Precisely Synchronized Oscillatory Firing Patterns Require Electroencephalographic Activation

Suzana Herculano-Houzel, Matthias H. J. Munk, Sergio Neuenschwander, and Wolf Singer

Max-Planck-Institut für Hirnforschung, 60528 Frankfurt/Main, Germany

Neuronal response synchronization with millisecond precision has been proposed to serve feature binding in vision and should therefore, like visual experience, depend on central states. Here we test this hypothesis by examining the occurrence and strength of response synchronization in areas 17 and 18 of anesthetized cats as a function of central states. These were assessed from the frequency content of the electroencephalogram, low power in the δ and high power in the γ frequency ranges (here 20–70 Hz) being considered as a signature of activated states. We evaluated both spontaneous state changes and transitions induced by electrical stimulation of the mesencephalic reticular formation. During states of low central activation, visual responses were robust but lacked signs of precise synchronization. At intermediate levels of activation, responses became synchronized and exhibited an oscillatory patterning in the range of 70–105 Hz. At higher levels of activation, a different pattern of response synchronization and oscillatory modulation appeared, oscillation frequency now being in the range of 20–65 Hz. The strength of response synchronization and oscillatory modulation in the 20–65 Hz range increased with further activation and was associated with a decrease in oscillation frequency. We propose that the oscillatory patterning in the 70–105 Hz range is attributable to oscillatory retinotopic input and that a minimal level of activation is necessary for cortical neurons to follow this oscillatory pattern. In contrast, the synchronization of responses at oscillation frequencies in the 20–65 Hz range appears to result from intracortical synchronizing mechanisms, which become progressively more effective as central activation increases. Surprisingly, enhanced synchronization and oscillatory modulation in the γ frequency range were not associated with consistent increases in response amplitude, excluding a simple relation between central activation and neuronal discharge rate. The fact that intracortical synchronizing mechanisms are particularly effective during states of central activation supports the hypothesis that precise synchronization of responses plays a role in sensory processing.

Key words: synchronization; γ frequency oscillations; EEG; cortical activation; visual perception; thalamocortical interactions; sleep

The synchronization of neuronal responses has been proposed as a mechanism complementary to rate modulation for the definition of relations among distributed responses. According to this hypothesis, synchronization of discharges with a precision in the millisecond range serves to jointly raise the saliency of responses, thereby defining for subsequent processing stages which responses are related (for review, see Singer and Gray, 1995). Synchronization in the millisecond range has been reported in several brain areas and species (Gray et al., 1989; Frien et al., 1994; Kreiter and Singer, 1994; Laurent and Davidowitz, 1994; Prechtl, 1994; Livingstone, 1996; Neuenschwander et al., 1996a,b; Freiwald et al., 1998) and is frequently associated with an oscillatory modulation of discharges in the γ frequency range. There is increasing evidence that these precise temporal relations among distributed discharges carry information that cannot be extracted from the firing rate of individual neurons. In the auditory cortex, the precise timing of spikes signals the familiarity of species-specific calls (Wang et al., 1995). In the insect olfactory system, composite odors appear to be encoded in the specific constellation of synchronous oscillatory discharges (Laurent, 1996), and in the visual cortex, synchronization of visual responses has been shown to reflect perceptual grouping criteria such as vicinity, continuity, colinearity, and common fate (Gray et al., 1989; Engel et al., 1991; Kreiter and Singer, 1996; Livingstone, 1996). Moreover, response synchronization correlates well with sensory disturbances such as strabismic amblyopia (Roelfsema et al., 1994) and with changes in perceptual dominance during interocular rivalry (Fries et al., 1997).

It is during waking and dreaming [rapid eye movement (REM) sleep], the two major brain states characterized by a desynchronized electroencephalogram (EEG) (Steriade et al., 1996), that visual experiences are possible. The EEG in these states is dominated by low-voltage activity in the γ frequency range and is referred to as “activated,” contrasting with the prominent high-voltage δ (1–4 Hz) activity that is observed during non-REM sleep (Steriade and McCarley, 1990; Llinás and Ribary, 1993). This predicts that neuronal response properties essential for perception should be expressed in the behavior of neuronal populations during states of central activation and should be absent when the brain is in a state that is incompatible with perception. To test this prediction, we investigated how visual responses in the cat primary visual cortex change in relation to EEG activation, as assessed from the frequency content of the EEG. EEG changes characteristic of behavioral arousal and of the transition from non-REM to REM sleep are caused by en-
hanced activity of modulatory projections originating in the mesencephalic reticular formation (MRF) (Moruzzi and Magoun, 1949; Hobson, 1992) and can be induced by electrical stimulation of the MRF (Moruzzi and Magoun, 1949). Therefore, we studied both spontaneous fluctuations of central states and those induced by electrical stimulation of the MRF. We have shown previously that MRF stimulation enhances the synchronization of neuronal responses in the visual cortex of anesthetized cats (Munk et al., 1996b). Here we extended this analysis to investigate the variation in strength, oscillatory modulation, and synchronization of visual responses in relation to central state changes.

Some of the results from this study have appeared in abstract form (Munk et al., 1996a)

MATERIALS AND METHODS

Animals. Eight adult cats were studied. Anesthesia was induced with 10 mg/kg ketamine and 2 mg/kg rompun injected intramuscularly and maintained under artificial ventilation with 70% N2O and 30% O2 supplemented with 1% halothane during all surgical procedures, as described previously (Engel et al., 1990). Heart rate, temperature, EEG, and end-tidal CO2 were monitored continuously. After surgery, halothane concentration was adjusted so that delivery of a 61-msec-long train (100 μsec pulses at 75 Hz, 1–3 mA) applied to the optic tract at the end of the experiments.

Multiunit activity was recorded simultaneously with up to three tungsten electrodes from a total of 53 sites in four adult cats. Neurons at different sites recorded simultaneously had nonoverlapping receptive fields, with an average center-to-center distance of 7.6 ± 5.1° of visual angle. Multiunit responses to repeated presentations of an invariant visual stimulus were recorded in 21 sessions spanning 3–10 consecutive hours. The level of anesthesia was kept constant during each session. Multiunit activity was filtered between 1 and 3 kHz, fed through a Schmitt trigger whose threshold was set higher than twice the noise level, and sampled at 100 kHz with a 1401 CED interface controlled by Spike 2 software (Cambridge Electronic Design, Cambridge, UK). The EEG was recorded at the same time between two epidural silver ball electrodes that were placed lateral and posterior to the multiunit recording sites, either across the hemispheres (one animal) or with a spacing of 3–5 mm in the same hemisphere (seven animals). The EEG signal was filtered between 0.1 and 1000 Hz and digitized at 1 kHz.

