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Sinusoidal stimulation on afferent fibers modulates the firing pattern of downstream neurons in rat hippocampus

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Electrical stimulation in the brain is an emerging therapy for treating a wide range of neurological disorders. Although electrical pulses are commonly used in the clinic, other electrical waveforms such as sinusoidal-waves have been investigated to improve the therapeutic efficacy, to reduce the risk of tissue damage induced by stimulation, and to decrease the consumption of electrical energy. However, the effects of sinusoidal stimulation on neuronal activity are still unclear. In the present study, we investigated the neuronal responses to the stimulation of 50-Hz sinusoidal-waves applied on the afferent fibers of the neurons in the hippocampal CA1 region of Sprague-Dawley rat *in vivo*. Results show that the stimulation increased the firing rate of both pyramidal neurons and interneurons in the downstream region of stimulation. Also, the stimulation eliminated the original theta rhythms (2-5 Hz) in the single-unit activity of the two types of neurons and entrained these neurons to fire at the stimulation rhythm. These results provide new clues for the mechanisms of brain stimulation to suppress the pathological rhythms in the neuronal activity, and for the application of sinusoidal waveforms in brain stimulation therapy.

Keywords

Deep brain stimulation; sinusoidal stimulation; unit spike; firing pattern; theta rhythm; hippocampus

1. Introduction

Electrical stimulation of the brain has excellent prospects for treating several neurological and psychiatric disorders such as Parkinson's disease, essential tremor, epilepsy, depression, and so on (Koeglsperger et al., 2019; Lozano et al., 2019). Although pulse stimuli (i.e., square waveforms) are commonly used in the stimulation, other electrical waveforms such as sinusoids have been investigated for improving the therapeutic efficacy and safety, as well as for developing new stimulation paradigms (Foutz and McIntyre, 2010; Jensen and Durand, 2007; Ramirez-Zamora et al., 2018). For instance, sinusoidal stimulations may activate neurons at a considerably smaller electrical intensity than pulse stimulation, thereby lowering the risk of tissue damage and decreasing energy consumption (Francis et al., 2003; La Corte et al., 2014).

Previous studies of animal experiments and computational simulations have shown the effects of sinusoidal stimulations on abnormal neuronal activity in the brain. For example, experimental studies have shown that sinusoidal stimulations may suppress epileptiform activity in the hippocampal CA1 region (Bikson et al., 2001; Guo et al., 2016; Lian et al., 2003). Simulation studies have shown that sinusoidal stimulations with low current intensity can alleviate the spontaneous oscillations in the pathological globus pallidus and subthalamic nucleus network in Parkinson's state (Liu et al., 2018). However, the underlying mechanisms are unclear. Both epilepsy and Parkinson's disease are related to the pathological rhythms of neuronal activity (Meissner et al., 2005; Moran et al., 2012; Popovych and Tass, 2014). For instance, theta rhythms of neuronal firing in the hippocampus are related to the generation of epilepsy (Andersen, 2007; Kitchigina et al., 2013). Abnormal theta and beta rhythms of neuronal firing correlate to the motor symptoms of Parkinson's disease in human patients and parkinsonian rodents (Malekmohammadi et al., 2018; Qasim et al., 2016). Therefore, we hypothesize that sinusoidal stimulations may replace the original rhythms of neuronal firing with a stimulation-induced one, thereby obtaining the therapeutic efficacy.

To test the hypothesis, stimulations of 50 Hz sinusoidal waveforms were applied in the afferent fibers of rat hippocampal CA1 region. Single unit spikes of both the pyramidal neurons and the interneurons in the downstream area of stimulation were recorded to examine the modulation effects of sinusoidal stimulation on the rhythmic firing of downstream neurons. The clear lamellar structure of the hippocampal region facilitates the investigations of neuronal responses to brain stimulation *in vivo* (Andersen, 2007). Also, the hippocampal region is one of the potential targets of stimulation for treating brain disorders such as Alzheimer's disease and refractory epilepsy (Hardenacke et al., 2013; Zangiabadi et al., 2019). Therefore, the results of the present study may provide new clues for the application of sinusoidal waveforms in brain stimulation therapy.

