Synchronicity of excitatory inputs drives hippocampal networks to distinct oscillatory patterns

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Abstract
The rodent hippocampus expresses a variety of neuronal network oscillations depending on the behavioral state of the animal. Locomotion and active exploration are accompanied by theta-nested gamma oscillations while resting states and slow-wave sleep are dominated by intermittent sharp wave-ripple complexes. It is believed that gamma rhythms create a framework for efficient acquisition of information whereas sharp wave-ripples are thought to be involved in consolidation and retrieval of memory. While not strictly mutually exclusive, one of the two patterns usually dominates in a given behavioral state. Here we explore how different input patterns induce either of the two network states, using an optogenetic stimulation approach in hippocampal brain slices of mice. We report that the pattern of the evoked oscillation depends strongly on the initial synchrony of activation of excitatory cells within CA3. Short, synchronous activation favors the emergence of sharp wave-ripple complexes while persistent but less synchronous activity—as typical for sensory input during exploratory behavior—supports the generation of gamma oscillations. This dichotomy is reflected by different degrees of synchrony of excitatory and inhibitory synaptic currents within these two states. Importantly, the induction of these two fundamental network patterns does not depend on the presence of any neuromodulatory transmitter like acetylcholine, but is merely based on a different synchrony in the initial activation pattern.

KEYWORDS
memory, oscillation, sharp wave-ripple, synchronization, theta-nested gamma

1 | INTRODUCTION

Many brain structures exhibit a variety of distinct network oscillations which orchestrate multineuronal activity patterns and, thereby, support cognition and behavior (Buzsáki & Draguhn, 2004). In the rodent hippocampus, different rhythms correspond to different states of vigilance or behavior, especially with respect to spatial memory formation and consolidation (Colgin, 2016). During active waking periods and REM sleep, the hippocampus displays gamma band (30–150 Hz) activity which is typically superimposed on an underlying theta frequency (4–10 Hz) oscillation (Buzsáki, Leung, & Vanderwolf, 1983; Vanderwolf, 1969). It is thought that this oscillation pattern provides...
a physiological framework for processing of sensory and spatial cues (Bragin et al., 1995; Hasselmo, Wyble, & Wallenstein, 1996). Throughout consummatory behaviors (e.g., rest or food intake) and slow-wave sleep theta/gamma rhythmic activity is replaced by sharp waves accompanied by ripple (150–200 Hz) oscillations (Buzsáki, Horváth, Urioste, Hetke, & Wise, 1992; Girardeau & Zugaro, 2011). This pattern supports readout of acquired engrams into the neocortex for sub-

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sequent memory consolidation (Buzsáki, 2015; Girardeau, Benchenane, Wiener, Buzsáki, & Zugaro, 2009; Khodagholy, Gelinas, & Buzsáki, 2017).

Past decades have elucidated several cellular, synaptic, and neu-

romodulatory mechanisms that contribute to these network phe-

nomena (Butler & Paulsen, 2015; Buzsáki, 2015; Buzsáki & Wang, 2012; Mann & Paulsen, 2007; Müller & Remy, 2018; Whittington, Cunningham, LeBeau, Racca, & Traub, 2011). All types of hippocampal network oscillations involve an interplay between inhibitory and excitatory neurons which generates rhythmic changes in spiking probability and, hence, defines oscillatory cycles (Butler & Paulsen, 2015; Whittington & Traub, 2003). Additional mechanisms generate specific types of oscillations, for example, cholinergic or GABAergic input from the medial septum generating theta oscillations (Colgin, 2013; Headley & Paré, 2017), typically with nested gamma oscillations in local networks (Bartos, Vida, & Jonas, 2007; Buzsáki & Wang, 2012; Whittington et al., 2011). The mechanisms which lead to the generation of ripples are less clear but do involve local, precisely timed cooperation of excitation and inhibition (Schlingloff, Kalli, Freund, Hajos, & Gulyás, 2014) and nonlinear dendritic integration processes in pyramidal cells (Jahneke, Timme, & Memmesheimer, 2015; Memmesheimer, 2010) or ultrafast signaling via gap junctions between pyramidal cell axons (Draguhn, Traub, Schmitz, & Jefferys, 1998; Traub, Schmitz, Maier, Whittington, & Draguhn, 2012).

Despite the wealth of information about these two oscillatory network states, the precise conditions for transitions between different rhythmic regimes are poorly understood. We thus developed an in vitro model for the induction and measurement of different network states. Using optogenetic stimulation tools we defined the respective initiation conditions for ripple versus gamma oscillations. Our data reveal a critical role for the synchrony of neuronal activity for the generation of sharp wave-ripple complexes while gamma oscillations are triggered by prolonged or smoothened patterns of neuronal activity.

## 2 MATERIALS AND METHODS

### 2.1 Experimental animals

All experiments described here were carried out using male C57/Bl6N mice (Charles River, Sulzfeld, Germany) in accordance with guidelines of the Federation of European Laboratory Animal Science Associations (FELASA). Surgical procedures and other experimental paradigms were approved by the state government of Baden-Württemberg (AZ G-188/15). Mice were housed in pairs at 21–24°C and 40–60% relative humidity in scantainers (Scanbur BK A/S, Denmark) on a 12 hr light/dark cycle and fed ad libitum.

