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Title: Widespread ripples synchronize human cortical activity

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Abstract

Hippocampal ripples index the reconstruction of spatiotemporal neuronal firing patterns essential for the consolidation of memories in cortex during sleep. Here, using human intracranial recordings, we show that ripples are also ubiquitous in the cortex during both waking and non-rapid eye movement sleep. During sleep, cortical ripples are generated on the down-to-upstate transition with phase-locked firing patterns indicating generation by pyramidal-interneuron feedback. They mark recurrence of spatiotemporal patterns from preceding waking, and group co-firing to facilitate plasticity. During waking, cortical ripples co-occur with hippocampal ripples during local activity peaks, and co-occur preceding memory recall. During sleep and waking, cortical ripples co-occur and phase-synchronize across widespread locations, including between hemispheres, providing a possible substrate for event-integration during memory and more generally in cognition.

Main

Ripples have been extensively studied in rodent hippocampus during non-rapid eye movement (NREM) sleep, when they mark the replay of events from the prior waking period, and are critical for memory consolidation in the cortex (*1-4*). They are associated with cortical replay (*5-7*), and with cortical sleep waves (spindles, downstates and upstates) (*8*), a relationship crucial for consolidation (*9*). Recently, ripples have also been found in the rat cortex, associated with hippocampal ripples, especially after learning (*10*). In humans, hippocampal ripples were found during NREM coordinated with cortical sleep waves (*11-13*), and during memory retrieval, preceding cortical ripples (*14*) with cell-firing reproducing spatiotemporal patterns from encoding (*15*). However, the human cortical ripples were found primarily in temporal association cortex during waking, and it is unknown if they also occur during NREM, in other cortical areas, or if the basic neurophysiology of human ripples is consistent with that described in rodents: phasic depolarization triggering a pyramidal-interneuron feedback loop. Crucial to the hypothesized role of ripples in coordinating consolidation and retrieval of memories composed of widely-distributed elements, the co-occurrence and phase-locking patterns of ripples across the cortical mantle are unknown. Finally, relationships between hippocampal and cortical ripples that may be crucial for guiding the replay of cortical firing patterns necessary for consolidation during NREM, and for memory recall during waking, remain unexplored.

Here we report ripples recorded intracranially from non-epileptogenic cortex and hippocampus in 17 patients undergoing monitoring for seizure focus localization (Supplementary Table 1). Bipolar derivations ensured measurement of local field potentials (LFP). Ripples were detected when there were at least 3 cycles of increased 70-100Hz amplitude without contamination by epileptiform activity or artifacts (SFig.1). Ripples were found during both waking and NREM in all cortical areas sampled (Fig.1A-B,E, SFigs.2-4, Supplementary Table 2), and hippocampus (Fig.1C-D,F, Supplementary Table 3). Across states and structures, ripple frequency was remarkably consistent (~80Hz), durations were similar (~65ms), and spontaneous cortical ripple occurrence rate was higher during NREM than waking (Fig.1E).

