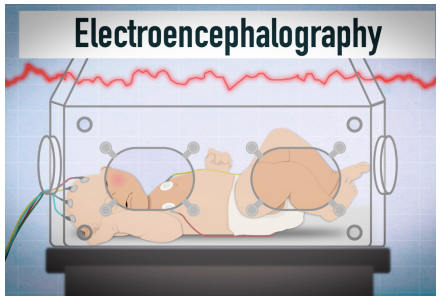
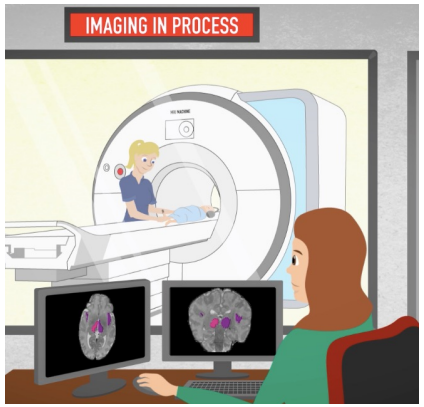
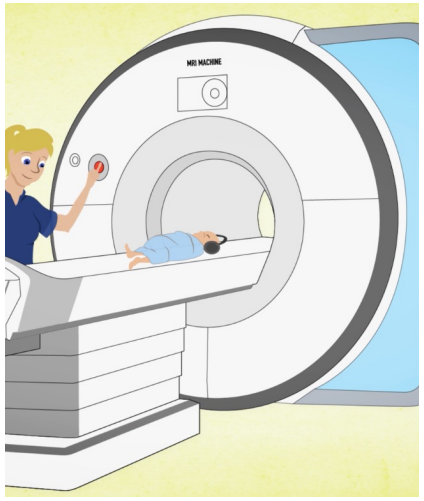
FDA Public Workshop: 13th - 14th October 2021

Analgesic Clinical Trial Designs, Extrapolation, and Endpoints in Pediatric Patients from Birth to Less Than 2 Years of Age







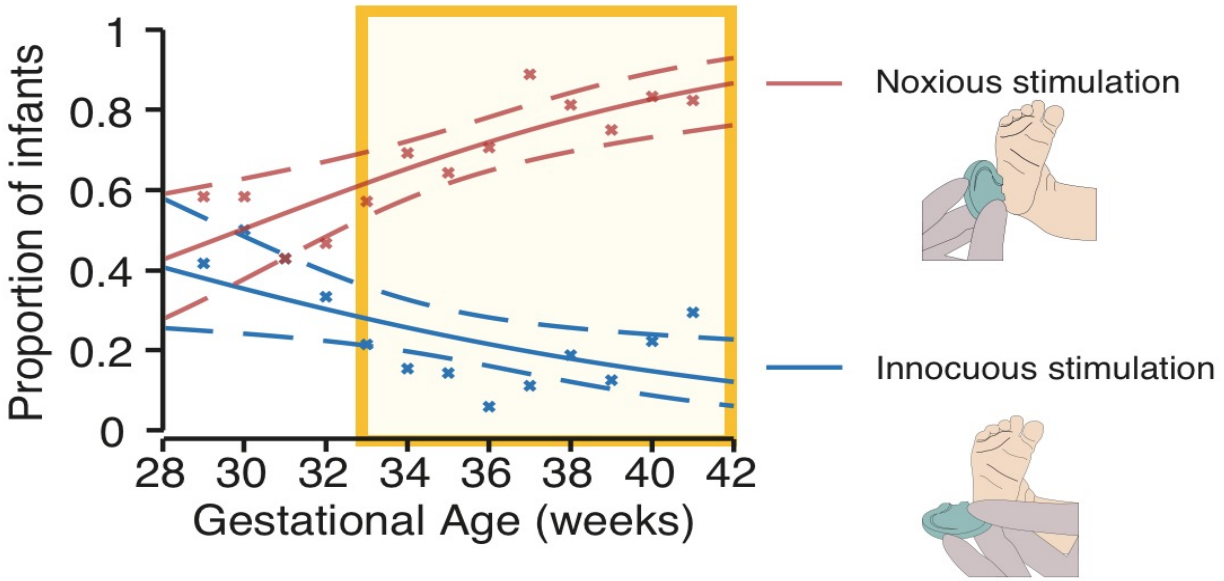
Brain-derived approaches to assess neonatal & infant pain

Dr Rebeccah Slater
Professor of Paediatric Neuroscience

UNIVERSITY OF OXFORD

Challenges with current pain measurement approaches

- Neonatal pain measurement is primarily reliant on observing changes in behavioural and physiological activity (e.g. heart rate).
- These measures are subjective, lacking specificity and sensitivity
  - Non-noxious stimuli (e.g. diaper change) can evoke high pain scores
  - Noxious stimulation may not elicit behavioral change in high % of neonates leading to low pain scores
- Advances in understanding neonatal physiology have occurred in recent years that may help improve measures of neonatal pain

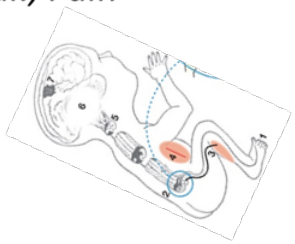


Quantifying noxious-evoked activity in the neonate

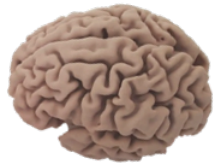
1980
Transcutaneous partial pressure of O2 & CO2
Rawlings et al., Am J Dis Child