MRF stimulation. Bipolar stimulation electrodes were positioned bilaterally in A (14.5; H, 5; L, 3) (Horsley-Clark) and the MRF (A, 2; H, 8; L, +3). The position of MRF stimulation electrodes was adjusted so that delivery of a 61-msec-long train (100 μsec pulses at 75 Hz, 1–3 mA; Singer, 1973) caused maximal facilitation of the cortical response (Fig. 1, top; see stimulus traces above raster plots). The EEG and multiunit responses were continuously evaluated on-line with a raster display.

Data analysis. All data analysis was performed using software programmed by one of us (S.N.) in LabVIEW (National Instruments) running on a Macintosh platform.

Oscillatory modulation and synchronization of multiunit neuronal responses to patches of moving gratings were analyzed by computing auto- and cross-correlation functions averaged over 10 consecutive trials, with a 100 msec interval between each trial. For the correlation analysis, a 4 sec analysis window was used to cover most of the response epoch, beginning 100 msec after visual stimulus onset to avoid the initial transient, stimulus-locked component of the responses. For quantitative analysis, a damped cosine (Gabor) function was fitted to the correlograms (König, 1994). Shift predictor averaged correlograms were calculated, and once established that these were flat, quantification was based on non-shift predictor-subtracted correlation functions. This allowed the strength of oscillatory modulation to be assessed from the ratio between the amplitude of the first satellite peak and the offset of the function fitted to auto-correlograms [modulation amplitude of the first satellite peak (MAS)]. Similarly, synchronization was assessed from the modulation amplitude (MA) of the central peak in the correlograms, using the ratio between the peak amplitude and offset of the fitted function for quantification. A correlogram was considered to reveal oscillatory (or synchronized) activity if the first satellite (or central) peak had a Z score >2 and an MAS (or MA) ≥0.1. Because all of our recordings consist of multiunit activity, the fitted central peak of the auto-correlograms, which excludes the 0 msec bin, indicates the degree to which the activity of neighboring neurons is synchronized. The average firing rate for each block of 10 responses was expressed as the average number of spikes within the analysis window per trial per second.

A total of 7281 auto-correlograms averaged over 10 consecutive presentations of the visual stimulus were analyzed, which amounts to an average of 137 auto-correlograms per recording site (range, 30–320 auto-correlograms per site). Of the 7281 averaged visual responses analyzed, 2409 (33%) had been obtained during MRF stimulation. From the visual responses at the 45 pairs of sites recorded simultaneously, 3331 averaged cross-correlograms were computed; of these, 30% corresponded to visual responses obtained during MRF stimulation.

At four recording sites, averaged auto-correlogram functions calculated over 4 sec suggested a superposition of oscillatory modulation in two different frequency ranges, around 50 and 90 Hz. To determine whether the two oscillation frequencies occurred simultaneously or successively during visual responses, we analyzed all responses in the recording session using a sliding window correlation algorithm. Averaged sliding auto- and cross-correlation functions were calculated for a 150 msec analysis window, which was placed at time 0 of each trial and moved in steps of 75 msec until the end of the visual stimulus. The analysis window was then normalized to the total number of spikes and averaged across corresponding windows in ten trials.

To assess the central state at the time of the visual responses, the power spectrum of the EEG was calculated over the same analysis window as the correlation functions (Fig. 1, EEG). Power spectra were averaged over the 10 consecutive trials in each block. The relative power in different frequency bands was obtained by normalizing the integral power in each band to the total power of the spectrum calculated between 1 and 120 Hz. Discrete peaks in EEG power were observed in four frequency bands, of 1–4, 4–8, 8–18, and 21–71 Hz; for the sake of simplicity, these bands will be referred to as δ, θ, α, and γ, respectively.

RESULTS

Oscillations in visual responses

Thirty-nine (74%) of the 53 sites recorded in areas 17 and 18 exhibited oscillatory visual responses in at least one of the averaged auto-correlograms obtained during the 3- to 10-hr-long recording sessions. In no case was oscillatory modulation phase-locked to the visual stimulus or to the screen refresh rate (see Materials and Methods). Overall, oscillation frequency ranged from 20 to 105 Hz but, at each oscillatory site it was either restricted to one of two frequency ranges, between 20 and 65 Hz at 30 sites and between 70 and 105 Hz at 3 sites, or alternated with no gradation between them at 6 sites (Fig. 2). Oscillatory modulation in the two frequency ranges differed markedly with respect...
Oscillatory modulation in the range between 70 and 105 Hz occurred at the beginning of the responses and lasted maximally 1 sec (Fig. 2, top right), similar to retinal oscillations (Neuenschwander et al., 1996b), whereas the modulation in the 20 – 65 Hz range tended to increase over several hundred milliseconds after response onset and lasted until the visual stimulus was turned off (Fig. 2, top left). Henceforth, we shall refer to oscillatory modulation in the 20 – 65 and 70 – 105 Hz frequency ranges as **γ** frequency and retinal-like oscillations, respectively. At four recording sites, retinal-like oscillations occurred at the beginning of single visual responses and were followed by **γ** frequency oscillatory modulation that persisted until the offset of the visual stimulus. In such cases, averaged correlation functions were calculated for two nonoverlapping windows that contained oscillatory modulation in either of the two frequency ranges, and for statistical analysis, the respective data were treated as if recorded independently. Altogether, **γ** frequency oscillations were analyzed at 36 recording sites, and retinal-like oscillations were recorded at nine sites.

When visual responses exhibited oscillatory modulation, of either **γ** frequency or the retinal-like type, the EEG displayed on average 88 ± 49% higher **γ** and 24 ± 21% lower δ power than when responses were nonoscillatory (p < 0.0001, Wilcoxon signed rank test; Fig. 3, bottom and top graphs). No consistent relations existed between the occurrence of **γ** frequency oscillatory response modulations and θ or α EEG power (Fig. 3, middle graphs).

**γ** frequency oscillations: effect of MRF stimulation on incidence and strength

The probabilities of oscillatory patterning differed markedly between sites and depended on the state of activation. The propor-
tion of averaged auto-correlograms exhibiting significant oscillatory modulation varied from 9 to 97% at the different recording sites exhibiting oscillatory responses. In the absence of MRF stimulation, 28% of the 2918 averaged auto-correlograms recorded from 36 sites exhibited γ frequency oscillations. With MRF stimulation, the incidence of γ frequency oscillations increased to 56% (p < 0.0001, Wilcoxon signed rank test), reaching 100% at several sites (Fig. 4A). At five sites, γ frequency oscillations occurred only with MRF stimulation. Additionally, MRF stimulation increased the strength of γ frequency oscillatory modulation by an average of 55 ± 98% across all sites (p < 0.01, Wilcoxon signed rank test; Table 1). Oscillation strength at this frequency range was increased significantly (p < 0.01) at 15 of the 31 sites showing oscillatory modulation in the absence of MRF stimulation (Fig. 4B) and decreased at none of the sites (Table 1; range, 30–482% increase with MRF).

