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Stimulus repetition modulates gamma-band synchronization in primate visual cortex

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When a sensory stimulus repeats, neuronal firing rate and functional MRI blood oxygen level-dependent responses typically decline, yet perception and behavioral performance either stay constant or improve. An additional aspect of neuronal activity is neuronal synchronization, which can enhance the impact of neurons onto their postsynaptic targets independent of neuronal firing rates. We show that stimulus repetition leads to profound changes of neuronal gamma-band activity (~40–90 Hz) synchronization. Electrocorticographic recordings in two awake macaque monkeys demonstrated that repeated presentations of a visual grating stimulus resulted in a steady increase of visually induced gamma-band activity in area V1, gamma-band synchronization between areas V1 and V4, and gamma-band activity in area V4. Microelectrode recordings in area V4 of two additional monkeys under the same stimulation conditions allowed a direct comparison of firing rates and gamma-band synchronization strengths for multiunit activity (MUA), as well as for isolated single units, sorted into putative pyramidal cells and putative interneurons. MUA and putative interneurons showed repetition-related decreases in firing rate, yet increases in gamma-band synchronization. Putative pyramidal cells showed no repetition-related firing rate change, but a decrease in gamma-band synchronization for weakly stimulus-driven units and constant gamma-band synchronization for strongly driven units. We propose that the repetition-related changes in gamma-band synchronization maintain the interareal stimulus signal and sharpen the stimulus representation by gamma-synchronized pyramidal cell spikes.

Significance

When a visual stimulus repeats multiple times, visual cortical neurons show decreasing firing rate responses, yet neither perception nor stimulus-related behavior is compromised. We show that stimulus repetition leads to increased neuronal gamma-band (~40–90 Hz) synchronization within and between early and higher visual areas. The enhanced gamma-band synchronization likely enhances effective stimulus signaling in the face of dwindling firing rates. We also show that synchronization to the gamma rhythm increases for spikes in general and for those of putative interneurons, whereas it decreases for spikes of putative excitatory neurons if they are not strongly stimulus-driven. Thus, inhibitory interneurons might create increasingly precise gamma-band synchronization, and thereby prune the stimulus representation by pyramidal cells to be sparser and more efficient.

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Stimulus Repetition Leads to Increasing Area V1 Gamma-Band Activity. We sorted trials according to trial number into eight equally sized and nonoverlapping trial bins. For each trial bin, Fig. 1A shows a representative raw local field potential (LFP) trace. Traces are from one recording site in area V1 from one recording session in monkey E1. Fig. 1B shows the trial bin averages of the absolute and baseline-normalized power spectra and demonstrates that repeated presentations resulted in increasing gamma-band responses. Fig. 1C shows the gamma power as a function of trial bin number. Visually induced gamma-band (52–74 Hz) power was highly correlated to the logarithm of the trial bin number ($r^2 = 0.98, P = 4.0 \times 10^{-06}$). Fig. SI shows the same analysis as in Fig. 1B (Inset), but averaged over all sites with significant visually driven gamma-band activity and averaged over three sessions. During these recording sessions, the monkey reported color changes of the fixation point, and the peripheral grating stimulus, which induced gamma-band activity, was behaviorally irrelevant. This suggests that the repetition-related gamma increase did not depend on attention being directed to the gamma-inducing stimulus. Gamma-band activity in these sessions was particularly strong because a full-field grating was used (13).

For the following analyses, we will use data from recording sessions during which the monkeys performed a selective visual attention task with grating patches of 3° of visual angle. If not otherwise stated, we use data from the task period when the stimuli were on the screen and attention had been deployed to one of them, and we pool across the two selective attention conditions. Fig. 1D depicts the spatial distribution of all ECoG electrodes on the brain of monkey E1, and Fig. 1E shows the visually induced gamma-band power change (stimulation vs. baseline, 52–74 Hz) for all ECoG sites. Fig. 1F shows the power spectra averaged over the significantly visually driven area V1 sites of monkey E1 for eight nonoverlapping trial bins (62 of a total of 63 sites; details are provided in Methods), averaged further across 25 sessions (6,266 trials). Fig. 1I shows the average gamma-band power and the corresponding SE across sessions. When the trial bin number was expressed on a logarithmic scale, there was a near-perfect log-linear relation to the gamma increase ($r^2 = 0.99, P = 1 \times 10^{-07}$). Next, we investigated the spatial

