Relation between gamma oscillations and neuronal plasticity in the visual cortex

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Use-dependent long-term changes of neuronal response properties must be gated to prevent irrelevant activity from inducing inappropriate modifications. Here we test the hypothesis that local network dynamics contribute to such gating. As synaptic modifications depend on temporal contiguity between presynaptic and postsynaptic activity, we examined the effect of synchronized gamma (γ) oscillations on stimulation-dependent modifications of orientation selectivity in adult cat visual cortex. Changes of orientation maps were induced by pairing visual stimulation with electrical activation of the mesencephalic reticular formation. Changes in orientation selectivity were assessed with optical recording of intrinsic signals and multiunit recordings. When conditioning stimuli were associated with strong γ-oscillations, orientation domains matching the orientation of the conditioning grating stimulus became more responsive and expanded, because neurons with preferences differing by less than 30° from the orientation of the conditioning grating shifted their orientation preference toward the conditioned orientation. When conditioning stimuli induced no or only weak γ-oscillations, responsiveness of neurons driven by the conditioning stimulus decreased. These differential effects depended on the power of oscillations in the low γ-band (20 Hz to 48 Hz) and not on differences in discharge rate of cortical neurons, because there was no correlation between the discharge rates during conditioning and the occurrence of changes in orientation preference. Thus, occurrence and polarity of use-dependent long-term changes of cortical response properties appear to depend on the occurrence of γ-oscillations during induction and hence on the degree of temporal coherence of the change-inducing network activity.

gamma oscillations | neuronal plasticity | unsupervised learning | orientation maps | visual cortex

Repetitive exposure to identical stimuli leads either to attenuation (habituation) or to enhancement (sensitization) of neuronal responses, depending on the significance attributed to the stimuli (1). Habituation and sensitization typically occur on short time scales (tens of milliseconds to minutes), and these changes in neuronal responsiveness are usually fully reversible (2). However, repetitive exposure to stimuli can also lead to long-lasting changes of neuronal responsiveness (3, 4). These longer-lasting changes also depend on the actual behavioral relevance of the stimuli: In perceptual learning tasks, repeated exposure to irrelevant stimuli leads to reduced performance (5), while repetition of behaviorally relevant stimuli improves performance (6, 7). In a pioneering behavioral study in kittens, Held and Hein (8) demonstrated that experience-dependent maturation of visual functions requires active exploration and fails to occur with passive exposure to visual stimuli.

The evidence for a control of neuronal plasticity by gating systems is supported by electrophysiological investigations. Stimuli fail to induce changes in neuronal response properties if they are behaviorally irrelevant (9, 10) or if modulatory systems controlling central states are blocked (11). Conversely, robust modifications are induced if stimuli are attended to (4, 7, 11, 12) or are combined with manipulations that enhance neuronal excitability either directly (3, 12–15) or, indirectly, via neuromodulators (11, 16). Under natural stimulation conditions, evoking vigorous responses alone is not sufficient to induce long-term modifications of response properties (17). Thus, use-dependent long-term changes of neuronal response properties are gated as a function of the behavioral relevance of the respective sensory activity (for a review, see ref. 18).

Two nonexclusive mechanisms have been discussed for the mediation of these gating functions. One possibility is that modulatory systems interact synergistically via metabotropic pathways with the Ca^{2+}-triggered second messenger cascades that convert synaptic activity into long-lasting changes of synaptic gain (19). The other possibility is that plasticity is gated by modulating the excitability and/or cooperativity of neuronal networks (20, 21). Activity-dependent changes of synaptic gain depend on the amplitude and source of dendritic Ca^{2+} surges (22). Strong increases trigger long-term potentiation (LTP), and more-slowly rising, smaller Ca^{2+} surges lead to long-term depression, while no change occurs when the calcium transients fail to reach a critical threshold (23–25). These calcium dynamics depend on numerous factors, one of them being the temporal contingency (cooperativity) of presynaptic and postsynaptic activity: the temporal correlation of activity between converging excitatory afferents, the correlation between excitatory postsynaptic potentials (EPSPs) and

Significance

Learning is thought to be mediated by activity-dependent modification of neuronal interactions. To avoid maladaptive modifications of synaptic transmission by spurious activity, synaptic plasticity has to be gated. In the case of supervised learning, these gating functions are accomplished by reinforcement through value-assigning systems. Here we show that the dynamic state of local circuits correlates with the occurrence of activity-dependent long-term changes in neuronal response properties. We find that repeated visual stimuli induce long-term changes of orientation preference of neuronal populations in visual cortex if stimuli induce synchronized population responses oscillating at γ-frequencies. This suggests that neuronal plasticity is controlled by a hierarchy of gating systems and assigns critical gating functions to resonance properties of local circuits.

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postsynaptic discharges, and the temporal relation between excitatory and inhibitory inputs (26). Accordingly, experiments with electrical stimulation have identified the synchronicity between presynaptic and postsynaptic activity as one of the factors that determine the occurrence and polarity of synaptic modifications (27, 28). This predicts that the occurrence and polarity of synaptic modifications should depend, at least in part, on the correlation structure of network activity. A particularly high degree of cooperativity is attained when networks engage in synchronized oscillatory activity. In the visual cortex, such dynamic states can be induced with appropriate visual stimuli. Here we focused on response synchronization in the γ-frequency range rather than on oscillations at lower frequencies, because visual stimuli, especially gratings, evoke strong ɣ-oscillations that are associated with millisecond precise synchronization of presynaptic and postsynaptic activation (29). Moreover, we had previously shown that the power of these oscillations can be enhanced by pairing the visual stimulus with electrical activation of the midbrain reticular formation (MRF) (29–31), allowing us to modulate the dynamic state of cortical circuits while keeping sensory stimuli unaltered.

