Sound-induced modulation of hippocampal θ oscillations

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The mechanism of response of hippocampal neurons to a specific feature in sensory stimuli is not fully understood, although the hippocampus is well known to contribute to the formation of episodic memory in the multisensory world. Using in-vivo voltage-clamp recordings from awake mice, we found that sound pulses induced a transient increase in inhibitory, but not excitatory, conductance in hippocampal CA1 pyramidal cells. In local field potentials, sound pulses induced a phase resetting of the θ oscillations, one of the major oscillatory states of the hippocampus. Repetitive sound pulses at 7 Hz (θ rhythm) increased the θ oscillation power, an effect that was abolished by a surgical fimbria–fornix lesion. Thus, tone-induced inhibition is likely of subcortical origin. It may segment hippocampal neural processing and render temporal boundaries in continuously ongoing experiences. *NeuroReport* **25:1368–1374 © 2014 Wolters Kluwer Health | Lippincott Williams & Wilkins.**

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Introduction

The hippocampus plays a role in encoding snapshots during daily life experiences and creating episodic memory [1]. One of the major network oscillations of the hippocampus is θ-rhythm (4–12 Hz) oscillations, which are likely to represent a memory-encoding state [2]. Indeed, the θ oscillation power correlates positively with the cognitive ability of animals [3] and humans [4,5]. In rodents, hippocampal neurons modulate their firing patterns depending on the location of the animal and collectively generate a cognitive map of space [6], and these firing patterns are modulated by θ rhythm [7]. Such internal representations regarding behavioral experience emerge and are updated through visual, auditory, olfactory, gustatory, and somatosensory information. In the present work, we investigated the effect of auditory stimuli to hippocampal θ field oscillations in awake mice. To this end, we first sought to examine how individual hippocampal neurons respond to sound, using in-vivo whole-cell patch-clamp recordings from CA1 pyramidal cells, because there is little literature about the intracellular responses of hippocampal neurons to sound in awake mice. We report here that auditory stimuli induce a transient inhibitory input to CA1 neurons and a phase resetting of θ field oscillations. Moreover, θ-rhythm tone pulses increase the θ oscillation power.

Methods

Animal ethics

The experiments were performed with the approval of the animal experiment ethics committee at the University of Tokyo (approval number: P26-5) and according to the NIH guidelines for the care and use of animals. Male ICR mice (21–45 days old) were housed in cages under standard laboratory conditions (12 h light/dark cycle) and had access to water and food *ad libitum*.

Surgery

Mice were anesthetized with ketamine (50 mg/kg, intraperitoneal) and xylazine (10 mg/kg, intraperitoneal) and were implanted with a metal head-holding plate weighing 175 mg [8,9]. After recovery, the mice were subjected to head-fixation training on a custom-made stereotaxic fixture. Training was repeated for 1–3 h/day until the implanted animal learned to remain quiet. The animal was rewarded with free access to sucrose-containing water during training, although the consumption amount of sucrose seemed unlikely to correlate with the success rate of habituation. Full habituation usually required 5–10 consecutive days. Then, the mice were anesthetized with a ketamine/xylazine cocktail and were craniotomized (1×1 mm^2), centered at 2.2 mm posterior and 2.0 mm lateral to the bregma for recordings from CA1, or at 3.8 mm posterior and 3–3.8 mm lateral to the bregma for recordings from the entorhinal cortex. The dura was surgically removed, and the exposed brain tissue surface was covered with 1.7% agar. Throughout the experiments, a heating pad maintained the rectal temperature at 37°C, and the surgical region was analgesized with 0.2% lidocaine. After the mice recovered from the anesthesia, recordings were made under head fixation in a sound-proof box. In experiments shown in Fig. 3b, the fimbria–fornix (FF) tract was bilaterally transected before recording. A retractable knife (~4 mm in width) was

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lowered to 3 mm depth from the cortex surface through a small burr hole in the skull (0.5 mm posterior, ± 2.2 mm lateral to the bregma) under stereotactic guidance. As auditory stimuli, sine-wave pure tones (duration: 10–300 ms; frequency: 4 kHz; intensity: 70–110 dB) were applied at an interval of 6–16 s from a speaker placed in front of the mice (25 cm away from the nose). In each block, tones with different conditions were presented in a random order.

