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SYNCHRONIZATION OF CORTICAL ACTIVITY AND ITS PUTATIVE ROLE IN INFORMATION PROCESSING AND LEARNING

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INTRODUCTION

The first measurements of the electrical activity of the brain, performed more than 60 years ago with recordings from the scalp, revealed prominent oscillatory activity (19), and until more recently the analysis of oscillatory patterns in the electroencephalogram and in field potentials recorded with intracerebral macroelectrodes has remained a major research tool of neurophysiology. Analyzing the time structure of these wave patterns has established close correlations between the frequency spectrum of the oscillations and changes in the central state of the brain. Different stages of sleep and arousal and also abnormal states such as coma and anesthesia could be identified by relying exclusively on the spectral composition of frequencies in the EEG (for review see 14). However, once it became possible to record the activity of individual nerve cells, interest in field potentials and temporal structures declined. The discovery that the firing rate of neurons in peripheral structures of the nervous system reflected the intensity of sensory stimuli and the speed and force of muscle contractions introduced the notion of rate coding. The evidence of a close relation between the position of a neuron in the brain and its functional properties led to the concept of place coding. The

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message conveyed by a neuron was thought to be defined entirely by the amplitude of the response and its provenance. As a consequence, in single unit studies, time received relatively little attention as a dimension for coding. This is reflected by the fact that neuronal responses to sensory stimuli or activities occurring in relation to motor acts are commonly averaged over successive trials in order to improve the signal-to-noise ratio. This averaging procedure destroys any temporal structure in the activation pattern that is not precisely locked to the stimulus or the motor response. Thus temporal codes were either ignored or undiscovered with the commonly applied methods of single unit analysis.

Recently, however, we have witnessed a dramatic change in attitude and interest. Attention has shifted again towards time as a coding dimension and many think that temporal relations between the responses of distributed neurons are as important a code as relations between response amplitudes. This renaissance of interest in the temporal aspects of nervous activity has several roots, some of which are elaborated in detail below.

Herein recent developments in this rapidly expanding field of research are reviewed with emphasis on the putative significance of self-generated temporal codes in cortical processing. The reason for this restriction is that there are numerous studies on the mechanisms of pattern generation in motor systems, especially in simple organisms, that demonstrate that neuronal processes are highly dynamic and that temporal codes matter (for review see 67). Inclusion of such a large field of research in this review would impose too much selection and arbitrariness.

OSCILLATIONS AND SYNCHRONY

The fact that fluctuations of field potentials can be recorded with macroelectrodes from the scalp or the dura or from within the brain indicates that a large number of neurons must be engaged in synchronized rhythmic discharges at the respective oscillation frequency. Otherwise, the weak currents associated with synaptic activity and action potentials of individual neurons would not result in recordable macropotentials. The occurrence of recordable amplitude fluctuations in macropotential recordings is thus always an indication for coherent activation of a large number of neurons. Such synchronized discharges can occur as a single event in which case they lead to a large, solitary potential. Examples are the ponto-geniculo-occipital waves that are generated in the brainstem in association with saccadic eye movements (82) and REM-sleep episodes (24, 83), or the potentials evoked by sensory stimulation (15). But synchronous discharges can also occur in a repetitive way in which case they give rise to oscillatory field potentials. The intervals between successive bursts can be more or less regular and lead to narrow or

broad band oscillations. The spontaneously occurring field potential oscillations appear to follow the rule that the amplitude of the fluctuations decreases with increasing frequency of the oscillation. This indicates that rapidly oscillating cell assemblies comprise fewer neurons than slowly oscillating cell assemblies.