Fig. 1. Stimulus repetition enhances gamma-band activity in visual cortex. (A) Raw LFP traces from one representative recording site from area V1 and eight representative trials from one recording session in monkey E1. During this session, monkey E1 performed a color change detection at fixation and the gamma-inducing grating stimulus was behaviorally irrelevant. (B) Corresponding absolute and baseline-normalized power spectra. Rel., relative. (C) Gamma power as a function of trial bin number on a logarithmic scale. Trials were sorted according to trial number into eight equally sized and nonoverlapping bins, and power was averaged per bin. (D) Brain of monkey E1 with ECoG electrodes and major sulci (as, arcuate sulcus; cs, central sulcus; ips, intraparietal sulcus; ls, lateral sulcus; lus, lunate sulcus; sas, spur of the arcuate sulcus; sts, superior temporal sulcus). Black labels point to the covered brain areas. (E–K) Data from sessions during which monkey E1 performed a selective attention paradigm. (E) Relative change in gamma power during stimulation compared with baseline, averaged over all trials. (F) Same as in B (Inset), but averaged over all visually driven area V1 sites and all sessions in monkey E1. Slopes of regression analyses are shown as in l, but separately for each site (G) and frequency (H). (I) Same as in C, but averaged over area V1 sites and sessions. (J) Trial-wise average of gamma-band power for the first 50 trials. Red squares show power during stimulation, and blue squares show power during baseline. (K) Each dot corresponds to a visually driven area V1 site in monkey E1. For each site, the regression analysis was performed separately and the scatter plot shows the respective slopes as a function of the intercepts. The intercept estimates the visually induced gamma-band power before the repetition-related increase occurred. This repetition-independent estimate of the stimulus-induced gamma-power change was predictive of the later repetition-related increase. Dots in D, E, and G show electrode positions, yet power estimates are based on sites (i.e., local derivatives). Absolute power values are shown in arbitrary units (a.u.) in B, C, and J.
and spectral specificity of the gamma increase. Fig. 1G color-codes the slope of regression lines that were obtained as shown in Fig. 1I, but separately for all ECoG sites. The topography of slopes (Fig. 1G) was very similar to the topography of visually induced gamma (Fig. 1E). This suggests that the increase was specifically related to visually induced activity rather than to drifts in the overall state of the brain or in the recording system. However, Fig. 1E shows the visually induced gamma-band activity averaged across all trials (i.e., including later trials in which the visually induced gamma-band activity was already affected by the repetition-related gamma increase). To avoid any circularity and to demonstrate the fine-grained dependence of the repetition-related gamma increase over trials on the visually induced gamma increase within trials, we performed the following analysis. For each of the sites showing clear visually induced gamma, we performed a separate regression analysis and extrapolated the regression line to the y-axis intercept for bin number zero, so as to use this intercept as an estimate of the visually induced gamma before any repetition-related increase occurred. We then investigated whether this intercept value predicted the repetition-related regression slope, by calculating a regression between the two parameters. Fig. 1K demonstrates a strong correlation ($r^2 = 0.92, P = 1.3e-34$), confirming that the repetition-related increase was systematically related to the strength of visually induced gamma-band activity. To investigate the spectral specificity of the increase, Fig. 1H shows the slopes for the visually driven sites, now as a function of frequency. The slope spectrum demonstrates that the repetition-related increase was specific for the gamma-frequency band, with a spectral shape very similar to the stimulus-induced gamma-power enhancements.

To test whether there was any stimulus-induced gamma-band power in the first few trials of a session, we averaged gamma-band power across sessions separately for each of the first 50 trials (Fig. 1J; red squares indicate absolute power during visual stimulation, and blue squares indicate absolute power during prestimulus baseline). This revealed that gamma-band activity was induced already by the very first stimulus presentation of a given session. This analysis also demonstrated that the increase was present for the absolute gamma-band power during visual stimulation ($P = 2.8e-20$ for monkey E1 and $P = 3.5e-11$ for monkey E2) and not for the absolute gamma-band power during prestimulus baseline ($P = 0.98$ for monkey E1 and $P = 0.11$ for monkey E2). This illustrates that the repetition effect on visually induced gamma power was not due to decreases in prestimulus, but rather to increases in poststimulus gamma-band power. Fig. S2 shows the same analysis for monkey E2, demonstrating a remarkable consistency across the two animals. In monkey E2, 39 area V1 sites were significantly stimulus-driven (of a total of 40 sites), nine recording sessions had been obtained (3,511 trials), and the gamma-frequency band extended from 68 to 82 Hz.