Electrophysiology

Patch-clamp recordings were obtained from neurons in the CA1 stratum pyramidale (AP: − 2.0 mm; ML: 2.0 mm; DV: 1.1–1.3 mm) using borosilicate glass electrodes (4–7 MΩ). Pyramidal cells were identified by their regular spiking properties and by post-hoc histological analysis. The intrapipette solution consisted of the following reagents (in mM): 140 Cs-methanesulfonate, 5 HEPES, 10 TEA-Cl, 1 EGTA, 10 Na_2-phosphocreatine, 1 MgATP (pH 7.2), and 0.2% biocytin. Sound-evoked excitatory and inhibitory postsynaptic conductances (EPSGs and IPSGs) were measured at clamped voltages of − 70 and 0 mV, respectively [8, 10]. Experiments in which the series resistance exceeded 70 MΩ or changed by more than 15% during the entire recording session were discarded. For local field potential (LFP) recordings, the pipettes (1.5–3.5 MΩ) were filled with artificial cerebrospinal fluid, which consisted of the following reagents (in mM): 127 NaCl, 1.6 KCl, 1.24 KH_2PO_4, 1.3 $MgSO_4$, 2.4 $CaCl_2$, 26 $NaHCO_3$, and 10 glucose. LFPs were recorded from hippocampal CA1 stratum pyramidale, radiatum, or lacunosum moleculare (AP: − 2.0 mm; ML: 2.0 mm; DV: 1.1–1.4 mm) or entorhinal cortex (AP: −4.0 mm; ML: 3.2 mm; DV: 1.4–1.5 mm). For recordings form entorhinal cortex, the electrodes were inserted at an angle of 8–10° in the sagital plane with the tip pointing in the posterior direction. The signals were amplified and digitized at a sampling rate of 20 kHz using a MultiClamp 700B amplifier (Molecular Devices, California, USA) and a Digidata 1440A digitizer (Molecular Devices) that were controlled by pCLAMP 10.3 software (Molecular Devices). Data were analyzed off-line using custom-made MATLAB (R2012b; MathWorks, Natick, Massachusetts, USA) routines.

Histology

After each recording, the biocytin-containing pipette was carefully removed from the brain, and the mice were anesthetized with an overdose of urethane. After they were completely anesthetized, they were perfused transcardially with chilled PBS, followed by 4% paraformaldehyde in 0.1 M PBS (pH 7.4). The brains were removed and stored overnight at 4°C in a 4% paraformaldehyde solution. Then they were coronally sectioned at a thickness of 100 μm. The sections were incubated with 0.3% H_2O_2 for 30 min. After permeabilization in 0.2% Triton X-100 for 1 h, they were processed with ABC reagent at 4°C overnight and with 0.0003% H_2O_2, 0.02% diaminobenzidine, and 10 mM $(NH_4)_2Ni(SO_4)_2$. The success rate for reconstruction of the recoded neurons was ~80% and depended on the durations and qualities of the recordings. We did not find a leaky staining of biocytin that may occur because of approach to the cells with intrapipette pressures.