2. Materials and methods

2.1 Surgical procedures

Experiments were performed on 9 adults Sprague-Dawley rats (male, 274 $\pm$ 56 g). The animals were anesthetized with urethane (1.25 g/kg, i.p.) and were placed in a rat stereotaxic apparatus

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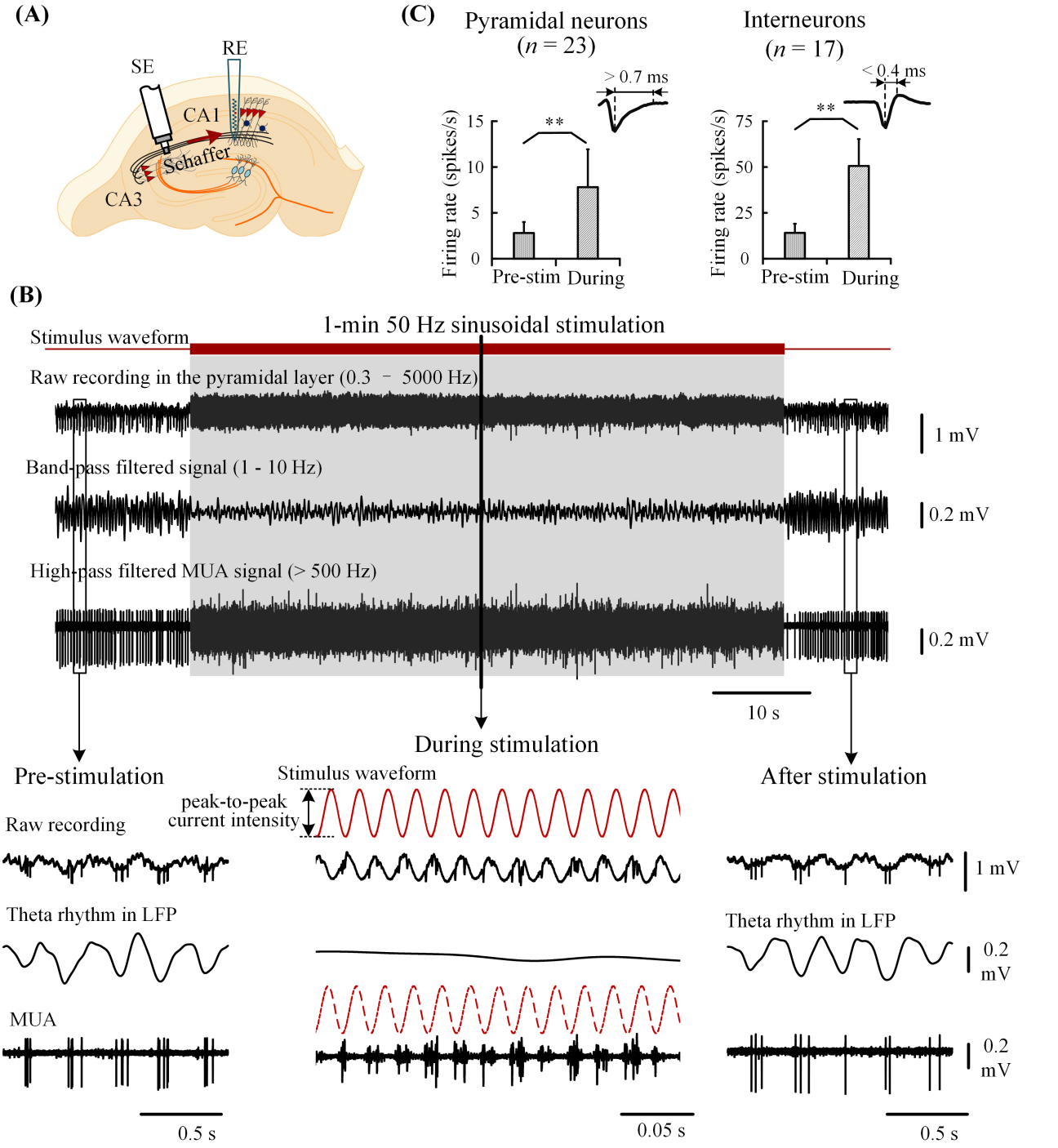