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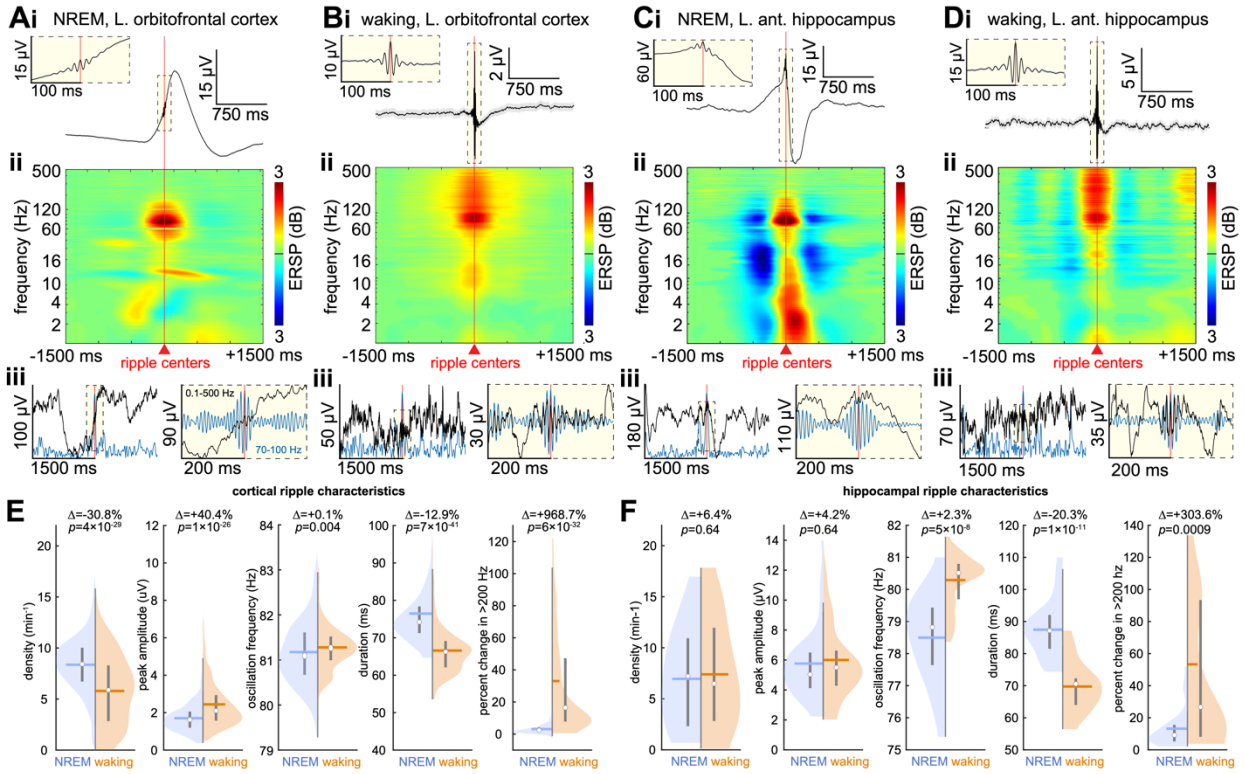

Fig. 1. Cortical and hippocampal ripple characteristics during NREM sleep and waking. (**A**) Orbitofrontal average broadband LFP (**i**) and time-frequency (**ii**) across ripples, and example broadband ripple (**iii**) unfiltered sweeps (black, left–3000ms, right–400ms), and 70-100Hz bandpass (blue, left-analytic amplitude, right-sweep), from one channel during NREM. (**B**) Same as (A) except during waking. (**C**) Same as (A) except hippocampal ripples. (**D**) Same as (C) except during waking. (**E**) NREM vs. waking cortical ripple density, peak 70-100Hz amplitude, frequency, duration, and percent change in peak >200Hz amplitude (*N*=273 channels; SEEG patients S1-17). (**F**) Same as (E) except hippocampal ripples (*N*=28 channels). Circles show medians; horizontal lines, means; vertical lines, interquartile ranges. FDR-corrected *p*-values, two-sided paired t-test. LFP=local field potential.

NREM is characterized by large downstates, often followed by upstates with spindles (*16,17*). Hippocampal ripples tend to occur on the cortical down-to-upstate transition with spindles in rodents (*7,8*) and humans (*11*). Cortical ripples occur on upstate and spindle peaks in cats (*18*) and rats (*10*). In humans, we found that cortical ripples were generated during down-to-upstate transitions (Figs.1A,2A-C, SFig.2A-C), often during spindles (Fig.2A,D; Supplementary Tables 4-5), with a preference for spindles preceding upstates (SFig.5). In humans, upstates (*19*) and spindles (*20*) induce strongly increased unit-firing. Using microelectrode array recordings from granular/supragranular layers of lateral temporal cortex during NREM (SFig.4A, Supplementary Table 6), we found unit firing-rates also increased during ripples (Fig.2E-F).

The increased firing during NREM ripples and their occurrence on upstates and spindles implies an underlying phasic depolarization, which can generate ~80Hz oscillations in computational and experimental models via pyramidal-interneuron feedback inhibition (*2,21*). Depolarization causes basket cells to fire synchronously, inhibiting other basket cells and pyramids via $GABA_A$. Pyramids fire upon recovery, exciting basket cells as they recover, leading to another cycle. As predicted, we found that pyramids and interneurons were strongly phase-locked to cortical ripples (Fig.2E), with pyramidal significantly leading interneuron spiking (Fig.2G-H). Furthermore, interneurons

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fired at ripple peak, when pyramidal somatic inhibition would be maximal, as found in cats (*18*). Similarly, ripple amplitude was higher in waking than NREM (Fig.1E), consistent with relative depolarization of pyramidal membrane potential during waking. Phasic depolarization during waking ripples was also suggested by increased >200Hz amplitude, a proxy for neuronal spiking (Fig.1E-F). Thus, human cortical ripples are associated with strong tonic and phase-locked increases in pyramidal and interneuron firing rates, and are likely generated by a sudden depolarization triggering pyramidal-interneuron feedback oscillations. The increased firing, and especially its phase-concentration, produced short latency co-firing (Supplementary Table 7), which provides a necessary and sufficient condition for spike-timing-dependent plasticity, and therefore may underlie the crucial contribution of these nested waves to consolidation (*20*).