Results

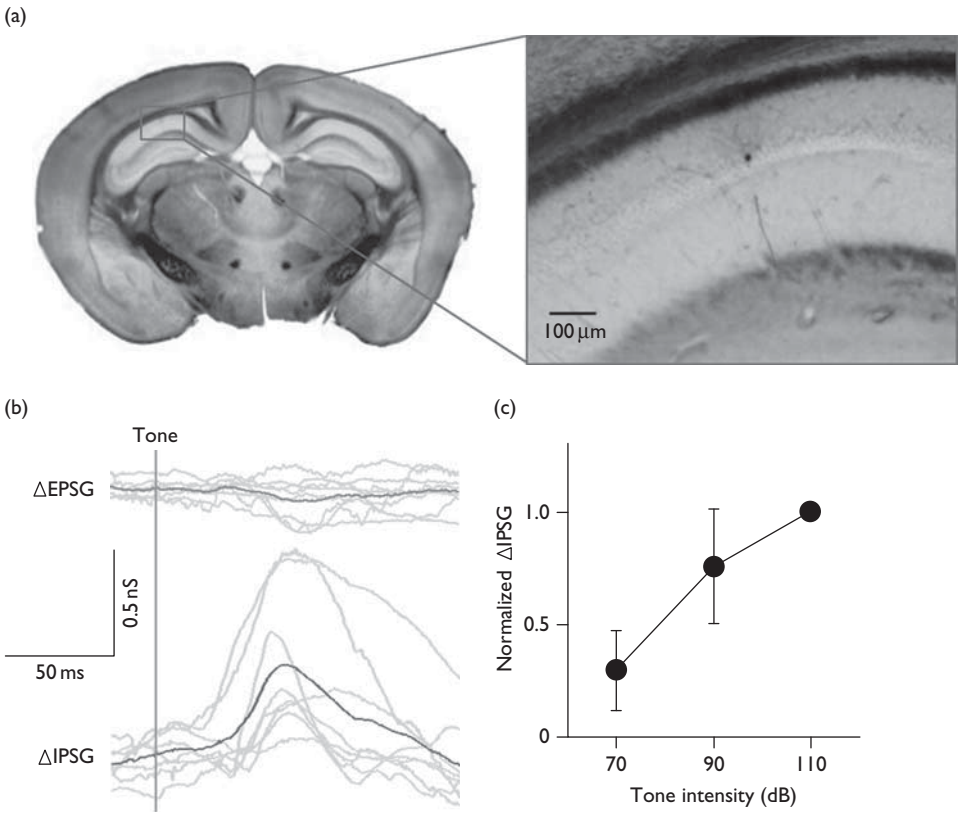
Tone-induced increase in inhibitory conductance of hippocampal CA1 neurons

Pyramidal cells were patch-clamped from the CA1 area of awake, head-fixed mice (Fig. 1a), and the mice were given 4-kHz sine-wave pure tones for 30 ms. The neurons were voltage-clamped, and excitatory and inhibitory synaptic currents were isolated. Tone stimulation induced a rapid and transient increase in IPSGs without an apparent change in EPSGs (Fig. 1b; $n = 8$ neurons from eight mice, 10–50 trials each). The transient IPSGs were consistently observed in all eight neurons recorded; the mean peak amplitude of IPSGs was 0.45 ± 0.12 nS, and the peak latency was 63.8 ± 3.1 ms after the tone onset (mean ± SEM of eight neurons). The peak amplitude of IPSGs increased with tone intensities (Fig. 1c; $n = 3$ neurons from three mice, 10–20 trials each).

Tone-induced phase resetting and entrainment of θ field oscillations

Because phasic inhibitory inputs are known to modulate oscillatory neuronal activity [11,12], we examined the effect of tone stimuli on hippocampal LFP oscillations. Mice were given 4-kHz tones for 300 ms, while LFPs were recorded from the CA1 stratum pyramidale, radiatum, or lacunosum moleculare (Fig. 2a). We first conducted a cross-correlation analysis to assess the trial-to-trial variability (Fig. 2b and c). The across-trial correlation coefficients were calculated for various time periods (Fig. 2a; bottom). They exhibited the highest peak for 1 s after the tone onset (Fig. 2b and c; $n = 17$ mice, $^{**}P < 0.01$, Dunnett's test), suggesting that hippocampal neurons were phasically synchronized by tone stimuli. We focused on the fluctuation of θ rhythm oscillations, one of the major hippocampal network oscillations. For each trial, Fast Fourier Transform analyses of LFPs revealed that a single-pulse tone stimulus did not induce a significant change in the power of θ field oscillations; the change ratio of the θ power (4–12 Hz) during the 3-s period after the tone onset to before the tone onset was − 0.05 ± 0.06 (mean ± SEM of 17 mice, $P = 0.41$, $t_{16} = 0.84$, paired t-test). However, in the stimulus-triggered average of the LFP traces, the θ power was significantly enhanced by tone stimulation; the change ratio was 1.42 ± 0.39 (mean ± SEM of 17 mice, $P = 0.002$, $t_{16} = 3.6$, paired t-test). Moreover, we found that tone stimuli forced θ oscillations into the identical phase, irrespective of the instantaneous phase at the stimulation onset time (Fig. 2d). Rayleigh's phase analysis [13] indicated that the phase congruity persisted for ~400 ms