Fig. 1. Increase of neuronal firing by 50-Hz sinusoidal stimulations.(A) Schematic diagram of the stimulation electrode (SE) at Schaffer collaterals and the recording electrode (RE) in the CA1 region. (B) A typical recording of neuronal responses to a 1-min 50-Hz sinusoidal stimulation with raw recording (0.3-5000 Hz), LFP around the theta frequency (1-10 Hz), and MUA (500-5000 Hz). The shadow denotes the stimulation period. The red curves denote the sinusoidal waveforms applied at the Schaffer collaterals. Note that the sinusoidal artifacts in the raw recordings are out of phase with the sinusoidal waveforms from the inner pole of the bipolar SE because the location of the recording site in the pyramidal layer was near the outer pole level of the SE. (C) Comparisons of the firing rates of pyramidal neurons and interneurons between the baseline recordings of pre-stimulation and the recordings during stimulation. $^{**}P < 0.01$, paired *t*-test.

(Stoelting Co.). The temperature of the rat body was maintained at ~37 °C. A part of the skull above the left-brain hemisphere was removed to implant the recording and stimulating electrodes. The recording electrode (RE), a 16-channel array (Model A1x16-Poly2-5mm-50s-177, NeuroNexus Technologies), was implanted into the left hippocampal CA1 region (AP 3.5 mm and ML 2.7

mm from bregma, DV ~2.5 mm from the surface of the brain). The stimulation electrode (SE), a concentric bipolar electrode of stainless-steel with a distance of 100 μm between the inner and outer poles (Model CBCSG75, FHC), was implanted into the afferent axons (i.e., the Schaffer collaterals) of the CA1 region (AP 2.2 mm and ML 2.0 mm from bregma, DV ~2.8 mm from the surface of the brain) for orthodromically stimulating the CA1 neurons. The final positions of the two electrodes were judged according to the patterns of the evoked potentials and the unit spike signals that appeared serially in the recording array (Kloosterman et al., 2001). Two separate screw anchors were fixed in the nose bone and served as the ground electrode and reference electrode.

2.2 Recording and stimulating

The electrical signals collected by the recording electrode were first amplified 100-fold by a 16-channel microelectrode amplifier (3600, A-M system) with a band-pass filtering range of 0.3-5000 Hz. The amplified signals were then sampled with a rate of 20 kHz by a PowerLab data-acquisition system (PL 3516, ADInstruments).

The sinusoidal waveforms of stimulation were originated from a signal generator (DG1032Z, REGOL Technologies). The potential waveforms were then input to an analog stimulus isolator (2200, A-M Systems) to generate the continuous current sinusoids with symmetrical waveforms between their positive and negative phases that were delivered into the stimulation electrode. The sinusoidal frequency was 50 Hz. The applied stimulation of the sinusoidal waveform was verified by a measurement in a cup of saline to mimic brain tissue with the same electrodes as used in the rat experiments. The peak-to-peak current intensity of the sinusoidal waveforms was adjusted to 40-70 μA (57.2 $\pm$ 10.7 μA, n = 9) to modulate the unit firing neurons without evoking population spikes. The duration of the sinusoidal stimulation was 1 min.

Also, the signal of sinusoidal stimulation, i.e., the outputs of the DG1032Z signal generator, were simultaneously recorded with the neuronal signals. The polarity of the sinusoidal recording was the same as the inner pole of the concentric bipolar stimulation electrode. Because the surface area of the inner pole was much smaller than that of the outer pole, the inner pole contributed significant stimulation effects with a much higher current density surrounding the pole.

2.3 Analysis of unit spikes

On the recording electrode array, the signals of four adjacent channels located in the pyramidal layer of the CA1 region were used to extract the single unit spikes of pyramidal neurons and interneurons. The unit spikes of the two types of neurons were detected and sorted by the previously described methods (Feng et al., 2017; Wang et al., 2018). Briefly, the raw recording signals were filtered ($>$ 500 Hz) by a built-in high-pass digital filter of PowerLab Chart v7.0 software (ADInstruments) to remove the stimulation artifact of sinusoids and the local field potential (LFP) in the low-frequency bands to generate multiple unit activity (MUA) signals. Then, unit spikes in the MUA were detected by an amplitude threshold at 5-fold standard deviations of the MUA signals. Finally, the principal components and the amplitudes of the spike waveforms obtained from the 4-channel unit signals by a MATLAB program were used to sort the spikes of individual neurons by an open-source clustering software (SpkieSort 3D, www.Neuralynx.com). The unit spikes of pyramidal neurons and interneurons were distinguished according to the widths of spike waveforms. The unit spikes with a width of rising phase $>$ 0.7 ms and $<$ 0.4 ms were defined as the spikes of putative pyramidal neurons and putative interneurons, respectively (Csicsvari et al., 1998, 1999). The distributions of inter-spike intervals (ISI) of the sorted units were calculated to verify the clustering procedure. Spikes with an ISI histogram without clear refractory (~1 ms) were not taken as single unit spikes (Barthó et al., 2004).

