Neonatal development of CNS response modulation and cortical microstate engagement to repeated noxious procedures

Mohammed Rupawala[1], Maria Pureza Laudiano-Dray[1], Judith Meek[2], Maria Fitzgerald[1], Sofia Olhede[3,4], Lorenzo Fabrizi[1], & Laura Jones[1]

1 DEPARTMENT OF NEUROSCIENCE, PHYSIOLOGY AND PHARMACOLOGY, UCL, UK
2 ELIZABETH GARRETT ANDERSON OBSTETRIC WING, UCLH, UK
3 DEPARTMENT OF STATISTICAL SCIENCE, UCL, UK
4 INSTITUTE OF MATHEMATICS, EPFL, SWITZERLAND

Background

- Adults habituate to repetitive painful stimulation [1]. This is reflected by decreased pain ratings and decreased brain activity in pain areas.
- Neonatal nociceptive circuitry and responses rapidly develop at every level of the central nervous system (CNS) over the final trimester of gestation [2,3,4].
- Noxious input engages sequential and parallel processes that enable the system to adapt to the environment [5].
- Repeated noxious stimulation may offer insight into changes in brain nociceptive processing according to context [6].

Aims

Is the immature neonatal CNS capable of habituation to pain?

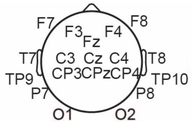
Does the neonatal brain process repeated painful procedures differently?

METHODS

- Subjects: 10 preterm (PMA 32.86 – 36.57, 5 female) and 11 term (PMA 37.57 – 44.28, 4 female) neonates.
- Paradigm: two clinically-necessary blood tests (heel lances), 4-15 minutes apart.

Magnitude differences between nociceptive responses measured at four levels of the CNS

Level:	Subcortical somatic	Subcortical autonomic	Spinal	Cortical
Measure:	Pain-related facial expressions [7]	Heart rate	Flexion withdrawal reflex	Pain-related brain activity
Instrument:	Video recording	Electrocardiography (ECG)	Surface electromyography (EMG)	Electroencephalography (EEG)



- Differences between **first (L01)** and **second (L02) lance** responses statistically tested using non-parametric statistics.

EEG microstates

- Measures of global brain activity.
- Dynamically varying short time periods (60-120 ms) during which the configuration of the scalp potential field remains semi-stable [8].
- Represent distinct cortical processes.
- Switching between microstates represents changes to brain network processes and information flow.

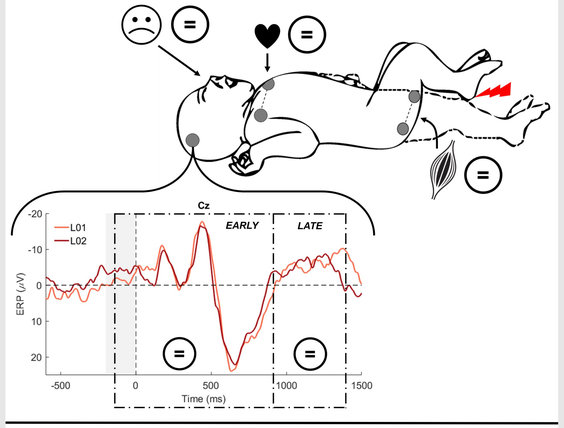
Discussion & Conclusions

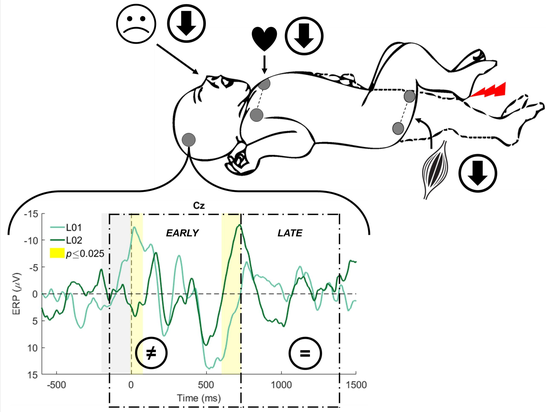
- Term neonates habituate to procedural pain suggesting a functioning pain modulatory system.
- Chronic pain in adults is associated with an inability to habituate to repeated noxious stimulation [9]. Premature neonates are therefore potentially more vulnerable to the numerous procedures required as part of their care as they do not habituate to repeated procedural pain.
- The late cortical nociceptive response is affected by repetition at any age (different microstate engagement), suggesting a change in how the brain responds to an identical stimulus.
- The neonatal nociceptive response could represent two levels of pain processing: (1) early sensory-discriminative and (2) late cognitive-affective [1,10,11].

