Single neurons throughout human memory regions phase-lock to hippocampal theta

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Background

- Functional interactions between cortex and hippocampus critical for episodic memory
- Influential theories suggest neural oscillations help guide communication between brain regions
- Rodents studies reveal neurons in multiple regions that phase-lock to hippocampal theta rhythm during memory-dependent tasks
- We explored a role for single-neuron phase-locking to hippocampal LFP rhythms in 18 epilepsy patients who played a virtual navigation game

Methods

Phase-locking determination

- For each neuron outside the HPC, wavelet convolution used to compute spike-coincident hippocampal LFP phases at 16 frequencies from 0.5-90.5Hz across entire recording session
- Mean resultant length (MRL) of spike-phase distribution calculated at each frequency and Z-scored (within-frequency) against null distributions of MRLs from circularly-shifted spike trains to determine phase-locking strength at each frequency
- Phase-locking *p*-value defined for each neuron by comparing maximum phase-locking strength (across frequencies) to the null distribution
- Significance set at α=0.05, false discovery rate corrected at study level

Abbreviations: AC = anterior cingulate; AMY = amygdala; EC = entorhinal cortex; HPC = hippocampus; LFP = local field potential; OFC = orbitofrontal cortex; PHG = parahippocampal gyrus

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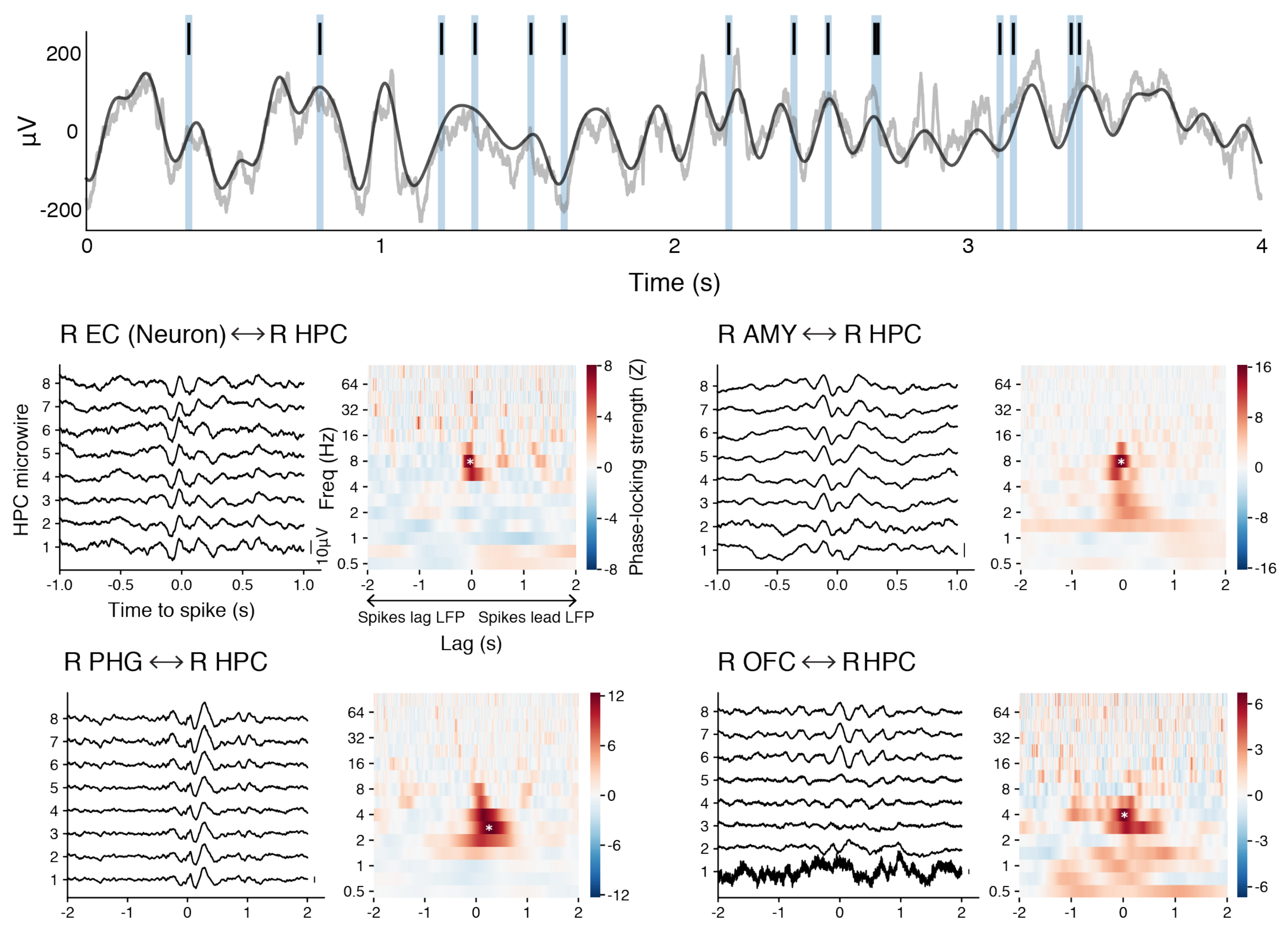
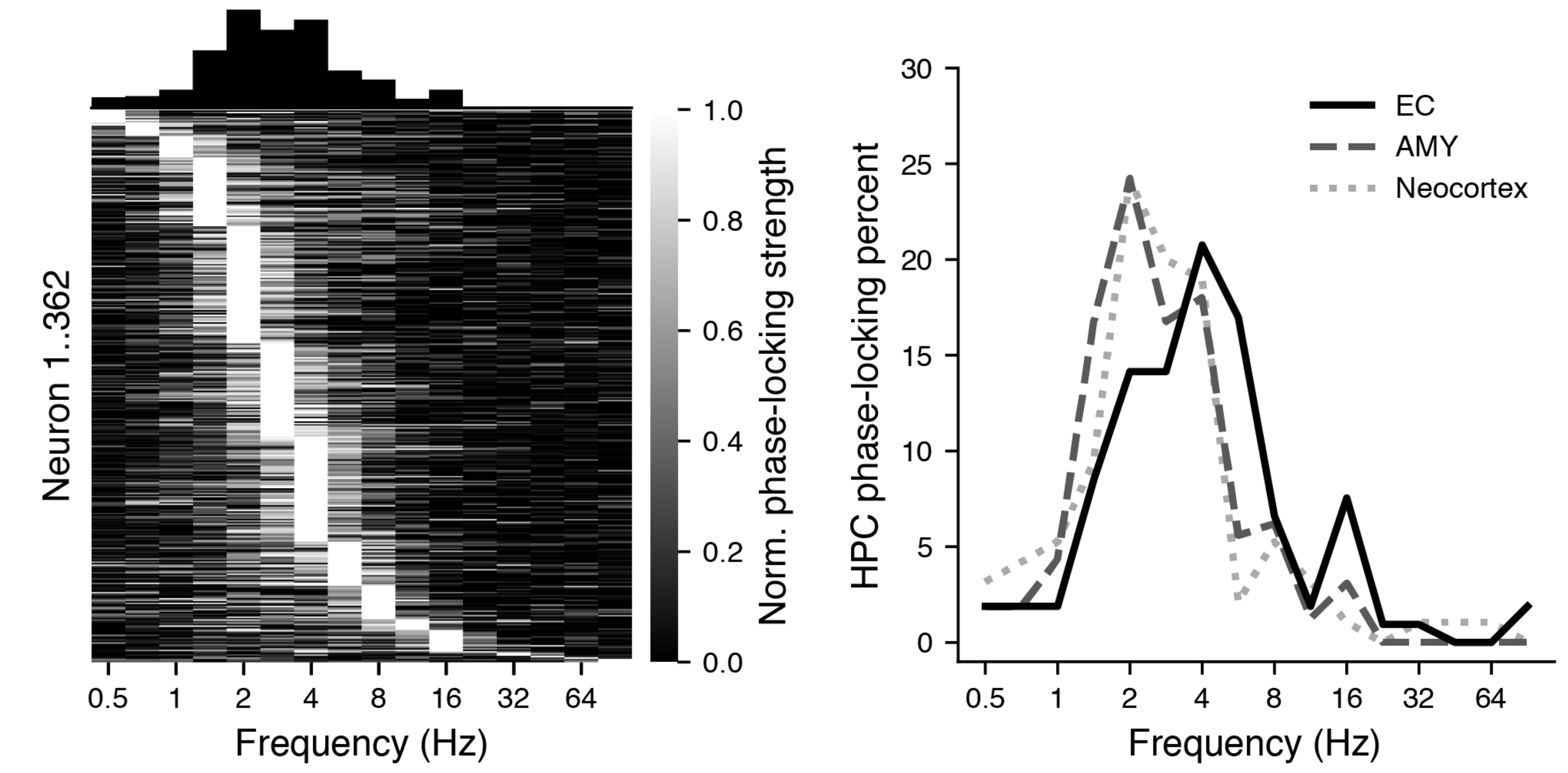
I. Nearly 30% of neurons outside the HPC (362/1,233) phase-locked to hippocampal oscillations