The fact that gamma increased with stimulus repetition both when the stimulus was a large unattended grating and when it was a smaller attended grating suggested that the effect did not depend on attention. We performed an additional analysis in this regard by analyzing the period when visual stimuli were already on the screen but no attentional cue had been given yet. Consistent with the other results, this showed the repetition-related gamma increase (Fig. S3). We also considered that the repetition-related increase was modulated by switches in stimulus features or in the allocation of attention. The respective analyses (Fig. S4) revealed only that the repetition-related increase was slightly larger for repetitions that involved a change in stimulus color, an effect that might be related to predictive coding (14).

**Stimulus Repetition Leads to Increasing Area V1–V4 Gamma Coherence and Area V4 Gamma Activity.** Gamma power in one area might contribute to communication with connected areas through interareal coherence (7, 8, 11, 12, 15, 16). Therefore, we tested whether the increase was also present for the coherence between area V1 and area V4. All analyses were done after bipolar derivation, thereby excluding a common reference, which can otherwise lead to artifactual coherence estimates. Fig. 2A (Inset) shows the anatomical definition of area V1 (pink) and area V4 (blue) in monkey E1 (Methods). Fig. 2A shows the interareal coherence for the eight trial bins averaged over all sessions in this monkey, revealing that interareal coherence also increased monotonically with trial number (62 significantly stimulus-driven area V1 sites of a total of 63 sites and 16 significantly stimulus-driven area V4 sites of a total of 17 sites, 992 interareal site pairs, and 6,266 trials). We performed the same regression analysis as for power, and we plot the resulting slope spectrum in Fig. 2B. The dominant result was a coherence increase in the gamma-frequency band. In addition, there was a smaller decrease in a theta-frequency band.

Enhanced gamma coherence between areas V1 and V4 is expected to result in enhanced gamma power in area V4 (12). Fig. 2C shows LFP power spectra from area V4 of monkey E1 (16 significantly stimulus-driven sites of a total of 17 sites and 6,266 trials), and Fig. 2D shows the corresponding slope spectra, confirming a repetition-related increase in area V4 power in the gamma-frequency band. Fig. S5 shows the repetition-related changes in area V1–V4 coherence and area V4 power for monkey E2, demonstrating that the gamma increase was consistent across the two animals (39 significantly stimulus-driven area V1 sites of a total of 40 sites, 16 significantly stimulus-driven area V4 sites of a total of 17 sites, 624 site pairs, and 3,511 trials).

We considered that the increases in local and long-range gamma-band synchronization could be related to changes in behavior. Therefore, we analyzed behavioral parameters in the same way as power and coherence, by binning trials and performing a regression analysis. This did not reveal any significant effect for response accuracy, for reaction times, or for the rate of microsaccades.

**Stimulus Repetition Leads to Increases in the Gamma-Peak Frequency.** Recent studies have shown that not only the strength but also the frequency of gamma-band activity can change systematically (e.g., with contrast) (8, 17). Correspondingly, we investigated the gamma...
frequency. Fig. S6 shows that for area V1 power, area V1–V4 coherence, and area V4 power, stimulus repetition makes the center of mass of the gamma band move to higher frequencies. This holds for both monkeys.

Stimulus Repetition Leads to Increasing MUA-LFP Synchronization in Area V4. Next, we investigated whether the increases in area V1 gamma power, area V1–V4 gamma coherence, and area V4 gamma power were also reflected in the gamma-band spike-LFP synchronization in area V4. To this end, we analyzed another dataset (monkeys M1 and M2) in which single-unit activity (SUA), multiunit activity (MUA), and LFPs were recorded from four electrodes simultaneously in awake monkey area V4, with electrodes spaced horizontally by 650 or 900 μm. Fig. 3 shows the effects of stimulus repetition on a sample MUA recording and its MUA-LFP synchronization. Fig. 3D shows that the firing rate of this MUA declined substantially over the course of 600 stimulus repetitions. Fig. 3B and C illustrates that at the same time, the MUA synchronization to the LFP gamma rhythm increased. This is quantified in Fig. 3D by the pairwise phase consistency (PPC) between MUA (recorded on one electrode) and the LFP (combined across the other electrodes). The PPC is a recently introduced synchronization metric (18, 19) that avoids any bias by trial number, spike number, or spike rate (details are provided in Methods). To avoid strong nonstationarities, the first 0.3 s after stimulus onset was excluded. Fig. 4A shows the MUA-LFP PPC using the same data epoch as Fig. 3D and the same trial-binning approach as for power and interareal coherence, averaged across all MUA-LFP pairs of both monkeys. Averaging over both monkeys was possible because their gamma-frequency bands were largely overlapping (40–60 Hz) (20). Stimulus repetition led to a clear increase in gamma-band MUA-LFP synchronization, which was highly significant in the regression analysis (Fig. 4B, \( r^2 = 0.91, P = 2.5e-04; n = 109 \)). Fig. 4C shows the regression slopes as a function of frequency and demonstrates that the increase was selectively present in the gamma-frequency band, whereas a low theta band showed a decrease. Fig. 4D shows that this result was consistent across the two monkeys. Enhanced gamma-band MUA-LFP synchronization does not necessarily entail enhanced MUA rates (21), and previous demonstrations of repetition-related firing rate decreases in inferotemporal cortex (22–24) suggest that similar decreases might occur in area V4. Fig. 4D shows the normalized MUA rates (±1 SEM) averaged across all sites and sessions in both monkeys M1 and M2. There was a highly significant decrease of MUA firing rates with increasing trial number (\( r^2 = 0.94, P = 8.2e-05 \)).

