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Novelty-induced phase-locked firing to slow gamma oscillations in the hippocampus: requirement of synaptic plasticity

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Summary
Temporally precise neuronal firing phase-locked to gamma oscillations is thought to mediate the dynamic interaction of neuronal populations, which is essential for information processing underlying higher order functions such as learning and memory. However, the cellular mechanisms determining phase locking remain unclear. By devising a virus-mediated approach to perform multi-tetrode recording from genetically manipulated neurons, we demonstrated that synaptic plasticity dependent on the GluR1 subunit of AMPA (α-amino-3-hydroxy-5-methyl-4-isoxazole propionate) receptor mediates two dynamic changes in neuronal firing in the hippocampal CA1 area during novel experiences: the establishment of phase-locked firing to slow gamma oscillations and the rapid formation of the spatial firing pattern of place cells. The results suggest a series of events potentially underlying the acquisition of new spatial information: slow gamma oscillations, originating from the CA3 area, induce the two GluR1-dependent changes of CA1 neuronal firing, which in turn determine information flow in the hippocampal-entorhinal system.

Running Title
Plasticity regulates slow-gamma phase locking

Introduction
Gamma oscillations are a type of neural oscillation observed in many brain regions, including the hippocampal-entorhinal circuits (Buzsáki and Wang, 2012). Individual neurons often preferentially
fire at specific phases of gamma oscillations, which is referred to as phase locking (Csicsvari et al., 2003). The phase-locking of a group of neurons to a common phase range temporally aligns their firings within millisecond windows in gamma cycles. Such temporally aligned firings among a group of neurons are effectively transmitted to downstream neurons as a coincident event (Fell and Axmacher, 2011). Therefore, gamma phase locking has been implicated in neuronal operations linking multiple neuronal populations, such as the formation of cell assemblies (Harris et al., 2003), the binding of sensory features (Gray et al., 1989), and inter-regional information transfer (Womelsdorf et al., 2007). These operations, which are assisted by gamma phase locking, are considered to be essential for information processing that associated with higher order functions such as learning and memory (Fell and Axmacher, 2011).

In the CA1 area of the hippocampus, gamma oscillations are shown to be divided into at least two types with separate frequency ranges: slow (25-50 Hz) and fast (65-140 Hz) gamma oscillations (Colgin et al., 2009). These two types of gamma oscillations in the CA1 area are thought to be driven by synaptic inputs from the CA3 area and the medial entorhinal cortex (MEC), respectively. The synchronization of slow and fast gamma oscillations between the CA1 area and these two upstream structures is differentially modulated by specific episodes related to different memory operations during behavioral tasks (Bieri et al., 2014; Kemere et al., 2013; Montgomery and Buzsaki, 2007; Yamamoto et al., 2014), suggesting that these two types of gamma oscillations are involved in different modes of information processing in the CA1 area. CA1 principal cells are phase-locked to slow and/or fast gamma oscillations (Colgin et al., 2009), and the strength of gamma phase locking is dynamically modulated during behavior (Ahmed and Mehta, 2012; Chen et al., 2011; Kemere et al., 2013).

Although the balance of excitatory and oscillatory inhibitory inputs is thought to contribute to phase-locked firing along gamma oscillations (Bartos et al., 2007; Buzsáki and Wang, 2012), the mechanism underlying phase locking is not thoroughly understood. As a process of changing synaptic strength, synaptic plasticity can alter the excitatory-inhibitory balance, and therefore, may regulate phase locking during the two types of gamma oscillations. To test this possibility, we decided to block long-term potentiation (LTP) in CA1 pyramidal cells and examine the effects on phase locking to gamma oscillations.

However, conventional pharmacological and transgenic methods have limited applications due to brain-wide effects, such as cognitive and behavioral impairments, which make it unclear whether the observed changes in neuronal firing are caused directly by the interference of the cellular machinery
or indirectly by the systemic deficits affecting input activity to the monitored neurons (Allen et al., 2014; Bach et al., 1995; Cain, 1997; Giese et al., 1998; Morris et al., 1986; Reisel et al., 2002; Resnik et al., 2012; Tsien et al., 1996). To circumvent this limitation, we devised a new approach combining viral vector-mediated local genetic manipulation with a unit recording technique. The viral vector was introduced locally to a relatively minor portion of the CA1 area in which synaptic plasticity was blocked selectively in pyramidal cells. The remaining majority of the CA1 area and surrounding structures remained intact, thereby enabling us to monitor the firing activity of manipulated neurons under normal brain function conditions.

Results

Viral vector-mediated local blockade of LTP

We constructed recombinant adeno-associated viral vectors (rAAVs) expressing either GFP-GluR1-c-tail or GFP under the control of the CaMKII promoter (Figure 1A). The GluR1-c-tail is a dominant-negative mutant of the GluR1 gene that suppresses LTP by interfering with the synaptic delivery of GluR1-containing AMPA receptors (Hayashi et al., 2000; Shi et al., 2001). GluR1-c-tail does not alter basal synaptic transmission mediated by either AMPA or NMDA (N-methyl-D-aspartate) receptors, or cellular membrane properties such as resting potential and input resistance (Hayashi et al., 2000; Mitsushima et al., 2011; Shi et al., 2001). By injecting a moderate quantity of the vectors, we achieved selective GFP expression within a minor portion (approximately 20%) of the dorsal CA1 area (Figure 1B, Figure S1A). The majority of GFP-expressing neurons were excitatory (Figure 1C-E), which comprised approximately 95% of the pyramidal cells within the infected area (Figure 1D). In contrast, GFP-positive cells were scarce in the CA3 area (Figure 1B, Figure S1A) and in the entorhinal cortex (0.12% of layer III neurons, Figure S1B, C), indicating that the upstream regions were largely unaffected by the retrograde transduction. Under these conditions, a small population of CA1 pyramidal cells is manipulated while normal brain functions are supported by the majority of normal CA1 neurons.