Fig. 1



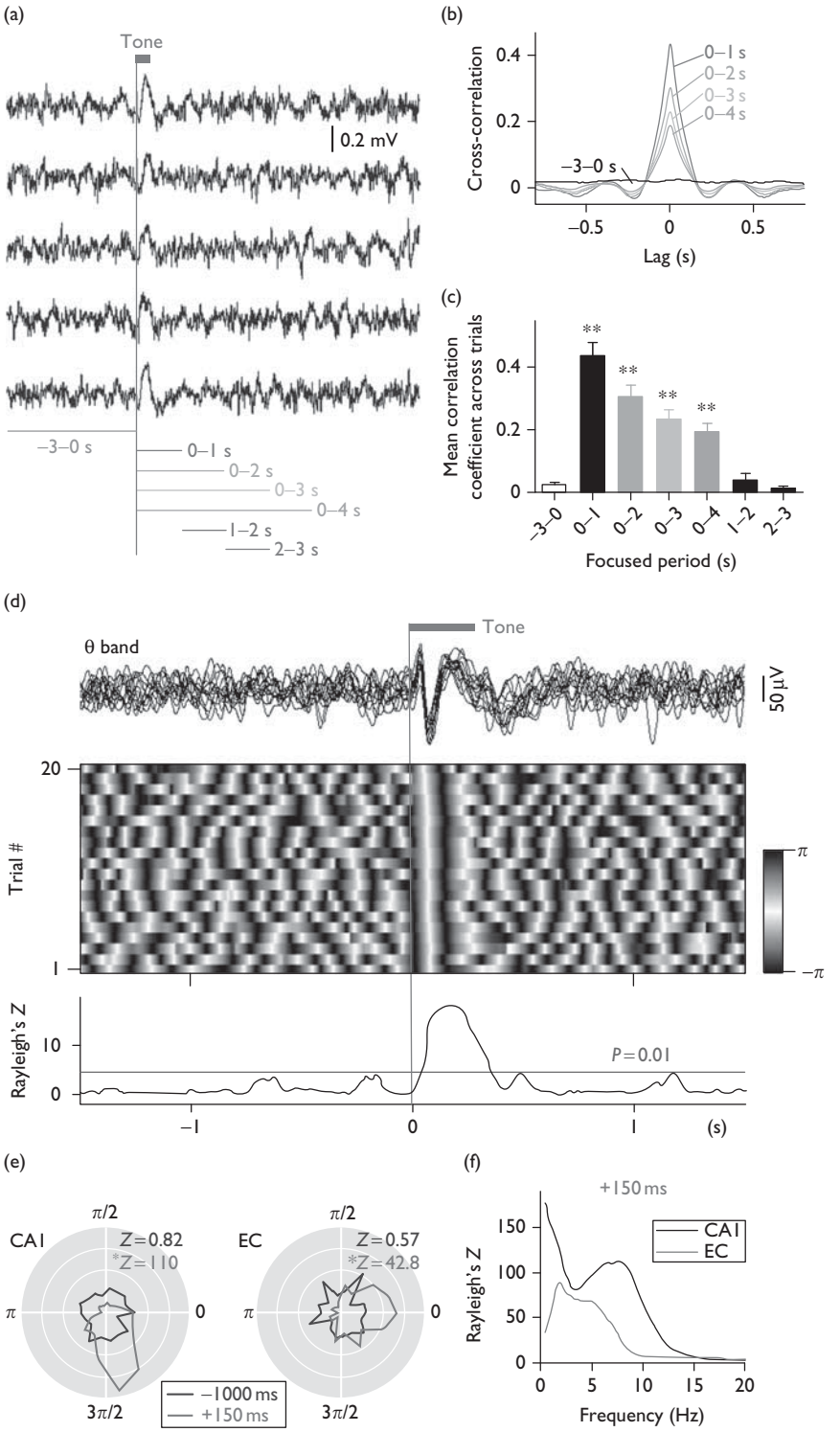
Tone-induced increase in inhibitory conductance of hippocampal CA1 neurons. (a) Biocytin reconstruction of an in-vivo whole-cell recorded CA1 pyramidal cell. (b) The mean traces of EPSGs and IPSGs in response to sound stimuli (gray bar: 30 ms, 4 kHz, 110 dB). Gray lines indicate eight individual cells from eight mice. For each cell, all traces observed (10–50 trials each) were averaged. The black lines indicate the averages of the eight cells. (c) The peak amplitude of ΔIPSG depended on the tone intensity. The error bars are SEMs of three cells from three mice. EPSG, excitatory postsynaptic conductance; IPSG, inhibitory postsynaptic conductance.