1984
Crying
Owens et al., Pain

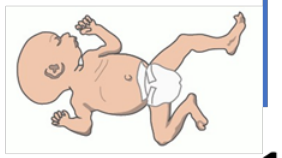
1993
Body movements
Craig et al., Pain

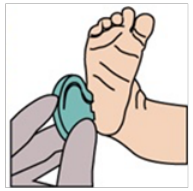


1996
Multimodal measures
Stevens et al., Clin J Pain



2010
EEG: Noxious-evoked potentials
Slater et al., EJP





1984
Increased heart rate
Owens et al., Pain

1987
Facial expressions
Grunau et al., Pain

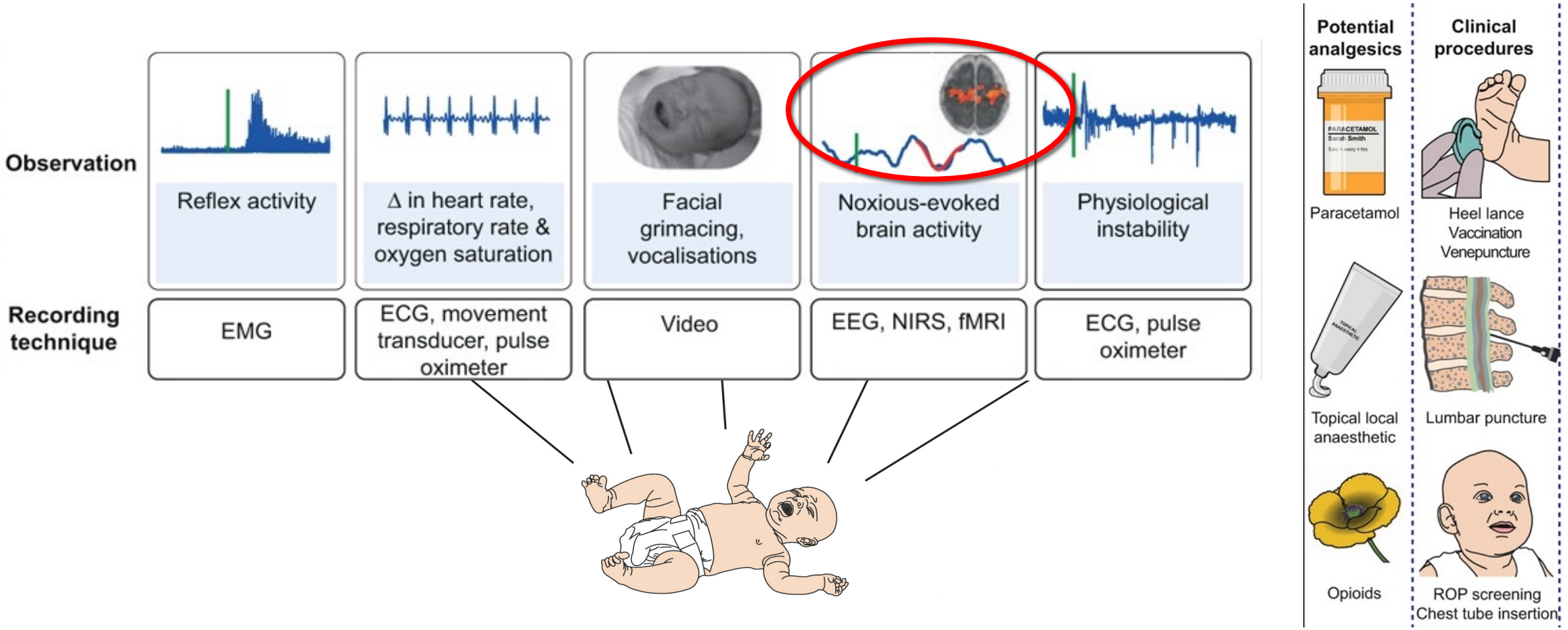
1994
Reflex withdrawal
Andrews et al., Pain

2006
NIRS: total haemoglobin conc.
Bartocci et al., Pain

2015
fMRI: BOLD
Goksan et al., eLife

O2: oxygen; CO2: carbon dioxide; NIRS: near-infrared spectroscopy; EEG: electroencephalography fMRI: functional MRI

Quantifying noxious-evoked activity in the neonate



Advances in brain-derived approaches to better understand neonatal pain

2006

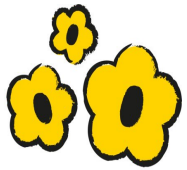
J Neuro, Pain

Recording noxious-evoked haemodynamic activity (NIRS).

2008

EJP

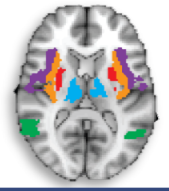
Recording noxious-evoked electrical brain activity (EEG).



2011

Current Biology

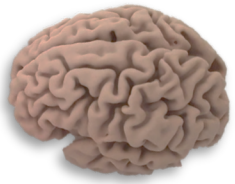
Early development of noxious-evoked brain activity.



2017

Current Biology

Impact of stress on noxious-evoked brain activity



2006

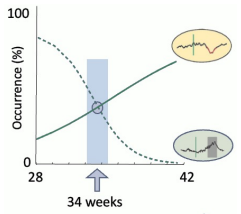
Pain

Long-term consequences of early life pain.

2010 & 2018

Lancet

Using brain-derived endpoints in clinical trials.