We examined the effect of GluR1-c-tail expression on LTP with extracellular recording in a slice preparation. Field excitatory postsynaptic potentials (fEPSPs) evoked by stimulation of the Schaffer collaterals were recorded from either the GluR1-c-tail or GFP expressing portions of the CA1 area. Although the enhancement of fEPSPs was induced in the GFP-expressing portions via theta-burst stimulation of Schaffer collaterals, no long-term enhancement occurred in the GluR1-c-tail expressing portions (Figure 1F). Thus, GluR1-c-tail expression blocked LTP. Basal evoked
responses were not significantly affected by GluR1-c-tail (Shi et al., 2001) (amplitude of evoked responses: GFP, 1.22 ± 0.58 mV; GluR1-c-tail, 0.60 ± 0.15 mV at 50 µA stimuli; two-sided, independent samples t-test, t_{8} = 1.05, P = 0.33).

**Intact neural oscillations in the CA1 area**

We used multiple tetrodes to monitor unit activity and local field potentials (LFPs) from the vector-injected areas of 11 freely-behaving rats (Figure S2, S3). In seven of these rats, we implemented a within-subject control design by injecting either the GFP- or GluR1-c-tail-expressing vector to the CA1 area in each hemisphere and bilaterally monitoring the neuronal activity in control (GFP) and manipulated (GluR1-c-tail) hemispheres in individual rats (Figure 2A). During the final recording days, we performed two sets of recording sessions. In the first set, the rats explored a familiar environment (room A), in which the rats were repeatedly trained prior to and after injecting the viral vectors to block LTP. Six 10-min sessions were performed with 5-min inter-session intervals. In the second set, we first performed a recording session in a familiar environment (room A) and then four sessions in a novel environment (room B) and another session again in the familiar environment. This sequence of six recording sessions was repeated three times (0 h, 6 h and 24 h), and these sessions are sequentially referred to as A_{1}, B_{1-4}, A_{2} (0 h), A_{3}, B_{5-8}, A_{4} (6 h) and A_{5}, B_{9-12}, A_{6} (24 h). Post-hoc histological analyses verified that all recording sites were within the GFP-positive CA1 areas (11 sites in the control hemispheres and seven sites in the GluR1-c-tail hemispheres, Figure S2). Single units classified as principal cells (putatively recorded from pyramidal cells, Figure S3, Supplemental Experimental Procedures) were included in the following analyses. The numbers of principal cells per tetrode did not differ between the GluR1-c-tail and GFP hemispheres (Figure S3).

During exploratory behavior, theta, slow gamma, and fast gamma oscillations were prominently observed in the CA1 area (Figures 2B, 2C). These three frequency ranges of LFPs were compared between CA1 areas infected with either the GFP or GluR1-c-tail-expressing vectors. The data from sessions A_{1-6} and B_{1-12} were pooled. The powers of the theta, slow gamma, and fast gamma oscillations were indistinguishable between the GFP and GluR1-c-tail-expressing hemispheres (Figure 2C-E, Figure S4). The waveform symmetry of band-pass-filtered LFPs (Figure 2F-H) were quantified by calculating the proportion of sampling time points that fell within each 30° phase bin (Figure 2G, % duration). The values of % duration were nearly uniform along the phase bins, and no differences were found between hemispheres in the theta, slow gamma, or fast gamma oscillations (Figure 2H, Figure S4). These results indicate that GluR1-c-tail expression does not affect gross
oscillatory activity in LFPs during exploration. Thus, using this virus-mediated local genetic manipulation method, we were able to examine how the blockade of GluR1-dependent synaptic plasticity affected neuronal firing patterns with normal neural oscillations.

**GluR1-dependent synaptic plasticity strengthens phase locking to slow gamma oscillations**

We then investigated phase-locked firing along slow and fast gamma oscillations while the rats foraged in environments. To quantify the strength of the phase locking, we calculated the mean resultant vector length of firing phases for individual neurons (see Experimental Procedures). The resultant length was lower in the GluR1-c-tail hemispheres for slow gamma oscillations (Figures 3A, 3B) but not for fast gamma oscillations (Figures 3C, 3D). Principal cells were classified as being phase-locked if their firing phase distribution along gamma oscillations significantly differed from a uniform distribution ($P < 0.05$, Rayleigh test). We found that the proportion of significantly phase-locked cells to slow, but not fast, gamma oscillations were lower in the GluR1-c-tail hemispheres (Figures 3E, 3F). These results suggest that phase locking to slow, but not fast, gamma oscillations is mediated by GluR1-dependent synaptic plasticity.

Because synaptic plasticity is considered to be a cellular mechanism for memory, we were interested in whether GluR1-dependent synaptic plasticity was involved in memory-related processes. Therefore, we next focused on phase locking during exposure to a novel environment in which rats learn new spatial information. In the familiar environment (session A1), the powers of slow (Figure 4A) and fast gamma oscillations (Figure 4B) were constant throughout the recording sessions [slow gamma oscillations: $F_{3.0, 36.3} = 2.41, P = 0.08$; fast gamma oscillations: $F_{2.7, 32.4} = 1.56, P = 0.22$ for the effect of time, two-way (time × hemisphere) repeated-measures ANOVA] and were indistinguishable between the GFP and GluR1-c-tail hemispheres (between hemispheres: $F_{1, 12} = 0.12, P = 0.74$ for slow gamma oscillations, $F_{1, 12} = 0.02, P = 0.89$ for fast gamma oscillations; $F_{3,0, 36.3} = 0.88, P = 0.46$ for slow gamma oscillations, $F_{2.7, 32.4} = 0.51, P = 0.66$ for fast gamma oscillations for the hemisphere × time interaction, two-way repeated measures ANOVA). During the first few minutes after the rats were exposed to a novel environment in room B for the first time (session B1), the power of slow gamma oscillations transiently increased compared with that in the preceding session (A1) in the familiar environment in both the GFP and GluR1-c-tail hemispheres. Then, the power gradually reduced to the level observed in the familiar environment (Figure 4A). Running speed, which has been reported to modulate the power of slow gamma oscillations (Ahmed and Mehta, 2012), did not account for this power increase (Figure S5). This transient power increase did not occur for fast gamma oscillations (Figure 4B).
Phase locking to slow gamma oscillations, measured by resultant length, was stronger in the GFP hemispheres than in the GluR1-c-tail hemispheres during session B₁ (Figures 4C, 4D). This difference was not observed during sessions in the familiar environment (A₁₋₆) or later exposures to room B (B₂₋₁₂) (Figures 4C, 4D). The difference in session B₁ was not attributed to the variance of the number of recorded spikes (Figure S6). The percentage of phase-locked cells was also lower in the GluR1-c-tail hemispheres than the GFP hemisphere during session B₁ (Figure 4E). These results indicate the involvement of GluR1-dependent synaptic plasticity in phase locking to slow gamma oscillations during novel experiences. The percentage of phase-locked cells was also lower in the GluR1-c-tail hemisphere than the GFP hemisphere during exposure to room A (A₁₋₆), but not in later sessions in room B (B₂₋₁₂) (Figure 4E). Thus, the GluR1-dependent synaptic plasticity may be involved in phase locking to slow gamma oscillations in a familiar environment under some conditions, although the effects were not as robust as those in a novel environment and were not observed in resultant length. For fast gamma oscillations, neither the strength of phase locking nor the percentage of phase-locked cells differed significantly between the control and GluR1-c-tail hemispheres in any of the compared sessions (Figures 4D, 4E).