The peri-stimulus time histograms (PSTH, bin = 1 ms) of the unit spikes per neuron and minute was calculated. The distribution relationship between unit spikes and sinusoidal phases was evaluated by a statistical method of circular distribution, i.e., a circular PSTH. For control, a mimic circular PSTH was obtained by relating the unit spikes in the 1-min pre-stimulation period to a 1-min mimic 50 Hz sinusoidal signal with continuous 20 ms cycles.

The firing rhythms of both types of neurons were analyzed by using a spectrum of auto-correlograms (ACs) of the binary sequences of unit spikes as following (Leblois et al., 2010; McConnell et al., 2012). The values of ACs were first calculated and normalized to eliminate the influence of firing rates. The mean components of ACs were removed. The length of ACs was 2 seconds (-1 to 1 s). Then, the power spectrum density (PSD) of ACs of the individual neurons was calculated by Welch's modified periodogram by using a Hanning window with an overlap of 50%. The cumulative power in the frequency band of theta rhythm (2-5 Hz) of the urethane anesthetized rats (Buzsáki, 2002) and around the sinusoidal frequency (49-51 Hz) were compared between the periods of 1-min sinusoidal stimulation and the 1-min pre-stimulation of baseline recording.

All values were given as mean $\pm$ standard deviation. Statistical significance in differences between two data groups was evaluated using the paired t-test or t-test performed by SPSS software.

3. Results

3.1 Sinusoidal stimulations entrain the firing of both pyramidal neurons and interneurons

During the period of sinusoidal stimulations at the Schaffer collaterals of the hippocampal CA1 region (Fig. 1A), the neuronal firing in the downstream area increased (Fig. 1B). The unit spikes of neurons rode on the noticeable fluctuations of sinusoidal artifacts in the raw recordings. The extracted MUA signal clearly showed that most of the unit spikes appeared around the trough of the applied sinusoidal waveforms (Fig. 1B, expended plots on the lower middle, red sinusoidal curves denote the stimulations applied at the Schaffer collaterals). After the end of the stimulation, the unit firing of neurons fell immediately. It returned to the baseline level and returned theta rhythm in the LFP within tens of seconds. In the 9 experiment preparations, we obtained single-unit spikes of 40 neurons, including 23 putative pyramidal neurons and 17 putative interneurons. During the 1-min 50 Hz sinusoidal stimulation, the mean firing rate of unit spikes of the pyramidal neurons and the interneurons significantly increased from 2.8 $\pm$ 1.2 spikes/s and 14.1 $\pm$ 5.0 spikes/s in pre-stimulation to 7.8 $\pm$ 4.1 spikes/s and 50.6 $\pm$ 14.7 spikes/s during stimulation, respectively (Fig. 1C). Also, the increments of pyramidal neurons (5.0 $\pm$ 3.8 spikes/s) were significantly smaller than that of interneurons (36.2 $\pm$ 15.9 spikes/s, P