(Fig. 2d, bottom). In a total of 405 tone-stimulus trials pooled from LFPs in the CA1 in 17 mice, the phase distributions of θ oscillations at −1000 and 150 ms relative to the tone onset showed that the initially uniform phase distribution was biased 150 ms after tone stimulation (Fig. 2e; $P = 1.3 \times 10^{-48}$, Rayleigh's $Z = 110$, Rayleigh's test for circular uniformity), indicating that tone-induced phase resetting is consistent across trials and animals. The same phase analyses were repeated for different oscillation frequencies at 150 ms after the tone onset (Fig. 2f). Rayleigh's Z spectrum was peaked at around 7 Hz, suggesting that tone-induced phase reset is specific to the θ oscillation range.

The rodent hippocampus and the entorhinal cortex may emit synchronized oscillations [14,15]. Indeed, we found that tone induced a θ phase resetting in the entorhinal cortex (Fig. 2e; $P = 2.5 \times 10^{-19}$, Rayleigh's $Z = 42.8$ at 150 ms after the tone onset). However, the increase in Rayleigh's Z scores was not specific to the θ band, and the increased level was lower than that in CA1 (Fig. 2f). Therefore, the LFP modulations in the entorhinal cortex cannot fully account for the CA1 θ resetting.

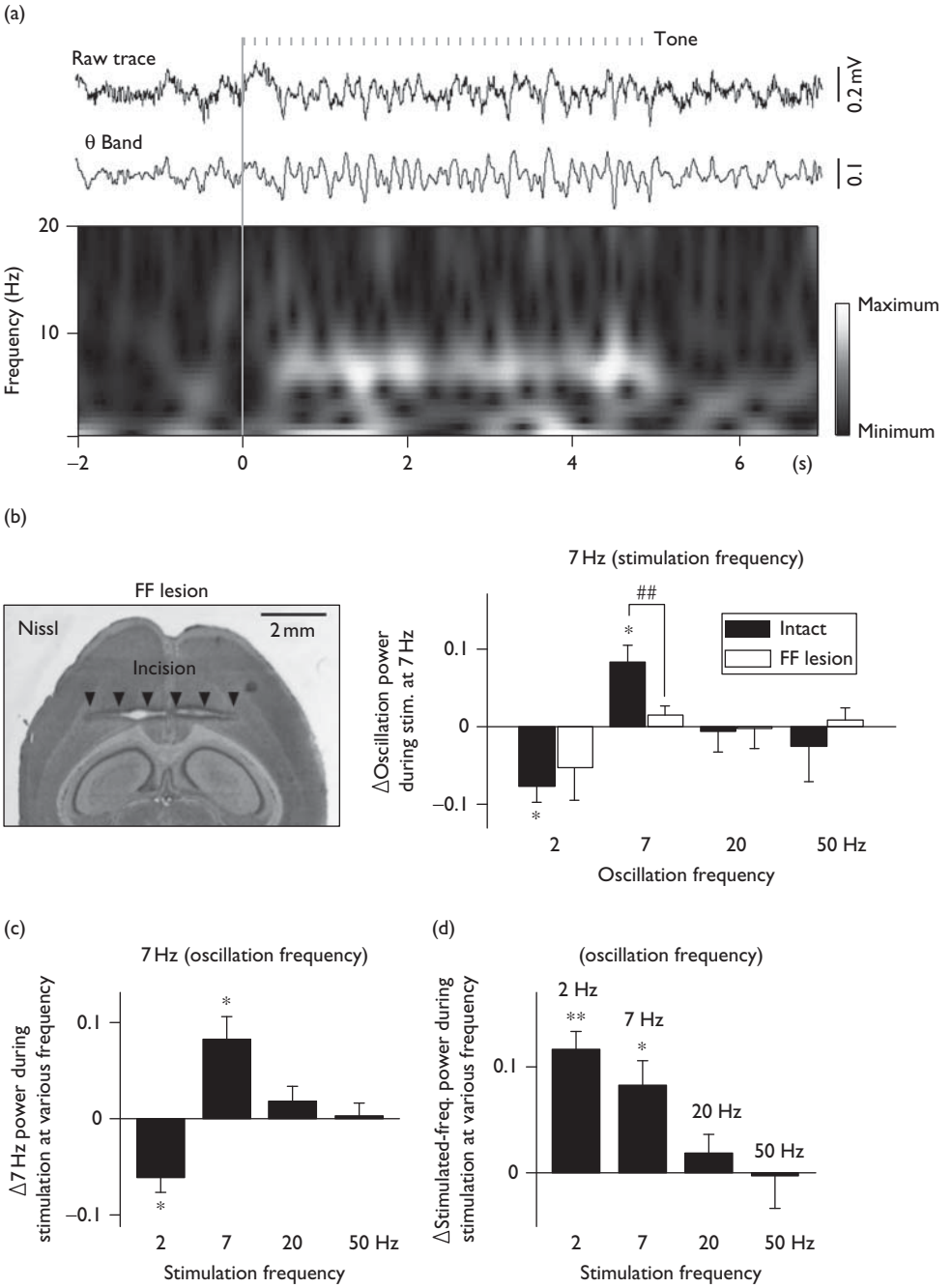
θ-Frequency stimulation of the hippocampal inhibitory network is reported to synchronize principal cells [16,17]. We next applied repetitive tone stimulation at a θ frequency of 7 Hz. The 7-Hz stimulation with 20-ms tone pulses for 5 s increased the θ power in the CA1 stratum pyramidale (Fig. 3a). This power enhancement was not observed for oscillation frequencies other than 7 Hz (Fig. 3b; right). Interestingly, the 7-Hz stimulation significantly reduced the 2-Hz power. Thus, hippocampal oscillations seemed to interact across frequencies. Therefore, we examined whether θ oscillations are induced by other stimulation frequencies. Tone pulses were repeated for 5 s at 2, 7, 20, and 50 Hz. The θ resonance was induced by 7-Hz stimulation but not by 2-, 20-, or 50-Hz stimulation (Fig. 3c). Incidentally, 2-Hz stimulation enhanced the 2-Hz oscillation power, whereas neither 20- nor 50-Hz stimulation altered the 20- or 50-Hz oscillation powers, respectively (Fig. 3d).