### 2.2 Intracranial virus delivery

Adeno-associated viruses of serotype 5 carrying the CamKII–hChR2 (H134R)-EYFP construct were purchased from the vector core facility of the University of North Carolina (http://www.med.unc.edu/genetherapy/vectorcore). Viruses were dispensed in 350 mM NaCl and 5% D-Sorbitol in PBS with titers of 4 × 10^{12} virus genomes/ml. Virus injections into the hippocampus were performed bilaterally.

Mice aged 4–6 weeks received a preoperative dose of bur-

prenorphine (0.1 mg/kg, Indivior Eu Ltd, UK) and were subsequently anesthetized with isoflurane in medical oxygen (4% for induction, 1.5–2.5% for maintenance, flow rate 1 L/min, Baxter, Germany)

Depth of anesthesia was assessed regularly by checking toe pinch reflexes. Body temperature was maintained at 38°C using a heating pad (ATC-2000, World Precision Instruments, Sarasota, FL). Anesthe-

tized animals were mounted on a stereotaxic frame (Kopf Instruments, Tujunga, CA), the skull was exposed by a sagittal incision and the posi-

tions of bregma and lambda were identified. Anterior/posterior (AP, –2.8) and lateral/medial (LM, ±3.2) coordinates were marked and a small hole of ~0.5 mm diameter was drilled with a dental drill (Hager&Meisinger GmbH, Neuss, Germany). A 10 μl microsyringe (Nanoill, World Precision Instruments) was loaded with 1.2–1.5 μl of virus suspension and positioned above the drill hole. The virus was evenly distributed at three dorsoventral (DV) depth coordinates (~3.3/~3.1/~2.9) at 200 nl/min using a micropump (SYS-Micro4, World Precision Instruments). After sufficient diffusion of the virus into the brain tissue, the syringe was slowly withdrawn and the skin flaps were sewn together. Mice received an additional dose of buprenorphine 6 hr postoperatively and were regularly monitored for abnormal behavior or skin defects in the days following the proce-

dure. Gene expression following virus injection was allowed for 2–4 weeks.

### 2.3 Electrophysiology

#### 2.3.1 Slice preparation

Virus injected mice were anesthetized by gradual flooding of the cage with CO2. After loss of righting reflex, the animals were decapitated, the brain was swiftly removed from the skull and stored in ice cold (4°C), carbogen (95% O2/5% CO2) gassed, artificial cerebrospinal fluid (ACSF) containing in mM: 124 NaCl, 1.8 MgSO4, 1.6 CaCl2, 10 glucose, 1.25 NaH2PO4, 26 NaHCO3 (pH 7.4 at 37°C). Horizontal slices of 400 μm thickness were produced with a Leica VT1000S vibratome (Leica, Nussloch, Germany) and stored in a modified Haas-

type interface chamber for a recovery period of at least 2 hr at
FIGURE 1  Legend on next page.
32 ± 1 °C where they were perfused with ACSF at -1.5 ml/min by gravity flow.

2.3.2 | Microelectrode array recordings

Extracellular field potentials were recorded with a microelectrode array (MEA) amplifier (USB-ME60-Up-BC, Multichannel Systems, Reutlingen, Germany) using 60 channel perforated MEAs (60pMEA200/30R-Ti, Multichannel Systems) under submerged conditions. Electrodes of these MEAs (30 μm diameter) are arranged in an 8 x 8 grid and spaced at 200 μm. ACSF perfusion of the upper MEA side was achieved with a peristaltic pump (REGLO Analog, Ismatec, Wertheim, Germany) set to 4 - 5 ml/min whereas the lower side was perfused by a combination of gravity flow and a vacuum pump (CVP, Multichannel Systems) which also provided suction for firm attachment of the slice to the MEA electrodes. Temperature of perfused ACSF was set to 32 °C and was controlled with heating elements (PH101, Multichannel Systems). Slices were placed such that the MEA electrodes covered the majority of the hippocampal formation. Data were sampled at 25 kHz and stored on a PC with the MEA_Rack software (Multichannel Systems).

2.3.3 | Patch-clamp recordings

Blind whole-cell patch-clamp recordings were carried out using pipettes pulled from borosilicate glass (Science Products, Hofheim, Germany) with 2.5 - 4 MΩ resistance. Electrodes were gently advanced through the CA1 pyramidal cell layer until an increase in resistance was registered upon which suction was applied to form a gigaseal. Pipettes were filled with an intracellular solution containing in mM: 130 Cs-Methanesulfonate, 2 KCl, 10 EGTA, 10 HEPES, 2 MgATP, 4 NaCl (pH 7.3 with CsOH). Recordings were performed with an ELC-03XS amplifier (npi, Tamm, Germany) and sampled at 20 kHz with a power 1401 analog/digital converter (CED). The liquid junction potential was calculated to +10 mV using JPCalc (Barry, 1994). Voltage clamp recordings of IPSCs were performed at a nominal holding potential of 10 mV whereas EPSCs were recorded nominally at -74 mV (chloride reversal potential was calculated to be around -82 mV).