Particularly low frequency oscillations in the delta range (0.5 to 4 Hz) are observed during slow wave sleep, but also during pathological stages such as anesthesia or coma. Oscillatory activity in the theta range, around 6–7 Hz, is prominent in limbic structures such as the septum, the hippocampus, and the entorhinal cortex during states of attentive arousal. Oscillatory activity in the 10 Hz range, also known as α-activity, occurs during drowsiness or states of relaxation and is particularly pronounced over occipital cortical areas (for a review of the extensive literature see 14, 15). Up to this frequency range, oscillatory activity is of large amplitude and can readily be recorded with macroelectrodes, which indicates that the discharges of a large number of neurons are synchronized and phase-locked to these frequencies. This contrasts with the low amplitude, high frequency fluctuations in the EEG, which characterize high levels of arousal and attention. During these states, the Fourier spectrum of the EEG covers a broad range of frequencies extending from 10 up to 60 Hz. This pattern is commonly referred to as desynchronized EEG and is thought to reflect temporally incoherent activity of spatially distributed neurons. However, analysis with refined methods including digital filtering and intracerebral recording with microelectrodes has revealed the presence of rather regular oscillatory activity also under conditions characterized by desynchronized EEG. These investigations have disclosed oscillatory activity in the β and γ range, i.e. at frequencies between 15 to 30 Hz and 30 to 60 Hz, respectively. These high frequency oscillations occur spontaneously both in humans and higher mammals such as cats and monkeys when the subjects are in a state of focused attention (21, 105, 123, 125, 132, 133, 143), or when they are performing new and complicated motor acts (107). Oscillatory components in the γ-frequency range are also contained in field potential responses evoked by sensory stimuli. This has been shown to be the case for the cortical responses following acoustic (15, 16, 17, 54, 55, 56, 101, 116) and visual stimulation (40, 53, 59, 64, 65), for visual responses in the optic tectum of pigeons (110) and for the event-related P-300-wave that is thought to reflect high level cognitive processes related to selective attention (17). Particularly regular and prominent field potential oscillations in the range of 40 Hz also occur in the olfactory bulb during the inspiration phase of the respiratory cycle (3, 51, 52).

There is thus ample evidence from a variety of brain structures, especially those showing a laminar organization such as the neocortex, the tectum and the olfactory bulb, that groups of cells engage in high frequency synchronous

ctivity even during states when the EEG is desynchronized. With the xception of the olfactory bulb, however, the amplitudes of these high equency oscillations are usually small, thus indicating that the groups of eurons engaged in such synchronous activity are small or dissipated.

These observations indicate that neurons in cortical networks have the ndency to engage in synchronous activity in different distinct frequency ands whereby the probability of occurrence of synchronous activity in a articular frequency range depends on the central state of the brain, on the resence of sensory signals, and on the occurrence of motor acts. This raises ie question as to the functional significance of these synchronization henomena. As far as synchronization in the low frequency band up to 4 Hz ; concerned, it is commonly held that such states of global synchrony are iappropriate for information processing. At these low frequencies very large opulations of cells discharge in unison, and these self-generated rhythmic ischarges are scarely influenced by sensory stimuli. The fact that such large cale synchronization in the low frequency band occurs during sleep and in oma and anesthesia seems to support this notion. It should be emphasized, iowever, that there have been proposals for a functional significance of low requency oscillations in natural sleep in relation to processes of memory nanagement and consolidation (75). The situation is different for the high requency oscillations in the β- and γ-band because these are particularly ironounced in awake performing brains, appear to occur on a less global cale, and show close relations with sensory and motor processes (see below).

THE ORIGIN OF OSCILLATIONS

Oscillatory activity usually results from reciprocal interactions between xcitatory and inhibitory mechanisms. Such interactions are realized either oy coupling between excitatory and inhibitory membrane conductances within he same neuron or by network architectures comprising inhibitory interneu- ons and feedback connections (for review see 94, 95). In the former case, ieurons tend to exhibit oscillatory firing patterns even if isolated, and therefore cells with such membrane properties are addressed as pacemaker cells. In the latter case, the oscillatory behavior is an emergent property of the network architecture. But in most cases, a combination of both mechanisms occurs. This has been demonstrated for thalamic oscillators where recurrent inhibition is implemented together with pacemaker neurons (for reviews see 103, 146). Less data are available on neocortical oscillations. Experiments in slices have revealed the existence of cells with pacemaker currents tuned to different oscillation frequencies including the γ-band (96, 134). Moreover, there is evidence from in vivo studies that cortical networks have a tendency to engage in rhythmic activity at various preferred frequencies between 10 and 40 Hz

(122). However, it is still unknown to what extent these preferences for distinct resonance frequencies are determined by pacemaker neurons and network properties, respectively. Detailed simulations of cortical networks with oscillatory behavior have been performed for the hippocampus (152) and recently also for the neocortex (26, 100, 161, 162).