**Intact spatial firing in a familiar environment**

Hippocampal principal cells fire when animals traverse specific locations in the environment; these neurons are called place cells (O'Keefe and Dostrovsky, 1971). New spatial firing patterns of place cells rapidly form when animals encounter a novel environment (Frank et al., 2004; Wilson and McNaughton, 1993), and these patterns can be stable for days (Muller et al., 1987; Ziv et al., 2013) or even months (Thompson and Best, 1990). The rapid formation and stability may reflect the acquisition and storage of spatial information into neurons during novel experiences. We investigated how the attenuated phase locking by GluR1-c-tail is associated with spatial firing patterns in CA1 principal cells. The spatial distribution of firing was monitored while rats foraged during six 10-minute sessions in a familiar environment in room A. In both the GFP and GluR1-c-tail hemispheres, the majority of principal cells selectively fired when the rats traversed certain areas in the environment (Figure 5A), which were defined as place fields (see Supplemental Experimental Procedures).

The mean ($t_{83} = -0.64, P = 0.53$, two-sided, independent samples $t$-test) or peak ($t_{83} = -0.36, P = 0.72$, two-sided, independent samples $t$-test) firing rates did not differ between the GFP and GluR1-c-tail hemispheres (Figures 5B, 5C). This is consistent with the findings that GluR1-c-tail expression does not alter basal synaptic transmission (Shi et al., 2001) or cellular membrane properties (Mitsushima
et al., 2011). Place field size (Figure 5D; between hemispheres, $F_{1,83} = 1.63$, $P = 0.21$; session × hemisphere, $F_{5,415} = 0.74$, $P = 0.59$ in two-way repeated measures ANOVA), spatial information (GFP, $1.20 \pm 0.08$ bits/s; GluR1-c-tail, $1.16 \pm 0.16$, between hemispheres, $F_{1,83} = 0.06$, $P = 0.81$; session × hemisphere, $F_{5,415} = 0.73$, $P = 0.60$ in two-way repeated measures ANOVA) and spatial correlation between the first and last sessions (GFP, $0.55 \pm 0.03$; GluR1-c-tail: $0.58 \pm 0.05$, $t_{83} = -0.46$, $P = 0.64$, two-sided, independent samples t-test) did not differ between the GFP and GluR1-c-tail hemispheres, indicating that GluR1-dependent synaptic plasticity does not regulate the basic properties of the spatial firing of CA1 principal cells in a familiar environment.

**Dispersed spatial firing in a novel environment and development with repetitive experience**

Next, we investigated spatial firing patterns in a novel environment. Place field size was analyzed during sessions in a novel room (B1-B4) and a familiar room (A1, A2; i.e., two sessions flanking the B1-B4 sessions). Neither the mean firing rate (GFP, $1.01 \pm 0.12$ Hz; GluR1-c-tail, $0.93 \pm 0.12$) nor the peak firing rate (GFP, $7.08 \pm 0.69$ Hz; GluR1-c-tail, $6.55 \pm 0.68$) in room B differed between the hemispheres ($P > 0.1$ for both, two-sided, independent samples t-test). We found location-specific firing during all sessions (A1-2, B1-4; Figure 5E). In session B1, however, the place field size was significantly larger in the GluR1-c-tail hemispheres than in the GFP controls (Figures 5E, 5F and S7). The large place fields became gradually smaller over the span of the sessions; by session B4, the fields were indistinguishable from those of the controls (Figures 5E, 5F; $P = 0.53$, post-hoc Bonferroni test). In contrast, the place field size in the GFP controls did not change over sessions B1-B4 (Figure 5F; $P > 0.05$, post-hoc Bonferroni test for all B1-4 pairs). The sequences of the six sessions in room A and B were repeated at 6 and 24 h after the initial sessions. At 6 h, the place field size was again larger in the first session in room B (B5) in the GluR1-c-tail hemispheres compared with those of the controls (Figure 5G) and became indistinguishable from those of the controls by the fourth session in room B (B8, Figure 5G; $P = 0.22$, post-hoc Bonferroni test). At 24 h, the place field size did not differ between the hemispheres (Figure 5H).

The long-term stability of spatial firing patterns is a feature of place cell activity. Previously, the role of synaptic plasticity in the formation of stable spatial firing patterns in CA1 principal cells was suggested by a study demonstrating impaired long-term stability of spatial firing patterns in rats systemically administered an NMDA receptor antagonist (Kentros et al., 1998). To examine the effect of GluR1-c-tail expression on the long-term stability of spatial firing patterns, we quantified the spatial correlation between the 0 h (A2, B4) and 6 h (A4, B8) or 24 h (A6, B12) time points. There were no differences between the hemispheres in either the familiar or novel room (Figure 5I; $P > 0.1$.
for all main and interaction effects, 3-way ANOVA on hemisphere × room × time point). These observations suggest that the GluR1-dependent synaptic plasticity of CA1 principal cells *per se* is not essential for the long-term stability of spatial firing patterns.