In order to examine the relation between network dynamics and neuronal plasticity, we induced long-lasting modifications of the neurons' orientation preference with repeated presentation of drifting gratings and investigated the relation between the occurrence of synchronized ɣ-oscillations during conditioning and the occurrence of changes in orientation preference. We find a positive correlation between the occurrence and polarity of long-lasting changes in neuronal response properties and the power of ɣ-oscillations during conditioning but no correlation between discharge rate and response modifications.

Materials and Methods

Changes in orientation preference were induced with repeated presentation of moving grating stimuli that were paired with electric stimulation of the MRF. In order to determine the orientation preference of cortical neurons, we performed simultaneous optical and electrical recordings in visual cortex of 8 adult cats under anesthesia (see *SI Appendix* for details), during conditioning combined with electric stimulation of the MRF. All experimental procedures were in accordance with the European regulations for the protection of animals, approved by the local authorities (Regierungspräsidium Darmstadt) and overseen by a veterinarian. In 4 animals, the orientation selectivity of cortical neurons was assessed with both optical imaging of intrinsic signals and multiunit recordings from areas 17 and 18; in 2 cats, only optical imaging was performed, and, in 2 cats, only multiunit recordings were performed.

Optical imaging was performed according to standard procedures as described previously (32). Orientation preference maps were calculated by dividing the sum of images from the same stimulation condition by the sum of all images. From different single-condition maps, preference maps were calculated for orientation and direction by pixel-wise vectorial addition (33). For quantification of response selectivity, we calculated the vector strength for each pixel (see *SI Appendix* for details). For display, orientation preference was color-coded, and orientation selectivity was expressed by adjusting brightness according to the respective vector strength.

Electrocorticogram (ECoG) recordings were obtained from silver ball electrodes placed at the fringe of the craniotomy above visual cortex. Multiunit activity (MUA) and local field potential (LFP) recordings were derived from microwires implanted in the same region of visual cortex exposed for optical imaging, allowing for direct comparison of optical and electrical signals. The MRF was activated by bilateral electrical stimulation of the parabrachial nucleus. The effectiveness of this stimulation was assessed in each animal by its facilitating effects on cortical responses evoked by electrical stimulation of the optic chiasm as reported previously (29).

Orientation tuning of units and the topology of orientation maps were determined by visual stimulation with whole-field square wave gratings (0.15 cycles per degree) moving at 15°/s in both directions orthogonal to their stripe orientation at 4 different orientations (0°, 45°, 90°, 135°) presented binocularly. Response properties were assessed by pseudorandomized presentation of all orientations over ∼50 min. For the induction of changes in orientation selectivity, the same stimuli were used, but only 1 of the 4 orientations was presented for the same duration and number of repetitions (272), and, in addition, MRF was stimulated 100 ms before the onset of stimulus movement (*SI Appendix*). To assess the effects of repetitive visual stimulation alone, the same sequence of stimuli was applied as during conditioning, but without MRF stimulation.

Signal power of oscillatory activity in LFP and ECoG recordings was estimated in multiple frequency bands (δ, ϑ, α, β, 3 different γ-bands; *SI Appendix*) between 1 Hz and 100 Hz in a 2-s window starting 500 ms after stimulus motion onset. MUA responses to gratings moving in different directions were evaluated in the same 2-s window as the LFP/ECoG responses.

All data discussed in the paper will be made available to readers upon request.

Results

In 29 conditioning sessions performed with MRF stimulation in 6 cats, optical imaging of intrinsic signals revealed that conditioning led to an enlargement of orientation domains activated by the conditioned orientation, and responses to this orientation increased in strength (Fig. 1*A*). The average response increase was 8% ($P = 0.0005$, 1-sample sign test; Fig. 1*B*). At the same

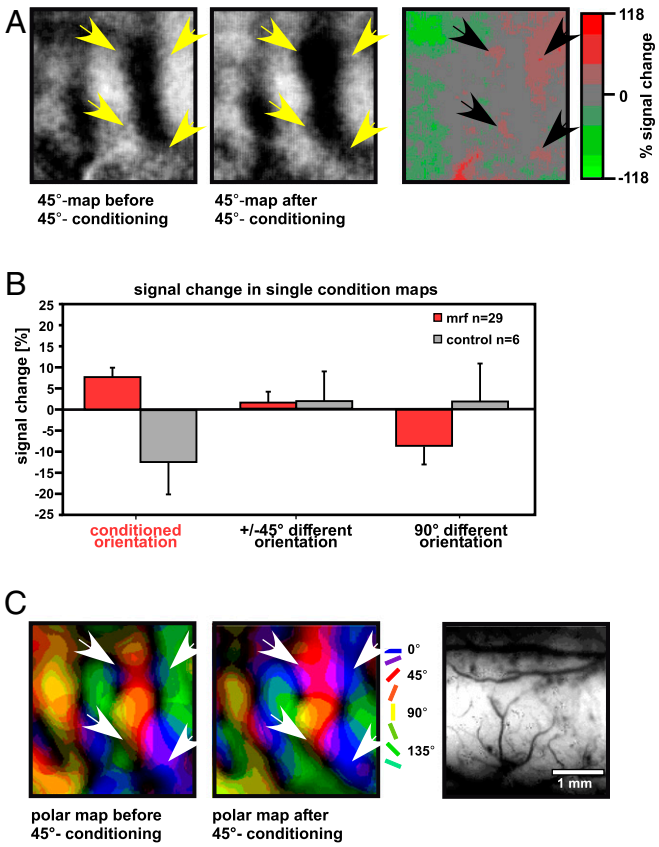

Fig. 1. Effects of repetitive visual stimulation concomitant with activation of the MRF on orientation preference maps. (*A*) Single-condition orientation maps resulting from stimulation with a 45° grating (*Left*) before and (*Middle*) after a 45-min period of conditioning with MRF activation. (*Right*) The changes between the former maps, with red codes for increases and green for decreases in activity in the respective pixel. Note that the increase of activity is particularly strong in regions surrounding the 45° domains (arrows). (*B*) Summary of the signal changes in 3 different compartments of the orientation map after conditioning (red bars) and after simple repetitive visual stimulation without additional MRF activation (gray bars) across the whole dataset. Error bars give the respective SEMs. (*C*) Polar maps for the case shown above (*Left*) before and (*Middle*) after conditioning with MRF stimulation. (*Right*) A video image of the recorded cortical region shown in *A*–*C*. Note the increase of the red tones (arrows) in the vicinity of the 45° domain as indication for orientation preference shifts, and the stronger saturation of the tones within the 45° domain as an indication of increases in response selectivity.