2015, 2017

eLife, Acta Paed

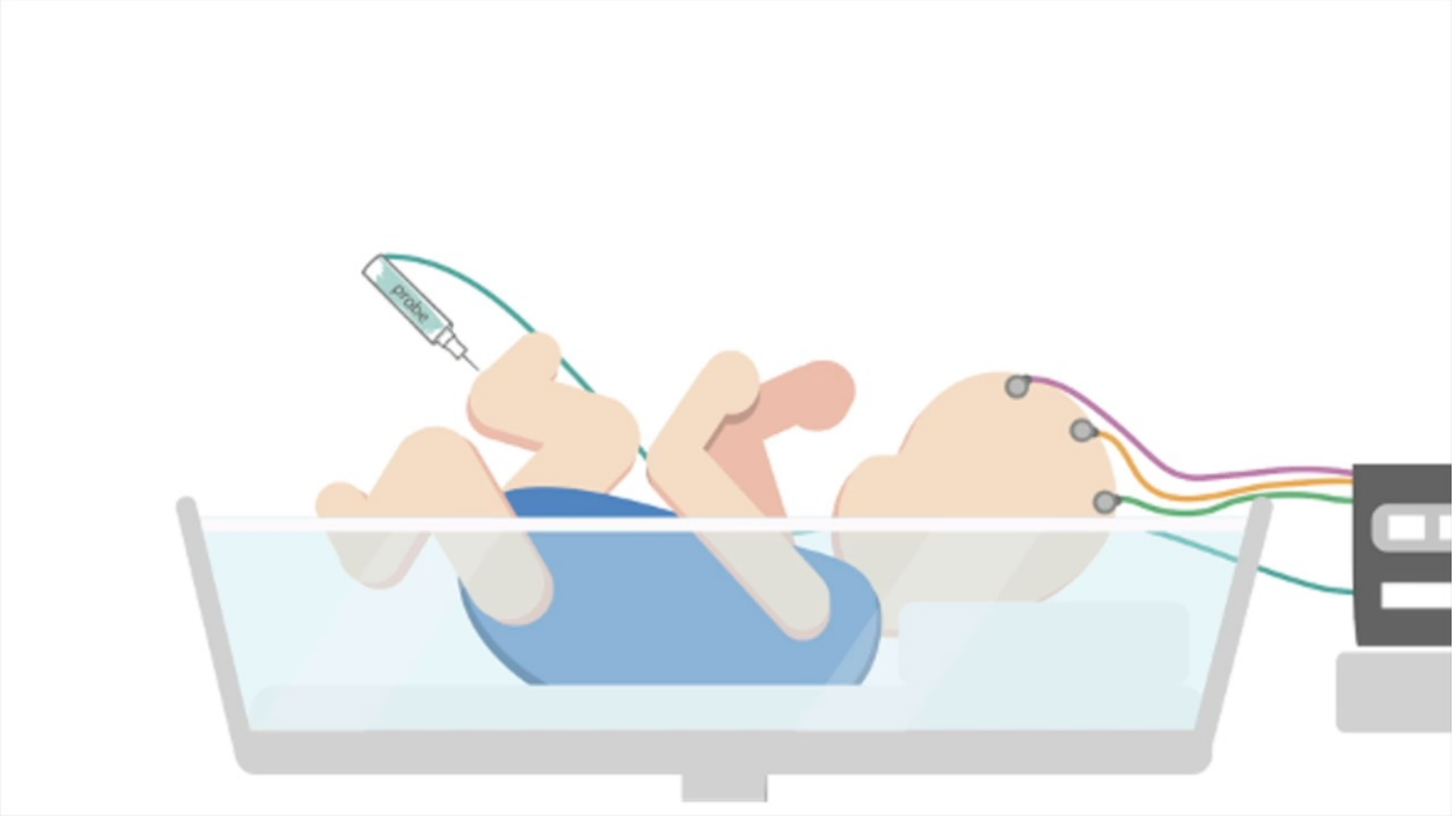
Measuring noxious-evoked brain activity using fMRI.

2021

Nature Comms

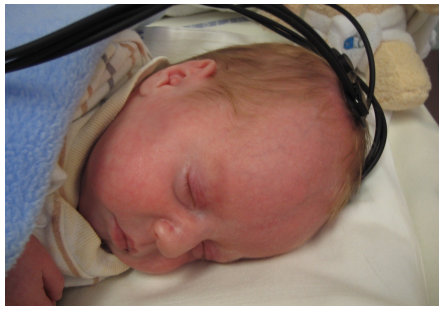
Understanding individual variability in pain responses.

Measuring noxious-evoked brain activity in the infant brain

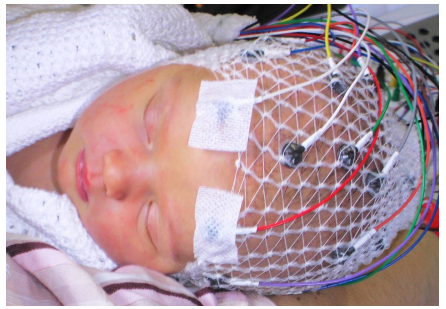


Measuring noxious-evoked brain activity

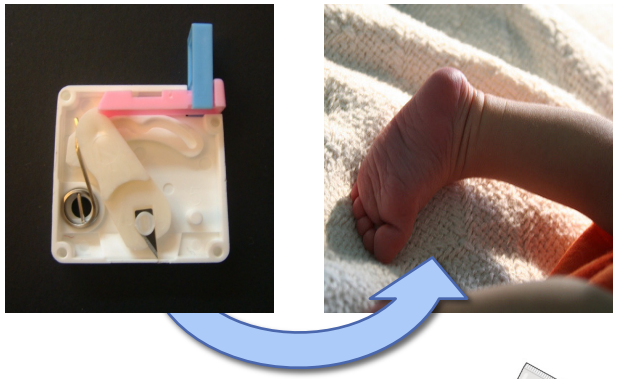
Near-infrared spectroscopy

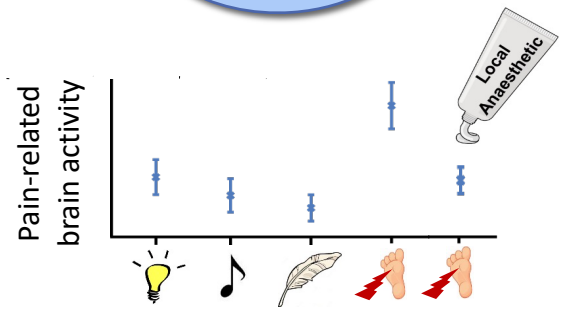


Electroencephalography (EEG)