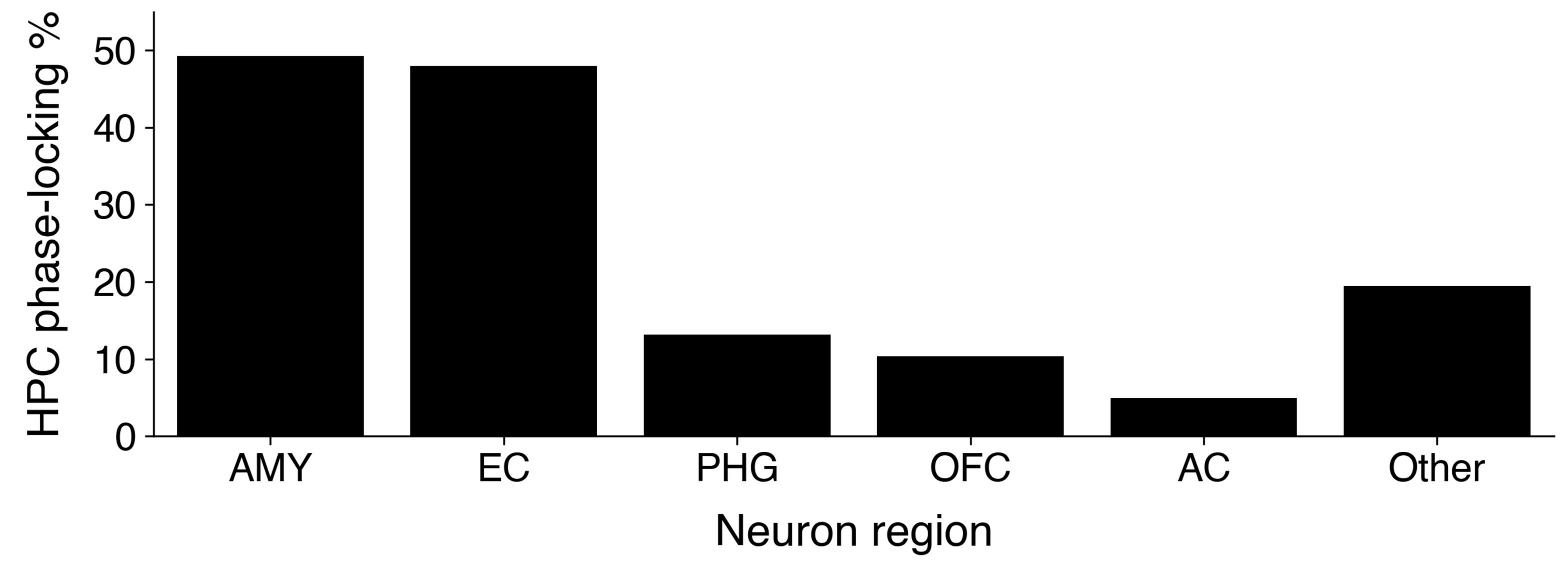
(Top) 4s example trace shows spikes from an EC neuron alongside simultaneously-recorded hippocampal LFP. Note alignment between spikes and theta peaks. (Bottom) Phase-locking to the HPC in 4 example neurons for which we plot spike-triggered average LFPs from 8 adjacent HPC electrodes (left) and phase-locking strengths by LFP frequency and spike-LFP lag (right).