The increased incidence and strength of γ frequency oscillatory modulation with MRF stimulation could be attributed to the stable enhancement of EEG activation produced by this treatment. During the 30–60 min period when MRF stimulation preceded each presentation of the visual stimulus, the EEG became characterized by strong and stable γ frequency activity
power content exhibited marked variation over time in each shaded column. In the absence of MRF stimulation, the EEG test), accompanied by decreased relative decrease, 276 significantly stronger and at none with weaker g (indicated in each graph); open symbols). When visual responses exhibited an oscillatory (average increase, 67% 56%; p < 0.001, Wilcoxon signed rank test), accompanied by decreased relative δ content (average decrease, 27 ± 27%; p < 0.01, Wilcoxon signed rank test; Fig. 5, shaded columns). In the absence of MRF stimulation, the EEG power content exhibited marked variation over time in each frequency band. Epochs of strong γ EEG activity also occurred spontaneously but then never lasted longer than 10 consecutive minutes. During these epochs neuronal responses often exhibited γ frequency oscillations (Fig. 5, nonshaded columns).

Correlation with EEG activation γ frequency oscillatory modulation of visual responses occurred reliably once EEG δ power was below and γ power above a critical level (Fig. 6). A critical γ limit could be defined, for 22 of 36 sites, as the relative γ power of the EEG above which visual responses had a 90% probability of exhibiting oscillatory modulation. At different sites, the critical γ limit for the occurrence of oscillatory modulation ranged from 4 to 29%, averaging 20 ± 8% relative γ power of the EEG. A similar critical δ limit, below which oscillatory modulation had a 90% probability of occurring in visual responses, could also be defined, albeit for fewer sites (n = 15). The average critical δ limit ranged between 10 and 32%, averaging 25 ± 11% relative δ EEG activity.

Once above the γ or below the δ critical limit of EEG activation, γ frequency oscillations varied in strength as a function of γ and δ EEG activity (average correlation coefficients, 0.361 ± 0.339 and −0.261 ± 0.392, respectively; p < 0.001; Table 2). According to a p < 0.01 significance criterion, γ frequency oscillations increased at 19 of 36 sites and in no case decreased with increasing γ EEG power content. Likewise, γ frequency oscillations increased in strength at 18 of 36 sites with decreasing δ and at only one site with increasing δ (Table 2, Fig. 6). At a few sites the strength of γ frequency oscillations correlated also with changes in θ or α EEG power, but there was no consistent trend across recording sites (Table 2).

Oscillation frequency versus oscillation strength So far, other studies have not found an explanation for the variability in oscillation frequency across visual responses at a given site (Engel et al., 1990; Livingstone, 1996). We found that oscillation frequency in the γ frequency range decreased significantly (p < 0.01) with increasing oscillation strength at 20 of 36 sites (Fig. 7A; average Spearman correlation coefficient for the 20 sites, −0.539 ± 0.175). In no case was stronger oscillatory modulation significantly associated with increased oscillation frequency (Fig. 7B).

Effect of MRF stimulation on visual response oscillation frequency Because oscillation frequency was related to oscillation strength, and the latter depended on EEG activation, we next examined whether oscillation frequency was modulated together with EEG activation by MRF stimulation. The overall effect of MRF stimulation was a significant decrease in the average oscillation frequency in the γ range (Table 1). Eleven of 31 sites that exhibited γ frequency oscillations in the absence of MRF stimulation underwent a significant (p < 0.01) reduction in oscillation frequency with MRF stimulation, which on average decreased from 43 ± 5 to 36 ± 5 Hz (Fig. 8A); oscillation frequency remained unchanged at the other 20 sites (Table 1).

The variability in oscillation frequency was consistently reduced with MRF stimulation (Fig. 8B), the sample variance of oscillation frequency decreasing by a factor of 3 at individual recording sites (p < 0.0001, Wilcoxon signed rank test). The stabilizing effect of MRF stimulation on EEG activation and on oscillation frequency of the multunit responses may reflect the stabilization of the dynamics of underlying cortical circuits.
Relation between oscillation frequency and EEG activation

Interestingly, there was no consistent correlation across the entire sample between oscillation frequency and EEG γ power, the average correlation coefficient being 0.140 ± 0.475 across the 36 sites exhibiting γ frequency oscillations (p = 0.6177, one-sample rank test). This was, however, not attributable to independence between oscillation frequency and γ EEG power; rather, these two parameters were positively or negatively correlated at different sites (Fig. 9A). With increasing γ power of the EEG, oscillation frequency in the 20–65 Hz range increased significantly (p < 0.01) at 10 and decreased at 9 of 36 sites (Fig. 9B).

Retinal-like oscillations

Effect of MRF stimulation on incidence and strength

Retinal-like 70–105 Hz oscillations were affected by MRF stimulation in a strikingly different manner. With MRF stimulation, retinal-like oscillations were suppressed completely at seven of nine sites and decreased in strength at one (Fig. 4B, crosses). At the six sites that showed both γ frequency and retinal-like oscillations during spontaneous variations in EEG activation, only the former persisted during MRF stimulation.

Correlation with EEG activation

EEG activation was stronger during responses exhibiting retinal-like oscillations than during nonoscillatory responses (Fig. 3, triangles), suggesting that the occurrence of retinal-like oscillations in cortical visual responses also required EEG activation. However, the strength of these retinal-like oscillations was only weakly correlated with EEG power in the different frequency bands (Fig. 6). The lack of a consistent covariation between EEG activation and strength of retinal-like oscillations was probably attributable to the suppression of these oscillations once EEG activation exceeded a certain value.