2.4 | Patterned optogenetic stimulation

For region specific optogenetic stimulation, we used a custom made holographic illumination system based on a reflective spatial light modulator (X10468, Hamamatsu Photonics, Japan) driven by custom written MATLAB (The Mathworks Inc., Natick, MA) software (Figure 1a). Expression of ChR2-EYFP was assessed by imaging through a spinning disk confocal microscope (CSU-X1, Yokogawa, Toyko, Japan) with a 515 nm diode-pumped solid-state laser (iBeam smart, Toptica Photonics, Munich, Germany). The region of interest was outlined by hand. The required illumination pattern was Fourier transformed (Gerchberg & Saxton, 1972) and the resulting phase image was generated by the spatial light modulator via a digital video interface. Optogenetic stimulation was then carried out with a 473 nm diode-pumped solid-state laser (DL473, Rapp Optoelectronics, Hamburg, Germany) which was directed toward the spatial light modulator displaying the illumination pattern. After elimination of the 0th order, the reflected pattern was focused through a 16 ×16 microscope objective (N16XLD-PF, Nikon, Tokyo, Japan) toward the slice. Stimulus profiles (ramps, sinusoids, etc.) were generated by modulating the laser with analog and digital inputs originating from an analog/digital converter (1401 power 3, CED, Cambridge, UK). Light intensities were measured with a photodiode power sensor (S121C, Thorlabs, Newton, MA) at the tip of the N16XLD-PF microscope objective. This experimental setup allows creating arbitrary illumination patterns by focusing the light source on the desired area(s) without loss of power. For the present experiments we used simple,
almost rectangular illumination patterns. In principle, these could also have been achieved more simply by inserting a mask blocking surrounding light.

2.5 | Data analysis and statistics

Analysis of field potential and patch-clamp recordings was carried out offline using custom written MATLAB scripts. MEA data were processed and imported into MATLAB using the Neuroshare MATLAB API (http://neuroshare.sourceforge.net/Matlab-Import-Filter/NeuroshareMATLABAPI-2-2.htm).

Power and frequency of network oscillations was primarily based on complex Morlet wavelet transformations of raw data allowing assessment of changes in frequency composition over time. Raw traces were down-sampled by a factor of 10 and transformed using MATLAB’s cmor1-2.5 wavelet. The resulting time frequency graph was smoothed with a Gaussian kernel and displayed with a color map where brighter colors represent higher oscillation power. The units of the spectrograms are $\mu V^2$. Gamma oscillations were detected using these wavelet spectrograms. First, the time course of the maximal wavelet power was extracted between 30 and 80 Hz. Then, events where identified if the power exceeded a threshold of three standard deviations of event-free baseline noise. Ripple waves detected in the same fashion in the wavelet power band between 150 and 260 Hz. Additionally, ripple events had to be small “islets” within the spectrograms and not coming from events with lower leading frequencies that spread out into higher frequencies. Thus, only ripple events with a power of at least 1.5 times the value of the spectrogram power between 90 and 110 Hz were included in the analysis and counted as “real” ripple events.

Digital filtering was achieved with a custom-written algorithm based on Fourier/inverse Fourier transform. Synaptic currents were detected using a deconvolution based algorithm after low pass filtering at 200 Hz as described in (Roth, Beyer, Both, Draguhn, & Egorov, 2016).

2.5.1 | Statistics

Data are represented as box plots in which medians are indicated by a line and the box limits denote the interquartile range. Whiskers of box plots extend to the most extreme data points not considered outliers. Outliers are defined as data points that are larger (or smaller) than 1.5 times the interquartile range away from the 75th percentile (or the 25th percentile). For normal distributions this corresponds to a data range of $\pm 2.7 \sigma$. In graphs that depict time courses or other courses, the median and the standard error of the median is shown. To estimate the standard error we performed bootstrapping (10,000 repetitions) on each dataset and quantified the mean and standard deviation of the median distribution. Values in the text are also specified as median ± standard error of the median (SEMd). Unpaired two-tailed Wilcoxon rank sum tests were used to assess statistical significance. A $p$-value <.05 was considered as significant.

3 | RESULTS

3.1 | Induction of different oscillatory states by two different optogenetic stimulus patterns

We recorded extracellular field potentials in acute mouse hippocampal slices placed on an array of 60 microelectrodes distributed evenly across the majority of the hippocampal formation (Figure 1b). Excitatory neurons expressed ChR2-EYFP for optogenetic stimulation which appeared fairly homogenous along the DG-CA3-CA1 axis ($n = 71$ slices from 23 mice; Figure 1c). In line with previous reports (Maier, Nimmrich, & Draguhn, 2003), hippocampal slices displayed spontaneously generated sharp wave-ripple complexes (SPW-R) with a characteristic frequency component at ~200 Hz (Figure 1g). We activated ChR2-expressing neurons by illumination of preselected, almost rectangular areas (see Section 2 for illumination device and more simple alternatives). When we applied brief light stimulation flashes of 5 ms at the pyramidal cell layer of CA3, network events similar to spontaneous SPW-R occurred in our field recordings (Figure 1f,h). At the site of stimulation we observed negative potential deflections which were likely caused by the local cation influx due to ChR2 activation. After propagation toward CA1, however, event waveforms resembled very closely the pattern of spontaneously occurring SPW-R. Thus, brief activation of excitatory neurons results in network activity patterns resembling typical sharp wave-ripple complexes.