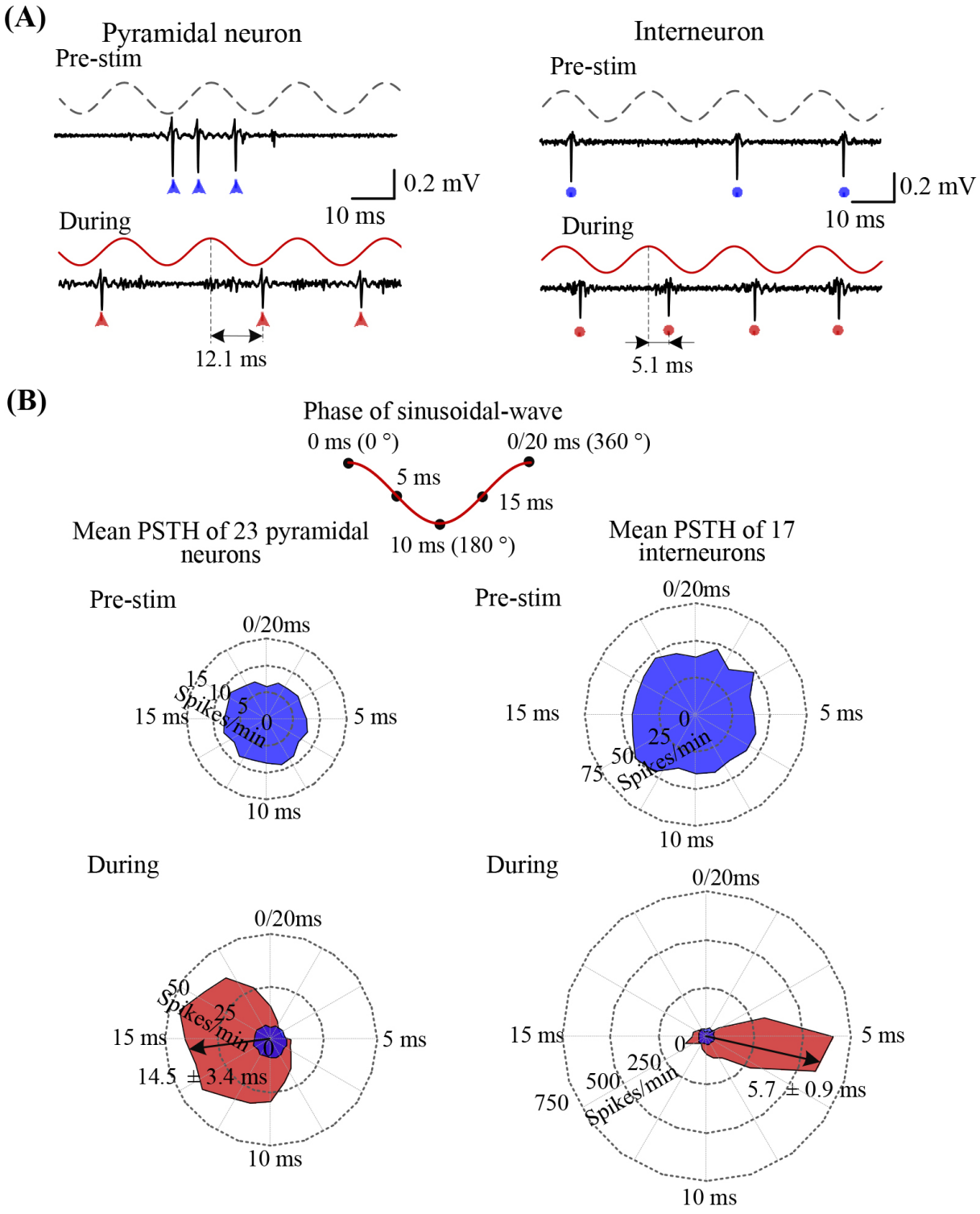

Fig. 2. Sinusoidal stimulation induced the phase-locked firing in downstream neurons. (A) Examples of neuronal firing at pre-stimulation of baseline recording and during stimulation. The dashed gray and solid red sinusoidal waveforms denote the mimic stimuli at baseline and the real stimuli during stimulation. (B) The mean circle PSTHs of the firing of both types of neurons at baseline and during stimulation. For comparison, the baseline PSTHs (in blue) are repeated in the PSTHs during stimulation. Black arrows denote the mean phases. Note that different scales are used in the PSTHs for clear illustrations.

< 0.01, t-test). The results indicated an excitatory effect of the sinusoidal stimulations on the downstream neurons. Next, we investigated the phase-locked relationship between the firing of the two types of neurons and the sinusoidal stimulation.

