

# Hippocampal potentials evoked by network-targeted stimulation vary by theta phase

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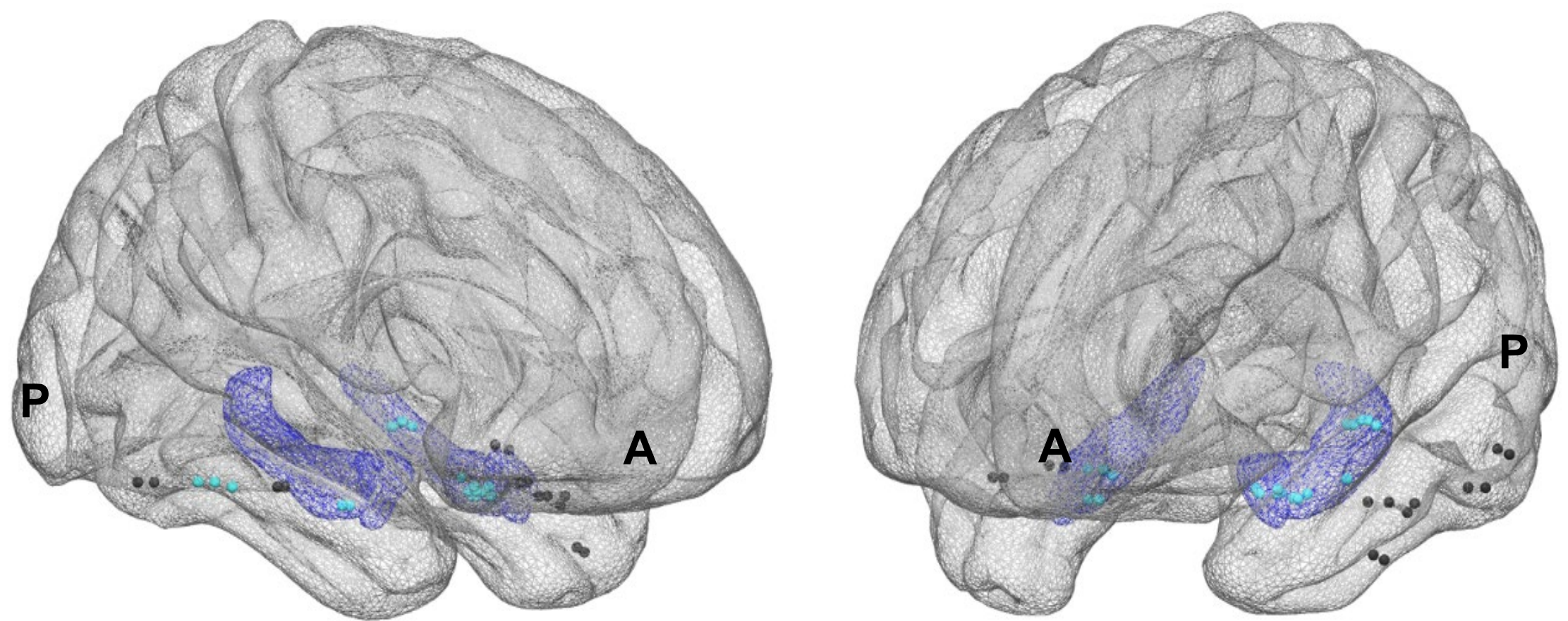
## Background

- Previous work in rodent models suggests that hippocampal excitability and connectivity with afferents vary with local theta oscillatory phase
- Stimulation targeting the hippocampus indirectly via its network can impact hippocampal memory function.
- However, it is not known whether theta phase has an impact on network stimulation efficacy
- We tested whether evoked potential amplitude in human hippocampus varies according to local theta phase at the time of stimulation