Hippocampal ripples in NREM mark the assembly of spatiotemporal firing patterns reproducing the sequential attributes of events from the preceding waking, supporting cortical replay and consolidation (*2,22*). However, cortical ripples have not been associated with replay during NREM. Our group previously identified waking spatiotemporal patterns of high gamma (70-190Hz) activity across widespread cortical areas that recurred more often in the following compared to preceding sleep night. These events also coupled to upstates, spindles and hippocampal ripples (*23*). In new analyses of these data (Supplementary Table 8), we found that the high gamma events that comprised these sequences of putative replay were strongly linked to cortical ripples (Fig.2I-J). Hippocampal assembly of the different elements of an event is possible, despite the local nature of most hippocampal ripples (*12,24*), because these elements (typically locations in an environment) are encoded by cells in close proximity. In contrast, encoding sites in the cortex are distributed across its vast surface, posing the question of how they are specifically selected by hippocampo-cortical projections.

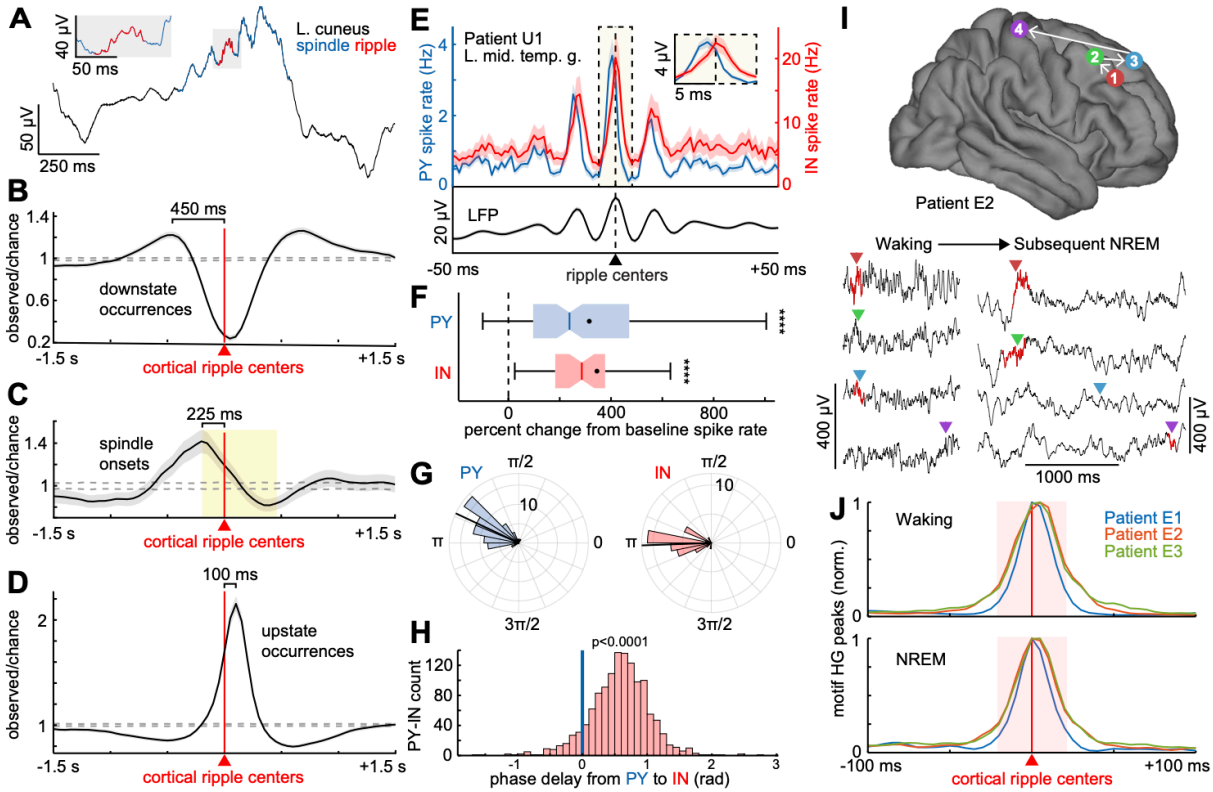

Fig. 2. Relation to sleep-waves, local generating mechanisms, and association with recurrence of spatiotemporal patterns from waking. (**A**) Example cortical ripple occuring