In the baseline recordings of pre-stimulation, the unit spikes of both pyramidal neurons and interneurons appeared uniformly in the phases of mimic sinusoidal cycles without an apparent phase-locked relationship (Fig. 2A *upper*). The mean PSTHs of the neuronal firing were distributed evenly in the mimic sinusoidal cycles (Fig. 2B *upper*). However, during the real 50-Hz sinusoidal stimulation, the firing of the two types of neurons was phase-locked with the sinusoidal waveforms (Fig. 2A *Lower*). The mean PSTHs showed that the most firing of pyramidal neurons appeared in the phase range of 180-320° (i.e., 10 - 18 ms) of the 20-ms sinusoidal cycles with a mean firing phase of 260 ± 61° (n = 23; Fig. 2B *lower left*), while the firing of interneurons appeared in the phase range of 80-120° (i.e., 4.5 - 6.7 ms) with a mean firing phase of 102 ± 16° (n = 17; Fig. 2B *lower right*). The results indicated strong phase-locked relationships between the firing of the two types of neurons and the sinusoidal waveforms of stimulations. Furthermore, the distribution peak in the interneuronal PSTH was narrower than that of the pyramidal neuron PSTH.

Taken together, the results showed that the sinusoidal stimulations of afferent axons entrained the firing of both pyramidal neurons and interneurons in the downstream region and increased their firing. Next, we investigated whether or not the entrainment effects of sinusoidal stimulation could alter the rhythms of neuronal firing.

3.2 Sinusoidal stimulation altered neuronal firing rhythms to the stimulation frequency

During the baseline recordings, the spontaneous firing of the two types of neurons had an unmistakable theta rhythm (2-5 Hz) in the auto-correlation function of the spike sequences (Fig. 3A *upper*). The rhythms generated a peak at 2-5 Hz in the spectrum of the unit spike sequences of neuronal firing (Fig. 3B blue curves). However, during the period of sinusoidal stimulations, the theta rhythm in the neuronal firing was replaced by a new rhythm at the sinusoidal frequency (i.e., 50 Hz; Fig. 3A *lower*), indicating by the peaks at 50 Hz in the spectrums (Fig. 3B red curves).

To confirm the changes of firing rhythms, we calculated the cumulative powers in the frequency bands of theta rhythm (2-5 Hz) and around the sinusoidal frequency (49-51 Hz) in the spectrums of the neuronal firing of all the pyramidal neurons and interneurons respectively in the pre-stimulation and during stimulation periods. The stimulations significantly decreased the mean power of theta rhythms (Fig. 3C) and significantly increased the mean power of 49-51 Hz (Fig. 3D) in the firing of the two types of neurons.

The results indicated that the sinusoidal stimulations altered the rhythms in neuronal firing from a theta rhythm of pre-stimulation to a new rhythm at stimulation frequency.

4. Discussion

The results of this study show that the sinusoidal stimulation of afferent fibers entrained the firing of downstream neurons and suppressed the original firing rhythms of both pyramidal neurons and interneurons in the rat hippocampus. The possible mechanisms of the finding are discussed below.

Sinusoidal stimulations can activate axons (the Schaffer collaterals) to generate action potentials. The action potentials then travel along the axons. They activate the post-synaptic neurons of the CA1 region in the downstream area of stimulation, thereby increasing neuronal firing and inducing phase-locked firing in the post-synaptic neurons (Fig. 1A). The post-synaptic neurons include both the inhibitory interneurons and the excitatory pyramidal neurons. The different intrinsic properties of the two types of neurons may contribute to their different responses to the stimulations. The interneurons are more ready to be activated than the pyramidal neurons due to their lower firing threshold (Csicsvari et al., 1998). The activation of interneurons would then inhibit the activity of pyramidal neurons through local inhibitory circuits (Ahmed and Mehta, 2009; Xu et al., 2009). Therefore, the firing increment of pyramidal neurons was significantly smaller than that of interneurons (Fig. 1C). Also, the strength of the phase-locked relationship between the firing of pyramidal neurons and the sinusoidal waveforms was weaker than that of interneurons (Fig. 2B).