In contrast, prolonged phasic stimulation with a 1 Hz sinusoidal illumination resulted in field potential synchronization within the gamma frequency band at ~50 Hz (Figure 1e). This activity did also propagate through the slice (Figure 1d,e) with a delay of 5.4 ± 1.6 ms between CA3 and CA1 (median ± standard error of the median [SEMd], 16 slices, 7 mice). This suggests synaptic transmission of evoked field potentials via Schaffer collaterals, in good accordance with published data (Both, Bähner, von Bohlen und Halbach, & Draguhn, 2008). Most notably, upon cessation of sinusoidal stimulation, the network returned to generating spontaneous SPW-R (Figure 1f,l). Thus, endogenous SPW-R reflect the basic network state of hippocampal slices in the absence of external stimulation. Sinusoidal activation of ChR2, in contrast, elicits a rapid and reversible network state transition from SPW-R to gamma oscillations.

3.2 | Effects of input strength and frequency on evoked network patterns

To investigate how different hippocampal network patterns depend on stimulus properties we applied light pulses or sinusoidal profiles with different light intensities and frequencies. As shown in Figure 2a, SPW-R were already elicited at low laser powers between 1 and 2 mW/mm². The success rate to evoke SPW-R at
such low intensities was 80 ± 7% (six slices of six mice). Application of stronger stimuli led to induction of hypersynchronous activity resembling a population spike which was followed by excitatory and inhibitory postsynaptic potentials and a short interruption of spontaneous network activity (Figure 2a, right panel). In addition, the ripple frequency component of the evoked potential decreases with increasing stimulus strength. The success rate of eliciting SPW-R also decreases to 40 ± 13% at the strongest intensity of 5 mW/mm² (Figure 2a,b). The corresponding amplitudes of evoked events started at 35 ± 4 μV for 1 mW/mm² and reached 64 ± 10 μV for 5 mW/mm² light intensity.

In order to examine the relationship between input strength and gamma oscillation parameters, we applied a 1 Hz sinusoidal light stimulus with varying laser intensity maxima ranging from 1 to 5 mW/mm² (Figure 2c). Within this range, normalized power in the gamma frequency band increased toward the state without light presentation. This rise depended on light intensity, starting at 67 ± 8% at 1 mW/mm² and reached ceiling level at 4 and 5 mW/mm² (Figure 2d, left panel, N = 6). Note that maximum gamma power was not always achieved with the highest laser intensity but with an intermediate input strength. The gamma frequency also increased from 40.6 ± 3.0 Hz at 1 mW/mm² to 50.1 ± 1.3 Hz at 5 mW/mm².
(Figure 2d, right panel). Throughout the range of tested stimulation strengths, oscillation frequencies remained within gamma range.

We next investigated the effect of stimulation frequency on optogenetically evoked gamma oscillations. Hence, sinusoidal stimulation patterns were varied ranging from 1 to 15 Hz (Figure 2e, \(N = 17\)). Interestingly, both gamma power and gamma frequency appeared relatively unaffected by input theta frequency (Figure 2f).

Taken together, sinusoidal optical stimulation generates typical gamma oscillations, in accordance with previous reports (Butler, Mendonca, Robinson, & Paulsen, 2016).

### 3.3 Emergence of gamma oscillations suppresses ripples

We showed that short rectangular pulses of light evoked SPW-R complexes whereas longer, sinusoidal stimuli evoked gamma activity. We next investigated how the network reacts to prolonged illumination with sudden onsets (Figure 3a,b, \(N = 13\)). Similar to short pulses, this stimulus pattern initially evoked a SPW-R (Figure 3a, right panels). However, immediately following this initial sharp wave the network started to display gamma oscillations (Figure 3a, right panel, inset). Mean delay to onset of gamma was ~120 ms and was largely independent from illumination power (Figure 3b; delay for 3 mW/mm² light intensity was 114 ± 9 ms). Similar to sinusoidal stimulation, the frequency of these gamma oscillations was weakly dependent on illumination power.

The data reported up to this point indicate that the profile of the stimulus waveform is crucial for whether hippocampal networks tend to produce gamma oscillations or SPW-R. Step-like light flashes evoke SPW-R while the more steadily increasing or prolonged stimulation induces gamma rhythms. In order to determine the exact conditions for this bifurcation in network dynamics we applied ramp-like stimuli with different slopes of the rising phase (Figure 3c, \(N = 15\)). As expected, hippocampal networks generated SPW-R activity in response to a nominally infinite rate of rise (<<1 ms) in laser power which appears as a rectangular time course. Decreasing the rate of rise such that the stimulus profile resembled a ramp with different