THE BINDING PROBLEM, ASSEMBLIES, AND TEMPORAL CODES

In order to appreciate the putative functional role of synchrony and oscillations in the neocortex, current concepts on the nature of cortical representations need to be considered. There is growing evidence that both perceptual and motor functions of the neocortex are based on distributed processes. These occur in parallel at different sites and always involve vast numbers of neurons that, depending on the complexity of the task, may be disseminated throughout the whole cortical sheath. In the visual system, for example, even simple sensory stimuli evoke highly fragmented and widely distributed activity patterns. Because of the columnar organization of cortical areas, neurons preferring the same features or coding for adjacent points in visual space are often segregated from one another by groups of cells preferring different features. In addition, different features such as contours, color, depth, and motion are often processed in separate, non-contiguous cortical areas (38, 50, 112, 156, 163, 165, 166). Thus a particular visual object elicits responses in a large number of spatially distributed neurons each of which encodes only a partial aspect of the object. This raises the intriguing question, commonly addressed as the binding problem, of how these distributed activities are reintegrated in order to generate unambiguous representations of objects in the brain. One widely accepted proposal is that there are areas in the brain where all these distributed activities reconverge onto neurons that respond in a highly selective manner only to those constellations of features that characterize a particular natural object (13). However, this concept faces several problems. First, cells in areas occupying higher levels in the processing hierarchy are often less selective for particular features than those at earlier stages. Second, apart from cells responding preferentially to features of faces and hands (18, 37, 68, 117, 124), no other object-specific cells have been found so far. Third, it has been argued that there would probably not be enough cells in the brain if all distinguishable objects including their many different views would each have to be represented by a specialized neuron. Fourth, even if objects and their different views are represented in a more economical way by interpolation in small groups of neurons (118), no single area in the visual processing stream has been identified so far that could serve as the ultimate site of convergence and that would be large enough to

accommodate the still exceedingly large number of required neurons. Fifth, one would have to postulate a large reservoir of uncommitted cells in order to allow for the representation of new, hitherto unknown objects. These neurons would have to maintain latent input connections from all feature-selective neurons at lower processing stages. For the representation of new objects, the subsets of these connections, which are activated by the unique feature constellation of the new object, would have to be selected and consolidated instantaneously.

Alternative concepts have therefore been developed. They are all based on the assumption that representations consist of assemblies of a large number of simultaneously active neurons that are distributed over many cortical areas (1, 22, 33, 42, 43, 44, 69, 73, 114, 115, 136, 137, 158). The essential advantage of assembly coding is that individual cells can participate at different times in the representation of different objects. The assumption is that just as a particular feature can be shared by many different patterns, a particular neuron can be shared by many different representations in that it participates at different times in different "assemblies" of co-active neurons. The code is thus relational, the significance of an individual response depends entirely on the context set by the other members of the assembly.

A basic requirement for representing objects by such assemblies is, of course, that neuronal elements that have joined a particular assembly are identifiable as members of this very assembly and distinguishable from members of other assemblies. Their responses have to be labeled so that they can be recognized as being related. This labeling is thought to be achieved by selective reciprocal connections between the neurons constituting an assembly. It is further assumed that these connections are endowed with adaptive synapses, the efficiency of which can change in a use-dependent way according to some kind of associative learning algorithm. Such adaptivity is required in order to allow for the modification of assemblies and hençe for the representation of new objects and patterns. Several proposals have been made concerning the mechanisms by which these connections could serve to label the responses of neurons that have joined into the same assembly. The proposal that is most pertinent to the experiments on response synchronization in the visual cortex was formulated a decade ago by von der Malsburg (158, 159), who suggested that the selective connections should establish temporal coherence on a millisecond time scale between the responses of the coupled cells, thereby making these responses distinguishable as coming from the same assembly. Thus neurons joining into an assembly should synchronize their discharges. Expressing relations between members of an assembly by such a temporal code has the additional advantage that several assemblies can be active simultaneously in the same cortical area without becoming confounded. Assemblies that code for different figures in a scene could each

engage in their own rhythm. Consequently, even if responses of neurons overlap on a coarse time scale they remain distinguishable as members of a particular assembly because their responses are correlated at a millisecond time scale with the responses of other cells of the same assembly, but not with cells of other assemblies. This concept of binding by synchrony has been developed further and generalized to intermodal integration (35) and even to integrative processes underlying phenomena such as attention (33) and consciousness (34). The implementation of this temporal coding principle in artificial neuronal networks has proven, that it is indeed very effective. It offers new solutions to segmentation problems that have been notoriously difficult to resolve with amplitude and position codes alone (12, 36, 41, 70, 85, 87, 88, 129, 130, 139, 140, 141, 148, 155, 159, 162).