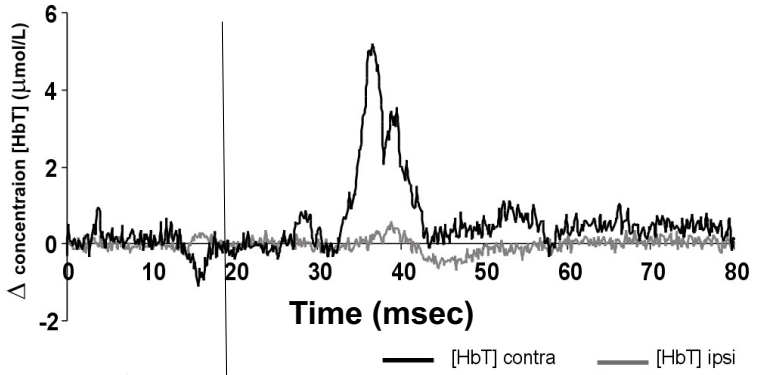


Clinically required noxious procedure (heel lance for blood sampling)

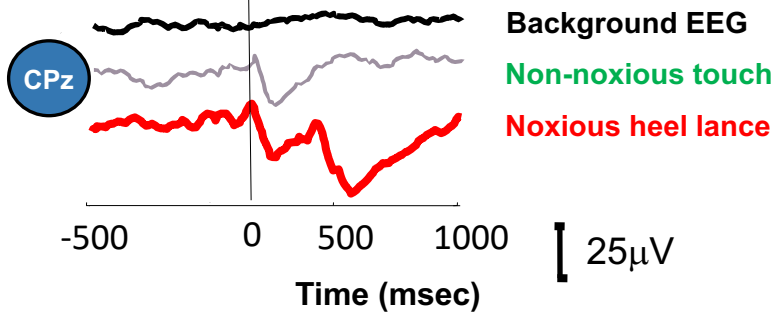




Near-infrared spectroscopy

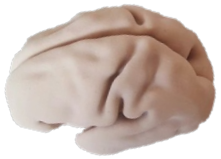


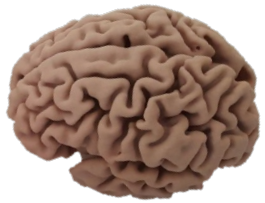
EEG

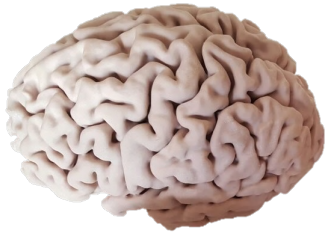


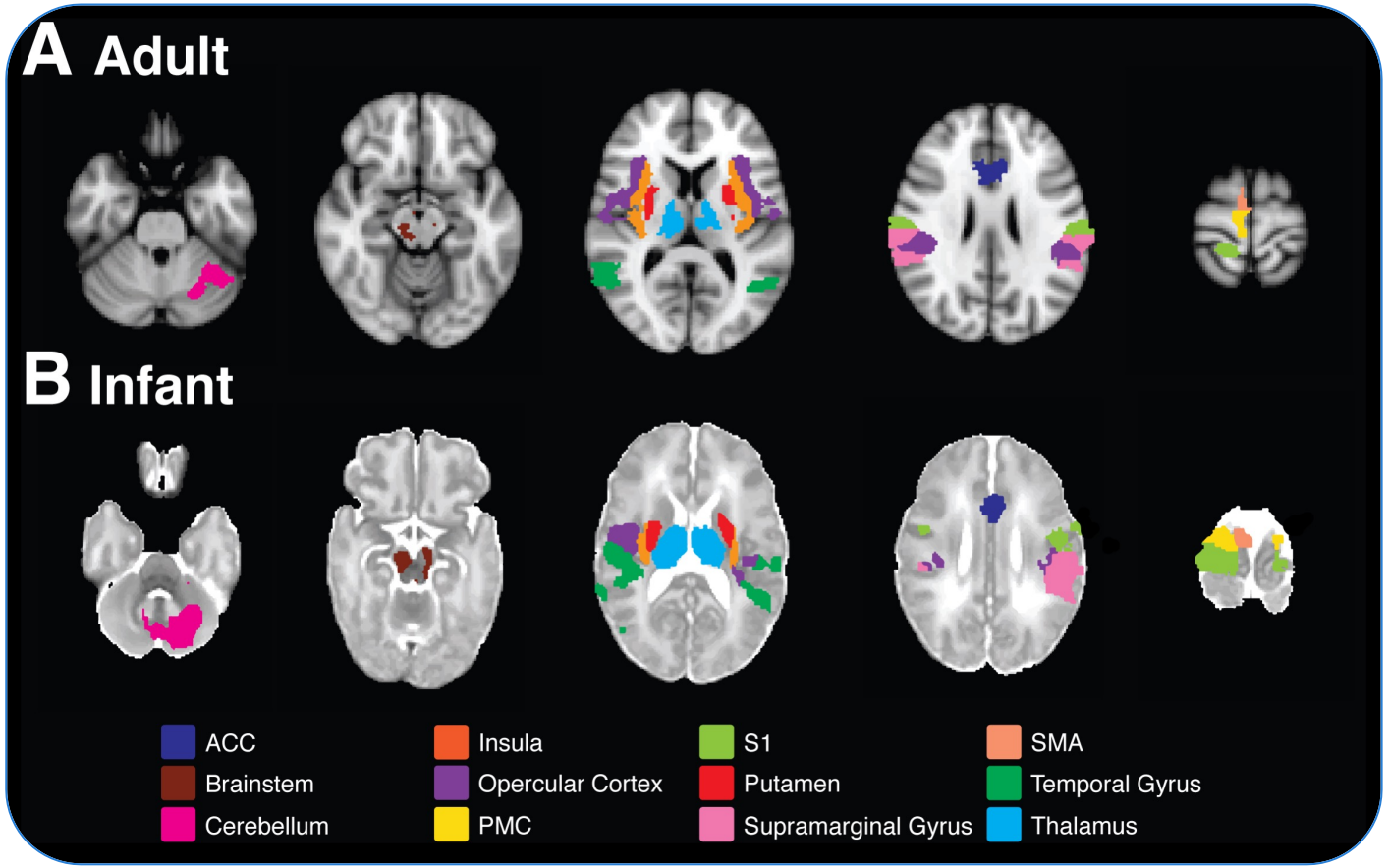
Slater et al. (2006) *Journal of Neuroscience*; Slater et al. (2010) *European Journal of Pain*