*Delayed formation of place cells in a novel environment*

When rats explore a novel environment, CA1 principal cells form patterns of place cell activity during the first several minutes (Frank et al., 2004). To closely investigate the formation of spatial firing during session B₁, the data from the 10-minute session was split into 5 blocks of 2 minutes (Figure 6A). The mean firing rate inside the place fields (fields determined from the entire 10-min data in session B₄) and the similarity of spatial firing pattern to session B₄ (calculated using a population vector cross-correlation) progressively increased in both hemispheres (Figures 6B, 6C; between 2-min periods, *P* < 0.001, two-way repeated measures ANOVA; *P* < 0.001, *post-hoc* Bonferroni test comparing 0-2 and 8-10 min periods in each hemisphere). This result indicates that spatially restricted firing patterns similar to the eventual place cell activity gradually emerged during the 10-minute B₁ session. Both parameters were significantly lower in the GluR1-c-tail hemispheres than those of the controls during the first 2 minutes (Figures 6B, 6C), which suggests that GluR1-c-tail expression delayed the formation of spatial firing patterns in the novel environment. The parameters showed smaller increases in the familiar environment (Figures 6D, 6E; between B₁, B₂₋₁₂ and A₁₋₆ sessions, *P* < 0.001 for both parameters, two-way ANOVA; *P* < 0.001, *post-hoc* Bonferroni test comparing the B₁ and familiar sessions), suggesting that stable spatial firing patterns in the familiar environment are more stable over 10-minute sessions. These observations indicate that GluR1-dependent synaptic plasticity contributes to the rapid formation of fine spatial firing patterns in a novel environment.

To investigate the possibility that gamma phase locking is related to the coding of spatial information, we examined the relationship between phase locking and spatial firing in individual cells. In the B₁ session, place field size was inversely correlated with slow gamma-resultant length in GFP controls (Figures 7A, 7B). This inverse correlation was maintained in the GFP-c-tail hemispheres (Figure 7A, 7B; *P* > 0.1, test of the difference between two independent correlation coefficients, two-tailed, see Supplemental Experimental Procedures). These results indicate that strong phase-locking to slow gamma oscillations is coupled with the formation of fine place fields and that this coupling is not dependent on GluR1-dependent synaptic plasticity (Figure S8). A weaker inverse correlation was also observed between the place field size and fast gamma-resultant length in GFP controls, but not in the GluR1-c-tail hemispheres (Figure 7C).
Discussion

The firing patterns of neurons in behaving animals are determined by interactions between cellular mechanisms and input activity. To examine the cellular mechanism underlying neuronal firing patterns in live brains, it is essential to maintain systemic brain functions while manipulating the cellular mechanism of interest. Although conventional approaches using pharmacological and transgenic manipulations have identified impairments in firing patterns in behaving animals, they often cause brain-wide/systemic changes including cognitive and behavioral impairments (Bach et al., 1995; Cain, 1997; Giese et al., 1998; Morris et al., 1986; Reisel et al., 2002; Tsien et al., 1996). Such systemic impairments make it unclear whether the observed effects are caused directly by the interference of the cellular mechanisms inside the neuron or indirectly by the altered input activity associated with the systemic impairments. To overcome this difficulty, we implemented local genetic manipulation and within-subject control design. By manipulating a minor portion of a target brain area and monitoring unit activity from it, systemic brain functions can remain intact because the majority of the target brain area is unaffected. Furthermore, the within-subject control design eliminates the possibility that the observed changes in firing patterns can be attributed to systemic changes, such as deficits in behavior, cognition, or learning.

In our study, we were able to genetically manipulate approximately 20% of the dorsal CA1 area (visualized via GFP expression) (Figure 1B, Figure S1). GluR1-c-tail expression in this small manipulated area did not affect the three types of neural oscillations (slow gamma, fast gamma and theta oscillations). Because these oscillations are considered to be driven primarily by input activity from upstream brain areas to the CA1 area, the intact oscillations indicate that input activity to CA1 principal cells is intact even after expressing GluR1-c-tail. Therefore, the virus-mediated local genetic manipulation method enables us to examine the cellular mechanism by which GluR1-dependent synaptic plasticity regulates neuronal firing patterns in the CA1 area, without having to consider indirect effects caused by systemic brain malfunctions.

Role of GluR1-dependent synaptic plasticity in phase-locked firing during slow gamma oscillations.

The expression of GluR1-c-tail impaired phase-locked firing to slow gamma oscillations in CA1 principal cells (Figures 3, 4). This finding indicates that GluR1-dependent synaptic plasticity promotes phase-locked firing to slow gamma oscillations (Figure 8A). A prevailing model states that the oscillatory inhibitory input from local interneurons is a primary determinant of phase-locked firing to gamma oscillations (Csicsvari et al., 2003; Lasztoczi and Klausberger, 2014; Pernia-Andrade and Jonas, 2014; Zemankovics et al., 2013). According to this model, local interneurons,
such as basket cells, provide widespread, rhythmic inhibition to CA1 principal cells in the gamma frequency range (Bartos et al., 2007), thereby creating a short time window of disinhibition within which a group of principal cells preferentially fire. This time window corresponds to a specific phase range in gamma oscillations, leading to phase-locked firing. Although inhibitory input from local interneurons is widespread over CA1 principal cells, firing within the time window does not occur in all principal cells or in all slow gamma cycles. The firing of specific principal cells during specific slow gamma cycles is assumed to be determined by the interaction of excitatory drives with inhibitory inputs (de Almeida et al., 2009). It is notable that the model does not require the involvement of synaptic plasticity in establishing the phase-locked firing of principal cells.

Our present results suggest that the rhythmic inhibitory inputs, together with the basal level of excitatory drives, may not be sufficient to achieve phase-locked firing but that the enhancement of excitatory drives through GluR1-dependent synaptic plasticity in principal cells is required for strengthening phase-locked firing to slow gamma oscillations. The enhancement of excitatory inputs to CA1 pyramidal cells during novelty exposure has been suggested in electrophysiological and structural studies (Kitanishi et al., 2009; Whitlock et al., 2006). Here, GluR1-c-tail expression transiently lowered the firing rate in the place field (the first two minutes) during novelty exposure (Figure 6). This observation may indicate that under normal conditions GluR1-dependent synaptic plasticity rapidly potentiates excitatory synapses in a novel environment and that this potentiation enables principal cells to fire during the time window of disinhibition generated by the interneurons.

