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Vanhatalo, Sampsa

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COMMENT OPEN



Why monitor the neonatal brain—that is the important question

Sampsa Vanhatalo^{1✉}, Nathan J. Stevenson², Ronit M. Pressler³, Nicholas S. Abend⁴, Stéphane Auvin⁵, Francesco Brigo⁶, M. Roberta Cilio⁷, Cecil D. Hahn⁸, Hans Hartmann⁹, Lena Hellström-Westas¹⁰, Terrie E. Inder¹¹, Solomon L. Moshé¹², Magda L. Nunes¹³, Renée A. Shellhaas¹⁴, Kollencheri P. Vinayan¹⁵, Linda S. de Vries¹⁶, Jo M. Wilmshurst¹⁷, Elissa Yozowitz¹⁸ and Geraldine B. Boylan¹⁹

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A key goal of neonatal neurocritical care is improved outcomes, and brain monitoring plays an essential role. The recent NEST trial¹ reported no outcome benefits using aEEG monitoring compared to clinical seizure identification among neonates treated for seizures. However, the study failed to prove the effects of monitoring on seizure treatment in the first place.

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Neonates with acute neurological disorders, such as encephalopathy due to hypoxia-ischemia, will commonly undergo continuous electroencephalography (EEG) monitoring to assess brain recovery and detection of seizures. EEG monitoring is necessary for a reliable diagnosis and monitoring of neonatal seizures², because the majority of EEG-confirmed neonatal seizures have no clinical signs, while EEG monitoring may confirm that many clinical events are non-epileptic in origin³. The International Neonatal Consortium, European Medicines Agency, US Food and Drug Administration, Brighton Collaboration, the International League Against Epilepsy, and American Clinical Neurophysiology Society agree that all studies involving the treatment of neonatal seizures should evaluate seizures from the EEG recordings^{2,4,5}.

Before these international recommendations, it was common for clinicians to question the added value of (a)EEG monitoring in newborn care. The NEST trial¹ attempted to address this question by assessing whether neurodevelopmental outcomes are improved by treating seizures with the aid of amplitude-integrated EEG monitoring (aEEG) compared to treating seizures identified by clinical recognition only. The underlying assumption was that seizure identification and management reduces secondary brain injury and improves neurodevelopment (Fig. 1), and that aEEG facilitates seizure diagnosis and treatment. The study found

no evidence of improved neurodevelopmental outcomes, and secondary analyses showed reduced cognitive outcomes in the group with aEEG monitoring. The secondary outcome findings can be linked to many well-established confounders, only some of which were mentioned in the paper. However, the most surprising finding of this study is the lack of difference in overall seizure burden between groups treated with aEEG monitoring support versus those with clinical consideration only.

It is now widely recognized that (a)EEG monitoring and seizure treatment should commence as early as possible because the seizure burden peaks during the first 24 h in infants with hypoxic-ischemic encephalopathy (the primary cause of neonatal seizures) with subsequent gradual resolution^{6,7}. This spontaneous resolution of seizures over time means that a late start of treatment would require prohibitively large study cohorts and only show a treatment response with limited clinical significance⁸. In the NEST study, aEEG was initiated after 24 h; therefore, NEST likely missed the bulk of the seizure burden, and it only assessed the remains of the spontaneously decaying seizures. Thus, the NEST study design per se precluded an opportunity to see an actual treatment effect in either study arm⁸.

In addition to missing seizures due to the late onset of aEEG monitoring, the EEG assessment method per se used in the

¹BABA Center in Pediatric Research Center, Departments of Clinical Neurophysiology and Physiology, Children's Hospital and HUS Imaging, Helsinki University and Helsinki University Hospital, Helsinki, Finland. ²Brain Modelling Group, QIMR Berghofer Medical Research Institute, Brisbane, QLD, Australia. ³Clinical Neuroscience, UCL GOS Institute of Child Health, Department of Clinical Neurophysiology, Great Ormond Street Hospital for Sick Children, London, UK. ⁴Division of Neurology and Neurophysiology Lab, Children's Hospital of Philadelphia, Philadelphia, PA, USA. ⁵Université de Paris, Service de Neurologie Pédiatrique, Hôpital Universitaire Robert Debré, APHP, Institut Universitaire de France (IUF), Paris, France. ⁶Department of Neurology, Hospital of Merano (SABES-ASDAA), Merano, Italy. ⁷Division of Pediatric Neurology, Cliniques universitaires Saint-Luc, Université catholique de Louvain, Brussels, Belgium. ⁸Division of Neurology, The Hospital for Sick Children and Department of Paediatrics, University of Toronto, Toronto, ON, Canada. ⁹Clinic for Pediatric Kidney, Liver and Metabolic Disorders, Hannover Medical School, Hannover, Germany. ¹⁰Department of Women's and Children's Health, Uppsala University, Uppsala, Sweden. ¹¹Department of Pediatric Newborn Medicine, Brigham and Women's Hospital, Harvard Medical School, Boston, MA, USA. ¹²Isabelle Rapin Division of Child Neurology, Saul R. Korey Department of Neurology, and Departments of Neuroscience and Pediatrics, Albert Einstein College of Medicine and Montefiore Medical Center, Bronx, NY, USA. ¹³Brain Institute (Brains), Pontifical Catholic University of Rio Grande do Sul, Porto Alegre, Brazil. ¹⁴Department of Pediatrics, Division of Pediatric Neurology, University of Michigan, Ann Arbor, MI, USA. ¹⁵Department of Pediatric Neurology, Amrita Institute of Medical Sciences, Cochin, Kerala, India. ¹⁶Department of Neonatology, University Medical Center Utrecht, Utrecht University, Utrecht, the Netherlands. ¹⁷Department of Paediatric Neurology, Red Cross War Memorial Children's Hospital, Neuroscience Institute, University of Cape Town, Cape Town, South Africa. ¹⁸Isabelle Rapin Division of Child Neurology, Saul R. Korey Department of Neurology, Montefiore Medical Center, Albert Einstein College of Medicine, Bronx, NY, USA. ¹⁹INFANT Research Centre & Department of Paediatrics & Child Health, University College Cork, Cork, Ireland.

