeks to less severe and more pervasive physiologic expressions of poor state regulation. The subtle expressions of brain dysfunction after resolution of the acute encephalopathic phase of a brain disorder [18,19] may help identify which neonates remain at higher risk for more pervasive neurodevelopmental problems. Asymptomatic infants who lack clinical evidence of an encephalopathy may also express neurophysiologic dysfunction in terms of dysmature EEG patterns and/or altered state regulation, which predict compromised outcome, as exemplified by neonatal cohorts with prenatal substance exposure [20,21], chronic lung disease and prematurity [22,23]. Recognition of electrographic findings such as inter-hemispheric asynchrony and excessive delta brush patterns or polygraphic findings such as dyssynergy (i.e. inappropriate physiologic behaviors for the given state) between cerebral and noncerebral measures reflect impaired functional brain organization [16] (Fig. 2a and b). Consequently, there is a clinical need to apply neonatal sleep analyses to the majority of high risk preterm and fullterm neonates who do not express a severe brain disorder on either clinical examination or routine EEG recordings.

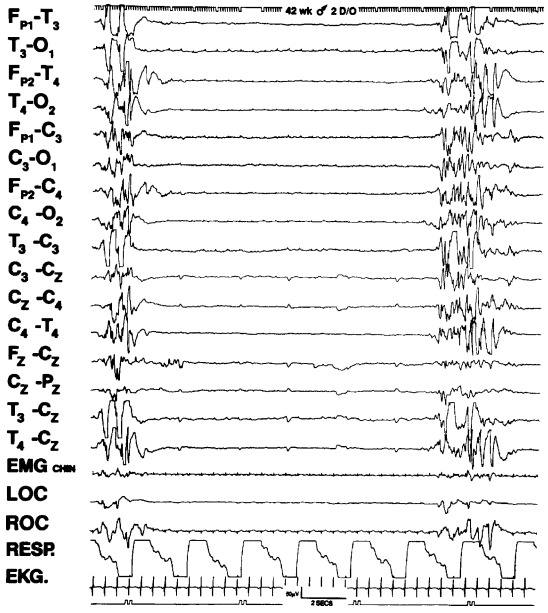

Fig. 1. EEG segment of a fullterm infant who has severe encephalopathy on day two of life demonstrating a suppression-burst pattern.

Computerized neonatal EEG-sleep analyses for this large neonatal cohort can provide novel and time-efficient strategies to acquire diagnostic and prognostic information. Use of an automated bedside device to assess state regulation would provide medical personnel with more effective means by which we could adjust medical practices in the NICU to optimize day-to-day care, as well as counsel families and other health professionals regarding early intervention strategies to lessen or eliminate neurological morbidities.

3. Digital analyses of electroencephalographic/polysomnographic studies—primarily for older patients

Improved technologies to store data, retrieve information and perform calculations by computer-based recording devices have allowed advances in automated sleep state detection for older patients [24]. These advances have been paralleled by a greater sophistication in mathematical modeling, including the study of nonlinearity of datasets, which can assist with the detection of novel events or periodicities in seemingly random background information. Such computations have been applied to the fields of epilepsy for seizure prediction and sleep medicine for apnea detection [25], but have not been uniformly applied to sleep state prediction.

The diagnosis of sleep physiology and pathology for older patients is based on a worldwide practice that uses a classification scheme defined by a polysomnographic consensus committee first lead by Rechtschaffen and Kales [26]. This group recommended a standard scoring methodology using visual analysis, by which 20–30 second epochs of polysomnograms are scored using multiple physiologic measures to define six sleep state stages, including wakefulness, light to deep sleep (i.e. nonREM sleep stages 1–4) and REM sleep over a 60—90 min cycle which will vary in length over the nighttime sleep period. Scored values are qualitatively derived with considerable variation among different scorers because of interscorer variability which will range from 67 to 91% [24]. In addition, visual scoring is time-consuming, tedious and difficult to perform on technically substandard recordings which also contain abnormal physiologic patterns.