time, the responses to orientations orthogonal to that of the conditioning grating got reduced by 12.5% (not significant, 1-sample sign test; Fig. 1*B*). This increase in response strength and enlargement of the cortical representation of the conditioning stimulus was also evident in the comparison of polar maps calculated by pixel-wise vectorial addition of the responses to the gratings of different orientation. As indicated by the increased brightness of pixels in the domains corresponding to the conditioned orientation, not only the amplitude but also the orientation selectivity of responses within the expanding domains had increased (Fig. 1*C*).

We then determined which regions in the orientation map underwent the strongest modifications. To this end, we measured the angular changes of orientation preference of individual pixels (Fig. 2*A*) and related these changes to their initial orientation preferences (Fig. 2*B*). This analysis revealed that changes in orientation preference occurred mainly at sites whose initial orientation preference differed by 10° to 30° from that of the conditioning stimulus, while changes were minimal in regions whose orientation preferences were orthogonal to or matched the orientation of the conditioning grating. This suggests that significant changes were confined to neuron populations whose tuning properties allow them to respond to the change-inducing stimuli and agrees with the critical role that postsynaptic activity plays in mediating neuronal plasticity (*Discussion*). Shifts in orientation preference were always toward the conditioned orientation, and the regions of maximal change spanned cortical distances of about 300 μm, which agrees with the spatial gradient of orientation preference shifts in the orientation map.

These modifications were consistent in the grand average computed over the whole set of experiments (Fig. 2*C*). Plotting angular changes against the difference between the initial orientation preference and the orientation of the conditioning grating confirmed that the most pronounced shifts occurred for pixels whose initial preference differed by 10° to 30° from the orientation of the conditioning grating. These changes were associated with systematic modifications of response selectivity as reflected by changes of the vector strength (Fig. 2*D*). Pixels with orientation preferences matching the orientation of the conditioning stimulus maintained or increased their selectivity, while pixels whose initial preference had larger offsets (>30°) from the orientation of the conditioning grating became less selective. This reduction in orientation selectivity was maximal for offsets around 60° (Fig. 2*D*). Thus, neuron populations whose tuning did not allow them to respond to the conditioning stimulus did not change their preferences but rather underwent a deterioration of their orientation selectivity.

When the conditioning gratings were presented without concomitant activation of the MRF, use-dependent modifications were less frequent and, when present, were of opposite polarity. In agreement with previous studies (29), repetitive visual stimulation without accompanying MRF activation (6 conditioning sessions of 50-min duration, 3 cats) resulted in a decrease of response strength for the conditioned orientation. No or only marginal changes in response strength were observed for stimuli differing from the conditioning stimulus by 45° or 90° (Fig. 1*B*). In regions whose original preferences differed by 10° to 20° from the conditioning stimulus, the preferences of the pixels shifted away from the orientation of the conditioning stimulus (Fig. 3 *A* and *B*). However, when conditioning sessions without MRF stimulation were followed by a session with MRF stimulation, these changes turned out to be reversible. The very same pixels, whose orientation preference had shifted away from the conditioning stimulus, shifted their preferences in the opposite direction back toward the conditioning stimulus (Fig. 3*C*). In the absence of further conditioning, the induced changes were stable for at least 6 h, which was the maximal duration of control measurements, unless they were overwritten by conditioning with another stimulus (Fig. 3*D*). This suggests that MRF stimulation influences the outcome of conditioning, determining the polarity of the modifications (Figs. 1*B* and 3 *A*–*C*). With MRF stimulation, neurons capable of responding to the conditioning stimulus become more responsive to this stimulus, and those with perfectly matching preferences become more selective, while responses of neurons not activated by the conditioning stimulus deteriorate. Without MRF stimulation, responses of neurons driven by the conditioning stimulus deteriorate, and responses of the neurons not activated by the conditioning stimulus do not change.

In order to identify reasons for the plasticity-enhancing effects of MRF stimulation, we investigated more closely the relation between the outcome of conditioning and cortical dynamics. Confirming previous results (29), MRF stimulation enhanced the power of stimulus-induced oscillations mainly in the ɣ-frequency range (above 20 Hz) and, to some extent, also in the β-range (~15 Hz), had variable effects on the power of oscillations in the alpha band, and caused a consistent reduction of power in the theta range (*SI Appendix*, Figs. S1 and S2) in the majority of conditioning sessions. The ɣ-power was, on average, significantly increased (1-sample sign test, $P < 0.0001$) by 70% in conditioning sessions with MRF stimulation as compared to the preceding mapping sessions without MRF stimulation. Conversely, ɣ-power even decreased by 16% (not significant) between the mapping