Table 1. Mean effect of MRF

<table>
<thead>
<tr>
<th>Parameters</th>
<th>% change with MRF</th>
<th>All sites</th>
<th>Increase</th>
<th>Decrease</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>n</td>
<td>%Δ</td>
<td>n</td>
<td>%Δ</td>
</tr>
<tr>
<td>Osc strength</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Low-frequency</td>
<td>31</td>
<td>54 ± 98*</td>
<td>15</td>
<td>117 ± 116</td>
</tr>
<tr>
<td>High-frequency</td>
<td>9</td>
<td>-83 ± 35***</td>
<td>0</td>
<td></td>
</tr>
<tr>
<td>Osc Frequency</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Low-frequency</td>
<td>31</td>
<td>-9 ± 8***</td>
<td>0</td>
<td></td>
</tr>
<tr>
<td>Sync strength, local</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>All sites</td>
<td>53</td>
<td>68 ± 107**</td>
<td>24</td>
<td>119 ± 116</td>
</tr>
<tr>
<td>No osc</td>
<td>14</td>
<td>20 ± 56 (NS)</td>
<td>1</td>
<td>124</td>
</tr>
<tr>
<td>Osc</td>
<td>39</td>
<td>76 ± 112**</td>
<td>23</td>
<td>119 ± 118</td>
</tr>
<tr>
<td>Sync strength, pairs</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>All pairs</td>
<td>19</td>
<td>55 ± 74**</td>
<td>8</td>
<td>119 ± 73</td>
</tr>
<tr>
<td>Firing rate</td>
<td>53</td>
<td>-18 ± 48*</td>
<td>13</td>
<td>24 ± 13</td>
</tr>
</tbody>
</table>

Effect of MRF stimulation on several visual response parameters. The mean percentage change of each parameter (%Δ) is indicated first for all individual recording sites and pairs of recording sites together (All sites) and then separately for those sites or pairs exhibiting significant (p < 0.01, Mann–Whitney U test) increases or decreases in each parameter. NS, nonsignificant (p > 0.01), Wilcoxon signed rank test. Osc, Oscillation; Sync, Synchronization.

* p < 0.01.
** p < 0.0001.
*** p < 0.001.

Figure 4. Effect of MRF stimulation on oscillatory modulation of visual responses. Scatterplots comparing percentile of averaged auto-correlation functions indicative of oscillatory modulation (A) and average oscillation strength (B) at each recording site, obtained with (ordinate) and without (abscissa) MRF stimulation. Each point represents one recording site. Circles, Sites exhibiting γ frequency oscillations only; crosses, sites exhibiting retinal-like oscillations only; triangles, sites exhibiting both types of oscillations.
Figure 5. Synchronous oscillatory modulation of visual responses appears and disappears simultaneously in areas 17 and 18 concurrently with changes in the level of cortical activation occurring spontaneously or in response to MRF stimulation. A. Comparison of the time course of changes in EEG power (top box) with response variables (bottom boxes) at three recording sites in left area 18 (LA18), right area 18 (RA18), and right area 17 (RA17): firing rates, oscillation strength, oscillation frequency, and synchronization between RA18 and RA17. As the EEG becomes dominated by activity in the γ frequency range, firing rates increase at recording site LA18 and decrease at recording sites RA18 and RA17; responses at (Figure legend continues)
Oscillation frequency

The oscillation frequency of retinal-like oscillations was at four of nine sites correlated at the $p < 0.01$ level with oscillation strength, stronger oscillations exhibiting lower oscillation frequency (average Spearman correlation coefficient, $-0.618 \pm 0.184$). Oscillation frequency in the 70–105 Hz range, however, was never correlated with EEG activity (see example in Fig. 9).

Relationship between retinal-like and $\gamma$ frequency oscillations

At the six sites that exhibited oscillatory modulation in both frequency ranges, retinal-like oscillations in general disappeared when $\gamma$ frequency oscillations appeared in the responses (Fig. 10). As cortical activation increased spontaneously, the temporal patterning of cortical responses changed in the course of successive visual responses first from nonoscillatory to retinal-like and then to $\gamma$ frequency oscillatory modulation (Fig. 10, first four columns). With MRF stimulation, which induced maximal EEG activation and strongest oscillatory modulation in the $\gamma$ frequency range, retinal-like oscillations were suppressed. As EEG activation declined, either spontaneously or at the end of the MRF stimulation period, retinal-like oscillations reappeared and persisted at levels of activation at which $\gamma$ frequency oscillations had already disappeared (Fig. 10, last column to the right).

At three of the six sites showing both $\gamma$ frequency and retinal-like oscillations, the latter occurred at levels of $\delta$ and $\gamma$ EEG activity intermediate to those observed when oscillatory modulation was absent or occurred in the $\gamma$ frequency range (Mann–Whitney $U$ test, $p < 0.01$; Fig. 10). Together with the fact that in the transition from weak to strong EEG activation retinal-like oscillations preceded $\gamma$ frequency oscillations, this finding sug-
Table 2. Mean correlation values

<table>
<thead>
<tr>
<th></th>
<th>n</th>
<th>δ</th>
<th>n</th>
<th>θ</th>
<th>n</th>
<th>α</th>
<th>n</th>
<th>γ</th>
</tr>
</thead>
<tbody>
<tr>
<td>Osc strength, low frq</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>All osc sites</td>
<td>36</td>
<td>−0.261 ± 0.392**</td>
<td>36</td>
<td>0.015 ± 0.314 (NS)</td>
<td>36</td>
<td>0.000 ± 0.378 (NS)</td>
<td>36</td>
<td>0.361 ± 0.339***</td>
</tr>
<tr>
<td>Positive r</td>
<td>1</td>
<td>0.502</td>
<td>3</td>
<td>0.434 ± 0.187</td>
<td>5</td>
<td>0.604 ± 0.110</td>
<td>19</td>
<td>0.631 ± 0.140</td>
</tr>
<tr>
<td>Negative r</td>
<td>18</td>
<td>−0.547 ± 0.146</td>
<td>5</td>
<td>−0.396 ± 0.140</td>
<td>5</td>
<td>−0.597 ± 0.157</td>
<td>0</td>
<td></td>
</tr>
<tr>
<td>Sync strength, pairs</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>All pairs</td>
<td>22</td>
<td>−0.256 ± 0.302**</td>
<td>22</td>
<td>0.064 ± 0.350 (NS)</td>
<td>22</td>
<td>0.012 ± 0.366 (NS)</td>
<td>22</td>
<td>0.364 ± 0.274***</td>
</tr>
<tr>
<td>Positive r</td>
<td>6</td>
<td>0.459 ± 0.182</td>
<td>4</td>
<td>0.473 ± 0.188</td>
<td>13</td>
<td>0.564 ± 0.107</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Negative r</td>
<td>9</td>
<td>−0.543 ± 0.159</td>
<td>5</td>
<td>−0.358 ± 0.066</td>
<td>5</td>
<td>−0.462 ± 0.064</td>
<td>0</td>
<td></td>
</tr>
<tr>
<td>Sync strength, local</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Low-frq osc sites</td>
<td>36</td>
<td>−0.156 ± 0.419 (NS)</td>
<td>36</td>
<td>0.061 ± 0.353 (NS)</td>
<td>36</td>
<td>0.038 ± 0.364 (NS)</td>
<td>36</td>
<td>0.341 ± 0.350***</td>
</tr>
<tr>
<td>Positive r</td>
<td>7</td>
<td>0.433 ± 0.180</td>
<td>10</td>
<td>0.426 ± 0.146</td>
<td>18</td>
<td>0.457 ± 0.236</td>
<td>18</td>
<td>0.617 ± 0.183</td>
</tr>
<tr>
<td>Negative r</td>
<td>15</td>
<td>−0.526 ± 0.203</td>
<td>6</td>
<td>−0.439 ± 0.190</td>
<td>10</td>
<td>−0.368 ± 0.152</td>
<td>1</td>
<td>−0.571</td>
</tr>
<tr>
<td>Firing rate</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>All sites</td>
<td>53</td>
<td>−0.095 ± 0.381 (NS)</td>
<td>53</td>
<td>−0.045 ± 0.289 (NS)</td>
<td>53</td>
<td>0.080 ± 0.314 (NS)</td>
<td>53</td>
<td>0.058 ± 0.435 (NS)</td>
</tr>
<tr>
<td>Positive r</td>
<td>11</td>
<td>0.453 ± 0.194</td>
<td>7</td>
<td>0.425 ± 0.141</td>
<td>27</td>
<td>0.523 ± 0.155</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Negative r</td>
<td>21</td>
<td>−0.428 ± 0.170</td>
<td>11</td>
<td>−0.377 ± 0.098</td>
<td>4</td>
<td>−0.532 ± 0.191</td>
<td>7</td>
<td>−0.518 ± 0.189</td>
</tr>
</tbody>
</table>