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during a spindle on a down-to-upstate transition. (**B**) Average downstate peak times plotted relative to local cortical ripple centers at *t*=0 across significant channels (*N*=258/273, patients S1-17). Dashed lines show 99% confidence interval of the null distribution (200 shuffles/channel). (**C-D**) Same as (B) except spindle onsets (*N*=80/273) (**C**) with shaded area indicating average spindle duration and downstate peaks (*N*=260/273) (**D**). (**E**) Mean broadband cortical ripples (black) and associated local PY (*N*=69) and IN (*N*=23) spike rates during NREM. (**F**) Single unit spike rates increase during cortical ripples (PY: *N*=133, mean=315%; IN: *N*=38, mean=345%; patients U1-3). (**G**) Circular mean 70-100Hz phase of spikes of each PY (*N*=73, mean=2.70rad, $p=2\times10^{-7}$, Hodges-Ajne test) and IN (*N*=36, mean=3.18rad, p≈0) during local cortical ripples (minimum 30 spikes per unit). PY spiking preceded IN spiking by 0.48rad ($p=2\times10^{-7}$, Watson-Williams test). (**H**) Circular mean ripple phase-lags of spikes from each PY (*N*=73) to each IN (*N*=36) (*N*=1280 unit pairs, mean=0.58±0.46rad, $p=1\times10^{-268}$, one-sample one-sided t-test). (**I**) Example spatiotemporal sequence ("Motif") of high gamma peaks identified during waking that recurred in the subsequent sleep with involvement of ripples shown in red (*23*). (**J**) Average motif peak times plotted relative to local cortical ripple centers. Errors show SEM. IN=putative interneuron, PY=putative pyramidal.

Hippocampal sharpwave-ripple occurrence and ripple coupling between parahippocampal gyrus and temporal association cortex are increased prior to memory recall in humans, (*14,25*). In rats, cortical ripples co-occurred between hippocampus and ~1mm^2 of parietal cortex in sleep following learning (*10*), and in cats, ripple co-occurrence was limited to short distances (*18*). Here, we demonstrate that, in addition to hippocampo-cortical coupling (Fig.3B), cortical ripples have frequent and strong coupling (occurrence within ±500ms), between all cortical areas sampled (Fig.3A, Supplementary Table 9), including between hemispheres. Short latency coupling led to ripple co-occurrence (overlapping ≥25ms), which was greater during waking than NREM (Fig.3C, Supplementary Table 10). Two cortical sites co-rippling made it more likely for other sites also to co-ripple (Supplementary Table 11), with multiple (>2) locations co-rippling at a much higher rate than would be expected from chance (Fig.4H, SFig.6). Critically, cortical ripple co-occurrence was infrequently and weakly associated with distance (Fig.3D, Supplementary Table 12), resulting in broad co-activation between lobes and hemispheres, consistent with a role in co-activation of multiple distributed elements constituting a memory.

In humans, anterior hippocampal ripples often occur on sharpwaves (*11*), whereas posterior hippocampal ripples are often associated with spindles (*12*). Sharpwave-ripples are more associated with sleep waves in prefrontal cortex areas supporting contextual aspects of episodic memory, whereas spindle-ripples can phase-lock with spindles in parietal areas supporting detailed autobiographical recollection. Here, we found that hippocampal sharpwave-ripples preceded cortical ripples by ~250ms (Fig.3E), whereas spindle-ripples were synchronous (Fig.3F), reinforcing a previous suggestion that they make sequential contributions to consolidation.