Stimulus Repetition Modifies Spike-LFP Synchronization in a Cell Class-Specific Way. In area V4, single units could be sorted, based on their waveforms, into narrow-spiking (NS) cells, which are putative interneurons, and broad-spiking (BS) cells, which are putative pyramidal cells (25, 26). We performed such a differentiation and analyzed firing rates and gamma-band synchronization separately for the two cell groups. Fig. 4E shows the average waveforms and the waveform duration histogram for the available single units, sorted into NS cells (red) and BS cells (blue). Fig. 4F shows the SUA-LFP PPC in the gamma-frequency band (difference relative to the first trial bin) separately for NS and BS cells: Gamma synchronization increased for the NS cells (\( r^2 = 0.8, P = 0.003; n = 16 \)) and showed a strong tendency to decrease for the BS cells (\( r^2 = 0.5, P = 0.05; n = 26 \)). Fig. 4G shows the corresponding spike rates; interestingly, the firing rates of NS cells decreased (\( r^2 = 0.55, P = 0.035 \)), whereas there was no significant change in BS cell firing rates.

To reconcile the decreasing BS cell gamma synchronization with the increasing MUA gamma synchronization, we reasoned that weakly active and/or weakly stimulus-driven BS cells, which contribute fewer spikes to the MUA, might show strong decreases in synchronization, whereas strongly active and/or strongly driven BS cells, which contribute more spikes to the MUA, might show fewer decreases or even increases in synchronization. To test this hypothesis, we calculated a multiple linear regression between the firing rate and the regression slope. Concretely, we defined the independent firing rate (FR) variables \( \text{FR}_{\text{baseline}} \) and \( \text{FR}_{\text{stimulation/FR}_{\text{baseline}}} \) and the dependent variable [slope of the regression between synchronization strength and log (repetition bin number)]. Fig. 4H shows in blue the \( t \) values of this multiple linear regression for the BS cells. The dark blue line is for the independent variable \( \text{FR}_{\text{stimulation/FR}_{\text{baseline}}} \) and reveals that, indeed, when a BS cell was more strongly stimulus-driven, it showed a more positive slope of the repetition-related gamma change (\( P = 0.0042 \)). The same analysis for the NS cells (Fig. 4H, red lines) did not reveal significant effects. To follow up the result for the BS cells, we performed a median split based on the stimulus-driven firing rate change and averaged the PPC vs. repetition slopes separately for the two groups of cells. This revealed a significant negative slope for the weakly driven BS cells (\( P = 0.015; \text{mean slope} \pm \text{SEM} = -0.0028 \pm 0.001 \)) and an absence of a significant repetition-related change for the strongly driven BS cells (\( P = 0.9; \text{mean slope} \pm \text{SEM} = 0.0001 \pm 0.0001 \)). We also sorted the BS cells into those with a decreasing slope (\( n = 15 \); three cells were individually significant) and those with an increasing slope (\( n = 11 \); one cell was individually significant).
The index \((\text{FR}_{\text{stimulation}} - \text{FR}_{\text{baseline}})/(\text{FR}_{\text{stimulation}} + \text{FR}_{\text{baseline}})\) was, on average, 0.23 ± 0.12 for BS cells with negative slope and 0.49 ± 0.11 for BS cells with positive slope (difference not significant).

**Discussion**

We found that in the course of a recording session, during repeated stimulus presentations, gamma-band activity in area V1 increased by approximately a factor of 2. The strength of gamma-band activity was linearly related to the logarithm of the repetition bin number. This repetition-related gamma increase was spatially specific for the sites with visually induced gamma, and the strength of the repetition-related increase was systematically related to the strength of the visually induced gamma before any repetition-related increase. Furthermore, the repetition-related gamma increase did not appear to be dependent on selective visual attention. A very similar repetition-related increase was also present for the interareal gamma-band coherence between areas V1 and V4 and for the gamma-band activity in area V4. In a separate dataset from area V4, we showed that multunit synchronization to the gamma rhythm increased by roughly 30%, whereas the multunit rate decreased by roughly 12%. When separating single units into BS and NS cells, the NS cells showed qualitatively the same synchronization and rate changes as the multunit. The BS cells showed a strong trend for a repetition-related decrease in gamma synchronization, which was significant for the weakly stimulus-driven cells but absent for the strongly driven ones.