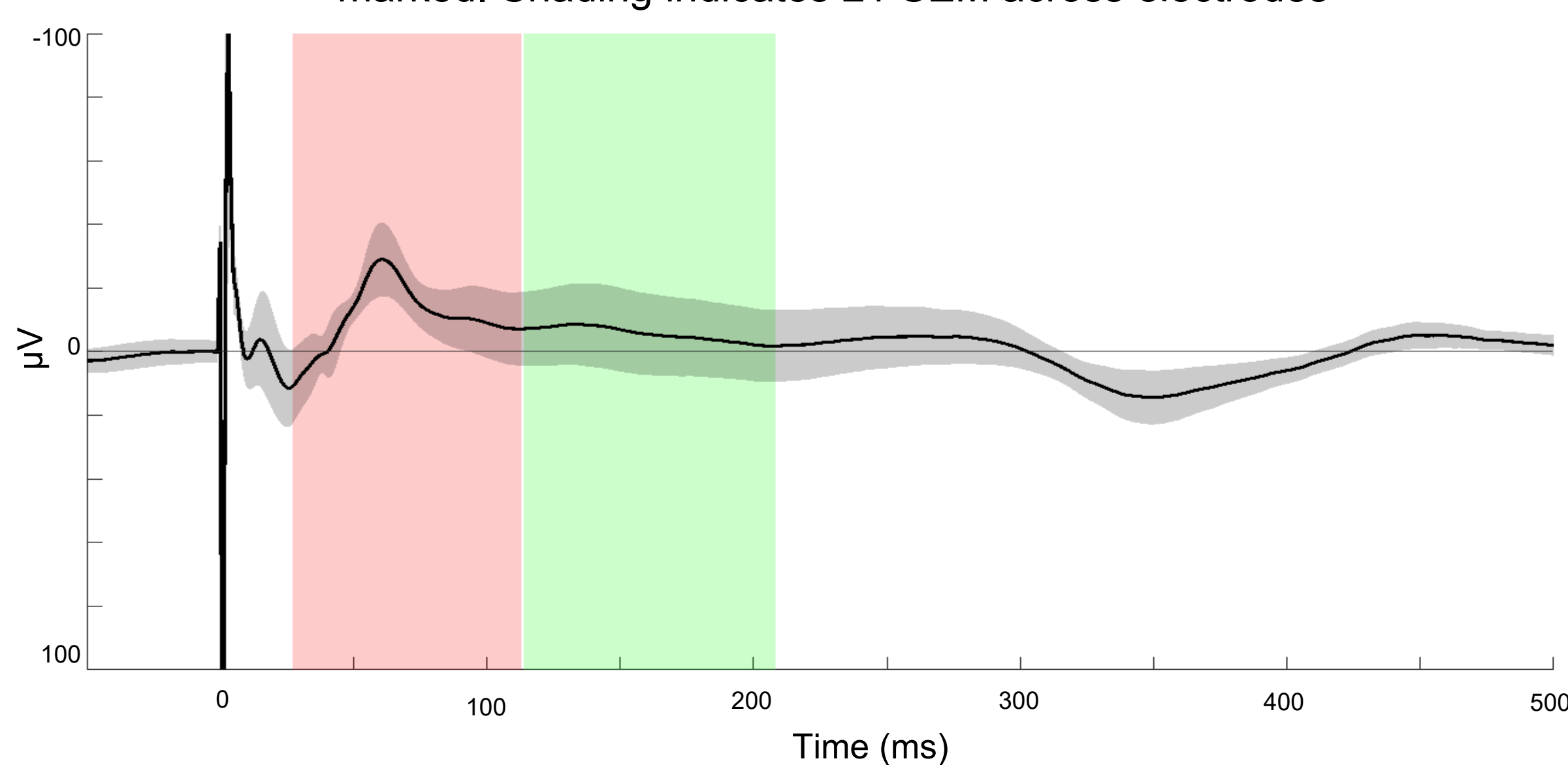
## Methods

- Data were collected from individuals with refractory epilepsy (N=8) undergoing invasive monitoring via implanted depth electrodes (sEEG)
- In each subject, bipolar, single-pulse direct electrical stimulation was administered through an electrode pair in lateral temporal cortex (LTC) and adjacent white matter (stimulation delivered at jittered 1Hz; 5mA intensity; ~1500 total pulses delivered per subject)