Noxious-evoked brain activity in adults compared with infants

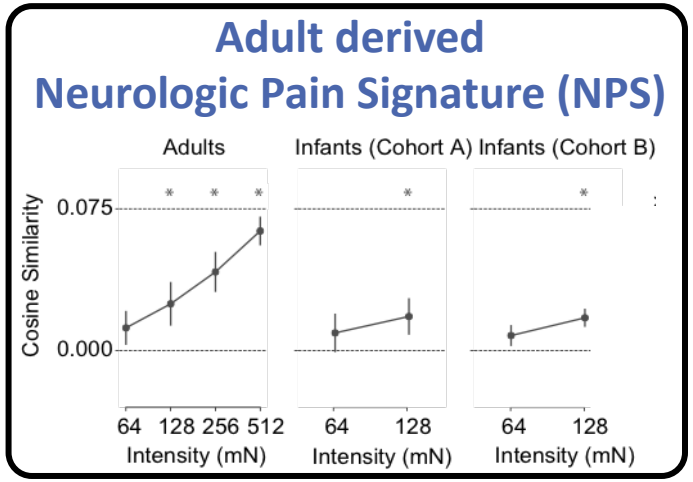








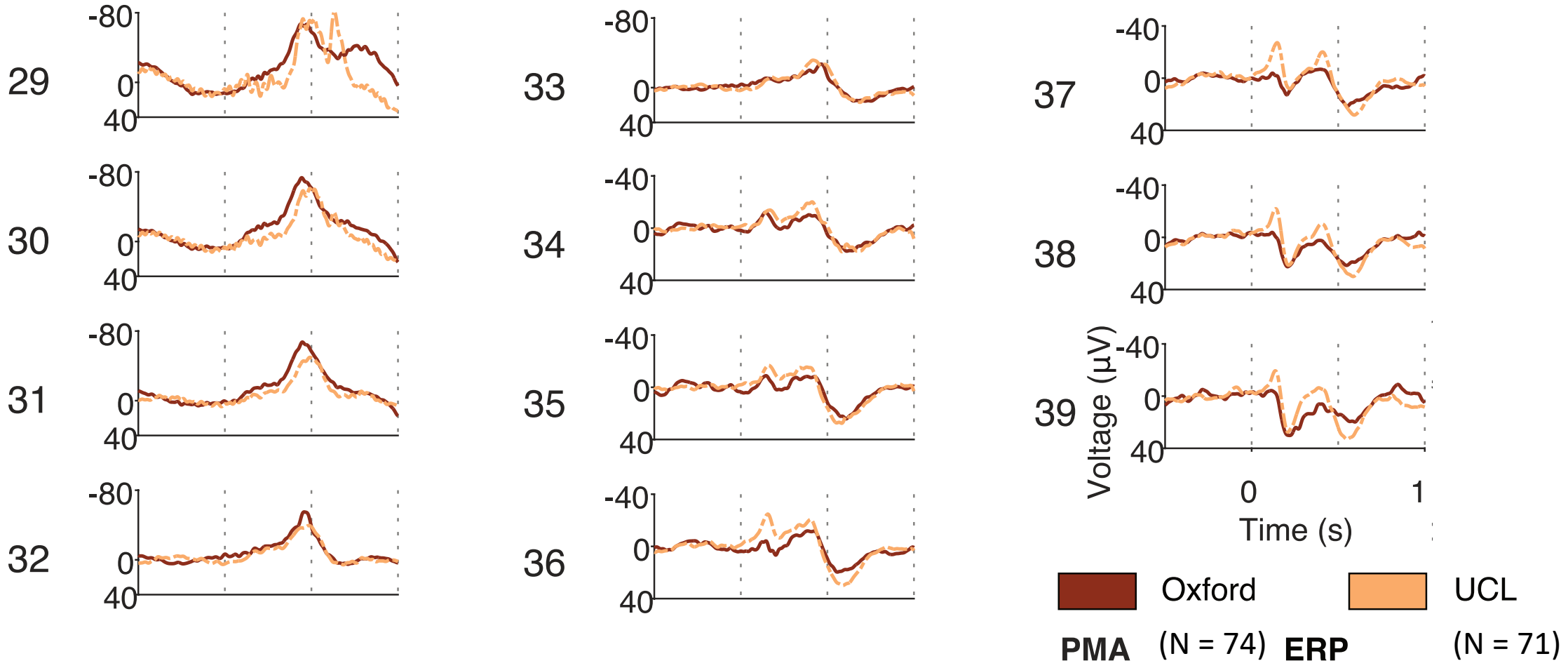
Similar patterns of noxious-evoked brain activity are recorded in neonates and adults when the same intensity nociceptive input is applied to the body, and adults verbally report that the stimuli are mildly painful.