EXPERIMENTAL SEARCH FOR SYNCHRONIZATION

Since assemblies are solely defined by relations between the responses of their constituting elements, they can only be identified by recording simultaneously from spatially distributed neurons in the brain and by evaluating relations between these responses (1, 4). Such correlation studies have been performed, but until recently they failed to disclose interactions of the kind postulated by the temporal binding hypothesis. The main reason is probably that most of these cross-correlation analyses had been performed to identify anatomical connections rather than to test the concept of temporally coded assemblies. Hence, stimulation and evaluation procedures were not designed to disclose dynamic interactions that depend on stimulus configuration. Many of the cross-correlation studies have actually been based on the analysis of spontaneous activity, which is appropriate for disclosing anatomical connectivity but not stimulus-induced dynamic coupling. Most of the interactions revealed by these analyses occurred only over very short distances and could be accounted for by assuming that the considered cell pairs receive either common excitatory or inhibitory input, or excite or inhibit one another, or have their firing probability influenced by common modulatory input (2, 7, 60, 92, 104, 109, 131, 150, 151, 153, 154).

A new motivation to reinvestigate the hypothesis of temporal coding by cross-correlation analysis came from the observation that spatially adjacent neurons in the cat visual cortex have a strong tendency to engage in highly synchronous oscillatory discharges (64, 65). This observation indicated that responses of feature-specific neurons have a distinct temporal patterning that could, in principle, be used for the labeling of assemblies by a temporal code. Moreover, it proved that groups of neurons can temporarily synchronize their responses as postulated by the hypothesis of temporal coding. This opened the possibility to investigate synchronization phenomena at the single cell

level in the visual cortex, one of the best explored structures of the brain, whose putative functions are well defined by a large body of psychophysical data and theoretical concepts.

The phenomenon of local response synchronization has since then been observed at the multi-unit level in several areas of the visual cortex of anesthetized (40, 49) and awake cats (121), in the optic tectum of awake pigeons (110), and recently also in the visual cortex of anesthetized (93) and awake behaving monkeys (91). When presented with their preferred stimulus, neurons spaced close enough to be recorded simultaneously with a single electrode tend to engage in synchronous discharges. These are grouped in bursts that follow each other at intervals of 15–30 ms and hence appear as oscillations in the γ-frequency band. Each of these bursts is associated with a large negativity in the field potential, which is recorded from the same electrode (61, 65). Hence, the local field potential (LFP) exhibits pronounced oscillations in the range of 30 to 60 Hz. The frequency of these oscillations usually fluctuates over a range of 5 to 10 Hz even within a single oscillatory response. Episodes with constant frequency last only for 100–300 ms and can recover several times throughout the response to a continuously moving stimulus (61, 62, 91). Neither the time of occurrence of these synchronized response episodes nor the phase of the oscillations are related to the position of the stimulus within the neuron's receptive field. When cross-correlation functions are computed between responses to subsequently presented identical stimuli, these shift predictors reveal no relation between the respective time series (61, 65). It has further been shown in anesthetized and awake cats (45, 63, 90, 91, 121) and anesthetized and awake monkeys (90, 91) that similar response synchronization can occur also between spatially segregated cell groups recorded with different electrodes within the same visual area. These episodes of synchronization usually occur at times when the local groups of neurons are also engaged in synchronous repetitive bursting. Hence, the cross-correlograms typically show a broad peak centered around zero delay, which is flanked on either side by troughs reflecting the synchronous bursts and the pauses between the bursts. When the duration of these pauses is sufficiently constant throughout the episode of synchronization, the cross-correlograms show a modulation with multiple peaks and troughs.

The Feature Dependence of Response Synchronization

Detailed studies in anesthetized cats and recently in monkeys have revealed that synchronization probability for remote groups of cells depends on the spatial segregation and the feature preference of the respective cell groups as well as on the configuration of the stimuli (45, 38, 63, 90). Stimuli, which according to common Gestalt criteria appear as single figures, lead to

synchronization among the responding groups, while stimuli appearing as independent figures or as parts of different figures fail to establish synchrony among the groups they excite (48, 63). Gestalt criteria investigated so far comprise continuity, vicinity, and common motion.