Repetition-related increases in area V1 gamma-band activity and area V1–V4 gamma-band synchronization are expected to lead to an increasing impact of area V1 input onto area V4 (7, 11, 12). Because this increasing impact is rhythmic in the gamma-frequency band, it is expected to result, in area V4, in increasing gamma-band activity and increasing gamma spike-field synchronization but not necessarily in increasing overall firing rates, in line with the results reported here. It is conceivable that the overall firing rate decrease in area V4 is related to the increased gamma-rhythmic impact and the increased local gamma spike-field synchronization. We have shown previously that spikes that are maximally synchronized to the local gamma rhythm are more stimulus-selective than less gamma-synchronized spikes (27). With repeating stimulation, increasing area V1–V4 coherence, and corresponding impact, the less gamma-synchronized spikes in area V4 seem to disappear, leaving the more gamma-synchronized spikes from the more stimulus-driven neurons (Fig. 4H). The precise mechanisms of this pruning of non–gamma-synchronized spikes are unclear. They might well be a consequence of the increasing gamma-band synchronization, or they might be independent of the mechanisms behind gamma and its repetition-related increase.

From a methodological point of view, the present results are important for the interpretation of previous studies and for the optimal design of future studies on gamma-band synchronization. Typically, neurophysiological studies use multiple repetitions of a given experimental condition. Where previous studies confounded their experimental conditions with repetitions (e.g., by presenting conditions in blocks of trials without sufficient counterbalancing), this might have resulted in apparent condition effects that actually were repetition effects. Where previous studies properly randomized conditions across repetitions, the repetition-related effect described here might have led to an underestimation of the significance and/or size of the effect of the respective experimental conditions. For future studies on gamma-band synchronization, the present results emphasize the importance of proper condition randomization in the experiment design and of taking repetitions into account in the data analysis. A discussion of related studies (22–24, 28–36) is provided in SI Discussion and Fig. S8.

In Fig. 4, we analyzed the changes in gamma synchronization separately for MUA, NS cells, and BS cells. NS cells are putative interneurons, although this cannot be proven in the awake monkey preparation at this moment. Networks of interneurons are the core generators of gamma-band synchronization (26, 37). Consistent with this, the gamma synchronization of the NS cells
increased similar to the gamma power/coherence within/between ECoG signals. Intriguingly, the BS cells showed repetition-related increases in gamma synchronization that depended on their stimulus-driven activation. Weakly driven BS cells showed repetition-related decreases in gamma synchronization, whereas strongly driven BS cells kept their gamma synchronization unchanged across repetitions. Thus, across repetitions, the gamma-synchronized spike output contained fewer and fewer spikes from weakly stimulus-driven BS cells and relatively more spikes from strongly stimulus-driven BS cells, which amounts to a sharpening of the stimulus representation in the gamma-synchronized spike output (27). We have recently described a very similar effect of selective attention on cell type-specific gamma-band synchronization (26). It is particularly the gamma-synchronized spikes that have an impact on postspontaneous target neurons, and in this postspontaneous target group of neurons, the different input neurons always mutually reduce impact through normalization mechanisms (38). Thus, if the gamma-synchronized spike output contains relatively more spikes from strongly stimulus-driven BS cells, this lends those cells a stronger effective impact.

Methods

A detailed description of the methods used in this study is provided in SI Methods. If not stated otherwise, data are from recording sessions in which the monkeys performed a selective visual attention task. They kept fixation on a central dot while two patches of drifting gratings were presented, of which one fell into the receptive field of the recorded neurons. In monkeys E1 and E2, ECoG grid electrodes were implanted over the left hemisphere to obtain LFPs (7, 39, 40). We use electrodes over areas V1, V2, and V4 and the temporal-occipital area (TEO). When we refer to area V1 (V4), this also includes some electrodes that might be over area V2 (TEO). LFPs from immediately neighboring electrodes were subtracted to obtain local bipolar derivations, which avoid a common reference in interareal coherence analysis. In monkeys M1 and M2, standard techniques were used to record with four microelectrodes simultaneously in visual area V4 (20, 41).

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