Result 1

*The subcortical and early cortical pain responses are reduced following a repeated noxious stimulus in term neonates but **not** preterm neonates.*

- ⬇ SIGNIFICANT DECREASE IN MAGNITUDE BETWEEN L02 AND L01
- = NO SIGNIFICANT DIFFERENCE
- ≠ SIGNIFICANT DIFFERENCE





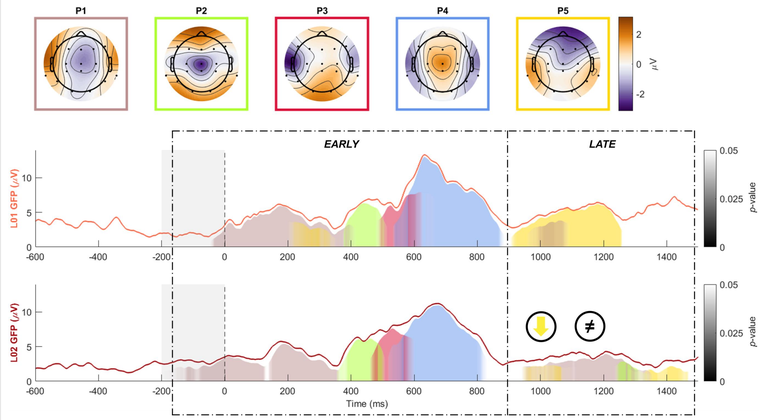
Result 2

The cortical processing of a repeated noxious stimulus involves:

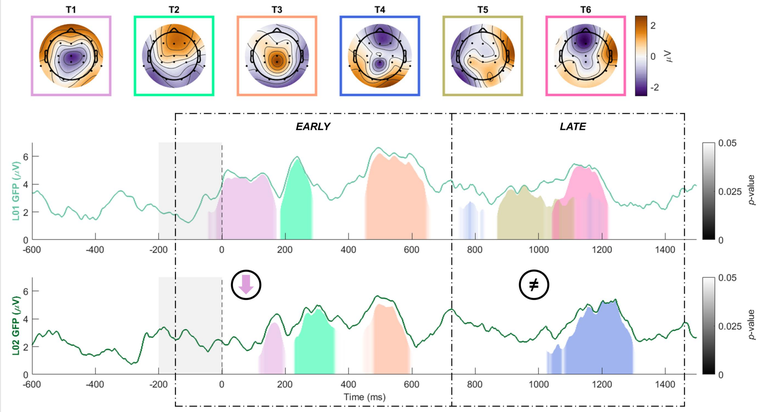
- *The engagement of a similar sequence of early microstates to that of the first stimulus.*
- *Engagement of distinct late microstates by both preterm and term neonates.*
- *Reduced engagement of early microstates in term neonates only.*

- ⬇ SIGNIFICANT DECREASE IN MICROSTATE ENGAGEMENT BETWEEN L02 AND L01
- ≠ DIFFERENT MICROSTATE ENGAGEMENT

PRETERM



TERM



1. Bingel, U., et al. (2007). *Pain*, 131, 21-30.
2. Verriotis, M., et al. (2016). *Neuroscience*, 338, 207-19.
3. Slater, R., et al. (2010). *Neuroimage*, 52, 583-9.
4. Cornelissen, L., et al. (2013). *PLoS ONE*, 8, e76470.
5. Kucyi, A. & Davis, K. D. (2015). *Trends in Neuroscience*, 38, 86-95.
6. Jones, L., et al. (2020). *European Journal of Pain*, 25, 149–59.
7. Grunau, R. V., & Craig, K. D. (1987). *Pain*, 28, 395-410.
8. Khanna, A., et al. (2015). *Neuroscience & Biobehavioral Reviews*, 49, 105-13.
9. Flor, H., et al. (2004). *Neuroscience Letters*, 361, 147-150.
10. Ploner, M., et al. (2002). *Proceedings of the National Academy of Sciences*, 99, 12444-8.
11. Rennefeld, C., et al. (2010). *Pain*, 148, 503-8.

University College London Hospitals NHS Foundation Trust
EPFL
erc European Research Council
MRC Medical Research Council