Phase-locked firing to slow gamma oscillations reflects the acquisition of new information

Synaptic plasticity has been regarded as a cellular mechanism for neurons to acquire new information. Based on this view, the involvement of synaptic plasticity in phase-locked firing during slow gamma oscillations, which we demonstrated in this study, suggests that the establishment of phase-locked firing during slow gamma oscillations may reflect the process of principal cells acquiring new information. Four observations support this possibility. First, we demonstrated that slow gamma oscillations in the CA1 area strengthen upon exposure to a novel environment and then are gradually reduced as rats become familiarized with the environment (Figure 4A). Second, GluR1-c-tail expression specifically blocked phase locking during the novel experience (Figures 4C, 4D). These two findings indicate that slow gamma oscillations and GluR1-dependent phase locking to them are associated with the novel experience during which principal cells would acquire spatial information and develop new spatially modulated firing patterns. Third, the impaired phase locking caused by GluR1-c-tail expression was accompanied by a deficit in the acquisition of spatial firing
patterns by CA1 principal cells (Figures 5, 6, 7). Finally, place field size was inversely correlated with the strength of phase locking to slow gamma oscillations (Figure 7B). The latter two observations suggest that phase locking to slow gamma oscillations is tightly coupled to spatial firing patterns, although further investigations are required to understand how these two aspects of neuronal firing are mechanistically linked. Interestingly, the correlation between the place field size and strength of phase locking was maintained in GluR1-c-tail hemispheres (Figure 7B). Intact correlation after the blockade of synaptic plasticity might be an indication that these two aspects of neuronal firing are not two independent phenomena regulated by GluR1-dependent synaptic plasticity but instead have a mechanistic relationship (Figure S8).

Phase locked firing to gamma oscillations has been considered important because it provides a brief time window in which multiple neurons fire closely in time. Such temporally-aligned firings among a group of neurons facilitate their strong interactions in postsynaptic neurons (ex. spike timing-dependent synaptic plasticity and temporal summation). Our results added an important adjustment to this notion, by implementing the requirement of synaptic plasticity in slow gamma phase locking, which indicates that slow gamma phase locking is not a passive consequence of a network state, but may rather reflect that the neurons acquired new information. For example, de Almeida et al. (2009) proposed a winner-take-all type of mechanism associated with neuronal firing during gamma oscillations. In this mechanism, neurons which happen to have the strongest excitatory input win (fire and suppress firing of others) and take a strong influence on the network function. Our finding gives an interesting tweak in this mechanism by implementing that the winner neurons may be determined by synaptic plasticity during the acquisition of new information. According to this idea, phase locking to slow gamma oscillations may function as a two-step, non-linear process in which, first, synaptic plasticity creates a gradient among a group of neurons in terms of the strength of excitatory input associated with the acquisition of new information. Then, the winner-take-all mechanism further strengthens the influence of neurons which acquired stronger excitatory input. Such a non-linear mechanism would be efficient in giving distinct influence to the winner neurons in a way relevant with newly-acquired information.

Previous studies focused on gamma oscillations monitored in familiar environments or after the completion of learning and suggested the role of slow gamma oscillations in the retrieval of learned information (Bieri et al., 2014; Shirvalkar et al., 2010). Together with our present study, slow gamma activity may switch its roles depending on behavioral demands and support two memory functions: the acquisition process that requires GluR1-dependent synaptic plasticity and the retrieval process of the acquired information. The brain-wide phenomenon called ‘state-dependent memory’ is well
known and refers to the fact that the network state prevalent during the acquisition of a memory facilitates the retrieval of this memory. In the CA1 area, slow gamma oscillations may reflect the state in which memory acquisition and retrieval are facilitated.

**Role of synaptic plasticity in information flow in the hippocampal circuit**

A recent multi-site recording study indicated that slow and fast gamma oscillations represent distinct inter-regional coupling along two afferent pathways to CA1 (Colgin et al., 2009). The CA3 and CA1 areas show coherent slow gamma oscillations, and the fast gamma oscillations in MEC and the CA1 area are synchronized. Thus, the phase-locked firing of CA1 principal cells to slow and fast gamma oscillations reflects the entrainment of these cells to upstream rhythms in CA3 and MEC, respectively. In this context, the present results indicate that GluR1-dependent synaptic plasticity determines information flow between sub-regions of the hippocampal-entorhinal circuit (Figure 8B).

The transient increase of slow gamma power upon exposure to a novel environment (Figure 4A) suggests strengthened coupling between CA3 and CA1 areas, which has been reported during the exploration of novel objects (Trimper et al., 2014). The selective impairment in phase locking to slow, but not fast, gamma oscillations suggests that GluR1-dependent synaptic plasticity at CA3-CA1 synapses strengthens the control of CA1 output via input from CA3. Thus, slow gamma oscillations facilitate information flow in the CA3-CA1-MEC pathway. Intact phase locking to fast gamma oscillations may occur because CA1 pyramidal cells have fewer endogenous AMPA receptors in distal dendrites (which receive MEC inputs) than in proximal dendrites where CA3 axons terminate (Nicholson et al., 2006). The specific strengthening of influence from one pathway may modulate how input activity from multiple sources is integrated in the local CA1 circuit (Brun et al., 2008; Nakashiba et al., 2008), which would be required for rapidly establishing new firing patterns during novel experiences.