Locations of **hippocampal** and **LTC (stimulating)** electrodes overlaid on template brain



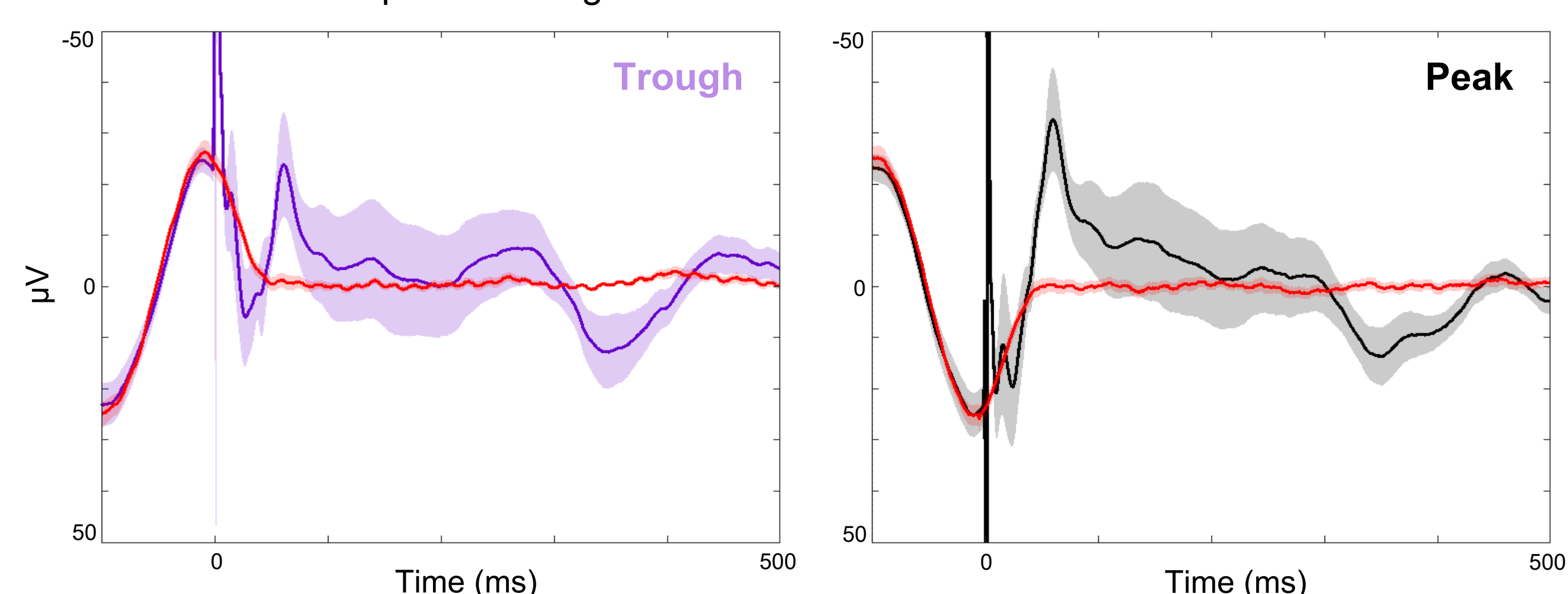
Average hippocampal evoked response to stimulation, with **early** and **late** components marked. Shading indicates  $\pm 1$  SEM across electrodes