Fig. 2



Tone-induced θ phase reset. (a) Representative local field potential (LFP) responses to the tones (gray bar: 300 ms, 4 kHz, 110 dB) were recorded from CA1 stratum pyramidale. (b) The mean cross-correlograms across all possible pairs of the trials were obtained for various time periods indicated in (a) ($n = 17$ mice). Data recorded from the CA1 stratum pyramidale, radiatum, or lacunosum moleculare were pooled. (c) The mean correlation coefficients in (b) (mean ± SEM of 17 mice, $^{**}P < 0.01$, Dunnett's test). (d) Representative LFP traces filtered in a band of 5–10 Hz (all 20 sweeps, top), their θ-phase pseudocolored map (middle), and their Rayleigh's Z score (bottom). The data were recorded from the CA1 stratum pyramidale. (e) Distributions of the phases of 7-Hz oscillations in the CA1 and the entorhinal cortex (EC) at −1000 and 150 ms after the tone onset. The data were pooled from a total of 405 trials in 17 mice for CA1 (−1000 ms: $P = 0.44$, $Z = 0.82$; +150 ms: $P = 1.3 \times 10^{-48}$, $Z = 110$, Rayleigh's test for circular uniformity) and from a total of 170 trials in five mice for EC (−1000 ms: $P = 0.56$, $Z = 0.58$; +150 ms: $P = 2.5 \times 10^{-19}$, $Z = 42.8$). (f) Rayleigh's Z spectra of CA1 and EC LFPs at 150 ms after the tone onset (CA1: $n = 17$ mice, EC: $n = 5$ mice).

Fig. 3



Tone-induced θ resonance in the CA1 stratum pyramidale. (a) Typical raw and 4–12-Hz band filtered traces of local field potential (LFP) recorded from CA1 stratum pyramidale and the wavelet-based power spectrum of the raw LFP in response to 110-dB tone stimulation at 7 Hz. (b) Left: a representative Nissl-stained horizontal section of the brain in a fimbria–fornix (FF)-lesioned mouse. Right: tone stimulation at 7 Hz selectively enhanced the 7-Hz oscillation power in the LFPs in intact mice but not in FF-lesioned mice. The oscillation powers were compared as the ratio of the 3-s period (2–5 s) after the tone onset to the control period (0–3 s) before the tone onset (2 Hz: $^{*}P = 0.017$, $t_5 = 3.53$; 7 Hz: $^{*}P = 0.018$, $t_5 = 3.47$, paired *t*-test, $^{\#\#}P < 0.01$, Duncan's test, $n = 6$ mice for intact and four mice for FF lesion). (c) Tone-induced changes in the θ power at stimulation frequencies of 2, 7, 20, and 50 Hz (2 Hz: $^{*}P = 0.016$, $t_5 = 3.58$; 7 Hz: $^{*}P = 0.018$, $t_5 = 3.47$, $n = 6$ mice). (d) Tone-induced changes in the power of each oscillation frequency at the corresponding stimulation frequency (2 Hz: $^{**}P = 1.2 \times 10^{-3}$, $t_5 = 6.56$; 7 Hz: $^{*}P = 0.018$, $t_5 = 3.47$, $n = 6$ mice). The error bars are SEMs.

Lack of tone-induced θ entrainment in fimbria–fornix-lesioned mice

The major afferents to the hippocampus are supplied through the temporoammonic pathway from the entorhinal cortex and the FF pathway from subcortical areas. Medial septal neurons, which project to the hippocampus through FF fibers, increase their firing rates in response to various sensory stimuli, including sound, touch, and light [18,19]. An imaging study demonstrated that medial septal GABAergic fibers projecting to CA1 stratum oriens respond to sensory inputs with transient calcium elevations [20]. Moreover, recent works indicate that repetitive stimulation of septal GABAergic neurons induces θ-rhythm oscillations in hippocampal LFPs [16,17]. We thus applied tone stimuli to mice in which the FF was surgically transected (Fig. 3b; left). The baseline θ power in these FF-lesioned mice was lower than that in intact mice (data not shown), as reported previously [21]. In these mice, CA1 neurons did not exhibit tone-induced θ resonance (Fig. 3b; right).