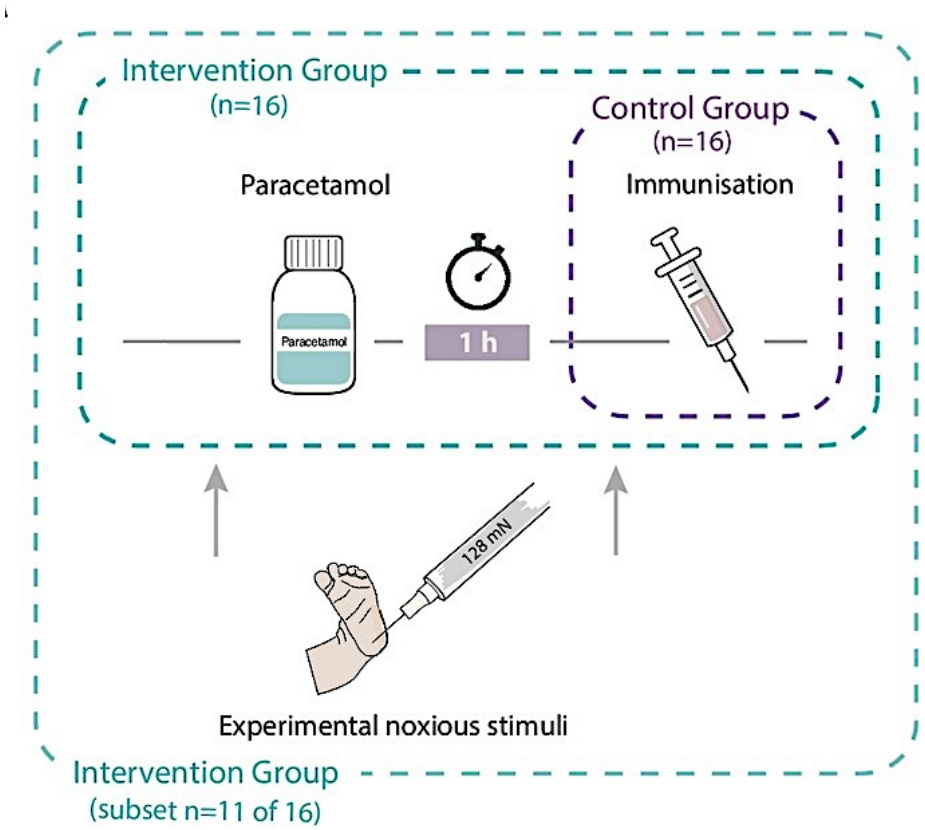
Goksan et al., (**2015, 2017**) *eLife*

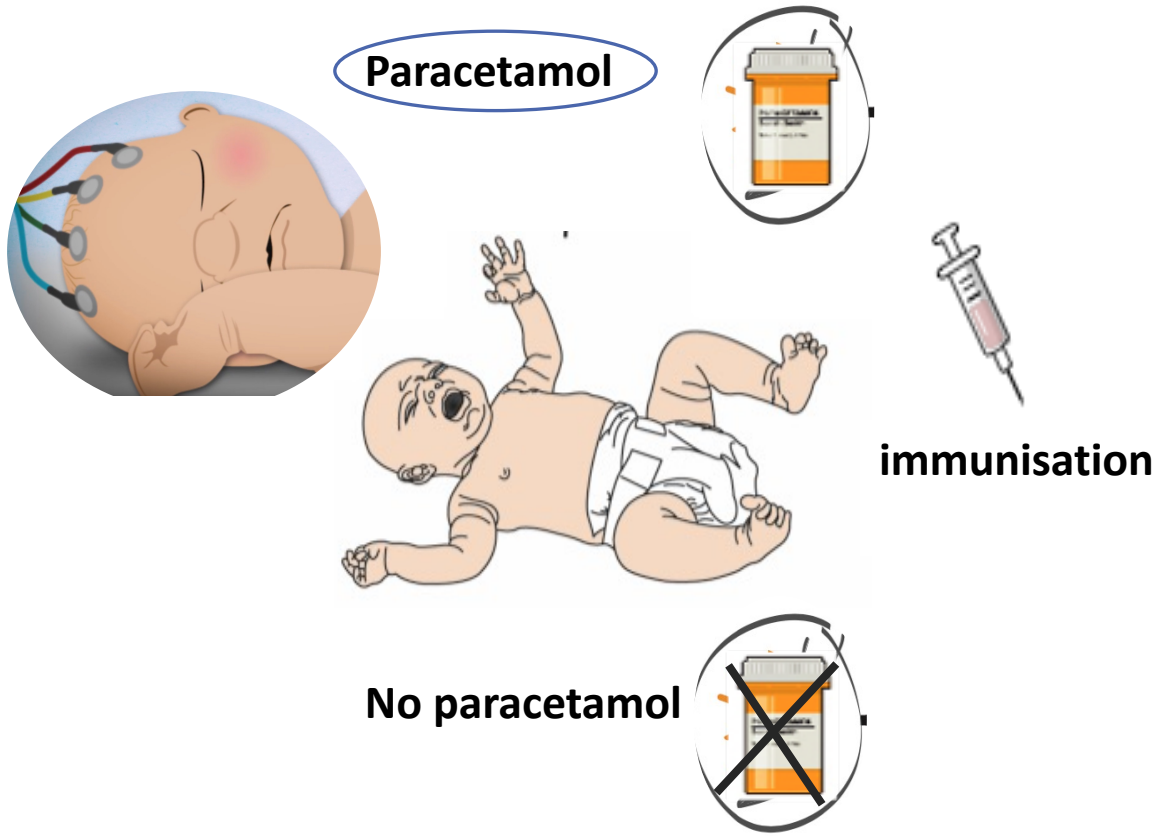
Duff et al., *Lancet Digital Health* (**2020**) *… in collaboration with Tor Wager*

