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Case Report
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# A Muscle Relaxant's Impact on Neonatal Babies' Cognitive Development

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## Abstract

Data on the effects of analgesics and sedatives on the brain are needed to develop safe and effective treatments during neonatal intensive care. Electroencephalography (EEG) is an objective but interpretation-dependent method for monitoring cortical activity. Quantitative computational analysis can reveal changes in the EEG that are otherwise undetectable. EEG recordings were retrospectively collected from her 21 infants (mean gestational age 38.7 weeks, range 27–42) who received dexmedetomidine during neonatal care. Registrations were converted to computational functions and analyzed visually, using two computational measures to determine relative and absolute changes in performance (regional EEG; rEEG) and cortico-cortical synchrony (Activation Synchronicity Index; ASI). were quantified respectively. Visual assessment did not reveal any drug effects. rEEG analysis found a negative correlation between baseline and reference frontal (rho = 0.612, p = 0.006) and parietal (rho = -0.489, p = 0.035) leads. ASI changes were negatively correlated with interhemispheric baseline values (rho = -0.753; p = 0.001) and frontal comparisons (rho = -0.496; p = 0.038). Dexmedetomidine brain effects as determined by neonatal EEG were associated with pre-DEX cortical activity, with higher levels of brain activity during baseline (higher rEEG) leading to more pronounced reductions with DEX. Computational measurements show drug effects on both global cortical activity and cortico-cortical communication. These effects were not evident by visual analysis.

**Keywords:** Brain monitoring; Sedative drug; Dexmedetomidine; Newborn; EEG analysis

## Introduction

Newborn, premature, and/or critically ill infants require weeks of care in the neonatal intensive care unit (NICU). This period is characterized by marked hemodynamic instability, increased susceptibility to environmental and treatment-related adverse events, and rapid brain development [1]. Previous research has shown that pain and stress in newborns can adversely affect neurodevelopment. This is evidenced by structural abnormalities and abnormal neurobehavioral consequences. Analgesics and sedatives, most commonly opioids, are commonly used to reduce pain and stress during neonatal critical care [2]. However, these agents have immediate cardiovascular and respiratory side effects, as well as long-term negative effects related to apoptosis and decreased brain growth. To reduce opioid dosage, alpha 2 agonists (clonidine and dexmedetomidine; DEX) have recently been introduced as add-on treatments in neonatology. These drugs are considered safe. However, its use in the NICU was 'empirical' and not 'evidence-based' as recommended by the European Medicines Agency (EMA) [3].

Since analgesics and depressants have brain effects, drug exposure assessments should add objective brain measures to extracerebral variables such as behavioral responses and cardiovascular effects. This is especially important in neonates, as neurobehavioral responses, including levels of consciousness, arousal, or pain, can be difficult to assess. Electroencephalography (EEG) and amplitude-integrated EEG (compressed visual representation of the EEG signal, aEEG) have been used to objectively assess drug effects in the brain [4]. Previous studies have shown that morphine and midazolam can cause inhibition of cortical activity. A recent study by Cortes-Ledesma et al. suggested a reduction in general and interindividual variables in brain activity after DEX administration. In addition, there are unpublished data from infants treated with DEX suggesting that global EEG abnormalities are disproportionately accentuated compared to clinical manifestations (Vanhatalo, unpublished observations) [5].

Brain monitoring of aEEG trends for seizure detection and assessment of cortical activity. The presence of a sleep-wake cycle is routinely practiced in the NICU. Although aEEG is useful for general qualitative bedside clinical assessment, interpretation of aEEG is still a subjective assessment, subject to large inter-rater less sensitive to influences [6]. With the goal of evidence-based and safe drug treatment, studies using objective quantitative methods and reducing the risk of interpretation-related differences are needed. Two such studies of his in the neonatal context were recently published. Filer, etc. We used the Activation Synchrony Index to describe how cortical synchrony is affected by morphine, and van't Westende et al. in a systematic review found quantitative EEG measurements to be associated with long-term outcomes. However, no quantified computational measures of the effects of DEX on neonatal brain function have been published [7].

In this study, we aimed to develop an objective and quantitative method to measure the effects of DEX administration on the brain. In particular, he aimed to capture two conceptually distinct mechanisms of brain function. Global levels of cortical activity and levels of interhemispheric communication measured by range EEG (rEEG) and Activation Synchrony Index (ASI), respectively [8]. Both are important components of healthy brain function in conventional EEG interpretation. Our hypothesis was that rEEG and ASI may reveal subtle contextual effects on cortical activity. H. Compared to sustained cortical activity upon drug administration [9].

## Materials and Methods

EEG data were collected retrospectively from the Helsinki University Central Hospital, Finnish Children's Hospital, and Neonatal Intensive Care Unit archives. The records included preterm and term

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infants with a mean gestational age of 38.7 weeks (range 27-42) who underwent DEX for clinical purposes with continued EEG use between April 2013 and September 2016 ( n = 21) cohort. of their clinical care.

Recordings were made with the NicOne EEG system. Collect four EEG signals with common reference at Fz (frontal midline) and Cz (central midline). EEG scans were performed at 250 Hz and the frequency band from 0.2 to 35 Hz was investigated because it is a common band range for clinical EEG. From EEG recordings of various lengths, we selected 2 h epochs before and after DEX administration [10].

## Discussion

Our findings show that the use of computer measurements for EEG analysis can reveal otherwise undetectable effects of sedatives, and in our case, the effects of DEX. Statistical analysis of shows a negative correlation between baseline and the effects of DEX administration that could not be detected by visual inspection of time trends. Apparently, human assessments are not efficient enough to detect detailed differences in temporal trends, and robust quantitative measures are needed. We showed that treatment with DEX affected neonatal cortical activity, with drug-related effects proportional to pre-drug brain activity.

From the nine different computational metrics presented in my master's thesis, I selected two that I believe are most relevant to the neonatal population. First, we hypothesized that an amplitude-based index from rEEG captures the effect, based on previous literature showing a general decrease in brain activity after exposure to drugs that affect the central nervous system. Second, clinical experience with visual EEG review suggests a possible reduction in interhemispheric synchrony with DEX, hence the activation synchrony index (ASI), and the only validated measure of interhemispheric synchrony. Initial visual trend analysis did not reveal any significant changes.

As expected with a sedation regimen, our results show that DEX administration affects cortical activity in neonates. However, we were also able to show that the effect depends on individual cortical activity upon drug administration. This effect is significant and can be quantified using both amplitude-based measurements (rEEG) and measurements of cortico-cortical activation synchronization (ASI). It is now well established that cortico-cortical synchronization is a fundamental feature of brain function. Burst-level synchrony, more accurately measured by the ASI metric, is thought to reflect a developmentally essential communication mechanism in early brain networks. Our results show that cortico-cortical network (ASI) synchrony or levels of general brain activity (rEEG) only decrease when there is a sufficient age-dependent level of synchrony or activity amplitude, it indicates that brain pathology depends and must be considered when using these metrics clinically or in research.

## Conclusions

The sedative effect of dexmedetomidine in neonates is manifested as a reduction in cortical activity that defies conventional visual EEG interpretation, but can be quantified with computer measurements. These analyzes indicate that the higher the level of brain activity and synchronization before drug administration, the greater the reduction associated with DEX administration. Further research is needed to evaluate and develop computerized EEG analysis to facilitate reliable and objective monitoring of effective and safe drug use in the NICU.

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