Mean Spearman coefficients for correlations between EEG power in the different frequency bands and several visual response parameters. The mean correlation coefficient is first given for all sites or pairs of sites pooled together and then separately for only those sites exhibiting a significant ($p < 0.01$, Mann–Whitney $U$ test) positive or negative correlation between visual response variables and EEG power. NS, Nonsignificant ($p > 0.01$), one-sample rank test. Osc, oscillation; Sync, synchronization; frq, frequency.

* $p < 0.001$.

** $p < 0.0001$.

*** $p < 0.001$.

Synchronization of visual responses across sites

If response synchronization plays a role in visual information processing, it should, like visual experience, be modulated with central state. We examined this hypothesis by looking at the variation in response synchronization during different levels of EEG activation. Twenty-four of the 45 pairs of sites recorded simultaneously exhibited at least one averaged cross-correlogram indicative of response synchronization in the millisecond range during the 3- to 10-hr-long recording sessions. This synchronization was not attributable to stimulus-locked rate covariations, as indicated by flat shift predictors. In all 24 pairs, the cross-correlograms exhibited significant satellite peaks, indicating that the underlying responses were oscillatory. This agrees with the observation that responses from at least one of the recording sites in each pair showed oscillatory patterning in the auto-correlogram.

When visual responses were synchronized across sites, the EEG contained on average 18 ± 22% lower δ and 66 ± 52% higher γ than when no synchronization occurred ($p < 0.01$, Wilcoxon signed rank test; Fig. 11, top and bottom graphs; $n = 20$; four pairs had to be excluded because all or almost all cross-correlograms exhibited synchronization). Two pairs of recording sites exhibited synchronous oscillations at both 20–65 and 70–105 Hz at both frequency ranges, the EEG contained lower δ and higher γ activity when responses were synchronized than when no synchronization occurred (Fig. 11, triangles).

Effect of MRF on incidence and strength

Of the total sample of 2025 averaged cross-correlograms analyzed for the 24 pairs, 1293 (68%) showed synchronization (range, 7–100% for the different pairs). In 18 of 21 pairs, synchronization of visual responses occurred more frequently during MRF stimulation (84%) than during spontaneous EEG fluctuations (60%), $p < 0.01$, Wilcoxon signed rank test; two pairs not tested under MRF stimulation and another exhibiting synchronization at all times were excluded; Fig. 12). For one pair of sites, synchronization occurred only when EEG activation was enhanced by MRF stimulation.

Additionally, the strength of synchronization across recording sites increased with MRF stimulation in 8 of 17 pairs exhibiting a sufficient number of synchronized correlograms to permit comparison (Table 2; average increase, 55 ± 74% over all 17 sites;
In none of the pairs did MRF stimulation reduce synchronization strength.

Correlation between strength of synchronization across sites and EEG activation

In addition to the dependence of the occurrence of response synchronization on EEG activation, the strength of response synchronization was correlated with $\gamma$ and $\delta$ EEG power (average correlation coefficients, 0.364 ± 0.274 and -0.256 ± 0.302, respectively; Table 2). According to a significance criterion of $p < 0.01$ (Spearman correlation test), the strength of synchronization across sites increased with $\gamma$ EEG activity in 13 of 22 pairs (Fig. 13A–C, Table 2; one pair showing synchronization only during MRF stimulation was excluded). In no case was increased $\gamma$ EEG power associated with reduced synchronization (Table 2). Synchronization became weaker with increasing $\delta$ EEG activity in nine pairs and stayed unchanged in the other pairs. The strength of synchronization across sites was occasionally correlated with changes in $\theta$ and $\alpha$ EEG power but with no consistent sign (Table 2).

Local synchronization of visual responses

Local synchronization of the multiunit responses recorded simultaneously from one electrode was assessed by calculating the relative modulation amplitude of the center peak of the auto-correlograms (see Materials and Methods). The strength of local synchronization increased with MRF stimulation by 68 ± 107% ($p < 0.001$; Table 1). According to a significance criterion of $p < 0.01$ (Mann–Whitney U test), local synchronization strength increased at 23 and decreased at only 3 of 36 sites exhibiting $\gamma$ frequency oscillations (Table 1). This suggests that local synchronization of oscillatory visual responses increased with EEG activation.

As expected from the coherent effects of MRF stimulation on synchronization and on the EEG, there was a close correlation between the increase in local synchronization strength and in $\gamma$ power of the EEG across visual responses (average correlation coefficient, 0.341 ± 0.350; $p = 0.0001$, Wilcoxon signed rank test). At 18 of the 36 sites exhibiting $\gamma$ frequency oscillations, the correlation between local synchronization strength and $\gamma$ EEG power was positive and significant at the $p < 0.01$ level (Fig. 13D–F). Local synchronization decreased with increasing $\gamma$ EEG power at only one site. In contrast, at 3 of the 14 sites that at no time showed oscillatory responses, local synchronization decreased significantly with increasing EEG $\gamma$ activity.