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**FIGURE 3** Optogenetic shifting of hippocampal network states by applying different stimulus profiles. (a) Example field potential traces (bottom) evoked by constant illumination of different lengths. The corresponding wavelet spectra are displayed on top of each trace with the time course of the illumination above. White lines indicate frequency borders for gamma oscillations. Note that each stimulation evokes a sharp wave-ripple complex that is followed by gamma oscillations if the stimulation duration exceeds ~125 ms. Inset in right panel: magnification of sharp wave and gamma oscillation from the sections indicated by rectangles in the complete trace. (b) Quantification of ripple lag and ripple power (left panels) and gamma lag and gamma power (right panels). Data are presented as median ± SEMed and were collected from 13 slices of 5 mice. (c) Example field potential traces (bottom) evoked by different rate of rise of stimulation intensity. The corresponding wavelet spectra are displayed on top of each trace with the time course of the illumination above. Note that ripple frequency components (150–300 Hz) are only present when applied stimuli featured a steep time course. Lower rates of rise lead to a more pronounced gamma (30–60 Hz) component. (d) Normalized power of ripple and gamma frequency components in local field potentials as a function of rate of rise of laser power. Data are presented as median ± SEMed and were collected from 15 slices of 7 mice. The calibration bars shown as insets of the wavelet spectra are given in units of \(\mu\text{V}^2\) [Color figure can be viewed at wileyonlinelibrary.com]
slopes led to a more pronounced gamma component in the LFP oscillations. Strikingly, stimulation with a ramp rising during 100 ms at a rate of 10 mW/mm²s (Figure 3c, middle panel) apparently evoked a SPW-R at the onset which then directly turned into a gamma oscillation. The stimulus-dependent transition between both frequency bands is summarized in Figure 3d. While normalized power in the gamma band (30–80 Hz) is essentially zero at high rates of rise, it becomes increasingly dominant at around 10 mW/mm²s. At the same time, power of ripple frequencies (150–300 Hz) declines with less steep stimulation slopes.

3.4 Gamma oscillations and ripples are not mutually exclusive network states

In freely behaving rodents, gamma oscillations and ripples can occur within the same behavioral or vigilance state (Buzsáki et al., 2003; Carr, Karlsson, & Frank, 2012; Isomura et al., 2006). Using our in vitro model, we therefore investigated their joint appearance under appropriate stimulation conditions. To efficiently induce gamma rhythms with different powers, we illuminated the slice with a 5 s-long ramping light stimulus and identified gamma and ripple oscillations using wavelet spectrograms (Figure 4, N = 13). Ripples were defined as discernable “islets” in the 150–260 Hz range while gamma oscillation power was quantified between 30 and 80 Hz (see Section 2). Indeed, ripples occurred regularly during phases of light-induced gamma oscillations at any time, that is, during low-power gamma oscillations (Figure 4a, blue box in the lower panel) but also during phases of strong gamma oscillations (Figure 4a, orange box) or in episodes without prominent gamma oscillations (Figure 4a, green box). To further quantify the interplay of ripples and gamma oscillations, we assessed the incidence of ripples and the power of gamma oscillations (Figure 4b). Ripples are more common at the beginning of the light stimulation, that is, during phases of low gamma power, and then strongly decrease their

**FIGURE 4** Gamma and ripple oscillations are not mutually exclusive. (a) Example trace of a 5 s ramping light stimulation. Four example events, marked by colored asterisks, are displayed in higher resolution in the lower panels. The left event shows a spontaneous ripple without light stimulation. The next three events show sharp waves occurring during increasing gamma activity while stimulation intensity increases. (b) Left panel: ripple incidence and gamma power during ramping light stimulation. Right panel: incidence of ripples during and outside gamma oscillations. (c) Phase and precision of ripple oscillations with respect to gamma troughs. Data are presented as median ± SEMed and were collected from 13 slices of 11 mice. The calibration bars shown as insets of the wavelet spectra are given in units of μV² [Color figure can be viewed at wileyonlinelibrary.com]
incidence with increasing gamma power. Further analysis showed that during phases of high gamma power, ripples mainly occurred superimposed with the gamma oscillation (Figure 4b, right panel and Figure 4a, red box). In those cases, ripples had a clear preference to occur during gamma troughs (Figure 4c).

3.5 | Instant neuronal synchronization during sharp wave-ripple oscillations

In order to gain more insight into the stimulation-induced synchronization of the CA1 network we performed whole cell voltage clamp

![FIGURE 5](wileyonlinelibrary.com) Neurons are instantly and highly synchronized during sharp wave-ripple oscillations. (a) Example traces of intracellularly recorded excitatory (EPSC, left) and inhibitory (IPSC, right) postsynaptic potentials during evoked sharp wave-ripple complexes (SPW-R). Blue bars indicate the 5 ms light pulse. Arrows and green circles indicate the onset of individual postsynaptic events identified by deconvolution. Lower traces depict the median and the 25th–75th percentiles of 25 evoked events from the same cell. Dashed lines indicate the onset of the average event. (b) Absolute time histograms of all events during 25 evoked SPW-R of a single cell. The 25 first events from each trial are shown in grey. Insets at the top depict the distribution of the first events averaged for one cell. The jitter of the first event is quantified by the time difference of 25th–75th percentile of the distribution. (c) Interevent histograms of all events from 25 trials of one cell. Note the clear and precise peak at around 4.5 ms. (d) Left: jitter of the first event averaged over six cells. Right: Time delay between the onset of the average EPSC versus IPSC from six cells (raw data) and of the first EPSC versus IPSC event averaged over six cells (events) [Color figure can be viewed at wileyonlinelibrary.com]
experiments of CA1 pyramidal cells. Cells where clamped to either 
−74 mV or +10 mV to record excitatory (EPSC) or inhibitory (IPSC)
postsynaptic currents, respectively (Figure 5, N = 6 cells, for liquid
junction potential correction see Section 2). In every cell, EPSCs and
IPSCs were recorded during 25 evoked SPW-R triggered by a light
pulse of 5 ms. EPSCs occurred shortly before IPSCs as can be seen
from the mean currents (Figure 5a, lower panel). Averaged over all
cells, the delay of EPSC onset vs. IPSC onset was 2.7 ± 1.2 ms
(p < .05, Figure 5d, right panel). IPSCs were 4.8 ± 2.1 times larger than
EPSCs (p < .05, Wilcoxon rank sum test). To quantify the synchroniza-
tion of postsynaptic currents by sharp-wave ripple complexes we
identified individual synaptic events by deconvolution (see Section 2)
and then analyzed interevent intervals (IEIs). Histograms of event
onset times showed similar rhythmic activity with interpeak intervals
of 4.9 ± 0.3 ms for IPSCs and 4.2 ± 0.1 ms for EPSCs (Figure 5b;
corresponding to 204 and 238 Hz, respectively). The onset jitter of
the first events was very low with 2.2 ± 1.0 ms for EPSCs and
1.9 ± 1.2 ms for IPSCs (Figure 5c,d, left panel). Similar to the average