The CA3-CA1 and MEC-CA1 pathways are implicated in distinct memory functions. As discussed above, slow gamma oscillations in the CA3-CA1 pathway may support the acquisition and retrieval of hippocampus-dependent long-term memory (Bieri et al., 2014; Carr et al., 2012; Montgomery and Buzsaki, 2007; Shirvalkar et al., 2010), and the MEC-CA1 pathway has been proposed to provide information regarding the current environment and temporally associated events through fast gamma oscillations (Colgin et al., 2009; Hafting et al., 2005; Kitamura et al., 2014; Suh et al., 2011; Yamamoto et al., 2014). The selective involvement of GluR1-dependent synaptic plasticity in phase
locked firing to slow gamma oscillations may reflect the distinct requirements of synaptic plasticity in these memory functions. Slow gamma oscillations in the CA3-CA1 pathway would require GluR1-dependent synaptic plasticity for entraining CA1 principal cells to slow gamma oscillations and to achieve the rapid acquisition of spatial memory. In contrast, fast gamma oscillations in the MEC-CA1 pathway may be able to recruit CA1 principal cells without the involvement of GluR1-dependent synaptic plasticity and work as a short-term memory buffer with persistent activity (Egorov et al., 2002; Yamamoto et al., 2014).

Our results indicate a series of novelty-induced events which may underlie memory formation, and identify GluR1-dependent synaptic plasticity as a key cellular mechanism (Figure 8). Novel experience induces slow gamma oscillations originating from CA3 area, and the oscillatory input from CA3 to CA1 area induces GluR1-dependent synaptic plasticity in CA1 pyramidal cells. This synaptic plasticity alters firing patterns of CA1 principal cells which are characterized by slow gamma phase locking and place field formation, and these GluR1-dependent changes may strengthen information flow through the CA3–CA1–MEC pathway. Accumulation of further insights into novelty-induced neural events at molecular, cellular and circuit levels would be required to fully understand how the hippocampal-entorhinal circuit works in memory formation.
Experimental Procedures

Recombinant adeno-associated viral vectors

High-titer rAAVs expressing either GFP-GluR1-c-tail or GFP were produced via the co-transfection of plasmids to AAV293 cells (Stratagene, La Jolla, CA, USA) using the calcium phosphate precipitation method (During et al., 2003; Hauck et al., 2003). Forty-eight hours after transfection, the viral vectors were purified with heparin affinity columns (1 ml HiTrap Heparin HP, GE Healthcare). The viral titers were determined via sandwich ELISAs (PROGEN, Heidelberg, Germany).

Slice electrophysiology

Male Long-Evans rats at three weeks of age were stereotaxically injected with rAAV into the dorsal CA1 area (3.7 mm posterior to the bregma, 2.4 mm lateral to the midline and 2.25-2.35 mm ventral to the dura) under anesthesia. Coronal hippocampal slices of 400 µm thickness were prepared 14-18 days after the viral vector injection. fEPSPs evoked by Schaffer-collateral stimulation were recorded in the GFP-expressing portions of the dorsal CA1 stratum radiatum. The theta-burst stimulation protocol (8 trains of 4 pulses at 100 Hz separated by 200 ms) was used to induce long-term potentiation (Larson et al., 1986).

Surgery and multi-tetrode recordings

rAAV microinjections into the dorsal CA1 area and tetrode/microdrive implants were stereotaxically performed in single surgeries under anesthesia. Male Long-Evans rats (500 ± 47 g) were injected with rAAVs (0.5 µl/site/hemisphere) into the stratum radiatum of the dorsal CA1 area (4.0 mm posterior to the bregma, 2.4 mm lateral to the midline and 2.5 mm ventral to the dura). Four tetrodes assembled on a microdrive were implanted dorsal to the vector-injected CA1 areas. In seven of the 11 rats used for the unit recording experiments, the GFP or GluR1-c-tail vector was injected in each hemisphere, and the tetrodes were implanted bilaterally to obtain within-subject controls. Four of the rats were unilaterally injected with the GFP vector and unilaterally implanted in the injected side.

Electrophysiological data from behaving rats were acquired using an Axona DacqUSB recording system (Axona, Herts, UK). For unit recordings, the signals were amplified by a factor of 5,000-10,000 and were bandpass filtered between 600 and 6,000 Hz. The spike waveforms were sampled at 48 kHz (50 samples per spike, 8 bits/sample). The EEG signals were recorded from a tetrode located at the CA1 area together with unit activity. The signals were amplified by a factor of 1,000-2,000, low pass filtered at 500 Hz and sampled at a rate of 4,800 Hz (16 bits/sample). A notch filter was
applied at 50 Hz. The rat locations were monitored by tracking two small light-emitting diodes on a headstage connected to a microdrive. Tracking was accomplished through an overhead camera at a sampling rate of 50 Hz.

The rats were trained daily to forage in an open field (1 m × 1 m) located in room A prior to and after surgery. At 30 ± 2 days after surgery, two sets of recording data used for the analysis were acquired from the rAAV-injected dorsal CA1 area. First, the rats foraged for six 10-min sessions in room A (familiar room experiment). A total of 119 units were recorded in the experiments. Of these, 67 and 16 units classified as principal cells in the GFP and GluR1-c-tail groups, respectively, were included for analysis. Second, rats foraged in familiar room A and another open field located in room B (a novel room) for a total of 18 sessions (A1-6, B1-12 sessions). The recordings were performed sequentially in the order A-B-B-B-B-A, and each session was 10 min. This sequence was repeated at 6 and 24 hours after the initial sequence (novel room experiment). The numbers of principal cells analyzed were 58 and 36 in the 0-hour sessions, 62 and 32 in the 6-hour sessions and 65 and 36 in the 24-hour sessions for the GFP and GluR1-c-tail groups, respectively. All recording sites were verified with post-hoc histology.

Analyses

The units classified as principal cells were analyzed. For the spatial domain, the cell rate maps were constructed for each recording session as the Gaussian-kernel smoothed number of spikes divided by the duration spent in each spatial bin. Then, the parameters, including place field size, mean infield rate and PV cross-correlation, were calculated using the rate maps. For phase locking, the EEG signals recorded from CA1 were bandpass filtered to extract slow (27-48 Hz) and fast (65-138 Hz) gamma oscillations. To quantify the strength of spike phase locking to gamma oscillations, the mean resultant vector lengths of the spike phases was calculated. The data are shown as the mean ± standard error of the mean unless otherwise stated.

See the Supplemental Experimental Procedures for comprehensive methods.

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Figure 1. Virus-mediated local genetic blockade of GluR1-dependent synaptic plasticity.