Synchronization versus oscillatory modulation

In the pairs exhibiting synchronized visual responses, the cross-correlograms often showed an oscillatory modulation, and the corresponding auto-correlograms were oscillatory at least at one of the two sites. We wondered therefore whether the strength of
synchronization and of oscillatory modulation were related, as suggested by previous studies (König et al., 1995; Volgushev et al., 1998). Comparison of the two variables revealed that the amplitude of \(\alpha\) frequency oscillatory modulation at one or both sites was positively correlated at the \(p < 0.01\) level with the strength of synchronization across sites in 14 of 18 pairs (0.699 ± 0.122, average Spearman rank correlation; Fig. 14, top). Six of the 24 pairs were excluded because the number of correlograms indicative of synchronous responses was too small for statistical evaluation (\(n < 15\)). Likewise, the strength of oscillatory modulation was also positively correlated at the \(p < 0.01\) level with local synchronization at 30 of the 39 sites exhibiting oscillations (average Spearman correlation coefficients: \(\gamma\) frequency oscillations, 0.699 ± 0.148; \(\delta\) activity, 0.652 ± 0.229; \(n = 4\); Fig. 14, bottom). In no case was there a significant (\(p < 0.01\)) negative correlation between the strength of synchronization and the strength of oscillatory modulation of the visual responses (Fig. 14, right).

Figure 10. Transition from nonoscillatory to retinal-like and then to \(\gamma\) frequency oscillatory responses with increasing EEG activation. Top row, Averaged EEG power spectra at consecutive time points without MRF stimulation. Center rows, Averaged sliding window auto-correlograms for responses from sites recorded simultaneously from area 17 in the two hemispheres [right area 17 (RA17), left area 17 (LA17)]. Bottom row, Averaged sliding window cross-correlograms for the two recording sites. Sliding window size, 150 msec; step size, 75 msec; bin width, 2 msec. All sliding window correlation functions are normalized to the total number of spikes in the period. The time course of visual stimulation is indicated at the bottom. Oscillatory modulation was in general absent when the EEG was dominated by \(\delta\) activity (left column). When the \(\gamma\) EEG content increased, the initial phase of the light responses exhibited retinal-like oscillations at \(\sim 95\) Hz that appeared simultaneously at the recording sites in both hemispheres (compare first three columns). As \(\gamma\) EEG power increased further, retinal-like oscillatory modulation decreased again and gave way to a sustained oscillatory modulation in the \(\gamma\) frequency range (30–40 Hz, fourth column). Retinal-like oscillations at this time had disappeared from the responses at site RA17. At site LA17 there is a smooth transition between retinal-like and \(\gamma\) frequency oscillations that is readily seen in single responses. As EEG activation decreased again (right column), \(\gamma\) frequency oscillations disappeared, whereas the transient retinal-like oscillations are again well expressed in the visual responses at both sites.
Interdependence of oscillation frequency, oscillatory modulation, synchronization, and EEG activation

An increase in synchronization strength often went along with a decrease but never with an increase in oscillation frequency of the visual responses. For local synchronization, this relation reached significance \( (p < 0.01) \) at 25 of 39 oscillatory sites and for synchronization across sites in 15 of 18 pairs (average Spearman correlation coefficients, \(-0.644 \pm 0.204\) and \(-0.614 \pm 0.174\), respectively; Fig. 15, right column).

At 21 of 36 recording sites, increasing local synchronization was correlated at the \( p < 0.01 \) level with both increasing oscillatory modulation and decreasing oscillation frequency and at 12 of these sites additionally with increasing \( \gamma \) EEG power (Fig. 15, top row). Likewise, in 12 of 18 pairs stronger intersite synchronization was correlated with both lower oscillation frequency and stronger oscillatory modulation at least at one of the sites and additionally with higher \( \gamma \) EEG power in 7 of these pairs (Fig. 15, bottom row).

For the nine sites where the \( \gamma \) oscillation frequency of visual responses decreased with increasing \( \gamma \) power of the EEG, the strength of the oscillations and of the synchronization increased consistently with decreasing oscillation frequency and increasing \( \gamma \) EEG power (Fig. 16, compare auto-correlograms from left to right). As the \( \gamma \) power of the EEG increased, the modulation of the \( \gamma \) frequency oscillations became stronger, and their oscillation frequency decreased. Local synchronization also increased significantly with both increasing oscillatory modulation and decreasing oscillation frequency at seven of the nine recording sites and with increasing \( \gamma \) EEG power at six of these sites. Likewise, the strength of synchronization across sites increased for 12 pairs with increasing oscillatory modulation and decreasing oscillation frequency in at least one of the sites and with increasing \( \gamma \) EEG power in seven of these pairs (Figs. 15, 16, compare correlograms from left to right).

Taken together, our results demonstrate that oscillatory modulation, oscillation frequency, and synchronization are interrelated. Moreover, all three variables depend on EEG activation, whereby this dependence is most consistent for the strength of oscillation and of synchronization. Because visual responses have been reported to change in strength with central states, we next examined how oscillatory modulation and synchronization related to response firing rates.

Firing rates

Correlation with EEG activation

Overall, variations in response firing rate were not significantly correlated with EEG \( \gamma \) power (Table 2). This was, however, not attributable to independence between firing rates and \( \gamma \) EEG
Figure 13. Relationship between EEG activation and strength of synchronization across (A) or within (B) recording sites. A, Data from three different recording site pairs recorded in different sessions (columns). Each point in the scatterplots represents the strength of synchronization in visual responses (MA, ordinate) and concurrent relative power of the EEG in the various frequency bands (abscissa) averaged over 10 consecutive trials. Insets, Spearman correlation coefficients; *p < 0.01. B, Distribution of Spearman correlation coefficients obtained for each recording pair from all data points (with and without MRF stimulation). Filled bars, p < 0.05. C, Correlation between Spearman coefficients calculated from all data points combined (with and without MRF stimulation, ordinate) and Spearman coefficients obtained exclusively from trials without MRF stimulation (abscissa). One recording pair exhibited synchronization only during MRF stimulation and is therefore not included. Insets, Linear correlation coefficients; p < 0.01 and 0.02, respectively. D–F, Local synchronization of visual responses. Conventions as in A–C. Two of the three sites in A exhibited oscillatory modulation (left and center columns), one did not (right column). F, insets, Linear correlation coefficients; p < 0.0001.
power; rather, these two parameters were often significantly cor-
related but with opposite signs at different sites (Fig. 17). With
spontaneously increasing $\gamma$ power of the EEG, response firing
rates increased significantly ($p < 0.01$) at 27 and decreased at 7 of
53 sites (Table 2). At 21 of these 34 sites, changes in firing rates
were also significantly ($p < 0.01$) correlated with changes in $\delta$
EEG power, and as expected, this relation was inverse to that
found for the dependence on $\gamma$ EEG power. At five other sites,
firing rates correlated only with $\delta$ and not with $\gamma$ power, positively
at three sites and negatively at two. At another two sites, response
firing rates correlated exclusively with changes in $\theta$ EEG power,
negatively at one site and positively at the other. At three sites,
response firing rates correlated exclusively with $\alpha$ EEG power, in
all three cases positively, and at one site the firing rate was
positively correlated with changes in both $\theta$ and $\alpha$ EEG power.
On several occasions, discharge rates at different, simultaneously
recorded sites changed in opposite directions as a function of
EEG activation (see Fig. 5).