II. Phase-locking to the hippocampus almost exclusive to the theta band



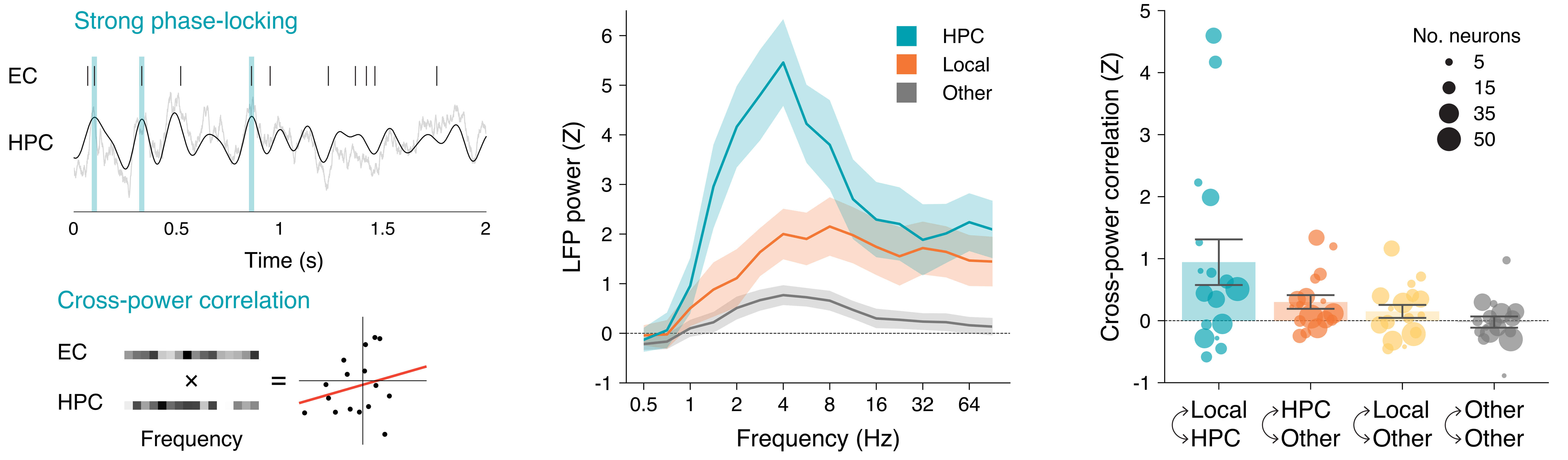
(Left) Phase-locking strength by frequency shown for each significantly phase-locked neuron. (Right) Percent of EC, AMY, and neocortical neurons that phase-locked maximally to the HPC at each frequency.

III. Phase-locking rates greatest in, but not limited to, regions structually connected to the HPC



Percent of neurons from each region that phase-locked significantly to ipsilateral hippocampal LFPs at any frequency from 0.5-90.5Hz over the entire recording duration (mean=25min).

IV. Strong phase-locking coincided with regionally-specific increases in theta power, high frequency activity, and cross-power correlations between the HPC and local region



(Left) Illustrated methods for determining strong phase-locking and cross-power correlations. (Middle) Z-scored LFP powers in the HPC, local region, and remaining regions during strongly phase-locked firing (20% of spikes closest to each neuron's mean theta phase) compared to randomly drawn spike subsets. Means and SEMs shown across subjects. (Right) Z-scored cross-power correlations between the local region and HPC (cyan) and other region pairs during strongly phase-locked firing compared to randomly drawn spike subsets. Means and SEMs shown across subects; each circle indicates the mean for one subject with circle area proportional to the number of neurons.

Conclusions

- Spike-time synchrony with hippocampal theta rhythm a defining feature of cortico-hippocampal functional interactions in humans
- Strong theta phase-locking coincided with regionally-specific changes in LFP power in the HPC and phase-locking region
- Results broadly agree with findings in rodents, despite human hippocampal theta being slower and more sporadic
- We propose that theta phase-locking gates communication with the HPC during memory encoding and retrieval