(A) Structures of recombinant adeno-associated viral vectors.

(B) Localized expression of GFP-GluR1-c-tail (green). Coronal sections containing an injection site (middle) and 720 µm anterior (left) or posterior (right) to the injection site. Blue, fluorescent Nissl staining. (B, C) Figures were created by tiling images from adjacent areas using a tile scanning function of a confocal microscope.

(C) CA1 area expressing GFP-GluR1-c-tail (green). Inhibitory neurons were immunostained for 67-kDa glutamic acid decarboxylase (GAD67, red). Note that the GFP-positive cells in the pyramidal cell layer do not express GAD67 (arrowheads and the inset), indicating that they are pyramidal cells.

(D) Three-dimensional analysis of GFP expression in dorsal CA1 pyramidal cells. Green dots, GFP-expressing pyramidal cells; red dot, an injection site; grey lines, cortical surface; blue lines, pyramidal cell layers; AP, anteroposterior; ML, mediolateral; DV, dorsoventral axis. Tick marks, 1 mm. Bottom, proportions of pyramidal cells expressing GFP projected onto a horizontal plane.

(E) Proportion of CA1 inhibitory (top), cortical excitatory (middle) and cortical inhibitory neurons (bottom) expressing GFP. The same AP-ML region as that in (D) was projected onto a horizontal plane.

(F) Impaired long-term potentiation in the GluR1-c-tail-expressing portion of the CA1 area. *P = 0.036, t8 = 2.52, two-sided, independent samples t-test for mean fEPSP slopes between 46-60 min after theta burst stimulation. Data are shown as mean ± SEM. Insets: averaged fEPSP wave forms prior to (dotted lines, -15 to -1 min) and after (solid lines, 46-60 min) stimulation.

Figure 2. Intact neural oscillations after the local blockade of GluR1-dependent synaptic plasticity.

(A) Schematic of the within-subject control design.

(B) Examples of unfiltered traces showing strong slow gamma (top) and fast gamma (bottom) oscillations.

(C) Theta (left), slow gamma (middle), and fast gamma oscillations (right) from the CA1 area injected with GFP (blue) and GluR1-c-tail (red) vector. For slow and fast gamma oscillations, LFP signals were band-pass filtered at the corresponding frequency ranges. Magnified traces in the dotted-line rectangles are shown in (F).

(D) Power spectrum of local field potentials from the CA1 area. Blue, GFP; Red, GluR1-c-tail. Arrowhead indicates the peak of theta oscillations.
(E) The power of theta (left), slow gamma (middle), and fast gamma oscillations (right). None of the power values were affected by the GluR1-c-tail ($P > 0.1$ for each two-sided, independent samples $t$-test; GFP, $n = 126$ recordings; GluR1-c-tail, $n = 126$ recordings). Data are shown as mean ± SEM.

(F) Magnified traces of slow (top) and fast gamma oscillations (bottom) illustrating that the waveforms in the GFP (blue) and GluR1-c-tail (red) hemispheres are indistinguishable.

(G) A schematic explaining the waveform analysis in (H). After assigning phases to band-pass-filtered local field potential traces, the proportion of sampling time points in each $30^\circ$ phase bin was calculated ($\%$ duration). If the wave forms are symmetric sinusoids, the $\%$ durations have equal values at all phase bins.

(H) The proportion of sampling time points in $30^\circ$ phase bins for theta, slow gamma, and fast gamma oscillations. No differences were detected between hemispheres (phase × hemisphere, $P > 0.1$ for each two-way repeated measures ANOVA). Uniform distributions over phase bins indicate that the sinusoid waveforms of these oscillations are symmetrical. Note that the red symbols are covered by the blue symbols.

**Figure 3. Impaired phase locking of principal cell firing to slow, but not fast, gamma oscillations.**

(A, C) Phase distribution of principal cell firing along slow (A) and fast (C) gamma oscillations. The phase locking to slow ($P = 0.003$, permutation test) but not fast ($P = 0.072$) gamma oscillations was impaired in the GluR1-c-tail hemispheres. The gamma oscillation trough was defined as $0^\circ/360^\circ$. (A-D) Data are shown as mean ± SEM.

(B, D) The resultant vector length quantifying the strength of phase locking to slow (B) and fast (D) gamma oscillations. The resultant length was lower in the GluR1-c-tail hemispheres for slow gamma oscillations ($^{*}P = 0.034$, $t_{1444} = 2.12$, two-sided, independent samples $t$-test) but not for fast gamma oscillations ($P = 0.66$, $t_{1444} = 0.44$). Dotted lines show chance level.

(E, F) The GluR1-c-tail decreased the proportion of significantly phase-locked principal cells to slow (E, $^{*}P = 0.044$, $\chi^2$ test) but not fast (F, $P = 0.49$) gamma oscillations. (A-F) A pooled analysis of all principal cells sampled in the familiar (sessions $A_{1-6}$) and novel room (sessions $B_{1-12}$).
Figure 4. Selective impairment of phase locking to slow gamma oscillations during the first exposure to a novel environment.

(A) The power of slow gamma oscillations in the familiar (left, A₁) and novel (right, B₁) environment. Top traces are examples of band-pass-filtered LFPs demonstrating slow gamma oscillations from GFP hemispheres during the first minute of each session. Bottom graphs demonstrate the transient increase in the power of slow gamma oscillations during novel room exploration in both hemispheres ($F_{9, 108} = 6.26, P < 0.001$ for the effect of time, two-way repeated measures ANOVA). The power was indistinguishable between the GFP and GluR1-c-tail hemispheres ($F_{1, 12} = 0.36, P = 0.56$ for between hemispheres, $F_{9, 108} = 0.03, P = 1.0$ for time × hemisphere interaction, two-way repeated measures ANOVA). (A, B, D) Data are shown as mean ± SEM.

(B) The power of fast gamma oscillations did not change with time during session B₁ ($F_{9, 108} = 1.32, P = 0.24$ for the effect of time, two-way repeated measures ANOVA). The power was indistinguishable between the GFP and GluR1-c-tail hemispheres ($F_{1, 12} = 0.26, P = 0.62$ between hemispheres, $F_{9, 108} = 0.53, P = 0.85$ for time × hemisphere interaction, two-way repeated measures ANOVA). The average power did not change between sessions A₁ and B₁ ($P = 0.25$, A₁ vs. B₁, two-way (session × hemisphere) ANOVA).