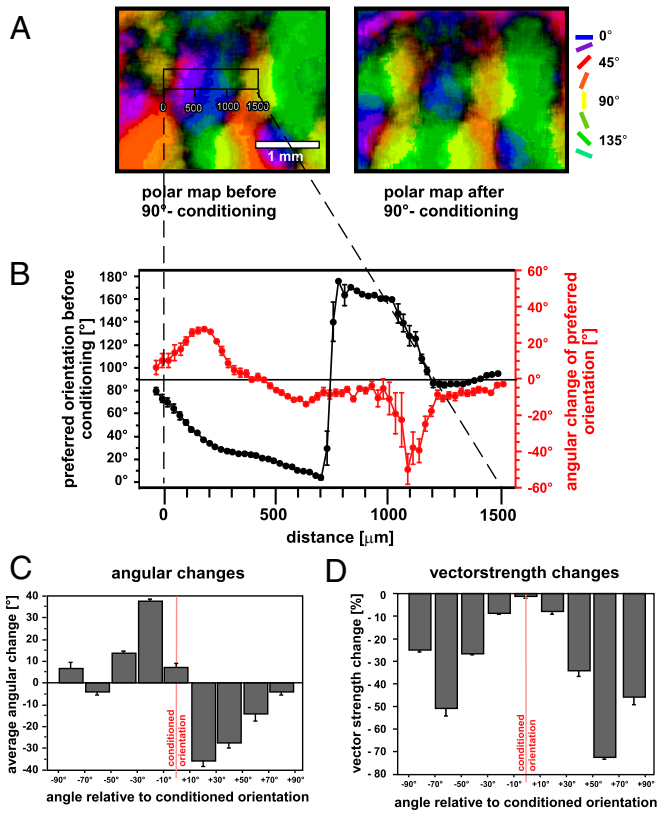

Fig. 2. (*A*) Polar maps from another experiment (*Left*) before and (*Right*) after pairing of visual and MRF activation. In this case, the stimulus orientation was 90°, represented in yellow. (*B*) Plots of the initial orientation preference (black) and the changes in orientation preference (red) along the window indicated in *A*, *Left*. Note that changes are most prominent in pixels exhibiting orientation preferences of ±45° around the orientation of the conditioning stimulus. (*C*) Summary of angular changes after conditioning in 29 conditioning sessions from 6 different experiments. Error bars give the respective SEM. (*D*) Summary of vector strength changes after conditioning from the same dataset as in *C*; again, error bars indicate the respective SEMs.

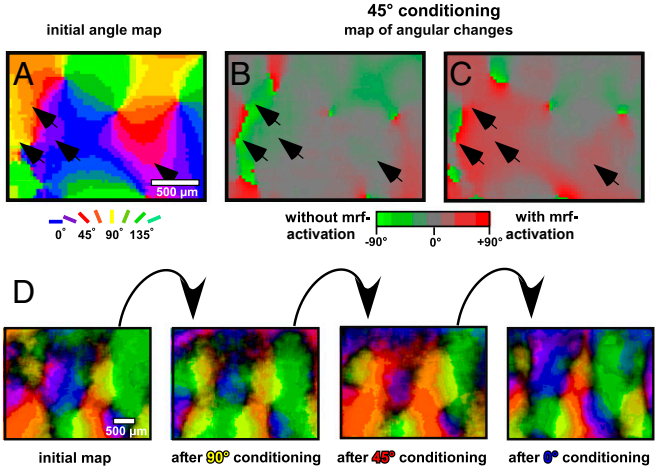

Fig. 3. Effects of repetitive visual stimulation on orientation preference maps with and without concomitant MRF activation. (*A*) Initial angle map. (*B*) Angular changes after repetitive visual stimulation without concomitant MRF activation. The applied visual stimulus had an orientation of 45°. Red tones indicate positive angular changes, and green indicates negative angular changes. (*C*) Angular changes after repetitive visual stimulation paired with MRF activation; color scheme as in *B*. Note that changes after repetitive stimulation without and with MRF activation differ strongly from each other. Arrows indicate the same locations in *A*–*C*. (*D*) Effects of sequential conditioning with different orientations. Note that the representational changes followed the respective conditioning stimulus.

sessions and conditioning sessions without MRF stimulation (*SI Appendix*, Figs. S2 and S3). The power of theta oscillations (3.5 Hz to 7.5 Hz) decreased when gamma increased (see *SI Appendix*, *SI Results* and Fig. S4 for all other frequency bands). This analysis suggested that MRF stimulation could have facilitated the induction of changes in orientation preference by entraining cortical networks in synchronized ɣ-oscillations.

To directly assess the neuronal underpinnings of the observed changes in orientation maps based on optical imaging, we recorded MUA with floating wire electrodes (n = 171 sites in 4 cats, 28 conditioning sessions with and 4 conditioning sessions without MRF stimulation) either in parallel with the optical measurements or, subsequently, selecting recording sites according to the previously determined orientation maps. The MUA results were more heterogeneous (Fig. 4*A*) than those obtained with optical recordings. This was to be expected, because the latter average the activity across a large number of neurons. However, the changes observed at the neuronal level were in agreement with the optical data. Units whose preferences differed by less than 30° from the conditioned orientation (n = 33) displayed remarkable shifts in response preference toward the conditioned orientation when conditioning stimuli were paired with MRF stimuli that caused strong increases in the power of induced ɣ-oscillations (Fig. 4 *A*, *Left*). In addition, these units tended to sharpen their tuning (*SI Appendix*, Fig. S5). Units whose orientation preferences differed by more than 30° and up to 60° from the conditioned orientation (n = 45) tended to show a broadening of their orientation tuning, but no changes in response preference (Fig. 4 *A*, *Middle*). Units with preferences differing by more than 60° from the conditioned orientation (n = 38) showed a change in neither tuning nor preference (Fig. 4 *A*, *Right* and *SI Appendix*, Fig. S5). As the optically recorded modifications, the changes of the units' orientation preferences were stable over several hours unless the cortex was exposed to further conditioning. No significant changes of orientation tuning were observed after conditioning sessions in which MRF stimulation was omitted.