✉email: sampsa.vanhatalo@helsinki.fi

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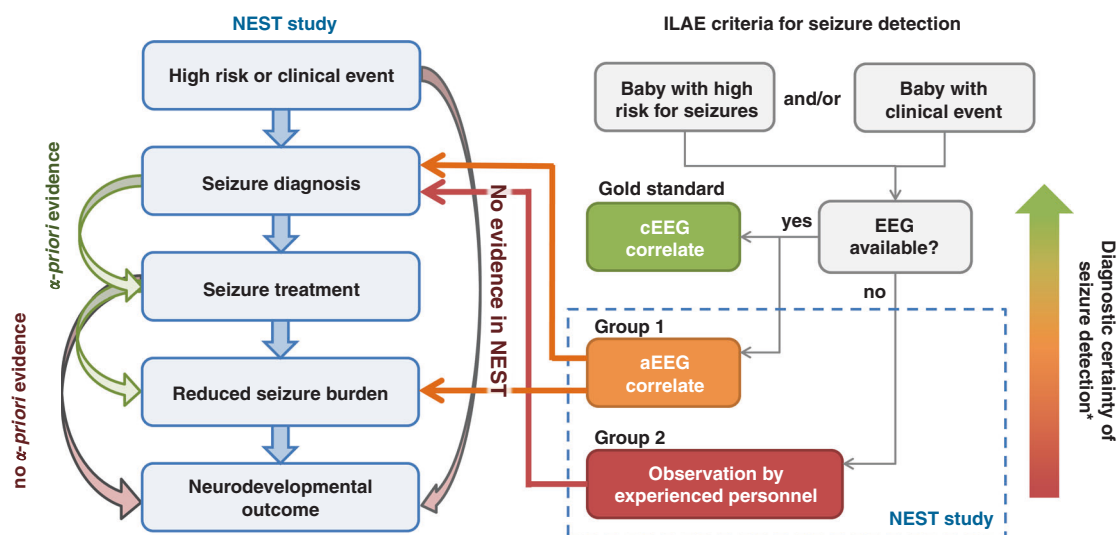


Fig. 1 The left side flowchart summarizes rationale in the NEST study and its relationship with the international guideline of seizure detection (right side flowchart). Colors from red through orange to green code for established reliability in seizure detection. The arrows depict the assumed causal links from the clinical suspicion to the neurodevelopmental outcome. The green arrows on the left side show links with prior research evidence. The gray arrow shows the critical a priori missing evidence that should have been known before commencing the NEST study. Arrows on the right side show the links that were examined in the NEST with negative findings. Notably, NEST study relies on seizure detection by aEEG that only has modest- or low-level reliability. This effectively precludes the potential to use NEST design for examining its study question. *Diagnostic certainty according to Brighton Collaboration case definition of neonatal seizures. Level 1—gold standard, definite seizure (seizures confirmed on EEG with or without clinical manifestations); level 2—probable seizure (aEEG confirmed or clinically assessed focal clonic or focal tonic seizures); level 3—possible seizure (clinical events suggestive of epileptic seizures other than focal clonic or focal tonic seizures); level 4—not seizure (reported clinical events that do not meet case definition); level 5—not seizure (clinical events evaluated by EEG and diagnosed as not a seizure).

NEST study introduces a major confounder in seizure burden estimates (Fig. 1). Although aEEG is often useful for clinical brain monitoring, including the recognition of longer seizures, international guidelines have established that the aEEG alone cannot provide accurate enough estimates of seizure burden. The NEST study amplifies this bias by only considering the longer seizures that were evident on the compressed aEEG trace that likely led to a considerable proportion of the seizure burden going undetected, untreated, and not accounted for in the analyses. Moreover, the report does not provide key details regarding the aEEG, for instance, which recording channels were used, how aEEG review was actually done at the bedside, whether seizure detection algorithms were (or were not) used, when treatment(s) were administered, and how seizure burden and response to treatment were subsequently quantified. Furthermore, analyses of aEEG background patterns are not reported despite their strong associations with outcome⁹.

