

Supplementary Materials for

Nociceptive brain activity as a measure of analgesic efficacy in infants

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Other Supplementary Material for this manuscript includes the following:

(available at

www.sciencetranslationalmedicine.org/cgi/content/full/9/388/eaah6122/DC1)

Data file S1 (.mat format). Template of nociceptive brain activity in infants (provided as a separate file).

Data file S2 (.m format). MATLAB code to project the template onto new EEG data (provided as a separate file).

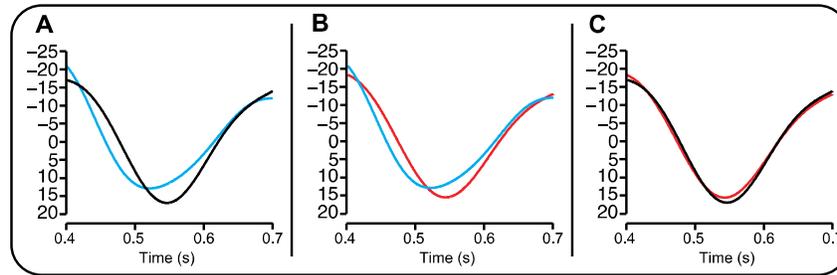


Fig. S1. Comparison of the noxious brain activity evoked by the clinical and experimental stimulus modalities.

The noxious-evoked brain activity was independently characterized using PCA after the clinical heel lance (blue) and the experimental noxious stimuli (black). The independently derived waveforms were compared with each other and with the template (red). (A) Comparison of the morphology of the noxious activity evoked by the clinical heel lance (blue) and the experimental noxious stimuli (black). (B) Comparison of the morphology of the noxious activity evoked by the clinical heel lance (blue) and the template (red). (C) Comparison of the morphology of the noxious activity evoked by experimental noxious stimuli (black) and the template (red). [All waveforms are calculated from the data in Study 1. For the clinical heel lance (blue), the PC waveform was identified by comparing the response to the heel lance with that of the control heel lance and background activity. For the experimental noxious stimuli (black), the PC was identified by comparing the response to the experimental noxious stimuli with the response to the tactile stimulation and background activity. The PCs have been scaled to match the template magnitude.]

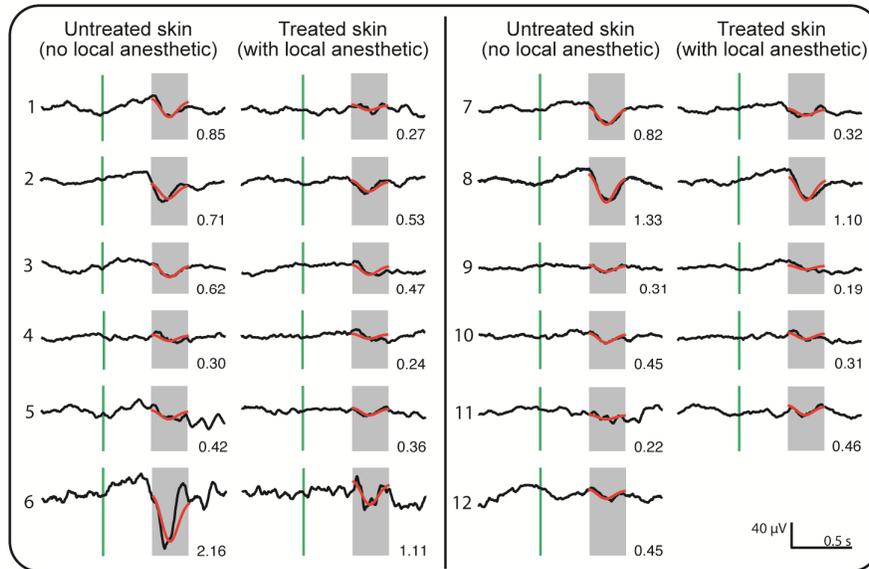


Fig. S2. Evoked activity in individual infants demonstrating sensitivity to analgesic modulation.

Average evoked activity to the experimental noxious stimuli applied to each foot - one untreated and the other treated with topical local anesthetic - in the 12 infants in Study 5. The green vertical lines indicate the point of stimulation. The evoked activity (black) is overlaid with the template (red). The average magnitude of the nociceptive brain activity is reported for each infant. In all but one infant (participant 11), the magnitude of the noxious evoked brain activity was reduced by application of the topical local anesthetic. In one infant (participant 12), the study was stopped before stimulation on the treated skin because the infant was restless.

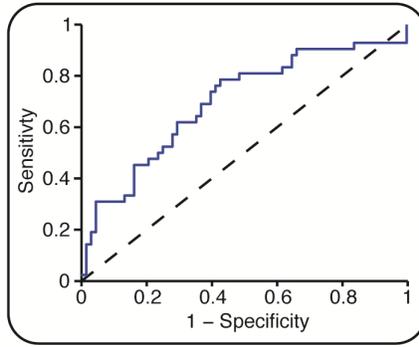


Fig. S3. ROC curve.

The receiver operating characteristic (ROC) curve (blue) for the responses to noxious and non-noxious stimuli in preterm and term infants (from Studies 2, 3, and 4). The sensitivity and specificity were calculated from the responses to noxious (clinically-required heel lance and experimental noxious stimuli) and non-noxious (control heel lance, auditory, visual, tactile) stimuli for varying thresholds between -2 and 2. The mean individual infant responses for the experimental stimuli were first calculated to obtain a subject average response. The area under the curve is 0.70, indicating reasonable predictive power.

Infant	Clinically-required heel lance	Experimental noxious stimuli	Control heel lance	Experimental tactile stimuli
1	✓		✓	
2	✓		✓	
3	✓		✓	
4	✓		✓	
5	✓		✓	
6	✓		✓	✓
7	✓		✓	
8	✓		✓	
9		✓		✓
10		✓		✓
11		✓		✓
12		✓		✓
13		✓		
14		✓		
15		✓		
16		✓		
17		✓		
18				✓

Table S1. Identification of the stimulus modalities applied to each infant in study 1.

EEG was recorded in response to noxious (clinically-required heel lance and experimental noxious stimuli) and non-noxious (control heel lance and experimental tactile stimuli) stimuli in 18 infants in Study 1. The clinically-required heel lance and control heel lance were applied once per infant. The experimental noxious stimuli and tactile stimuli were applied in trains of approximately 10.