**FIGURE 6**  Ramp stimulation leads to a delayed but sudden synchronization of neurons to a gamma rhythm. (a) Recording schematic indicates
the stimulation site in CA3 and the recording electrode in CA1 pyramidal cell layer. (b) Example local field potential (top) and intracellular
potentials (bottom) during ramp stimulation. Inhibitory (IPSC, left) and excitatory (EPSC, right) postsynaptic currents were recorded by different
holding potentials. Time windows indicated by red boxes were used to quantify the synchronization of presynaptic cells into network oscillations.
(c) LFP power in the gamma range (30–80 Hz) appears around 200–300 ms (dashed line), similar to postsynaptic currents. Once oscillations
can be detected from the LFP, the network immediately synchronized to a stable gamma oscillation at ~50 Hz. The calibration bar shown as an inset
of the wavelet spectrum is given in units of $\mu$V$^2$. (d) Mean IPSCs and EPSCs averaged over six cells. PSCs appear around 200–300 ms after ramp
onset and EPSCs emerge around 50 ms before IPSCs. (e) Inhibitory (left) and excitatory (right) postsynaptic events show different synchronization
at different time points of the ramp stimulation. During the first 50 ms, events show an exponential decay in the interevent histograms (bottom),
consistent with a Poisson distribution, that is, random firing of presynaptic cells. Increasing synchronization of inputs to the gamma oscillations
is reflected by a growing peak in the interevent histogram. IPSCs are stronger synchronized than EPSCs. (f) EPSCs precede IPSCs by around 2.5 ms.
(i) inhibitory (left) and excitatory (right) currents with respect to the lfp. (ii) time lag between EPSCs and IPSCs. (iii) precision and (iv) phase of post
synaptic currents [Color figure can be viewed at wileyonlinelibrary.com]
raw currents, the first detectable EPSC events occurred at 2.5 ± 2.3 ms before the first IPSC events (p < .05, Figure 5d, right panel). Finally, the IEI histogram showed a very pronounced and narrow first peak with a full width at half maximum of 1.4 ± 0.4 ms for IPSCs and 2.0 ± 0.3 ms for EPSCs. These data indicate an instant occurrence of highly synchronized network activity at the very onset of sharp wave–ripple oscillations (Figure 5b, grey peaks and box plot insets).

3.6 Sudden synchronization of CA1 neurons to gamma rhythm during stimulus ramps

Similarly to SPW-R we quantified the synchronization of cells by gamma oscillations from the same cells reported above (Figure 6, N = 6 cells). In each cell, EPSCs and IPSCs where recorded during six ramp-shaped stimulations. Similar to network oscillations measured by the local field potential (Figure 6c) patterns of postsynaptic currents synchronized abruptly into gamma oscillations (Figure 6d). During the course of the ramp, both EPSCs and IPSCs built up in amplitude and incidence. Both types of synaptic currents showed strong and stable gamma oscillations that appeared abruptly after about 200–300 ms of light presentation. In CA1, the onset of EPSCs preceded that of IPSCs by 46 ± 19 ms (p < .05, Wilcoxon rank sum test). Similar to SPW-R stimulation, IPSCs were 5.0 ± 1.1 times larger than EPSCs (median of IPSCs 270 ± 49 pA vs. EPSCs 50 ± 5 pA; p < .05, Wilcoxon rank sum test) and IPSC/EPSC ratio was similar between SPW-R and gamma oscillations. To quantify the synchronization of postsynaptic currents with the field gamma rhythm we again identified individual synaptic events by deconvolution (see Materials and Methods) and then analyzed IEIs at three different time ranges: from 0 to 0.4 s, from 0.6 to 1 s, and from 3.8 to 4.2 s of stimulation (Figure 6b,e). Interestingly, the IEI histogram of IPSCs during the first time interval showed an exponential decay, consistent with a Poisson distribution and, hence, random firing of excitatory as well as inhibitory cells. During the second time interval, IPSCs display a more rhythmic behavior as indicated by a peak in the IEI histogram. Toward the end of the ramp stimulation the pronounced peak in IEI indicated gamma-synchronous rhythmicity of postsynaptic currents. Increasing rhythmicity could also be observed for EPSCs, albeit to a lesser degree. The IEI at the peak of the distribution was 23.9 ± 0.7 ms for IPSCs and 20.7 ± 1.6 ms for EPSCs which corresponds to 42 ± 1 Hz for IPSCs and 49 ± 4 Hz for EPSCs, consistent with the gamma frequency observed in local field potentials. During the fully synchronized interval, the half-width of the peak in IEI distribution was 6.0 ± 1.0 ms for IPSCs and 7.9 ± 1.1 ms for EPSCs, indicating a similar degree of synchronization with gamma.