Automation of sleep state staging has been proposed over the last 30–35 years by various authors, primarily using rule-based methods applied from subjective interpretations of sleep studies. Some of these earlier automated strategies suggested period analysis [27], EEG spectra with multiple discriminant analysis [28] and a combination of analog and digital techniques [29]. More recent methodologies for sleep scoring suggest pattern recognition [30], wave detection with a Bayesian approach [31], interval histogram methods

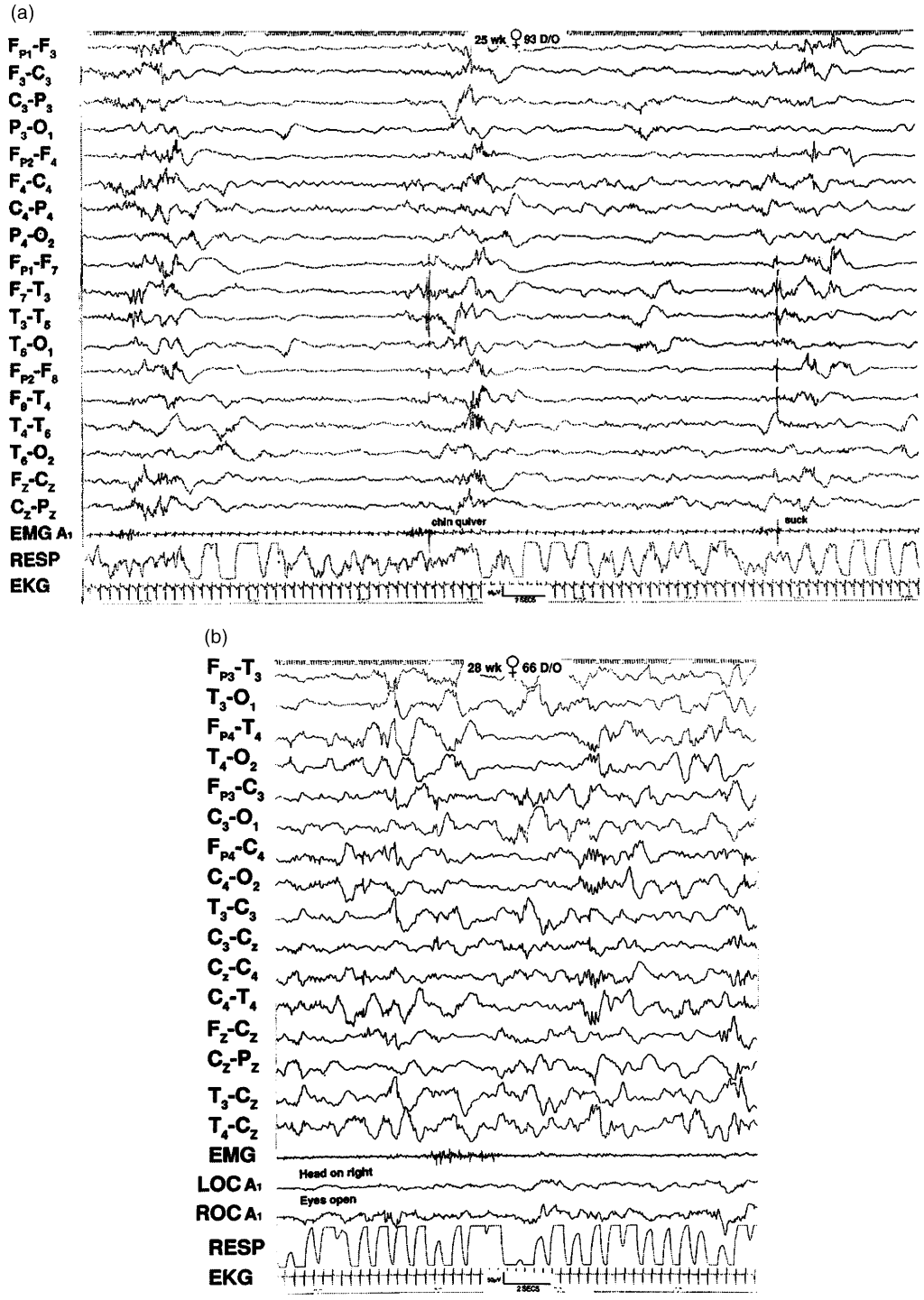

Fig. 2. (a) Dysmaturity seen in a corrected fullterm infant showing excessive interhemispheric asynchrony, delta brushes, and discontinuity; (b) is an example of dysserngy (i.e. irregular respiratory rate during quiet sleep for a corrected age fullterm infant).