Effect of MRF stimulation
The general effect of MRF stimulation was a decrease in response
firing rates by $18 \pm 48\%$; however, firing rates could either
increase or decrease at different sites during this treatment (Table
1). At the $p < 0.01$ significance level (Mann–Whitney $U$ test),
MRF stimulation had significant effects on average response
firing rate at 33 of the 53 sites, causing an increase at 10 sites
(average, $27 \pm 21\%$; Fig. 18A). Because MRF stimulation caused in most cases
an increase in EEG $\gamma$ power, this implies that MRF stimulation
affected firing rates and $\gamma$ frequency oscillations and synchroni-
zation differently. This is in line with the fact that changes in
firing rate with MRF stimulation were not always in the same
direction as changes associated with spontaneous EEG activation.
Of 27 recording sites at which response rates increased with
spontaneously increasing $\gamma$ EEG activity, 8 showed an increase
and another 8 showed a decrease in firing rate with MRF stimu-
lation (Fig. 17c), indicating that there is no simple correlation between firing rates and EEG activation. Of the seven sites at which response rates decreased with increasing EEG γ activity, six also showed a decrease with MRF stimulation. The remaining site was unaffected by MRF stimulation. However, irrespective of whether MRF stimulation enhanced or reduced firing rates, it stabilized the responses, reducing sample variance by 56 ± 40% (p < 0.0001, Wilcoxon signed rank test; Fig. 18B).

Relation among firing rate, oscillations, and synchronization
Variations in firing rate alone could not account for the variations in oscillatory modulation or synchronization. When γ frequency oscillation strength increased with increasing EEG γ power (n = 19 sites), firing rates increased at six sites, decreased at five sites, and remained unchanged at eight sites (significance criterion, p < 0.01, Spearman correlation test). Likewise, of the 13 recording pairs for which synchronization across sites increased coordinately with EEG activation, response rates changed jointly at both sites in 4 pairs (as in Fig. 5), changed in opposite directions in 7 pairs, and were not at all affected at either site in 2 pairs when EEG activation increased. These observations indicate that there is no simple relationship between firing rates and oscillations or synchronization during visual responses, excluding the possibility that increased oscillatory modulation and synchronization of responses with increased central activation was simply a consequence of enhanced responses.
DISCUSSION

Our results demonstrate that synchronous oscillations of visual responses are state-dependent, and that this dependence cannot be attributed to modulation of response firing rates. In fact, there is a clear dissociation in the state dependence of the amplitude of responses on the one hand and their temporal patterning on the other. During states when the EEG was dominated by δ waves, visual responses were still vigorous but exhibited no oscillatory
modulation or synchronization. Furthermore, progressive increases in EEG activation are more consistently reflected at the unitary level in the strength of gamma frequency oscillations and of both local and intercolumnar synchronization than in the firing rate of the underlying visual responses. Thus, transitions from central states that are compatible with sensory processing to states that are not are reflected better by changes in the precise temporal patterning of visual responses than by changes in firing rates.

Oscillatory modulation and synchronization of responses in the mammalian visual cortex are dynamic phenomena that exhibit a high degree of variability in both strength and frequency (Engel et al., 1990; Livingstone, 1996). The present study shows that this variability is tightly linked to state changes. Oscillatory modulation of visual responses and their synchronization do not occur during high levels of delta EEG activity characteristic of slow-wave sleep but are prominent when the EEG exhibits strong gamma activity, characteristic of waking or dreaming states. There is in addition a tight and positive correlation among the strength of oscillatory modulation, the strength of response synchronization, and the amount of gamma power in the EEG, indicating a very dynamic and direct relationship between the temporal patterning of visual responses and the state of cortical activation. The most parsimonious interpretation of this finding is that states characterized by a desynchronized EEG such as arousal or REM sleep facilitate the oscillatory patterning and the synchronization of neuronal responses in the gamma frequency range.

When interpreting variations of neuronal response patterns over several hours, recording stability is a concern. It is unlikely that the observed variability resulted from uncontrolled electrode slip because of the tight and systematic covariance among the various response parameters. Another reason for response variability could have been that a subpopulation of previously silent neurons became responsive during EEG desynchronization. If these newly recruited cells were intrinsically oscillatory, such as chattering cells (Gray and McCormick, 1996), this could account for the close correlation between EEG states and oscillatory patterning of responses. In this scenario, the appearance of an oscillatory modulation should be systematically associated with increased firing rates in the multiunit recordings, but this was not the case. On the contrary, often the increase in oscillatory modulation and synchronicity in the gamma frequency range was associated with a decrease in firing rate, especially with MRF stimulation. The most likely interpretation is, therefore, that activated states are associated with a change in the temporal patterning of individual neuronal responses. This agrees with the evidence obtained from intracellular recordings in the auditory and somatosensory cortex that individual neurons undergo a change in membrane potential fluctuations from large-amplitude, slow (~1–5 Hz) oscillations to low-amplitude, fast (20–40 Hz) oscillations when the state of cortical activation changes, either spontaneously (Steriade et al., 1996) or in response to electrical stimulation of the nucleus basalis (Metherate et al., 1992).