## Trial phase-sorting and sham-correction

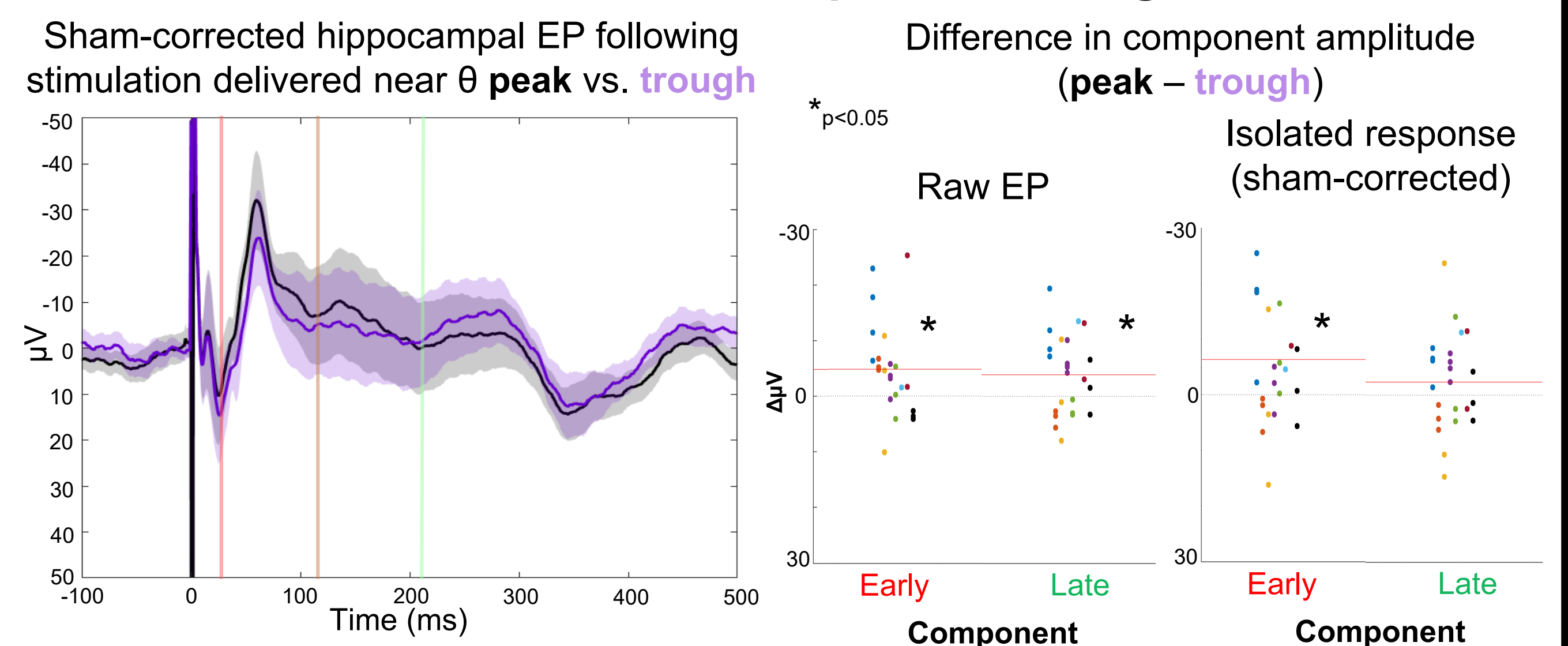
- Trials were binned at  $\pi/4$  intervals according to estimated 3-8Hz theta phase at the time of stimulation onset
- To isolate the evoked signal from the ongoing oscillatory component, we generated **stimulation-free sham trials** with distributions of theta phase at t=0 matched to the stimulation trials

Mean hippocampal response to LTC stimulation delivered near the local theta **trough** (left) and **peak** (right). Average of phase-matched, **stimulation-free sham trials** overlaid for each plot. Shading indicates  $\pm 1$  SEM across electrodes.