(C) Representative firing phase distribution of single principal cells along slow gamma oscillations. Green, curve fitting with von Mises distribution.

(D) The resultant vector length quantifying the strength of phase locking to slow (left) and fast (right) gamma oscillations. A, sessions A₁-6; B, sessions B₂-12. *$P = 0.03$, $t_{74} = 2.17$, two-sided independent samples t-test. Resultant lengths for phase locking to slow gamma oscillations were significantly different among sessions (A, B₁ and B) in the GFP hemispheres ($P = 0.023$, one-way ANOVA). A significant increase in session B₁ was detected compared with session B₂-12 ($P = 0.026$, post-hoc Bonferroni test), although the difference between A and B₁ did not reach statistical significance ($P = 0.13$, post-hoc Bonferroni test). No differences were detected between hemispheres for fast gamma oscillations ($P > 0.1$ for each session, two-sided, independent samples t-test) or among sessions in the GFP hemispheres ($P = 0.079$, One-way ANOVA). Dotted lines show chance level.

(E) Proportion of significantly phase locked cells to slow (left) and fast (right) gamma oscillations. A, sessions A₁-6; B, sessions B₂-12. *$P < 0.05$, $\chi^2$ test.
Figure 5. Dispersed spatial firing in a novel environment and long-term stability of place fields.

(A) Spatial firing patterns of principal cells in familiar room A. Color-coded rate maps of five cells each from GFP and GluR1-c-tail hemispheres [0 Hz (blue) to peak rate (red)]. Peak rates (in Hz) are indicated below the individual maps.

(B, C) Mean (B) and peak (C) firing rates in a familiar room A. No significant differences were found between the GFP and GluR1-c-tail hemispheres. **Data are shown as mean ± SEM.**

(D) Place field size in room A. No significant differences were found between the GFP and GluR1-c-tail hemispheres.

(E) Firing rate maps of principal cells during the first and fourth sessions in room B. Two consecutive panels in each row indicate rate maps of the same cell during B₁ and B₄ sessions.

(F-H) Place field size in room A and B at the 0 (F), 6 (G) and 24 h (H) time points. (F) Session × hemisphere, $F_{3, 276} = 3.31$, $P = 0.021$, two-way repeated measures ANOVA; *$P = 0.027$, post-hoc Bonferroni test. (G) Session × hemisphere, $F_{3, 276} = 4.17$; $P = 0.007$, two-way repeated measures ANOVA; **$P = 0.003$, post-hoc Bonferroni test. (H) Between hemispheres, $F_{1, 99} = 0.004$, $P = 0.95$; session × hemisphere, $F_{3, 297} = 1.76$, $P = 0.16$, two-way repeated measures ANOVA.

(I) Spatial firing patterns of principal cells over 24 h. Three consecutive panels in each row indicate rate maps of the same cell at 0, 6 and 24 h.

Figure 6. Delayed formation of place fields in a novel environment.

(A) Rate maps constructed from five 2-min blocks during session B₁ (left), and rate maps of the same principal cells from session B₄ used to define place fields (far right panels). Two cells each from GFP and GluR1-c-tail hemispheres are shown. The color code is scaled to the peak rates for session B₄ (indicated below maps in Hz).

(B) Mean firing rates inside and outside place fields in session B₁. The mean infield rate during the first two minutes was significantly lower in the GluR1-c-tail hemispheres than controls (time × group: $F_{12, 632} = 6.67$, $P < 0.001$, two-way repeated measures ANOVA; *$P = 0.027$, post-hoc Bonferroni test). **Data are shown as mean ± SEM.**

(C) PV cross-correlation between each 2-min block and the reference maps (B₄). The PV cross-correlation during the first two minutes was significantly lower in the GluR1-c-tail hemispheres than
that in the controls (time × group: $F_{4,3192} = 51.75, \ P < 0.001$, two-way repeated measures ANOVA; \*\*\* $P < 0.001$, post-hoc Bonferroni test).

(D) Mean infield rate in familiar rooms. No significant between-group effect ($F_{3,400} = 1.25, \ P = 0.29$, two-way (time × group) repeated measures ANOVA) or time × group interaction effect ($F_{12,1600} = 0.63, \ P = 0.82$) was detected. (D, E) Dotted lines, room $A_{1-6}$; solid lines, room $B_{2-12}$. (E) PV cross-correlation in familiar rooms.

**Figure 7. Correlation between phase locking strength and place field size in the novel environment.**

(A) Firing phase distribution along slow gamma oscillations (top, 0-720°) and rate maps (bottom) of individual principal cells in session $B_1$. The corresponding top and bottom panels are from the same cells. The numbers above the top panel indicate data points labeled as 1 to 10 in (B). Green line, curve fitting with von Mises distribution.

(B) Inverse correlation between place field size and resultant length for slow gamma phase locking in session $B_1$ in both GFP (left) and GluR1-c-tail (right) hemispheres. Significant correlations were detected with Spearman rank correlation method ($r_s$, correlation coefficient).

(C) The relationship between fast gamma resultant length and place field size in session $B_1$ in the GFP (left) and GluR1-c-tail (right) hemispheres.

**Figure 8. Roles of GluR1-dependent synaptic plasticity at the cellular and circuit levels.**

(A) Schematic showing the hypothesis that LTP induced by synaptic delivery of GluR1-containing AMPA receptors establishes the phase-locked firing of CA1 principal cells along slow gamma oscillations.

(B) Schematic showing a series of novelty-induced events leading to the proposed regulation of information flow by GluR1-dependent synaptic plasticity. Strengthening of slow gamma oscillations originating from CA3 during novelty exposure (1) drives the synaptic delivery of GluR1-containing AMPA receptors (2), which establishes the spatial and temporal firing patterns of CA1 place cells as an output to the MEC (3). These novelty-induced events leading to strengthening of information flow in the CA3-CA1-MEC pathway may mediate memory formation.
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