To test if cortical ripple co-occurrence was involved in memory recall, we analyzed paired-associates memory task data from 5 SEEG patients (Fig.3G, Supplementary Tables 1,13). Following stimulus cue presentation and preceding delayed recall, there was a significant increase in cortical ripple occurrence ($p=1\times10^{-11}$), and an even greater increase in cortico-cortical ripple co-occurrence ($p=0.0004$; linear mixed-effects; Fig.3H-I, SFig.7). Furthermore, cortical ripple occurrence ($p=0.002$) and cortico-cortical ($p=0.002$) and hippocampo-cortical ($p=0.008$) ripple co-occurrence modulations were greater preceding delayed versus immediate recall. Finally, cortico-cortical ($p=0.04$) and hippocampo-cortical ($p=0.004$) co-rippling was enhanced preceding successful versus unsuccessful recall, which was not the case for cortical ($p=0.08$) or hippocampal ($p=0.94$) ripples generally. These data suggest that ripple co-occurrence between

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cortical sites and between hippocampus and cortex may support long-term memory recall in humans.

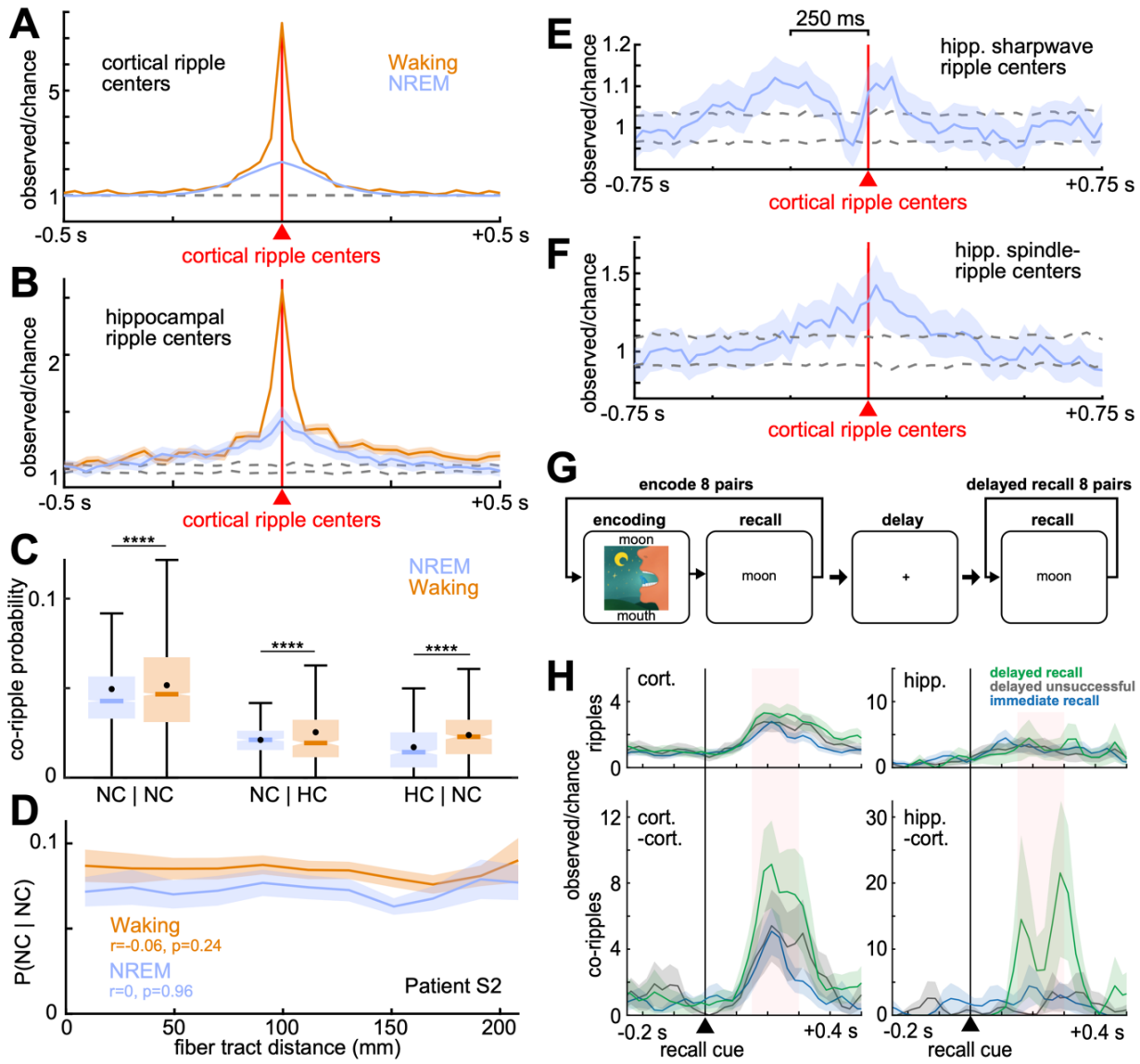

Fig. 3. Cortico-cortical and hippocampo-cortical ripples co-occur preceding memory recall. (**A**) Cortico-cortical ripple time delays between coupled (occurring within 500ms of each other without necessarily overlapping) sites during NREM (*N*=4487/4550 significant channel pairs) and waking (*N*=4478/4550; post-FDR $p<0.05$, randomization test). Dashed lines show 99% confidence interval of the null distribution (200 shuffles/channel pair). (**B**) Same as (A) except hippocampal ripples relative to cortical ripples (NREM: *N*=133/461; waking: *N*=403/461). (**C**) Conditional co-occurrence probabilities of cortico-cortical and hippocampo-cortical ripples (≥25ms overlap). (**D**) Cortical ripple co-occurrence probabilities vs. intervening fiber tract distance. (**E-F**) Same as (B) except for hippocampal sharpwave-ripples (*N*=91/461) (**E**) and spindle-ripples (*N*=56/461) (**F**) relative to cortical ripples during NREM. (**G**) Schematic of paired-associates memory task. Patients learned word pair associations and were subsequently cued with the first word to recall the second immediately following learning and then after a delay. (**H**) Cortical/hippocampal ripples/co-ripples locked to stimulus cue preceding successful immediate or delayed recall or unsuccessful delayed recall (cort./cort.-cort.: delayed *N*=365 trials, immediate