A negative shift in the extracellular potential may depolarize the membrane of neurons (axons). Therefore, the axons understimulation would be excited in the falling phase of sinusoidal waveforms. More and more axons would be recruited to fire along with the increase of the falling slope, thereby accumulating synaptic excitations on the post-synaptic neurons. Presumably, with a lower firing threshold, the post-synaptic interneurons reached the excitatory threshold and fired in the falling phase with a shorter latency. The pyramidal neurons fired following the trough of sinusoidal waveforms with a longer latency because of their higher firing threshold (Fig. 1B *bottom middle* and Fig. 2). Also, the resonance property of interneurons at ~10 - 50 Hz may facilitate the firing of interneurons following the 50 Hz stimulation (Orbán et al., 2001; Pike et al., 2000) with a mean firing rate ~50 Hz (Fig. 1C).

Another interesting finding is that the sinusoidal stimulation may suppress the original firing rhythms of downstream neurons. The generation of theta rhythm in the CA1 neurons is associated with the excitatory inputs from the upstream CA3 region via the Schaffer collaterals (Andersen, 2007; Buzsáki, 2002). The stimulation-induced activations in Schaffer collaterals can travel in both directions along the axons to the upstream and downstream regions (Li et al., 2007; Udupa and Chen, 2015). Thus, the cell bodies of upstream CA3 neurons also receive the modulations from the sinusoidal stimulations of the efferent axons of CA3 neurons (i.e., Schaffer collaterals), thereby eliminating their original firing rhythms. Presumably, the loss of rhythmic inputs from the upstream CA3 neurons may enable the CA1 neurons to follow the rhythm of stimulation frequency to fire action potentials. Abnormal pathological rhythmic activities in neuronal networks have been considered related to many brain diseases (Jakobs et al., 2019; Popovych and Tass, 2014). Therefore, the stimulation-induced alteration of firing rhythms may have clinical implications for eliminating abnormal rhythms and achieving therapeutic efficacy.

Previous studies have shown that biphasic pulse stimulations with a frequency higher than 50 Hz may generate depolarization block and rapidly attenuate the excitatory effects of stimulations in seconds (Feng et al., 2013; Jensen and Durand, 2009). In contrast, the 50 Hz sinusoidal stimulations with a mild intensity in the present study did not induce apparent attenuation of stimulation effects in the 1-min stimulation period (Fig. 1B). Presumably, it may be caused by the hyperpolarization effect of the half of the sinusoidal cycle to prevent the development of depolarization block during the sustained stimulation. A sinusoidal stimulation with

