

Benoit and colleagues (1) aimed to compare the influence of breastfeeding during heel lancing with oral sucrose in term-aged infants. They measured evoked changes in brain activity, behaviour, and physiology and report no significant group differences between these measures following heel lance. Of key importance here is how we interpret the report that the primary outcome measure – brain activity evoked by heel lancing – is not specifically evoked by the noxious input or different between the interventions.

The measurement and quantification of noxious-evoked brain activity is beginning to be implemented around the world, including in multiple centres in the UK (2,3), Switzerland (4), and USA (5), and has been used to measure the impact of skin-to-skin contact, stress and gentle touch on procedural pain (6–8). However, in this study no difference is demonstrated between the brain activity evoked by the noxious heel lance and non-noxious control stimulus; it is unclear how this study-specific marker can be interpreted as “pain-related”. This challenges the authors’ conclusions related to the efficacy of breastfeeding versus oral sucrose for modulating pain-related brain activity.

A number of methodological issues could have prevented the identification of a pattern of brain activity that is exclusively evoked by the noxious stimulus. For example, (i) activity is analysed at the Pz electrode, whereas most previous studies identify maximal noxious-evoked activity at the Cz electrode in term-aged infants (9,10), (ii) the level of data loss is substantial (17 of 39 infants (44%) compared with a comparable study where data loss was 1/30 (3%) (2)), and (iii) it is unclear how the Principal Component Analysis (PCA) was conducted making their statistical analysis difficult to interpret and limiting reproducibility. Figure 3 suggests PCA may have been performed in treatment groups separately which would invalidate the results. Including the averaged EEG data would have aided interpretation of the results.

This study highlights that while there is a well-placed desire to conduct randomised controlled trials (RCTs) that include changes in brain activity, there may be difficulties in adopting this approach. So where do we go next? For RCTs we need:

(1) Easy-to-use acquisition methods

- Accurate electrode placement and time-locking is essential (11) – about half of the data loss in this study was due to failure to identify the time of the heel lance. Development of a clinically-usable device that facilitates data acquisition and analysis would aid the adoption of these methods for clinical trials.

(2) Validated endpoints identified in independent data sets

- We have developed a publicly-available electroencephalographic measure which has been shown to exhibit initial validity, including evidence of specificity and modulation by an analgesic (9). Adopting established measures in RCTs allows for easier comparison and reproducibility across studies and negates the need for redefining study-specific pain-related markers in each study.

(3) Data sharing and collaboration

- Studies investigating the measurement of pain in neonates are extremely difficult to conduct. We have an ethical responsibility to the families who participated to ensure best practices are adopted. We recommend international collaboration and data sharing, of which an excellent example is the work of Fabrizi and colleagues (12).

Benoit and colleagues have collected a significant amount of valuable data. We recommend secondary re-analysis of this data to ensure that maximum value is extracted from this work. Using brain-derived measures to assess the efficacy of pain-relief will have a pivotal role in optimising pain management in infants.

Declaration of interests

All authors are actively involved in research using EEG to measure noxious-evoked brain activity in infants. RR, AW and CH (among others) published the template of noxious-evoked brain activity that we suggest using here. Our research is funded by the Wellcome Trust.

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