To investigate further the relation between ɣ-oscillations and the outcome of conditioning, we analyzed the relation between the occurrence and polarity of changes in orientation preference and the power of ɣ-oscillations (20 Hz to 48 Hz) during conditioning. An example with a sequence of 3 consecutive conditioning sessions is shown in Fig. 4*B* for a MUA recording. When MRF stimulation caused strong increases in ɣ-power above baseline, the units captured by this MUA recording shifted their preference toward the conditioned orientation. When MRF stimulation failed to increase ɣ-power, the units' orientation preference tended to shift away from the conditioned orientation.

To further substantiate this relation between the occurrence of ɣ-oscillations and changes in response properties, we reanalyzed the whole dataset by splitting conditioning sessions into 2 groups. One consisted of sessions with an enhancement of ɣ-power of at least 10% as compared to the preceding mapping period, and the other with less than 10% or even decreases in ɣ-power. This was possible because, even in the same animal and with MRF stimulation, certain conditioning sessions were associated with strong increases of ɣ-oscillations, while others were not (see, e.g., Fig. 4*B*). As reported in previous studies performed under very similar conditions, central states change slowly in cycles that may last several hours, even under anesthesia, and alternate between phases in which identical stimuli induce either strong or weak ɣ-oscillations (34). The reason for these spontaneous fluctuations is unknown, and we failed to establish any correlations with circadian rhythms, the sequence of conditioning sessions, or the duration of the experiments. Still, these spontaneous changes permitted stratification of conditioning sessions, while keeping all controllable variables constant.

In conditioning sessions with ɣ-increases, units with orientation preferences close to the conditioning stimulus (up to 30°) tended to shift their preferences toward the conditioned orientation (Fig. 4*C*). A fine-grained analysis revealed that units with preferences differing from the conditioning stimulus between 0° and 5° did not express significant shifts of their preferences (n = 10, 1-sample sign test), while those which differed by 5° to 30° from the conditioned orientation shifted their preference toward the conditioned orientation (n = 23, $P < 0.01$, 1-sample sign test). No significant changes were observed for cells with orientation preferences differing from the orientation of the conditioning stimulus by 30° to 60° (n = 45) and above 60° up to 90° (n = 38). In conditioning sessions without ɣ-elevation, no consistent shifts in orientation preference were noted (Fig. 4*C*). Similar results were obtained for optically measured map changes after stratification of conditioning sessions according to ɣ-power. We applied the same criteria as for the MUA analysis for the classification of conditioning sessions with either high or low ɣ-activity. This analysis revealed that only conditioning sessions associated with enhanced ɣ-activity led to a strengthening of the response to the conditioned stimulus (P = 0.0015, 1-sample sign test) and thus fully confirmed the findings obtained with MUA recordings.

MRF stimulation not only enhances ɣ-oscillations but sometimes also discharge rate (35, 36). Thus, the plasticity-enhancing effects of MRF stimulation could have been due to increased firing of neurons rather than the enhanced synchrony of firing associated with ɣ-oscillations. To distinguish between these 2 possibilities, we examined the relation of changes in orientation preference in relation to changes of either ɣ-oscillations or firing rate. We performed the same analysis as illustrated in Fig. 4*C*, but now separating units according to not only changes in ɣ-oscillations but also firing rate changes during conditioning. This analysis confirmed that plasticity-facilitating effects of ɣ-oscillations occur irrespective of firing rate changes (Fig. 4*D*). The shift in orientation preference of neurons preferring orientations between 10° and 30° off the conditioning orientation was significant at the $P < 0.05$ level for conditioning sessions where both ɣ-power and discharge rate of responses were enhanced and

