Single-channel event-related potentials versus cortical microstate analysis of nociceptive responses in human neonates

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BACKGROUND & AIMS

- Single channel vertex event-related potentials (ERPs) have been used extensively to study pain in neonates.[1,2,3]
- This work demonstrates that the pain signal reaches the cortex from very early stages of development.
- However, the pain experience is complex and involves the sequential and parallel engagement of different brain networks.[4]
- The ERP approach could be reductive and not allow to capture the multifaceted temporospatial dynamics of nociception.
- Studying changes in the entire scalp potential field (cortical microstate engagements and transitions) could provide an indication of the changes in network activity in the processing of a noxious stimulus.

We investigated whether cortical microstate analysis can provide further insights into neonatal pain processing beyond that offered by ERP analysis.

METHODS

- Subjects: 10 preterm neonates (32-36 completed postmenstrual weeks, 5-65 days old, 5 female).
- Paradigm: two clinically-necessary blood tests (heel lances), 3-18 minutes apart.
- Pain-related brain activity recorded using electroencephalography (EEG).
- Differences between first and second lance responses statistically tested using either a t-test (ERP analysis) or non-parametric statistics (microstate analysis).

ERP analysis (reference dependent)

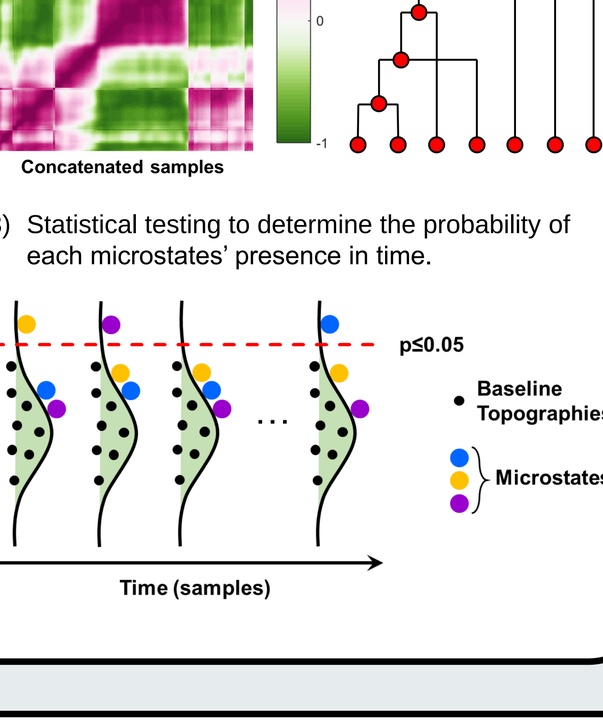
- Distinct negative (N) and positive (P) deflections occurring between 100 and 400 ms (N2-P2), and 300 and 700 ms (N3-P3) following a noxious stimulus in neonates.[3]
- Latency shifts or amplitude changes in these peaks can indicate changes to neural activity processing of stimuli.

Microstate analysis (reference independent)

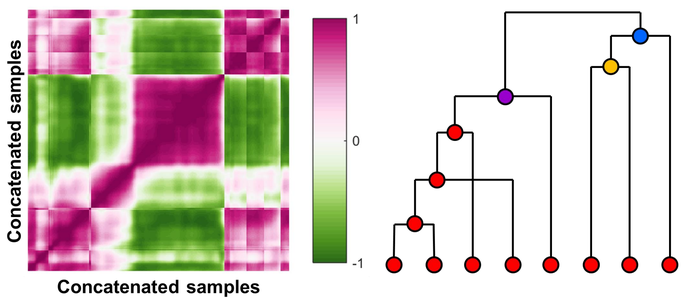
- Measures of global brain activity, defined as dynamically varying short time periods (60-120 ms) during which the configuration of the scalp potential field remains semi-stable.[5]
- Represent distinct cortical processes. Switching between microstates represents changes to brain network processes and information flow.

Microstate analysis steps:

1) Determining topographically consistent average samples across subjects/trials.