Discussion

Information about the intracellular responses of hippocampal neurons to sensory inputs is still sparse, and, to the best of our knowledge, previous studies were all conducted under anesthesia. In urethane-anesthetized rats, for example, hippocampal CA1 neurons exhibit a long-delayed hyperpolarization in response to somatosensory stimuli [22,23] and θ-rhythm membrane potential fluctuations after tail pinch stimulation [22]. Using awake mice, we demonstrated that CA1 pyramidal cells responded to the onset of a sound with a transient IPSG. We also found that sound induced a θ phase resetting and θ resonance.

Inhibitory input through the fimbria–fornix pathway

The hippocampus receives both excitatory and inhibitory projections through the FF pathway. Medial septal neurons are known to fire in response to various sensory stimuli [18,19,24]. Indeed, a previous report showed that hippocampal GABAergic afferents from the medial septum are responsive to auditory stimulation [20] and that repetitive stimulation of these axons induces θ field oscillations [16,17]. Thus, the medial septum is a candidate brain area that mediates sound-induced IPSGs in the hippocampus, although our data do not exclude the involvement of other subcortical regions.

The septohippocampal GABAergic terminals make synapses predominantly with inhibitory interneurons in the hippocampus [25] and are presumed to enhance hippocampal network excitability through disynaptic disinhibition. In contrast to this expectation, we observed that sound induced IPSGs, but not EPSGs (Fig. 1b). Besides GABAergic projections, however, previous investigations have demonstrated that the medial septum sends cholinergic and glutamatergic fibers to the hippocampus [26,27]. These excitatory inputs may activate hippocampal interneurons and thereby elicit a hippocampal network suppression.

Tone-induced phase resetting and inhibitory input

Phasic inhibition is reported to modulate hippocampal θ oscillations [11,12]. For instance, stimulation of a CA1 interneuron evokes a hyperpolarization of a postsynaptic CA1 pyramidal cell and resets its intrinsic rhythmic state [12]. Therefore, tone-evoked IPSGs may serve to reset the intrinsic oscillation phase of individual pyramidal cells and thereby synchronize neuronal activities. We found that repetitive tone pulses at 7 Hz increased the θ oscillation power (Fig. 3). Likewise, 2-Hz tone pulses increased the δ (2 Hz) oscillation power, but neither 20- nor 50-Hz pulses entrained the oscillations (Fig. 3d). Therefore, hippocampal networks may be easily entrained at the θ and the δ frequencies through rhythmic activation of interneurons [12,28,29]. In contrast, repetitive tone pulses at 2 and 7 Hz decreased the power of θ and δ oscillations, respectively (Fig. 3b and c). This result is consistent with the fact that the rhythmical θ activity state and the slow-wave δ activity state are mutually exclusive [2].

Sound stimuli consistently shifted the θ phase to a fixed angle. Thus, the phase resetting does not depend on the instantaneous neural state of the hippocampus. During hippocampus-dependent tasks, sensory stimuli are reported to induce a phase resetting of θ oscillations in the dentate gyrus [30]. Moreover, previous reports suggest that phase resetting induces appropriate dynamics for encoding and retrieval of memory [31]. The tone-induced phase resetting in the hippocampus and the entorhinal cortex may also contribute to cognitive processes by synchronizing ongoing oscillations in these two regions. Recent evidence indicates that place cell activities switch along θ cycles with environmental contexts [32] and that their repeated θ sequences are segmented by landmarks [33]. These findings suggest that θ cycles are a functional unit that represents the environment in segments. We speculate that sensory-evoked inhibitory inputs contribute to temporal segmentation of hippocampal neural processing and therefore the cognitive chunking of continuously ongoing experiences.

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Conflicts of interest

There are no conflicts of interest.

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