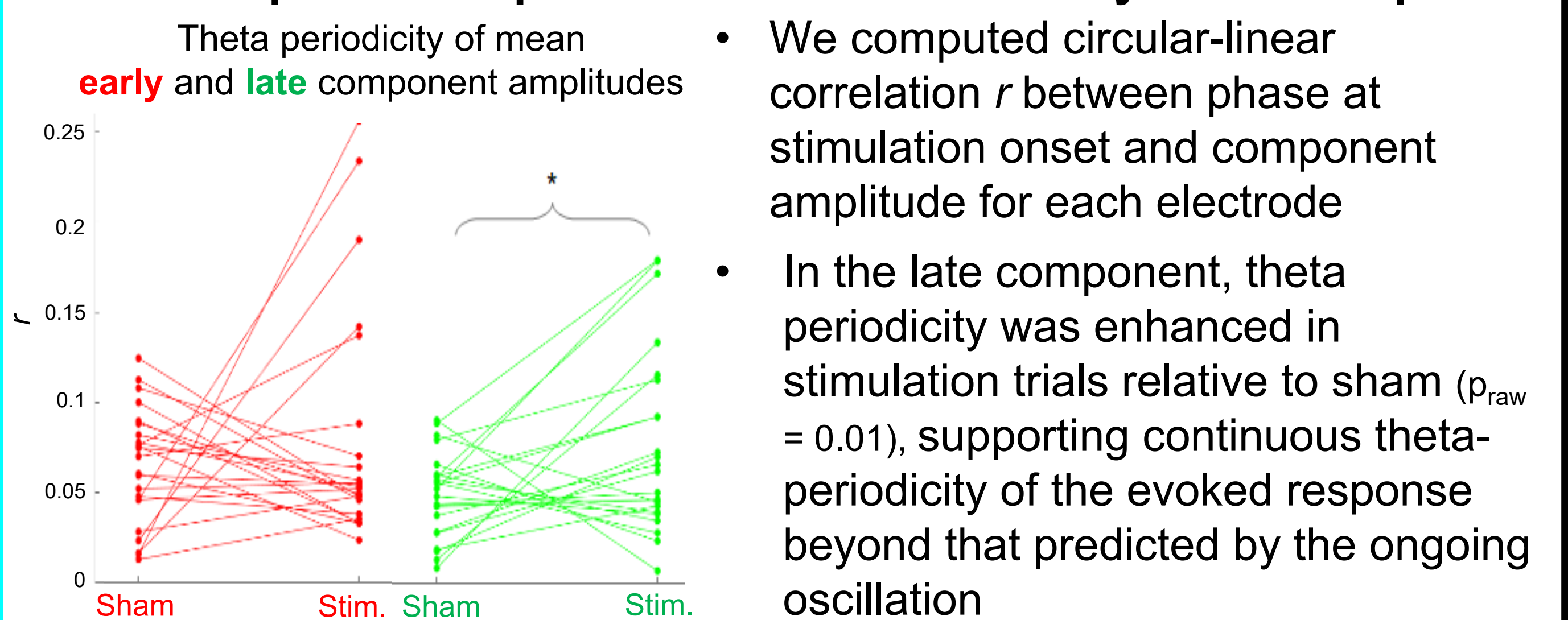
## Results

### Hippocampal late response amplitude is greater following stimulation at theta peak vs. trough

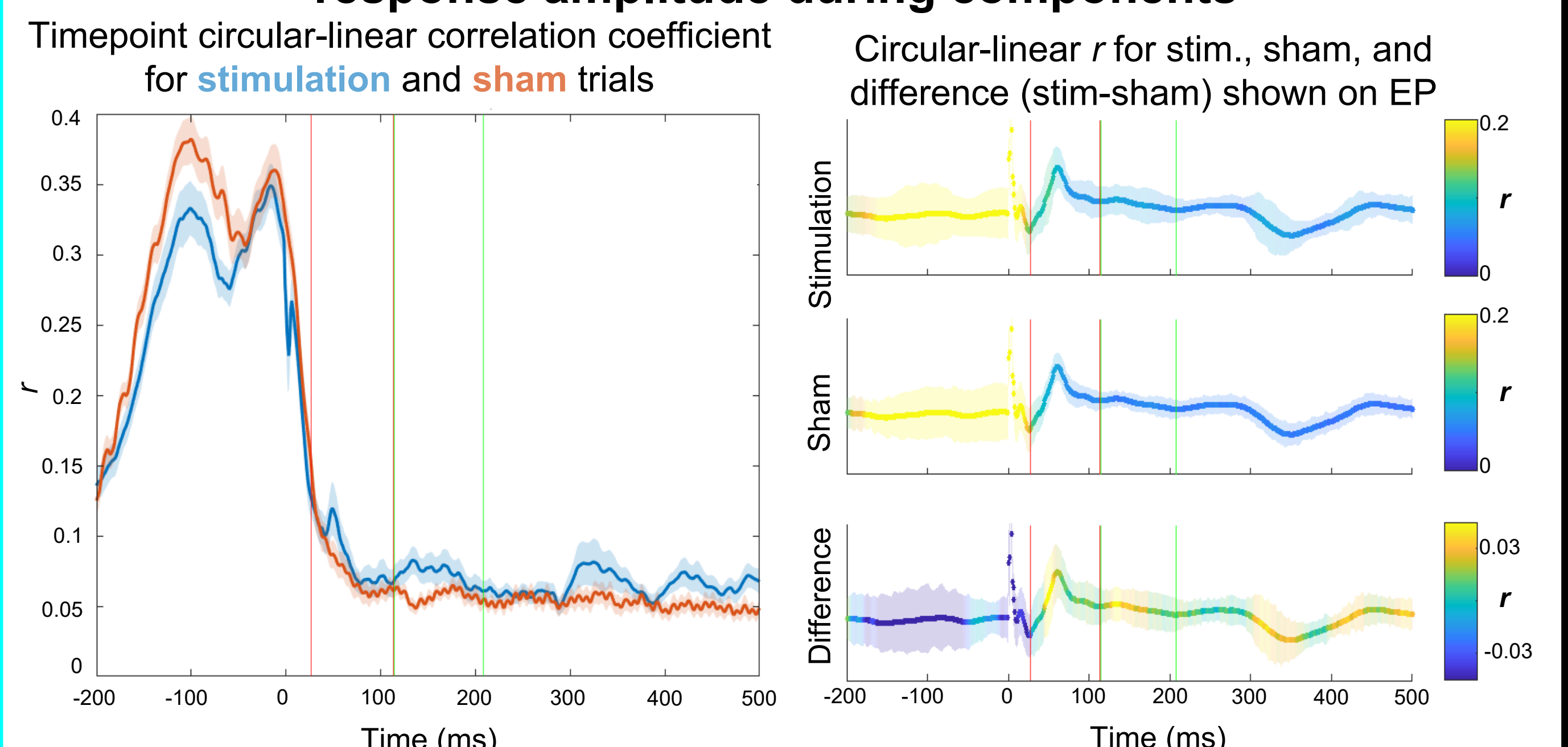


- Sham-correction effectively abolished the pre-stimulation theta oscillation (n.s.d. mean peak vs. trough amplitude from -50ms to 0ms)
- Early component amplitude was enhanced by peak stimulation relative to trough (paired t-test:  $p_{\text{raw}} = 0.01$ ,  $p_{\text{sham-corrected}} = 0.03$ )
- Late component amplitude was enhanced by peak stimulation in the raw (paired t-test:  $p_{\text{raw}} = 0.02$ ) but not sham-corrected EP

### CCEP component amplitude varies continuously with theta phase



### Theta phase at stimulation selectively impacts hippocampal response amplitude during components



**Left:** Circular-linear correlation  $r$  between estimated theta phase at t=0 and timepoint amplitude. Stimulation (blue) vs. sham (orange) trials

**Right:** Circular-linear  $r$  overlaid on grand average stimulation EP. Shading indicates  $\pm 1$  SEM of  $r$  across electrodes

## Summary

- LTC stimulation consistently evoked a hippocampal response with distinct early and late components
- Contrary to our hypothesis, late response amplitude was greater when stimulation was delivered at local theta peak relative to trough
- The hippocampal EP showed enhanced theta-periodicity selectively during components
- These findings suggest that local theta phase predicts the magnitude of evoked hippocampal response by stimulation of LTC afferents

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