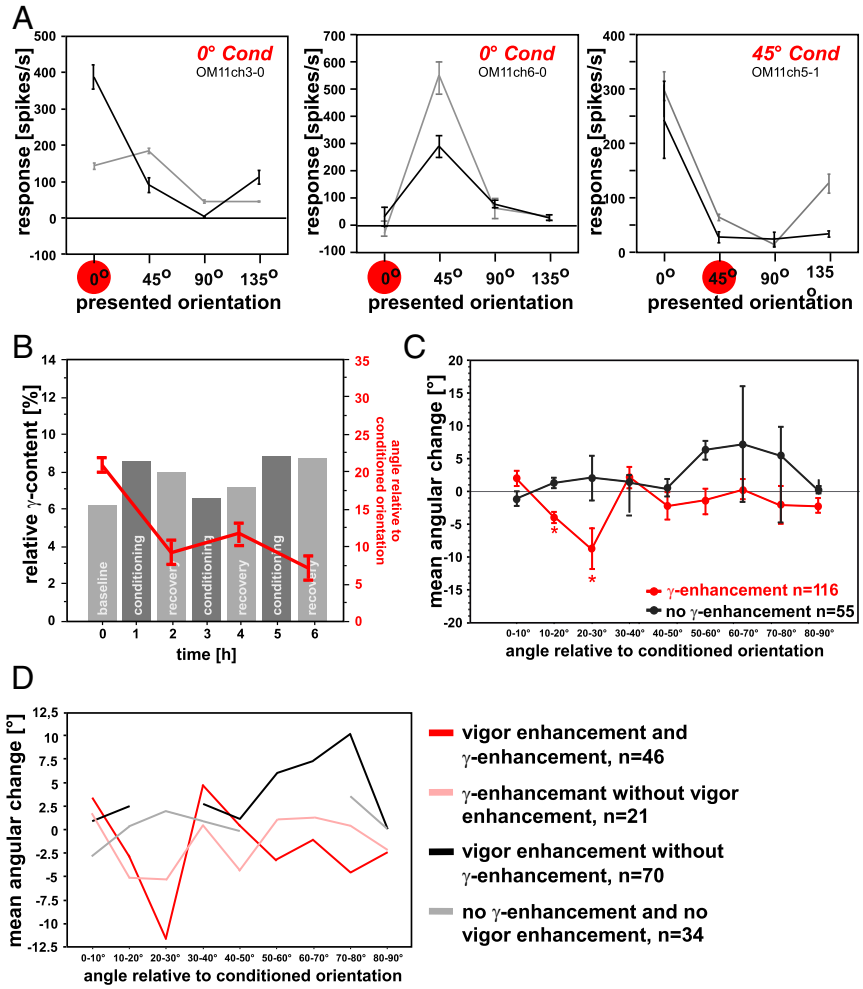

Fig. 4. Conditioning-dependent changes in the orientation preference of neurons as a function of orientation offset and changes of ɣ-power during conditioning. (*A*) Examples of individual MUA orientation tuning curves before (gray lines) and after (black lines) conditioning with MRF stimulation. The conditioned orientation is indicated in the right upper corner of each graph and underlined in red on the abscissa. (*B*) Comparison of the direction of shifts in orientation preference during conditioning relative to the conditioned stimulus (red line plot and red scale on the right) and as a function of relative ɣ-power in the electroencephalogram (bar plot and black scale on the left) for an individual MUA recording tracked over several hours. (*C*) Angular changes in orientation preferences of all recorded units ($n = 171$), grouped according to their initial distance from the conditioned orientation. The red line shows the preference changes in cases with an enhancement of power in the low γ-band [20 Hz to 48 Hz] of more than 10% during the conditioning, while the black line indicates the changes for cases without ɣ-enhancement or even a γ-decrease. Significant changes (1-sample sign test) are indicated by asterisks; error bars indicate the SEMs. (*D*) Angular changes after conditioning as a function of changes in firing rate (vigor) and power in the low ɣ-band during conditioning.

at the $P < 0.03$ level in conditioning sessions where only ɣ-power was enhanced without increases in discharge rate.

In order to obtain further information about the circuits involved in the mediation of the map changes, we performed the conditioning with whole-field gratings as before but compiled orientation maps before and after conditioning by stimulating only a small area of the visual cortex. We expected that this should allow us to monitor, selectively, the activity of the tangential intracortical connections that connect remote orientation domains with similar preferences (37–40). Because the intrinsic signal, unlike MUA, reflects also subthreshold synaptic activity (41), it should also reveal activity at sites not directly activated by the small mapping stimulus. If the changes in orientation preference are associated with gain changes at the level of intracortical tangential connections, we reasoned that we should see changes also at sites remote from those activated by the mapping stimulus. As shown in Fig. 5, stimulation of a small patch of the visual field evoked intrinsic signals within the whole field of analysis (20° diameter). The orientation maps compiled from this restricted stimulation closely resembled those evoked by the whole-field grating. As stimuli presented outside of classical RFs evoke no suprathreshold responses, this indicates that the intrinsic signals were caused by subthreshold activity and that this activity reflects the orientation preference of the respective target sites. This agrees with the evidence that long-range horizontal connections preferentially link orientation domains with similar preference (37–39). As indicated by the angular changes plotted in Fig. 5*B*, comparison of the maps evoked by the spatially restricted mapping stimuli before and after conditioning with the maps evoked by whole-field stimuli confirmed the strengthening of responses to the conditioning stimulus. Interestingly, these changes were more clearly expressed in domains not directly activated by the mapping stimulus (Fig. 5*C*). This indicates that conditioning had enhanced the activity and/or efficiency of tangential connections originating from domains whose orientation preference matched the conditioning stimulus within the directly activated portion of cortex.

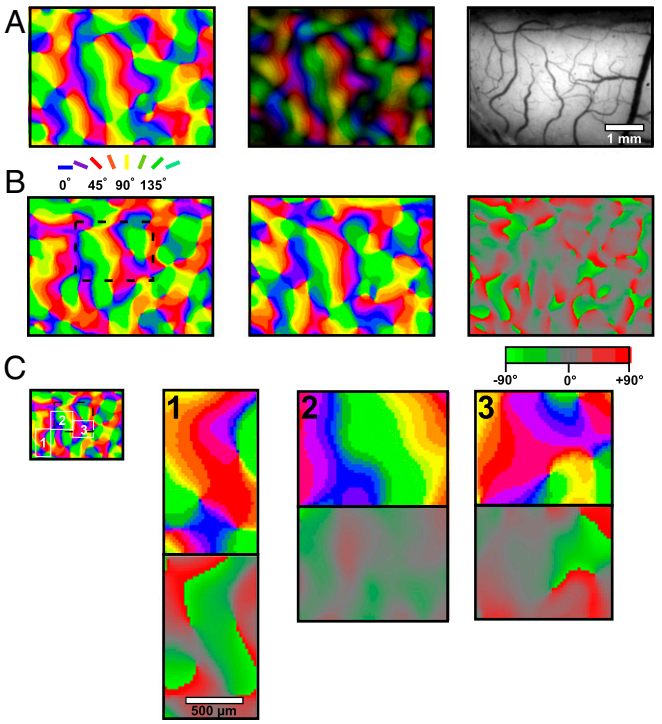

Fig. 5. Changes in orientation preference maps induced with whole-field stimuli but determined with a small patch stimulus. (*A*) (*Left*) Angle and (*Middle*) polar map recorded from area 18 using a whole-field grating. *Right* depicts the recorded cortical region. (*B*) Angle map obtained with a patch stimulus (*Left*) before and (*Middle*) after conditioning. The cortical representation of the patch is indicated by the dashed rectangle. Inside the patch, all orientations were presented as for the whole-field grating in *A*. (*Right*) The angular changes after conditioning according to the color scheme shown below. (*C*) Details of the changes shown at higher magnification. (*Left*) The angle map again with the stimulated region (dashed rectangle), and the white rectangles depict the regions (1 to 3) which are shown in the following images at higher magnification in *Left Middle*, *Right Middle*, and *Right*. Here, the initial angle maps and the respective angular change map are shown for zones 1, 2, and 3. Note that angular changes are more pronounced outside the directly stimulated region.