2) Hierarchical clustering of topographies using the pair-wise spatial correlation value between cluster centres.



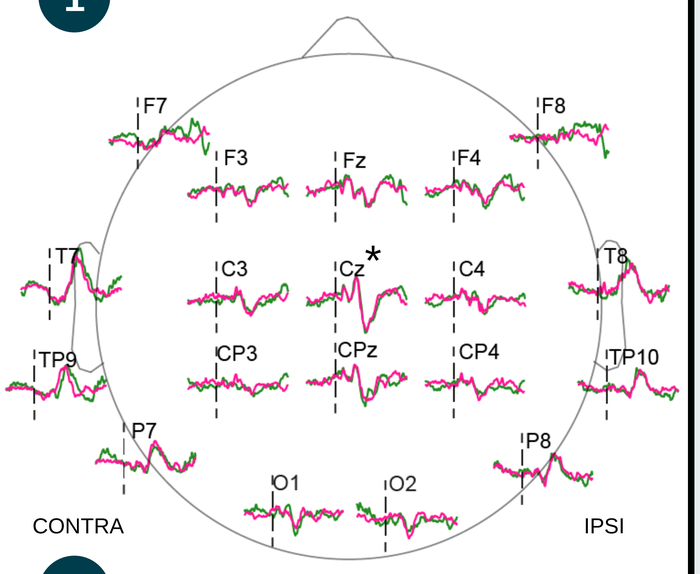
3) Statistical testing to determine the probability of each microstates' presence in time.

RESULTS

1

Topographic array of ERP averages

- Event-related potentials across groups in response to each heel lance show:
  - Peak potentials at a number of electrodes including Cz (*).
  - Shifts in the maximal electrode response over time.



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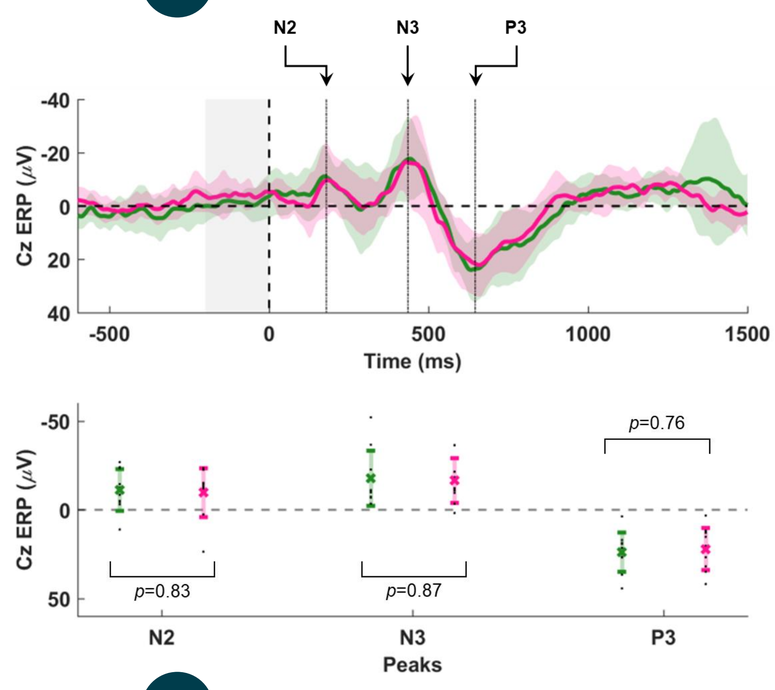
Vertex ERP analysis