To further quantify the timing of IPSCs and EPSCs during the third, strongly synchronized interval we computed the phase of events with respect to the gamma oscillation troughs in the field potential recordings (Figure 6f). Consistent to published data from in vitro (Fisahn, Pike, Buhl, & Paulsen, 1998) and in vivo (Csicsvari, Jamieson, Wise, & Buzsáki, 2003) recordings, EPSCs appeared shortly after the gamma trough and preceded IPSCs by 23 ± 7° which corresponds to 2.6 ± 0.7 ms. Similar to the stronger peak in the IEI histograms, IPSC showed a higher precision in phase coupling than EPSCs (Figure 6fiii, see also Section 2).

4 DISCUSSION

Hippocampal networks tend to adopt one of two activity patterns, theta-nested gamma oscillations or sharp wave–ripple complexes (SPW-R). The precise conditions under which either network pattern is generated are, however, unclear. In our experimental model, we induced hippocampal network oscillations without any supply of neuromodulators, by solely activating pyramidal cells with temporally and spatially confined optogenetic tools. Thus, we were able to define the exact conditions for triggering SPW-R or theta-nested gamma oscillations, respectively.

We report that the temporal pattern of excitatory input is a decisive parameter determining the subsequent type of network activity. If principal neurons are activated by a smoothly modulated stimulus, that is, with low synchrony, the network will tend to synchronize into a gamma rhythm and cells will be entrained with a jitter of around 8 ms. In contrast, if a small group of cells is activated synchronously, a SPW-R is generated that recruits cells with a comparatively low jitter of around 2 ms. This synchronization depends, however, on the number of recruited cells—activation of too many cells causes a population spike which is then aborted by strong feedback inhibition preventing subsequent oscillatory activity. Taken together this suggests that the conditions for activating the two oscillation types are strongly different which may explain why at a given time usually one of the two rhythms prevails.

Data from in vivo recordings (Buzsáki et al., 2003; Carr et al., 2012; Isomura et al., 2006) as well as our present findings show that both oscillation patterns can also co-occur. This phenomenon and, possibly, the underlying mechanisms may extend to other parts of the temporal lobe or the neocortex (Cunningham et al., 2004). We found such joint occurrences especially upon light stimulation at low to intermediate strengths.

This may be explained by local effects of different types of interneurons as well as crosstalk through of long- and short-range connections (Csicsvari, Hirase, Mamiya, & Buzsáki, 2000; Ellender, Nissen, Colgin, Mann, & Paulsen, 2010; Klausberger & Somogyi, 2008). It is well feasible that activity is generated in a local group of cells and then recruits neurons in large, dispersed areas which feed back to and synchronize with the region of origin. Such long-range interactions occur especially when the oscillations exhibit lower frequencies (Buzsáki, Anastassiou, & Koch, 2012; Kajikawa & Schroeder, 2011). Thus, a dispersed group of functionally connected cells might synchronize into a gamma rhythm while another group of cells generates ripple oscillations simultaneously, both groups contributing to the local field potential. In these scenarios any given neuron would, however, probably be either in the gamma or in the ripple state.
4.1.1. | Theta-nested gamma oscillations

One long-standing and established model for gamma oscillations is based on the interaction of pyramidal cells and inhibitory interneurons (Bartos et al., 2007; Mann & Paulsen, 2007; Whittington et al., 2011). In this pyramidal cell-interneuron network gamma (PING) model, feedback inhibition is triggered by the activity of excitatory neurons. The resulting inhibitory postsynaptic potentials prevent further action potential generation in pyramidal cells for a defined time window. When inhibition decreases, pyramidal cells start spiking again, thereby activating a new cycle of feedback inhibition and firing. In this model, the time constant of inhibitory synapses plays a crucial role for firing and, hence, network oscillation frequency. In line with this mechanism, network models with reciprocal excitatory-inhibitory connections lead to coherent oscillations at gamma frequency which reflect recorded activity in hippocampal and neocortical networks (Bartos et al., 2007; Buzsáki & Wang, 2012; Whittington et al., 2011). One important condition for the maintenance of gamma oscillations is a continuous excitatory drive from outside of the local network, for example, inputs from the entorhinal cortex to the hippocampus. This drive does not necessarily have to be rhythmic itself. According to some computational studies, a constant Poisson-distributed (i.e., random) excitatory input is enough to drive and generate gamma oscillations within local networks (Lee & Jones, 2013; Lowet et al., 2015). On the other hand, rhythmic input in the proper frequency range may positively interact with the local network dynamics and support gamma frequency output. Furthermore, local networks might act as a “regenerative repeater,” entraining temporally dispersed input signals into a common temporal regime. In our experimental model, the excitatory drive from outside the hippocampus was simulated by optogenetic activation of pyramidal cells. When light intensity is linearly increased, cells start to fire in a random fashion, depending on their different excitability, ChR2 expression levels, and local light intensity. In our recordings, this irregular firing was reflected in the random timing of excitatory postsynaptic currents during the first few hundred milliseconds of a slow ramp-wise stimulation. Afterward, the increasing strength and synchrony of feedback inhibition lead to network synchronization in the gamma frequency range.