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N=698 trials, patients S18-22; hipp./hipp.-cort.: delayed *N*=90 trials, immediate *N*=304 trials, patients S19,22). Linear mixed-effects models. Error shows SEM. ****post-FDR $p<0.0001$, two-sided paired t-test.

The precise timing of cortico-cortical communication between sites by oscillations has been hypothesized to underly integration of different components of events across sites ('binding'), originally suggested by inter-hemispheric phase-locking of visually-evoked gamma in cats (*26*). We measured phase-locking as the consistency of phase between each pair of sites, across all of their co-ripple events. We found significant phase-locking values (PLV; consistency of phase from 70-100Hz independent of amplitude) of co-occurring ripples between all sampled cortical regions, including between hemispheres, more frequently during NREM than waking (Fig.4A-C, Supplementary Table 14; post-FDR $p<0.05$, randomization test; non-significant results in SFig.8A-B). Like ripple co-occurrences, PLV modulations were not associated with distance (Fig.4D, SFig.9, Supplementary Table 12).

During waking, phase-lags tended to be ~0 or ~π, whereas in NREM phase-lags were often non-zero (Fig.4E). Ripples often phase-locked across multiple sites (Fig.4F,G). Widespread co-occurrence and phase-locking of cortical ripples could theoretically arise from a common hippocampal input. However, hippocampo-cortical pairs with co-occurring ripples were seldomly phase-locked (NREM: *N*=4/277 channel pairs; Waking: *N*=1/333; SFig.8C-F), whereas cortico-cortical co-occurring ripples often were (NREM: *N*=554/2106; Waking: *N*=269/1939), a ~20-45 fold difference. This is more consistent with coupled cortical oscillators, as is the strong positive correlation between cortico-cortical phase-locking and the number of sites co-rippling (Fig.4G). In sum, we have found widespread state-dependent networks of phase-locked 80Hz oscillations over large areas of the cortex (Fig.4H).