Discussion

Our results confirm that, under certain activation conditions, neuronal response properties and feature maps can undergo use-dependent long-term modifications in adult visual cortex (3, 4, 12, 13, 42–46) and demonstrate that probability and polarity of such changes are correlated with the occurrence of synchronized ɣ-oscillations. When the conditioning stimuli induced strong ɣ-oscillations, neurons with 10° to 30° orientation offset, and hence capable of responding to the conditioning stimulus, shifted their preference toward the orientation of this stimulus and increased their orientation selectivity. Neurons whose orientation preference matched that of the conditioning stimulus (within ±10°) did not change their preference but became more responsive and more sharply tuned. By contrast, when conditioning stimuli induced only weak or no ɣ-oscillations, neurons capable of responding to the conditioning stimulus became less responsive.

Confounds. MRF stimulation mimics arousal by activating, directly or indirectly, ascending modulatory projection systems that facilitate both ɣ-oscillations (29, 31) and synaptic plasticity (47). Thus, enhanced plasticity and the occurrence of ɣ-oscillations could be causally unrelated consequences of stimulating the ascending reticular activating system. Of particular interest in this context are the cholinergic projections, because acetylcholine facilitates both ɣ-oscillations and synaptic plasticity: Topical application of acetylcholine facilitates while blockade of cholinergic transmission abolishes stimulus-induced ɣ-oscillations, and cholinergic antagonists abolish the facilitation of ɣ-oscillations by MRF stimulation (31). Acetylcholine has also been shown to directly facilitate the induction of activity-dependent synaptic plasticity both in vitro (28, 48) and in vivo (49). This agrees with the evidence that states associated with increased release of acetylcholine, such as arousal and attention, are also favorable conditions for experience-dependent synaptic plasticity of cortical circuits (10, 16, 18, 20, 50). This raises the question of to what extent the facilitation of map changes in the present experiments was due to the entrainment of networks in synchronized ɣ-oscillations or to other mechanisms such as enhanced excitability or both.

Our data do not allow us to unequivocally distinguish between these possibilities, but the following considerations suggest that synchronized network oscillations are actually critical. First, there was no correlation between the occurrence and polarity of response modifications on the one hand and changes in discharge rate on the other, which argues against a simple relation between plasticity and excitability changes. Second, quantitative analysis of changes in discharge rate and ɣ-power during the conditioning sessions revealed that the power of stimulus-induced ɣ-oscillations but not discharge rate during conditioning reliably predicted the occurrence and polarity of the conditioning effects. The importance of ɣ-oscillations is further supported by the observation (*SI Appendix*, Figs. S2 and S3) that conditioning sequences without MRF stimulation that lead to habituation and cause a decrease of responses to the conditioning stimulus were associated with a decrease in ɣ-power below the level attained during the preceding mapping period. The analysis of power changes in the lower-frequency bands revealed that increases in ɣ-power were associated with a moderate but less consistent increase in beta activity, variable changes in the alpha band, and a clear decrease of power in the theta band. Thus, the most consistent relation between changes in the power of oscillatory activity and the occurrence of changes in orientation tuning existed for the increase in ɣ-power and the concomitant decrease in theta power. This suggests a critical role of ɣ-synchrony in the facilitation of use-dependent plasticity. As discussed below, synchronized ɣ-oscillations assure coincidence between presynaptic and postsynaptic activity with millisecond precision (28) and therefore provide particularly favorable conditions for the induction of synaptic modifications.

Hebbian Plasticity of Intracortical Connections as the Likely Mechanism of Modifications. Developmental studies have shown that, once established, the orientation preference of cortical neurons and the topology of orientation maps remain fixed despite deprivation-induced rearrangement of thalamic input (51, 52). This suggests that orientation maps become imprinted in and stabilized by the network of intracortical connections (53). Moreover, thalamocortical connections are no longer susceptible to experience-dependent modifications after the end of the critical period. This suggests that the conditioning-dependent recruitment of neurons into the domains activated by the conditioning stimulus is, with all likelihood, due to changes in the synaptic efficacy of cortical rather than thalamocortical connections. This conjecture is further supported by the finding that the conditioning-dependent map changes could be monitored by optical recording far beyond the region that was directly activated via thalamocortical afferents by a spatially restricted mapping stimulus (Fig. 5). This indicates that modifications have occurred at the level of cortical pathways whose activity is captured by the hemodynamic signal (41). Candidates are the tangential intraareal connections and/or feedback connections from higher cortical areas.

This conclusion is compatible with the evidence that synapses of intracortical connections remain susceptible to use-dependent modifications in the adult. Numerous in vitro studies provided

a detailed account of the activation conditions leading to strengthening and weakening of synaptic connections among cortical neurons. Supported by conclusions from earlier in vivo studies (17, 42), these in vitro experiments led to the formulation of dual threshold rules of synaptic plasticity, addressed as Artola–Bröcher–Singer (ABS) (23), Bienenstock, Cooper, and Munro (BCM) (54), and spike-timing–dependent plasticity (STDP) (55, 56) rules. Active synaptic connections strengthen when discharging in conjunction with strong postsynaptic depolarization, depress when postsynaptic depolarization is below a critical threshold, and undergo no change if neither of the 2 depolarization ranges is reached (23). Accordingly, use-dependent modifications of response properties of cortical neurons are facilitated by direct electrical (42, 43, 46) or pharmacological (44) activation of postsynaptic neurons or by stimulation of activating modulatory systems (10).