4.1.2. | Sharp wave-ripple complexes

We demonstrated that one short light stimulus triggers a temporally confined network response with characteristics of sharp wave-ripple complexes. What causes the network to shift into this distinct regime with a much faster superimposed network oscillation? Similar to gamma oscillations, ripples do involve the activation of interneurons (Bähner et al., 2011; Csicsvari et al., 2000; Ellender et al., 2010). In principle, the two patterns could be generated by activation of different subtypes of interneurons generating IPSPs in pyramidal cells with time constants of about 25 ms (leading to ~40 Hz gamma) or 5 ms (leading to ~200 Hz ripples), respectively. However, there is no evidence for two clearly distinct interneuron populations with such strongly different IPSP time constants (Hajos et al., 2013; Klausberger et al., 2003). Based on published computer models, two alternative mechanisms have been suggested for the generation of very fast network oscillations, both involving nonlinear mechanisms: electrical coupling between pyramidal cells axons (Draguhn et al., 1998; Traub et al., 2012; Traub, Schmitz, Jefferys, & Draguhn, 1999) or, alternatively, nonlinear dendritic signal integration of excitatory postsynaptic potentials (Jahnke et al., 2015; Memmesheimer, 2010; Nevian, Larkum, Polsky, & Schiller, 2007). Electrical coupling between axons will result in a very fast recruitment of coupled pyramidal cells by a small group of initially activated neurons (Schmitz et al., 2001). As a result, activity will percolate through the axonal network, giving rise to ectopically generated action potentials (Bähner et al., 2011) and generating a rhythm that depends on network topology (Draguhn et al., 1998; Traub et al., 1999). Recently, an alternative mechanism has been suggested based on purely chemical synaptic transmission (Jahnke et al., 2015; Memmesheimer, 2010). If a group of excitatory neurons is co-active within a few milliseconds, basal dendrites of target cells can amplify these inputs by triggering dendritic sodium spikes. This will strongly increase the probability of action potential generation and generate near-synchronous spiking and, hence, activation of postsynaptic cells. Additionally, nonlinear excitation-spike coupling is able to overcome strong perisomatic inhibition which builds up due to feedback inhibition. Eventually, however, inhibition will become strong enough to terminate activity in the network.

Both suggested mechanisms (which need not be mutually exclusive) predict major features of the resulting network event which are confined by our experimental data: (a) activity is initiated by synchronous activation of a small number of neurons (typically around 5% in a network with 5% recurrent connectivity); (b) after initiation, activity spreads without further external drive; (c) jitter of co-active neurons stays small over all oscillation cycles of the event (around 2 ms); (d) activity stops after a few cycles. These predictions are all in line with our present observations. They are also in line with the single population spike driven by very strong stimulation: if a larger group of cells is activated, it triggers enough feedback inhibition to overcome nonlinear dendritic integration and, hence, to terminate any further activity.

4.1.3. | Determination of network dynamics by initial excitation conditions

Taken together, we propose that different oscillatory states of hippocampal networks are triggered by the temporal pattern in which hippocampal neurons are activated. If local activity or inputs from upstream networks are asynchronous or smeared out over tens of milliseconds, the hippocampal network will be dominated by inhibitory feedback connections that set rhythmic windows of opportunity and thus synchronize the network into a gamma rhythm. If the inputs are sufficiently synchronous, activity is dominated by nonlinear mechanisms of dendritic or axonal depolarization, and feedback inhibition will only be able to suppress activity after sufficient cumulative
recruitment of interneurons. The observed ripple-frequency field potential oscillation is, nevertheless, largely generated by inhibitory postsynaptic potentials (Schlingloff et al., 2014) but will not be causal for the rhythmic entrainment of pyramidal cells (Viereckel, Kostic, Bähner, Draguhn, & Both, 2013).

Neuromodulators like acetylcholine facilitate state shifts from SPW-R to gamma (Traub et al., 2000; Zylla, Zhang, Reichenke, Draguhn, & Both, 2013). However, several other approaches have been used to induce gamma oscillations in hippocampal slices (LeBeau, Towers, Traub, Whittington, & Buhl, 2002; Whittington, Stanford, Colling, Jefferys, & Traub, 1997; Whittington, Traub, & Jefferys, 1995), including the present study. Thus, activation of cholinergic receptors is not required to induce gamma in hippocampal networks. Acetylcholine may rather serve to fine-tune network activity and support the formation of neuronal assemblies during theta- and gamma oscillations, or it may boost recurrent synapses during sharp wave-ripple complexes to facilitate retrieval of stored memories (Hasselmo & Stern, 2006).

In summary, we show that the type of emerging hippocampal network oscillations is particularly dependent on the activating pattern of excitatory cells. Highly synchronous activity leads to self-propagating SPW-R while continuous, random activation synchronizes the network into gamma oscillations within tens of milliseconds. Thus, the network can rapidly shift between two different, intrinsic activity patterns appropriate for the formation or retrieval of information, respectively, without the need of neuromodulatory regulation.

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CONFLICT OF INTEREST
The authors declare no competing financial or other conflict of interest.

DATA AVAILABILITY STATEMENT
The data that support the findings of this study are available from the corresponding author upon reasonable request.

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