[32], expert systems [33] and neural network approaches [34], as cited by Agarwal [24]. Compared to visual scoring agreements, accuracy of these automated techniques range from 75 to 85%.

Most rules applied to automated sleep state detection are based on thresholds of detection for selected physiologic measures that were subjectively chosen by the user. Applications to clinical practice have not been uniformly tested; deterioration in performance of these methods is anticipated because of technical and medical conditions. Agarwal [35,24] suggested a three-stage computer-assisted method of automated sleep detection to improve performance for adults. Naturally occurring patterns on the sleep recording, based on visually identified primitive features are

applied to an automated staging paradigm, based on the particular user's preference. These authors specifically chose automated programs for sleep spindles, respiratory patterns, periodic leg movements and REMS. A third stage of revalidation by visual analysis by the specific user after automated detection was then suggested to avoid the use of hard 'thresholds' that cannot adapt to the staging rules of each user's preference. This system applied feature detection methods during sleep of older patients, and cannot be applied to the neonate because of fundamental differences in sleep architecture, continuity, phasic activities and EEG patterns.

4. Automated neonatal state detection strategies

Comparatively less attention has been directed to automated analyses of neonatal EEG-sleep studies. Scher [36] reviewed the field prior to the most recent computer advances over the last decade, emphasizing the unique neurophysiologic expressions of state transitions that occur in the newborn that do not exist in the older patient. These differences include a shorter sleep cycle, prominent EEG delta rhythms, intra- and interhemispheric electrographic asynchrony, discrete neonatal waveform patterns (e.g. delta brush and theta bursts), a high percentage of periodic breathing, greater heterogeneity of rapid eye movements and unique motor patterns that reflect fetal rather than more mature postnatal movements seen during infancy. Sleep morphologies noted in older patients such as sleep spindles or vertex waves are not expressed during neonatal sleep. Conventional wisdom also historically assumed that only term infants (i.e. 37 weeks gestational age or older) express an organized neonatal sleep cycle, while rudimentary states are expressed in preterm neonates [16]. Applications of EEG-sleep analyses in the neonatal intensive care setting also remain a formidable challenge, given the adverse technical and clinical conditions, even for the experienced EEG technologist and neurophysiologist.

Automated strategies for sleep state detection in the newborn initially experimented with computer computations of spectral EEG energies, assuming stationarity of the signals [37]. Scher et al. [36] later suggested that time-dependent information concerning physiologic signals within epochs of neonatal sleep should alternatively use techniques that detect either stationarity or nonstationarity of a desired signal. Nonstationarity methods of analyses assume that the statistical relationships among neurophysiologic signals are nonlinear and change over time [38]. Computations which anticipate such nonlinearity can therefore address brief or rapid changes in neurophysiologic signals which have time-limited nonstationary behavior. Slower changes in signals require the use of longer time intervals for analysis, and nonstationarity becomes a more critical issue. While analyses have been applied to the neurophysiologic assessments of comatose adult patients [39], pharmacological studies [40], and adult sleep studies [41,42], little attention has yet been directed to the neonatal populations.

Neonatal sleep analyses from the 1970s into the first years of the present decade continued to assess functional brain organization and maturation using analysis methods that were based on assumptions of stationarity, without consideration of time-dependent changes [11,43–50]. One methodological preference was the Fast Fourier transform analyses (FFT) primarily to EEG signals, sometimes applying various filtering maneuvers, on primarily fullterm neonatal cohorts [51–55]. Selected reports of preterm neonates also used these conventional spectral EEG power analyses [56–62]. Calculations based on assumptions of stationarity were also applied to selected neonatal and infant risk groups for sudden infant death [63], apnea [60], hyperbilirubinemia [64], white matter necrosis [65] and asphyxia [66].

5. Cerebral function monitoring—a minimalist approach

Cerebral function monitoring (*CFM*) was previously reviewed over 25 years ago, [67], with studies as early as the late 1960s [68]. This somewhat oversimplified technique displays spectral analyses consisting of both frequency and amplitude changes from single-channel EEG recordings. The renaissance of this 'old' technology in the 1990s reintroduced the suggestion that bedside portable computerized EEG recording devices can offer trend-information regarding CNS function and maturation [66,69]. Optimal applications for such technologies should still require comparison studies with conventional EEG/sleep recordings, since the latter provide regional and hemispheric information, as well as valuable polygraphic information regarding state regulation [70].