Synchronization and oscillatory modulation of visual responses occurred in two distinct frequency ranges (20–65 and 70–105 Hz), and these two patterns differed markedly in their time course during individual responses, in their dependence on central states, and in the way they were affected by MRF stimulation. The oscillatory modulation in the high-frequency range resembles that described previously in the retina and lateral geniculate nucleus of the anesthetized cat (Neuenschwander and Singer, 1996), suggesting a subcortical origin. This is supported by the evidence that these high-frequency oscillations are synchronized between the retina and cortical areas 17 and 18, whereby the cortical oscillations exhibit a phase lag compatible with feed-forward synchronization (Castelo-Branco et al., 1998). In contrast, the low-frequency oscillations have no retinal counterpart. In the rare cases in which thalamic responses are correlated with the low-frequency cortical oscillations, phase relations indicate a cortical origin of the oscillatory patterning (Castelo-Branco et al., 1998). This agrees with the present evidence that the oscillation frequency and strength of 20–65 Hz oscillations were state-dependent, whereas the respective parameters of the 70–105 Hz oscillations were not. Thus, the oscillatory patterning and the synchronization in the low frequency range appear to be attributable to intracortical interactions, whereas the high-frequency oscillations are secondary to temporally patterned subcortical input.

The occurrence of both gamma frequency and retinal-like oscillations required a minimal level of EEG activation, but the respective thresholds were different. The activation of the mechanisms mediating gamma frequency synchronous oscillations required more activation than the ability of cortical neurons to follow high-frequency oscillatory subcortical input. During transitions from delta-dominated to gamma-dominated EEG activity, the retinal-like oscillations appeared first, and the gamma frequency oscillations appeared only a couple of minutes later (Fig. 10), in which case both oscillatory phenomena could coexist within single visual responses. When activation was further enhanced by MRF stimulation, gamma frequency synchronous oscillations became more prominent, whereas retinal-like synchronous oscillations became reduced or completely suppressed. We propose the following interpretation for the differential state dependence of retinal-like and gamma frequency oscillations. In the nonactivated state, in which the EEG is dominated by delta waves, geniculate neurons would still be able to relay the fast 70–105 Hz retinal oscillations, but cortical neurons can neither follow these oscillations nor engage in the interactions required for the generation of 20–65 Hz oscillations. At higher activation levels, cortical neurons become able to follow the high-frequency modulation of subcortical input, and with further activation, the intracortical synchronizing mechanisms become eventually effective and generate synchronous oscillatory responses in the gamma frequency range. Once the synchronous gamma oscillations appear, they override the oscillatory patterning of the thalamic input, but they are not entirely independent of it. On occasions, a fraction of the discharges of cortical cells oscillating in the range of 30 Hz can be synchronized with activity of other cortical cells or neurons in the lateral geniculate nucleus that oscillate at ~90 Hz (Castelo-Branco et al., 1998), suggesting that the high-frequency oscillatory thalamic input could affect the timing of low-frequency cortical oscillations.

Concerning the oscillations in the gamma frequency range, we consistently observed that responses at some recording sites were nonsynchronous, whereas those at other sites exhibited a strong oscillatory modulation. One possibility is that not all neurons are capable of engaging in oscillatory activity (Engel et al., 1990). Another possibility is that the activation thresholds of the intracortical mechanism responsible for gamma frequency oscillations and their synchronization differ among cell populations. This latter interpretation is supported by the observation that some recording sites exhibited oscillations already at intermediate levels of activation, whereas others became oscillatory only when activation was enhanced further by MRF stimulation. This scenario is further supported by the finding that the probability for a partic-
ular cell group to engage in synchronous oscillatory activity can be altered by conditioning. Repeated induction of highly synchronous responses by combining MRF and light stimulation was found to lead to a lowering of the threshold for the synchronization within the conditioned cell assembly, so that its neurons start to engage in synchronous oscillatory responses at levels of EEG activation lower than prior to conditioning (Herculano et al., 1997).

Despite their different origins, retinal-like and γ frequency oscillations were similar in that oscillatory modulation and synchronization in both frequency ranges increased in strength as oscillation frequency decreased. Interestingly, at some sites oscillation frequency increased within the 20–65 Hz range with increased activation, but in these cases the frequency change was correlated neither with oscillatory modulation nor with synchronization strength. These findings suggest that our recording sites comprised neurons from two physiologically distinct populations. One population could consist of intrinsically oscillatory neurons, which start to oscillate in response to a visual stimulus as soon as sufficient EEG activation occurs, and thereafter increase in oscillation frequency with increasing activation. This latter property is reminiscent of chattering cells, whose visual responses are modulated at higher oscillation frequencies with stronger current injection (Gray and McCormick, 1996). Oscillation frequency in this neuronal population would thus be determined by the interaction between intrinsic cellular properties and the level of EEG activation and would not necessarily correlate with the strength of oscillatory modulation. A second population would, in contrast, consist of neurons whose oscillation frequency is determined not intrinsically but by the actual size of the synchronously oscillating assembly in which they participate. Our data indicate that enhanced EEG activation facilitates neuronal synchronization, both locally and across different recording sites, including cells in different visual areas and even hemispheres. This implies that enhanced cortical activation is associated with recruitment of more neurons into synchronously oscillating assemblies. We propose that this recruitment is the likely reason for the increase in amplitude of the modulation of the correlograms and for the reduction in oscillation frequency (Woelbern et al., 1994; Traub et al., 1996). This interpretation is in agreement with the common observation that there is an inverse relation between oscillation frequency and the modulation amplitude of oscillatory patterning in EEG and field potential recordings. It also agrees with the finding that the very low frequency oscillations characteristic of slow wave sleep are synchronous over very large cortical distances (Steriade et al., 1993).

Although precise synchronization in the γ frequency range became consistently stronger with increased cortical activation, response firing rates could either increase or decrease. This challenges the notion that the main correlate of arousal is an increase in response rate. Rather, our data suggest that states of deep sleep mainly in that the temporally precise stimulus-induced and feature-specific synchronization of neuronal responses occurs exclusively in the former. This suggests that response synchronization is an integrated component of the processes supporting visual perception. Synchronization of visual responses in primary visual cortex is likely to affect profoundly the propagation and integration of synaptic activity at subsequent processing stages (Abeles et al., 1994; König et al., 1996; Singer et al., 1997). Recent evidence from experiments on binocular rivalry indicates that the degree of synchronization among neurons in primary visual cortex is one of the critical variables that determine which of the responses are processed further and control behavior (Fries et al., 1997). We propose that cortical processes supporting sensory experience depend not only on the ability of individual neurons to respond to the features to which they are tuned but also on the ability of cortical neurons to establish temporal relations between their discharges in a stimulus- and context-dependent way, with high temporal precision and spatial selectivity. Such patterning, in turn, appears to be possible only during activated states that are characterized by macroscopically desynchronized EEG activity. Further experiments will be necessary to determine to which extent response synchronization and its spatiotemporal patterning are modulated in addition by attentional mechanisms in the awake, performing brain.

REFERENCES


