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## EDITORIAL

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## Playing music to preemies: boosting of soothing the brain?

Progress in neonatal intensive care has rapidly shifted its focus from treating cardiorespiratory systems to optimising neurological stability in an attempt to improve neurodevelopmental outcomes. Protecting the brain has traditionally implied attempts to avoid brain injuries, such as intraventricular haemorrhage. However, advances in basic developmental neurobiology have made it clear that developmental adversities may become embedded in an activity-dependent manner, because early brain development is crucially dependent on endogenous brain activity. Early neuronal activity regulates the neurotrophic support necessary for neuronal survival, as well providing the guidance needed for precise targeting of growing neuronal networks (1). Hence, preserving physiological brain function, namely neuronal activity, is considered a key target in neurological care. Early neuronal activity is known to be sensitive to a host of factors that the newborn infant faces in the neonatal intensive care unit (NICU), such as cardiorespiratory compromise, other co-morbidities or drugs and other treatments.

The topical challenges in this context are to define measures that are biologically relevant and clinically practical when it comes to monitoring early brain function and to devise NICU practices that enable early brain function to be preserved. Long-term monitoring of a scalp-recorded electroencephalograph (EEG) is the only clinically available direct measure of brain function. Several metrics derived from the EEG signal have been shown to correlate with later neurodevelopment (2–4). EEG is often reviewed at the cot side using a time-compressed trend called amplitude-integrated EEG (aEEG) (2,3), which allows qualitative assessment of long-term changes, such as vigilance state fluctuations, often referred to as sleep–wake cyclicality (5,6). Analysis of cyclicality has become a feature of interest in the aEEG analysis as a general marker of neurological well-being (2,3).

Wide-ranging attempts have been made to improve care practices in NICUs. Their overarching aim was to stabilise the infant to improve early brain function, especially the infant's ability to sleep (7). In this issue of *Acta Paediatrica*, Stokes et al. (8) have continued in this direction by studying the behavioural effects of music exposure in preterm infants. They performed a randomised crossover trial where preterm infants were exposed to music and they then assessed the patient's behavioural state as well as brain activity using a long-term aEEG recording. The authors can be commended for carrying out a randomised trial on nursing, which as a nonpharmacological intervention is likely to provide important directions for future research to improve NICU outcomes. Their statistics on the outcomes



were carried out with care, and their general results were compatible with the idea that creating a soothing environment may help to stabilise the infant during NICU care, even if their data were not able to genuinely prove it.

The idea of optimising nonpharmacological care is one of the key challenges in modern medicine. The weight of evidence obtained from such trials depends on two factors: the reliability and quality of the outcome measures and the coherence and biological plausibility when discussing the observations.

Stokes et al. used cycling in brain states during the aEEG as the key outcome measure that defined the information value of all subsequent analyses and conclusions. The authors used visual scoring of aEEG trends, which is often used by clinicians because of its simplicity, but it is also known for considerable weakness. The score is essentially qualitative, coarse and subjective, with both significant intra-individual variability and interindividual variability. Moreover, the relationship between the given shape in aEEG trends and the actual—true physiological—sleep–wake cycles is heuristic rather than directly proven (5,6), which calls for high care in formulating the conclusions. These combined considerations imply that the further statistical analyses that was carried out by Stokes et al. may be statistically sound, but their physiological meaning remains unknown, at least in the context of their sleep–wake cyclicality story. In other words, the study found that playing music may have some effects, but the outcomes they measured were ambiguous by nature, as they were driven by qualitative visual reading, and they lacked proven physiological interpretations.

It is fortunate in this context that modern aEEG recordings are digital, allowing for future re-analysis with more objective quantitative metrics. Several neonatal EEG laboratories have recently developed algorithms that can identify sleep states from neonatal EEGs (9,10). There is even an openly available quantitative measure of brain activity cycling (5) that has been validated against visual sleep–wake cyclicality scores to enable genuinely objective and

continuous scalar for preterm vigilance state cycling. It would be straightforward to provide an objective and quantitative re-analysis of changes in brain activity cycling from the existing data.

Current evidence-based medicine calls for physiologically and conceptually coherent study designs and interpretation of the findings. It has been common in clinical studies using aEEGs from newborn infants that the actual findings and their interpretation are effectively disconnected and that the glue between the two is provided by implicit assumptions that may be conceptually loose or flawed. Likewise, Stokes et al. take us in directions that are difficult to back up with their data. For instance, they state that their findings show how music exposure leads to sleep–wake cyclicity patterns corresponding to increased postconceptional age. It is generally accepted that brain activity cycling becomes more stable during maturation, but the same cycling stability, or its visual clarity, is also observed at any age in more physiologically stable infants (2,3). As short exposure to music cannot magically and suddenly make the brain more mature, the findings by Stokes et al. should be interpreted as signs of brain stabilisation but within the limits of ambiguity inherent to their qualitative score.

The authors also state that brain maturation is biologically determined and not responsive to environmental modifications, which contradicts sharply with their own rationale and conclusions. It is neurobiologically well established that brain maturation is biologically determined (1), but it is hard to find evidence for the idea that brain maturation would not respond to the environment. Indeed, the whole rationale in the study by Stokes et al. is about modifying brain function environmentally, just like all the other studies that aim to improve neurological care in the NICU (7,11).

Improving the neurological care of NICU patients is very important. All future studies should also aim to minimise ambiguities and to maximise coherence throughout the study process, from recording data to their analysis, interpretation and conclusions. The paper by Stokes et al. is essentially a feasibility study that shows that it is possible to perform a randomised trial on music exposure during aEEG recordings. Their study provides a good size clinical EEG data set and this could provide promising and important novel evidence when it is re-analysed objectively and

quantitatively using modern, objective and quantitative computational analyses.

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