Given the sensitivity of these mechanisms of synaptic plasticity for temporal relations between presynaptic and postsynaptic activity, it follows that γ-synchronization should provide a particularly favorable condition for the induction of synaptic modifications. The entrainment of networks in γ-oscillations is associated with the precise synchronization of presynaptic and postsynaptic activity (57) and therefore facilitates the occurrence of LTP of synaptic transmission. Of particular importance is that, during γ-oscillations, the discharges of excitatory and inhibitory neurons become concentrated in different phases of the oscillation cycle. Pyramidal cells discharge in synchrony around the peak of the depolarizing cycle and inhibitory neurons with a lag of several milliseconds (58). Thus, during γ-oscillations, EPSPs generated by intracortical connections impinge as compound volleys on the dendrites of target pyramidal cells in a phase of the cycle when these are highly excitable, because inhibition generated during the preceding γ-cycle has faded and the new barrage of inhibitory postsynaptic potentials (IPSPs) has not yet arrived from the phase-lagging interneurons (59). As the postsynaptic neurons also discharge preferentially during this window of increased excitability, dendritic depolarization can be further amplified by back-propagating spikes (60). Moreover, these spikes are particularly likely to back-propagate into remote dendritic compartments during this phase of the oscillation cycle, because inhibitory interneurons pause during this phase (61) and shunting effects by IPSPs are minimal. Therefore, the conditions provided by γ-oscillations are ideally suited to reach the threshold for the strengthening of active connections as defined by the ABS, BCM, and STDP rules.

Accordingly, neuronal populations driven by the conditioning stimulus are likely to strengthen their input connections and their mutual interactions if engaging in γ-oscillations. By contrast, without oscillatory patterning, discharges are temporally more dispersed and EPSPs and IPSPs are more intermingled. This condition makes it less likely that responses to the conditioning stimulus reach the threshold for strengthening synaptic modifications and make it more likely that active synapses are weakened or do not change at all. This can account for the reduction of responses observed in conditioning sessions in which stimuli evoked only weak or no γ-oscillations, as was the case when MRF stimulation failed to facilitate γ-oscillations or when conditioning stimuli were presented without MRF activation.

This interpretation also accounts for the findings that neurons whose initial preference differed by less than 30° from the conditioned orientation profited from conditioning, while those with preferences offset by more than 30° were either unaffected or showed even inverse effects. According to the well-established tuning properties of neurons in the cat visual cortex, most cells with orientation offsets of <30° could respond to the conditioning stimulus, while those with offsets of >30° could not. Thus, the former but not the latter could profit from the synergies of contingent presynaptic and postsynaptic activity. This also explains why, in the orientation maps, the most prominent changes were apparent at the edges of the orientation domains corresponding to the orientation of the conditioning stimulus and were confined to regions extending up to 300 μm. Orientation preferences in visual cortex change gradually, and tangential distances of about 300 μm are about the range over which preferences change by 30°.

Interestingly, γ-oscillations are also involved in triggering other cellular processes that, like synaptic plasticity, involve activation of second-messenger cascades. Entrainment of cortical networks in synchronized γ-oscillations has been shown to enhance the hemodynamic response even if average discharge rates remained constant (41). Likewise, it was recently discovered that entrainment of cortical circuits in synchronized γ-oscillations leads to activation of microglia and a reduction of amyloid load (62). Whether these various effects depend on a common trigger mechanism, for example, on the generation of Ca^{2+} spikes as a consequence of enhanced synchrony, will have to be clarified in future experiments. Another explanation for the facilitation of plasticity through γ-oscillations may be an interaction with the expression of proteins such as Lynx1, which antagonizes the excitatory action of nicotinic acetylcholine receptors on GABAergic interneurons in the cortex. The expression of this protein increases with age and limits the critical period plasticity in visual cortex. A reduction of its expression level reinstates ocular dominance plasticity in the adult (63, 64). However, this hypothesis needs to be investigated in further studies.

Global versus Local Gating of Plasticity. Because of their widely bifurcating axons, modulatory systems are ideally suited to exert global gating of synaptic plasticity, as is required for reward-dependent supervised learning. However, the modulatory systems are less apt to gate synaptic plasticity with high topological selectivity, as is required for perceptual or attention-dependent learning. Only the cholinergic projections from the basal forebrain might provide sufficient topological specificity (65) to gate plasticity in a modality- or area-specific way. By contrast, γ-oscillations could gate adaptive changes in a circuit-specific manner, as is required for the unsupervised learning of frequently occurring feature constellations. The probability of cortical networks to engage in synchronized γ-oscillations depends not only on central states but also on stimulus context (66) and feedback from other cortical areas (67). The long-range tangential connections in primary visual cortex preferentially connect neurons responsive to features that have a high probability to cooccur in natural environments and therefore tend to be grouped perceptually according to the common Gestalt criteria of vicinity, continuity, and collinearity (39, 68). As a consequence of this preferential coupling and as demonstrated in numerous studies (for a review, see ref. 68), neurons coding for features that tend to be grouped perceptually synchronize their responses in the γ-frequency range when activated by feature constellations that match these Gestalt criteria, thereby signaling that their responses are related and groupable (67, 69). This notion is further supported by the recent evidence that neuron populations in the visual cortex engage in strong γ-oscillations if the features of the stimulus presented in the neuron's receptive field center are correctly predicted by the embedding context, that is, by the features of stimuli in the surround of the nonclassical receptive field (70, 71). Thus, stimuli whose features match the contextual predictions stored in the network architecture induce strong γ-oscillations. As the present data suggest, this, in turn, reinforces the connections signaling the match. In the context of predictive coding, this process would be interpreted as unsupervised up-dating of priors, the occurrence of γ-synchrony serving as the local "reinforcement" or "gating" signal.

In conclusion, while ascending modulatory systems support supervised or reinforcement learning by gating neuronal plasticity as a function of global states and reward, engagement in synchronous oscillations could mediate unsupervised learning by

gating plasticity as a function of the match between sensory evidence and local priors. How exactly the specific dynamic features of γ-oscillations are translated into lasting changes of response properties and connectivity needs to be clarified in future studies.

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