Since the initial EEG recordings by the Japanese and the French in the 1950s, [71,72] real-time EEG sleep studies offer important diagnostic and prognostic information regarding brain organization, maturation and possible evidence of physiologic dysfunction. It would be too simplistic to assume that a single-channel of EEG can adequately document most neonatal seizures for example, which are generally focal, document regional sharp wave phenomena such positive sharp waves (i.e. associated with intraventricular hemorrhage and periventricular leukomalacia), or adequately described EEG/sleep dysmaturity which reflect altered brain development. While more laborious, visual analysis interpretations of EEG-sleep recordings by skilled neonatal neurophysiologists continue to provide clinically useful information.

CFM devices, which can record two to four channels of data, may in fact more efficiently approximate major bihemispheric or regional cerebral changes, with bedside

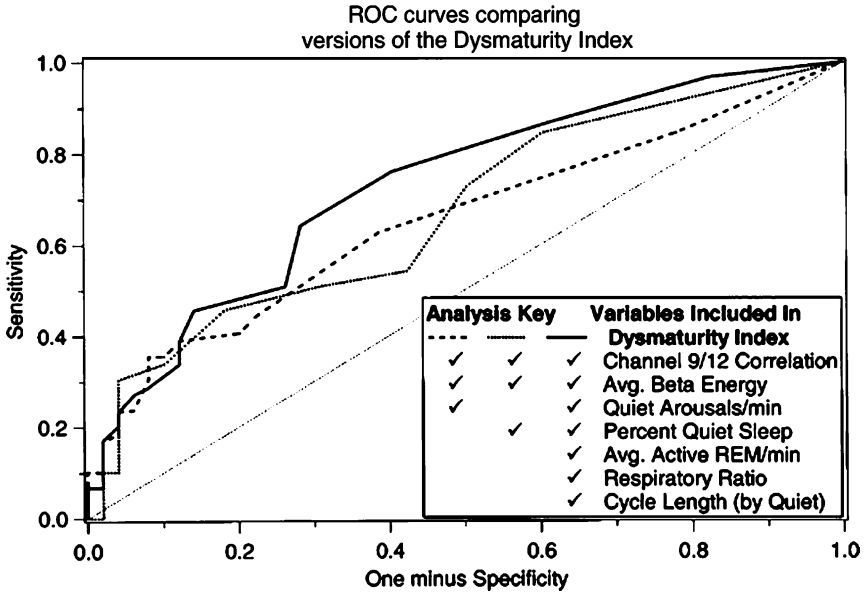

Fig. 3. Sleep study: ROC curves for DI. Receiver–operator characteristic curves for the dysmaturity index (DI) demonstrating greater area under the curve when seven vs. three sleep behaviors were compared between neonatal cohorts. Note the *Y* axis represents the preterm cohort while the *X* axis represents fullterm infants. (Reprinted with permission Scher et al., 2003).

convenience over long recording periods. This simplified tool could positively impact on neurointensive care practices by nurses and physicians in our modern neonatal intensive care units. These 'trending' devices still need to be compared with conventional EEG/polygraphic analyses in future studies. Automated analyses of cerebral and noncerebral physiologic measures must assume a more dominant position in the neonatal intensive care units, utilizing both linear and nonlinear mathematical algorithms to characterize state regulation [36].

6. Physiologic Brain Dysmaturity and automated analysis

Few reports have compared spectral measures of EEG with selected noncerebral measures that constitute state regulation [73,74]. Automated analysis methods of neonatal sleep have been applied to both cerebral and noncerebral measures to define state transitions, combining computations that detect and quantify stationary as well as nonstationary behaviors. Simultaneous assessment of multiple cerebral and noncerebral measures have been emphasized for neonatal state definitions [75], as applied to sleep analyses in older patients. Spectral analyses of EEG [76–79], cardiorespiratory behavior [80], temperature [81,82], arousal behavior [22,75,77,83] and REMs [23,75,79] have established that important physiologic differences during sleep exist between healthy preterm and fullterm cohorts. These differences, in turn, have been incorporated into a statistical model of functional brain dysmaturity, comprised of an index of seven selected physiologic measures [18,19,79,84,85], to characterize differences in brain organization and maturation between healthy preterm and fullterm cohorts (Fig. 3). Such an index may reasonably represent altered neuronal circuitry signifying altered developmental neuroplasticity because of conditions of prematurity, expressed as either delayed or accelerated physiologic behaviors during sleep.