Overall, the NEST study portrays a grand challenge in all contemporary medical research. The rapidly changing clinical landscape and accumulating research data make it difficult to design new studies with influential results. This is particularly true for neonatal research where the use of long-term neurodevelopment outcomes results in very long study cycles. Consequently, the initial study question may have lost its relevance by the time the trial is completed. In the case of NEST, the concurrently accumulated evidence rendered the initial study question a classic straw man hypothesis: The study was designed to test the hypothesis that aEEG improves neurodevelopmental outcomes by improving seizure identification and seizure management, thereby reducing seizure burden (Fig. 1). Instead, the study shows that aEEG begun >24 h after delivery did not affect treatment practices and outcomes, but it does not really address the question of whether or how early use of EEG monitoring impacts treatment success, i.e., seizure burden en route to better outcomes. Notably, this situation is changing rapidly worldwide, with further training of personnel as well as more widespread use of EEG devices with adequately validated algorithms for automated seizure detection¹⁰.

Why is this issue important to raise? We believe that there is a risk that the NEST study question per se may lead clinicians to erroneously conclude that EEG monitoring is unhelpful in neonatal neurological management. This misleading effect may be worse in low- and middle-income countries where the current upskilling of neonatal units is calling for de novo implementation of brain monitoring routines. Notably, the authors of NEST study concluded that “EEG remains the reference standard for the detection of neonatal seizures, and essential in the validation of neonatal research.” This important statement carries the readership onto the grand challenge question of neonatal neurological care: Why monitor the neonatal brain? Routine clinical practice has shown that EEG monitoring of neonates supports and guides individualized patient care by providing a functional measure of brain recovery after injury, reliable detection of seizures, and surveillance of sleep-wake cycling, as well as many other context-relevant observations^{9–11}. In addition, several novel aEEG and EEG biomarkers are being developed that hold promise for making EEG a proximal outcome measure for individualized patient care, benchmarking clinical trials, as well as predicting later neurodevelopmental compromise. These benefits are irrefutable and widely acknowledged, and conceivably, trying to measure their links to neurodevelopmental outcomes without considering the possible intermediary or causal mechanisms is unproductive. Indeed, there is a widely shared bedside experience in neonatal intensive care units that trusts in a well-known mechanism, the latent Hawthorne effect^{11,12}: mere attention to the newborn brain leads to improved newborn care.

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S.V. is an unpaid advisor for Stratus and ANT. R.M.P. is an investigator for studies with UCB and does consultancy work for Kephala LTD, Ireland. She served as a Speaker and/or on Advisory Boards for Natus, GW, Eisai, and UCB. G.B.B. has a consultancy with UCB and Nihon Kohden to provide advice on neonatal EEG monitoring. She is a

co-founder of a start-up company Kephala LTD, which provides EEG reviewing services for industry and academia. M.R.C. serves as a Speaker and/or on Advisory Boards for Eisai, UCB, and Biocodex, and does consultancy work for Sanofi Aventis. J. M.W. receives an honorarium for her role as Associate Editor for *Epilepsia*, advisory board for South African branch of Sanofi. S.A. receives an honorarium for his role as associate Editor for *Epilepsia*. He has served as consultant or received honoraria for lectures from Angelini Pharma, Biocodex, Biomarin Encoded, Eisai, GRINtherapeutics, GW Pharma, Neuraxpharma, Nutricia, Orion, UCB Pharma, Ultragenyx, Xenon, Zogenix. He has been an investigator for clinical trials for Eisai, Marinus, Takeda, UCB Pharma, Xenon, and Zogenix. K.P.V. received an honorarium from Medlink Neurology and Dravet Syndrome Foundation. C.D.H. receives an honorarium for his role as Associate Editor of the *Journal of Clinical Neurophysiology*, and has consulted on clinical trial design and conduct for UCB Biopharma and Takeda Pharmaceuticals. R.A.S. receives royalties from UpToDate for authorship of topics related to neonatal seizures; serves as Associate Editor for *Neurology*; and is a consultant for the Epilepsy Study Consortium. Her research is supported by NIH and the Pediatric Epilepsy Research Foundation. S.L.M. is serving as Associate Editor of *Neurobiology of Disease*. He is on the editorial board of *Brain and Development*, *Pediatric Neurology*, *Annals of Neurology*, *MedLink*, and *Physiological Research*. He receives compensation from Elsevier for his work as Associate Editor in *Neurobiology of Disease* and from *MedLink* for his work as Associate Editor; and royalties from two books he co-edited. N.J.S., L. H.-W., L.S.d.V., N.S.A., and F.B. declare no competing interests.

ADDITIONAL INFORMATION

Correspondence and requests for materials should be addressed to Sampsa Vanhatalo.

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