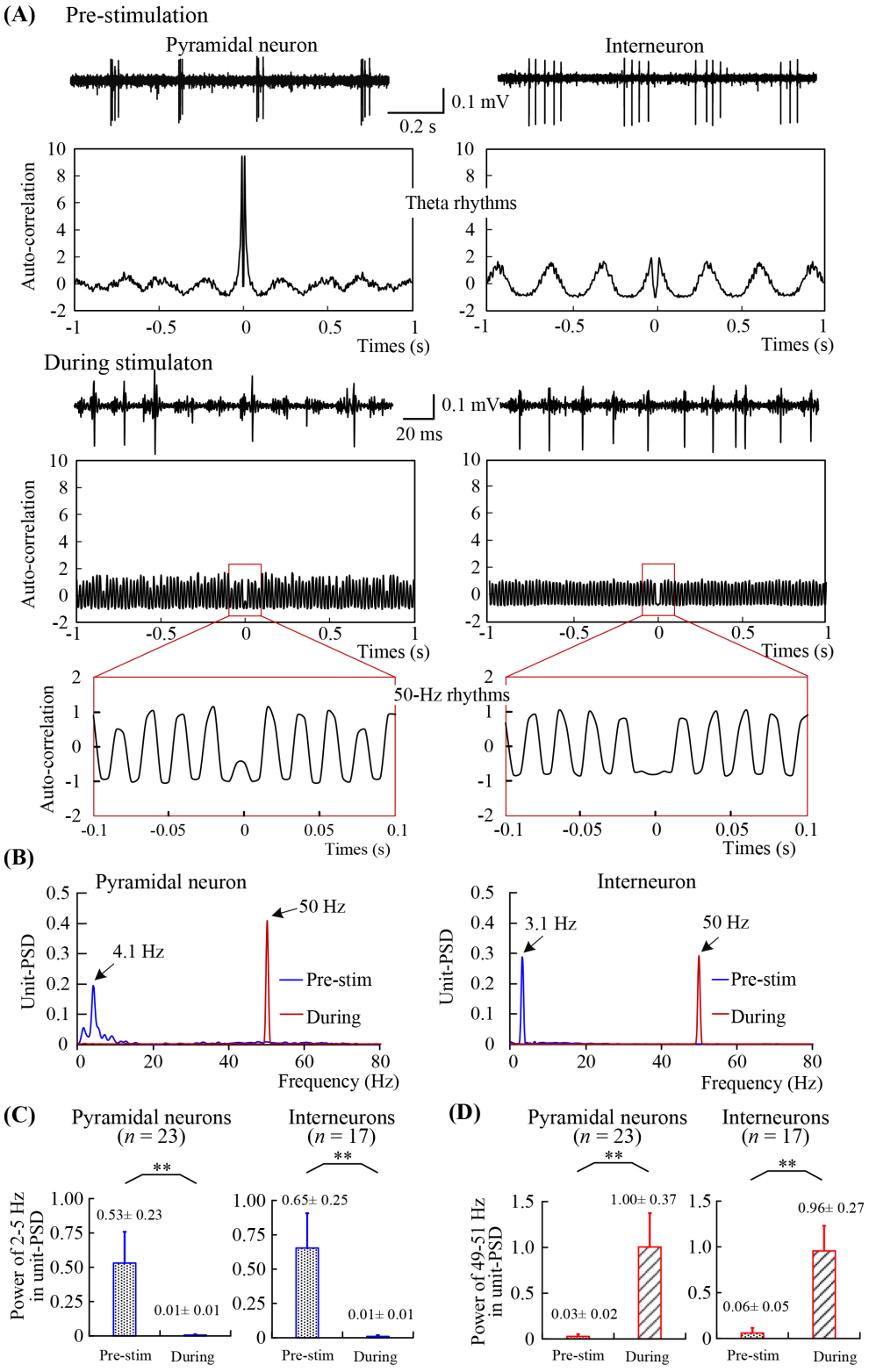

Fig. 3. Sinusoidal stimulation changed the firing rhythms of downstream neurons. (A) Typical examples of the neuronal firing and auto-correlation profiles of the two types of neurons at 1-min periods of pre-stimulation and during stimulation. (B) The unit-power spectrum densities (unit-PSD) of pyramidal neurons and interneurons showed in (A). (C) and (D) Comparisons of cumulative powers in the frequency bands of theta rhythm (2-5 Hz) and around the sinusoidal stimulation (49-51 Hz) between the periods of pre-stimulation and during stimulation for pyramidal neurons and interneurons, respectively. $^{**}P < 0.01$, paired *t*-test.

a higher frequency (e.g., 100 Hz) tended to induce neuronal responses similar to a pulse stimulation, presumably due to a short duration of the putative hyperpolarization phase. In comparison, a much lower frequency weakened the stimulation effects because of a lack of sufficiently rapid changes in extracellular potentials (data not shown).

Further studies are needed to investigate the effect of sinusoidal frequency on neuronal responses. Also, the neuronal reactions in other brain regions (e.g., basal ganglia) are needed to be investigated to reveal the universality of sinusoidal stimulation on neurons. Finally, more data is needed to verify the therapeutic efficacy of the sinusoidal stimulations.

5. Conclusions

The present study shows that the sinusoidal stimulations of afferent axonal fiber in the rat hippocampus *in-vivo* can modulate the firing of neurons in the downstream CA1 region and suppress their original firing rhythms. The finding provides clues for developing stimulus waveforms other than pulses to advance brain stimulation therapy.

Abbreviations

ACs: auto-correlograms; LFP: local field potential; MUA: multiple-unit activity; PSTH: Peri-stimulus time histogram; RE: recording electrode; SE: stimulation electrode.

Author contributions

ZF and ZW conceived and designed the experiments; ZW, LZ, and YY performed the experiments and analyzed the data. ZF and ZW wrote the manuscript. All authors approved the final version of the manuscript to be published and agreed to be accountable for all aspects of the manuscript.

Ethics approval and consent to participate

All animal procedures used in this study were conducted following the Policies on the Use of Laboratory Animals (China Ministry of Health). The protocol was approved by the Institutional Animal Care and Use Committee, Zhejiang University.

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Conflict of Interest

The authors declare no conflict of interest.

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