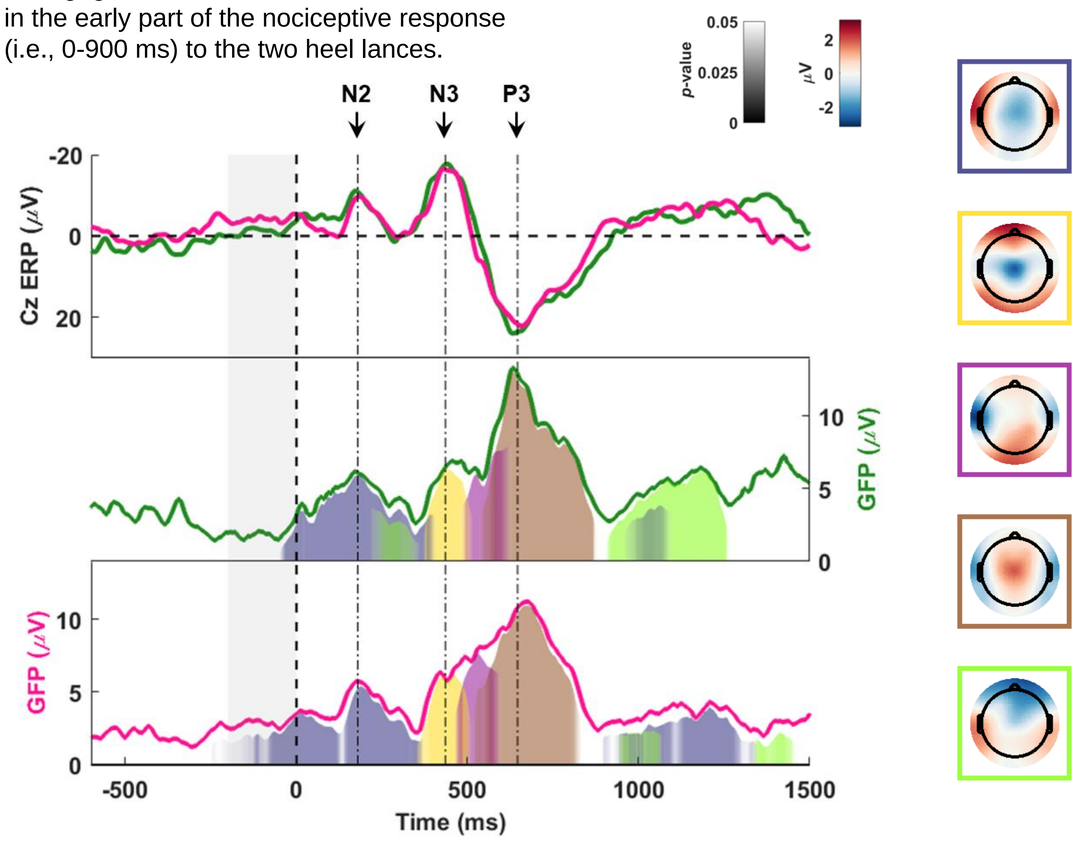
- Preterm neonates display 3 ERPs: an early ERP (N2) and a consecutive nociceptive-related ERP (N3P3) at the vertex.
- No clear peaks are observed 700 ms after the stimulus.
- No significant differences in the amplitudes of these peaks in response to the two heel lances.



3

Microstate analysis

- Heel lance elicit the engagement of 5 distinct microstates.
- Vertex ERPs map to three of them.
- No significant differences in the onset, duration or engagement extent of microstates activated in the early part of the nociceptive response (i.e., 0-900 ms) to the two heel lances.
- Microstate analysis further highlights:
  - Additional brain states between the N2 and N3 (green), and N3 and P3 (purple) potentials.
  - Repetition-specific cortical activity in the late part of the nociceptive response (i.e., >900 ms).



CONCLUSIONS

- Microstate analysis reveals the engagement of networks (i.e. topography configuration) following noxious stimuli which are missed with traditional ERP analysis.
- Microstate analysis reveals differences in late network engagements, which cannot be detected with traditional ERP analysis.
- ERP analysis suggests that there is no difference in the processing of noxious stimulation between repeated stimuli.
- Microstate analysis shows that while this is true for the initial response in preterm neonates, late processing diverges.
- A microstate approach overcomes constraints related to discrete single-channel peak identification and allows for the characterization of a complex continuous dynamic nociceptive processing stream.

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