Data reproducibility at independent sites: noxious-evoked brain activity

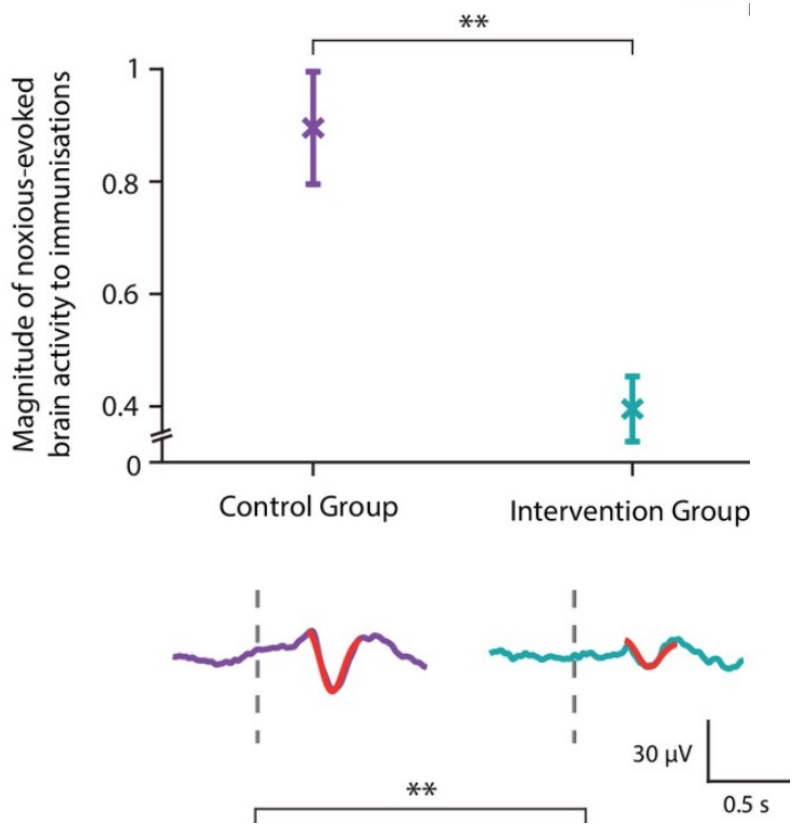


Pilot data: paracetamol modulates neonatal noxious-evoked brain activity

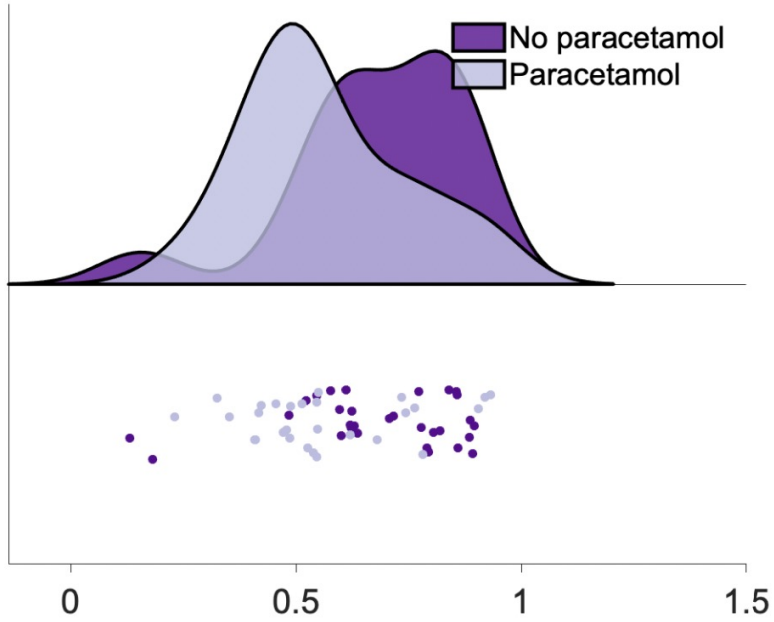




Pilot data: paracetamol modulates neonatal responses to immunisation

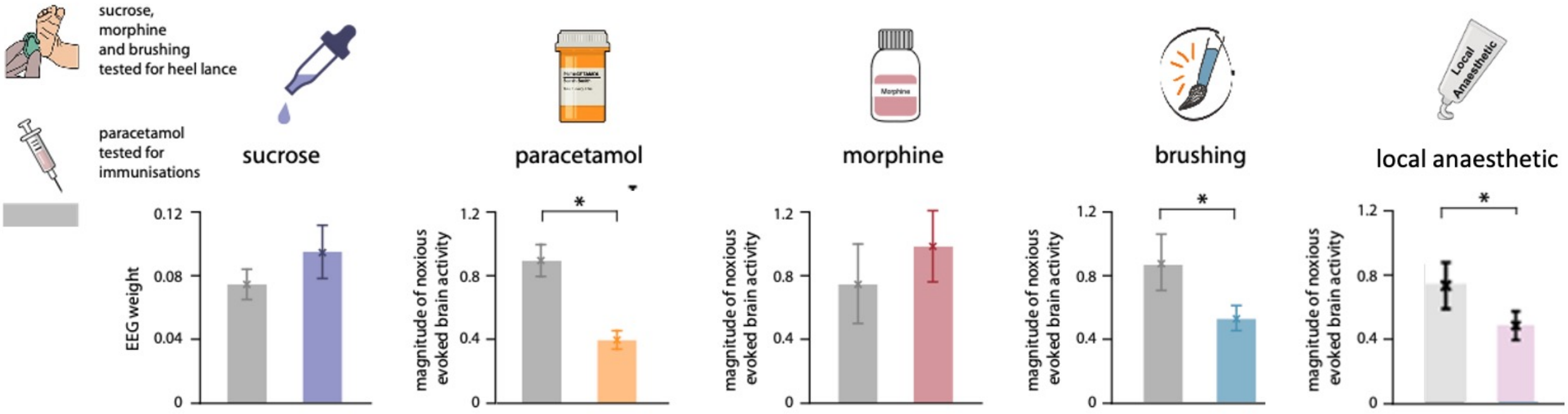


Probability that the procedure is noxious



Classifier correctly classified **85 %** of observations as noxious in neonates who did not receive paracetamol prior to the immunisation. The scores were significantly lower when the infants were treated with paracetamol (p = 0.025)