Nonlinear computations have also been applied for feature extraction of neonatal EEG signals [86], and arousal phenomena [83], as well as to predict state or outcome [87–89] (Fig. 4). Differences in sleep organization and

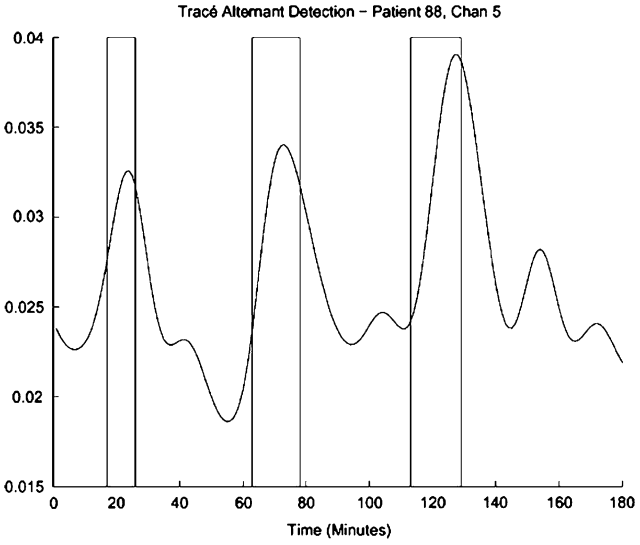

Fig. 4. Discrete wavelet transform (DWT) after smoothing (boxed areas—visually identified periods of tracé alternant) note the peaks in the DWT during periods of tracé alternant quiet sleep. (Reprinted with permission, Turnbull et al., 2001).

maturation between healthy preterm and fullterm neonatal cohorts can also be compared with medically ill cohorts of varying gestational ages [18,19,23], suffering from a variety of medical conditions.

7. Biologic relevance of an automated neonatal sleep detector

Advances in developmental neuroscience over the last 15 years have expanded our knowledge-base regarding the sequential steps in brain maturation, particularly at molecular or cellular levels. Later developmental stages extend into postnatal life and represent the complicated process of maturation characterized by remodeling or resculpturing of the brain, sometimes termed neuroplasticity (i.e. activity-dependent development). Use or disuse of specific neural networks leads to pruning and remodeling of the brain's neuronal circuitry. Apoptosis or programmed cell death also contributes to modifying brain structure and function during prenatal and postnatal periods [90,91]. During the last trimester of pregnancy and into postnatal life, dendritic arborization, synaptogenesis, myelination and neurotransmitter development rapidly occur in the immature brain [92] during which adverse conditions of prematurity (i.e. both during prenatal and postnatal time periods), medical illnesses and environmental stresses collectively alter the process of developmental neuroplasticity of specific neuronal networks. Given that remodeling of neuronal connectivity is ultimately required for the expression of complex physiologic behaviors at older ages such as sleep and cognition [93], aberrant remodeling may alternatively be expressed as neurocognitive, neurobehavioral or sleep problems.

Automated neurophysiologic methodologies to assess neonatal state organization and maturation offer an opportunity to create a surrogate marker of developmental neuroplasticity. Computational algorithms applied to selected physiologic measures of neonatal sleep provide insights into the manner by which neuronal networks change and adapt over long time periods during extrauterine life under adverse medical and socioeconomic conditions, in the context of prenatal conditions and genetic endowment. Application of the methods of nonlinear as well as linear dynamics to experiments in neurobiology will help characterize the biologic process of developmental neuroplasticity [94]. Computational analyses of complex stimuli, which reflect changes in neuronal circuitry, will enhance our understanding of the encoding and transmission of information by neuronal networks that subserve complex functions ranging from sleep to cognitive performance. The application of these processing techniques in the neonatal intensive care unit to assess EEG-sleep state organization and maturation will transform the NICU into neonatal neurointensive care facilities. Such technologies will ultimately improve the care provided by all types of health professionals working within this specialized facility.

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