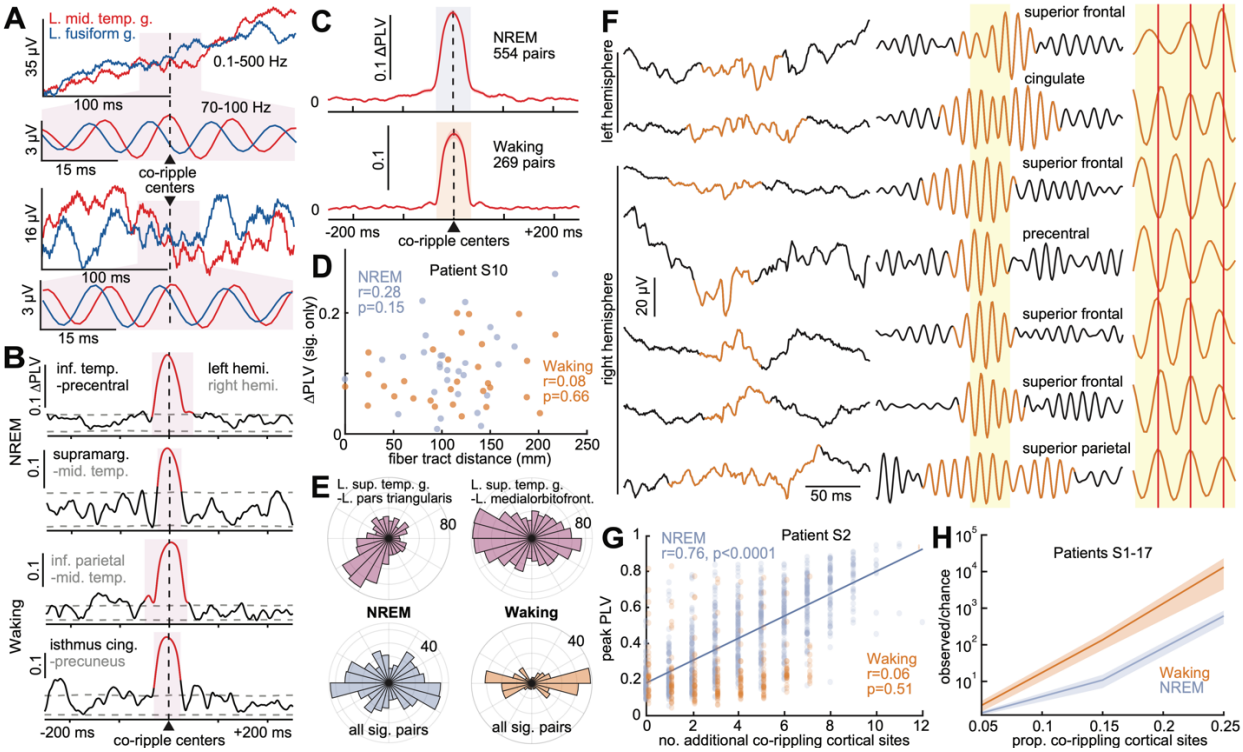

Fig. 4. Ripples synchronize across wide separations in the cortex. (**A**) Two individual ripples in broadband LFP and 70-100Hz bandpass. (**B**) Example 70-100Hz PLV time-courses calculated between ripples co-occurring between ipsilateral and contralateral cortical sites (≥25ms overlap)

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NREM and waking. Red shows significant modulation (post-FDR $p<0.05$, randomization test, 200 shuffles/channel pair). (**C**) Average ΔPLVs (relative to -500 to -250ms) for cortical channel pairs with significant PLV modulations. (**D**) ΔPLV vs. intervening fiber tract distance for significant pairs. (**E**) Polar histograms of waking and NREM phase-lags across co-ripples for two cortico-cortical pairs with significant PLV modulations (top) and across channel pair circular means (bottom). (**F**) Single sweep broadband and 70-100Hz bandpass show ripples co-occurring across multiple cortical sites during waking. Ripples are in orange. (**G**) Peak PLV as a function of the number of additional cortical sites co-rippling (NREM: N=10/17 patients significant; Waking: N=3/17, post-FDR $p<0.05$, significance of the correlation coefficient). (**H**) Observed over chance cortical ripple co-occurrence according to the number of sites co-rippling.

Here we provide the first report that cortical ripples are widespread during NREM in addition to waking in humans, forming widespread co-occurring and phase-locked networks across all lobes in both hemispheres. Ripples co-occur but seldom phase-lock between hippocampus and cortex. Cortical ripples occur during brief periods of local activation, indexed by upstates during NREM and high gamma during waking. Increased unit-firing was phase-locked to cortical ripples, with pyramids leading interneurons, consistent with oscillatory feedback models for ripple generation. Ripples during NREM were associated with spindles and down-to-upstates, and evoked high levels of single-unit co-firing during ripples, facilitating plasticity and consolidation. Cortical ripple co-occurrence preceded memory recall, and spatiotemporal activity patterns identified during waking linked to ripples during the following sleep. Thus, cortical ripples may provide a substrate for memory integration across widespread regions in the cortex with distinct roles during waking and sleep.

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