Using brain activity as a measure of analgesic efficacy in infants



Slater et al. (2010) Lancet; Cobo et al. (2021) eLife; Hartley et al. (2018) Lancet; Gursul et al. (2018); Curr Bio Hartley et al. (2018) STM

Collaboration with regulators, industry, clinicians and academics

Preterm health: time to bridge the evidence gap

Rebeccah Slater • Fiona Moultrie • Ralph Bax • John van den Anker • Aomesh Bhatt

Published: September 26, 2020 • DOI: https://doi.org/10.1016/S0140-6736(20)31977-2 • Check for updates

CrossMark

Preterm health: time to bridge the evidence gap

ER Productions Limited/Getty Images

Despite the development of revolutionary life-sustaining advances in neonatal medicine, medications are frequently administered in an ad-hoc and suboptimal way. Most drugs prescribed in neonatal care have not been submitted to the stringent regulatory processes of drug licensing that are standard in adult medicine.[1] Although clinical research and licensing regulations differ between countries, the scarcity of licensed medications and inevitable use of off-label

but repetitive underdosing. Doing research in preterm infants presents considerable ethical, logistical, and commercial challenges. Specific barriers include the challenging ethics of gaining consent from vulnerable parents of critically ill infants,[9] high rates of morbidity and mortality, a greater risk of adverse drug events in this population,[10] issues surrounding clinical equipoise with the widespread use of drugs without evidence,[11] the acceptability of placebo use,[12] and concerns over liability

Slater, Moultrie, Bax, van den Anker & Bhatt (**2020**) *Lancet*

Make pain matter

Brain-derived approaches can be used as end points in clinical trials.

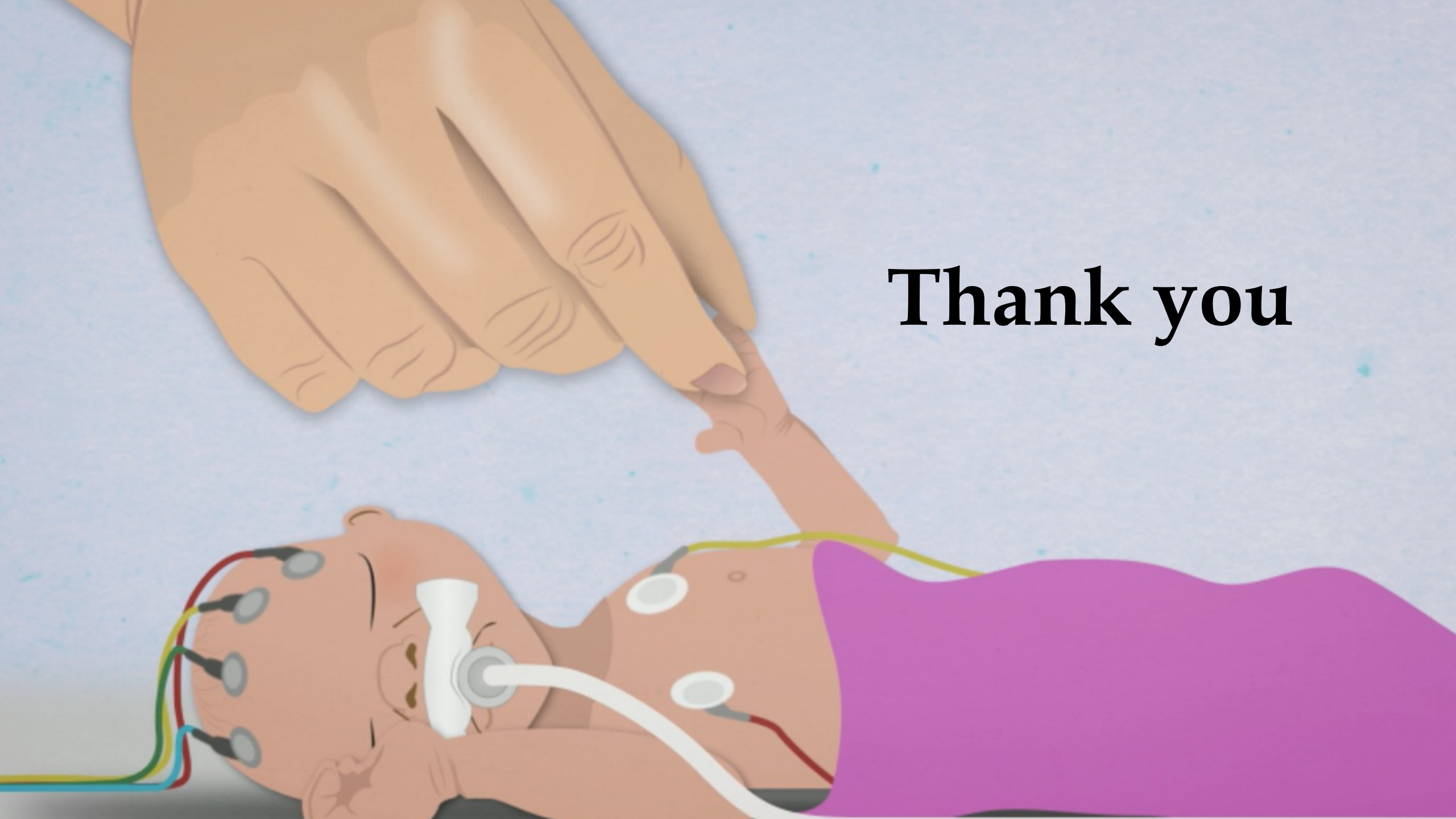
Make pain understood

Develop methods to improve treatments, through better understanding of the pharmacokinetic and pharmacodynamic properties of analgesics.

Make pain visible

Advances in imaging and analytical methods provide an opportunity to test the efficacy of analgesics across a range of clinical procedures.

Make pain better


Thank you