In agreement with a central prediction of the assembly hypothesis is the recent demonstration that two different, spatially overlapping stimuli can be represented by two independently synchronized assemblies of cells and that individual groups can switch between different assemblies depending on stimulus configuration (48). If groups of cells with overlapping receptive fields but different orientation preferences are activated with a single moving light bar, they synchronize their responses even if some of these groups are suboptimally activated (48). However, if such a set of groups is stimulated with two independent stimuli that move in different directions, they no longer form one coherently active assembly, but split into two independently synchronized assemblies; those groups join the same synchronously active assembly that shows a preference for the same stimulus. Thus the two stimuli become represented by two spatially interleaved but temporally segregated assemblies. Groups representing the same stimulus synchronize their responses, while no consistent correlations exist between the activities of assemblies representing different stimuli. Local response parameters of the individual groups such as the amplitude or the oscillatory patterning of the responses are unaffected by changes in the global configuration of the stimuli. Thus it is not possible to tell from the responses of individual groups whether they were activated by one coherent stimulus or by two different stimuli. The only clue for this distinction is provided by the evaluation of synchronicity of the responses of the activated groups. These results indicate that response synchronization between simultaneously activated groups depends not only on the feature preference of the respective groups but also and, to a crucial extent, on stimulus configuration. One methodological caveat following from this is that cross-correlation analysis does not reliably reflect anatomical connectivity (see also 4). The conclusion is that the coupling between distributed cell groups is dynamical and can change in a stimulus-dependent way.

Synchronization Between Areas

The hypothesis of assembly coding further implies that assemblies should be distributed entities extending across different cortical areas. In agreement with this prediction, response synchronization in the γ-frequency range has also been found between groups located in different cortical areas. In the cat, interareal synchronization has been observed between cells in areas 17 and 18 (40, 109), between cells in area 17 and area PLMS, an area specialized

for motion processing (49), and even between neurons in A 17 of the two hemispheres (47). In all of these cases, synchronization depended on receptive field constellations and stimulus configurations, similar to the intraareal synchronization (49, 47). Assemblies of neurons with temporally coherent responses can thus be widely distributed and comprise cell groups located in different cortical areas.

The Substrate for Response Synchronization

It is commonly assumed in cross-correlation studies that synchronization of neuronal responses with zero-phase lag is indicative of common input (57). It has been proposed, therefore, that the observed synchronization phenomena in the visual cortex are due to common oscillatory input from subcortical centers. This notion has received support by the discovery of oscillatory activity in the 40 Hz range in thalamic neurons (58, 59, 145). However, synchronization by common subcortical input would alone be incompatible with the postulated role of synchronization in binding because it would neither allow for the required combinatorial flexibility nor for the dependency on feature constellations. The concept of assembly coding requires that the binding together of elements constituting an assembly is achieved through reciprocal connections between the elements of an assembly and not only by common input. This, however, was thought to be unlikely because it seemed difficult to establish synchronization with zero-phase lag by reciprocal interactions between spatially distributed neurons given the rather long conduction delays in the coupling connections. Recently, however, evidence has been obtained that response synchronization with zero-phase lag can indeed be achieved by cortico-cortical connections despite considerable conduction delays. It has been demonstrated that the response synchronization between cell groups in area 17 of the two hemispheres is abolished by severing the corpus callosum and hence is brought about by this reciprocal cortico-cortical projection (47). Response synchronization between the two hemispheres follows the same rules as synchronization between cells in area 17 of the same hemisphere, i.e. synchrony is established only by stimuli that, according to Gestalt criteria, appear as components of a single object. This further emphasizes the putative significance of response synchronization for perceptual grouping because it agrees with the postulate that components of objects that extend across the vertical meridian of the visual field and are projected to different hemispheres need to be bound together in the same way as components of objects that are projected only to one hemisphere. In the meantime, simulation studies are available that confirm that it is possible to establish synchrony without phase lag in the absence of common input and despite variable conduction delays in the synchronizing connections (89, 126, 129, 130).

Experience-Dependent Development of Synchronizing Connections

The theory of assembly coding implies that assemblies are bound together by the coupling connections between the constituting elements. Therefore, the criteria according to which particular features are grouped together reside in the functional architecture of the connections. If this architecture is specified entirely by genetic instructions, perceptual grouping criteria will have to be regarded as genetically determined. If the architecture is modifiable by activity and hence experience, criteria for the segmentation of the visual scene into distinct figures could be acquired by learning. The numerous interindividual similarities in the layout of cortico-cortical connections indicate that basic principles of organization such as laminar termination patterns and maximal spatial extent are determined genetically. But there is also evidence for extensive epigenetic modifications. In mammals, cortico-cortical connections develop mainly postnatally (27, 78, 98, 119) and attain their final specificity through an activity-dependent selection process (28, 80, 99, 120).

Direct evidence that this selection is based on a correlation analysis and leads to disruption of connections between cells that exhibit mainly decorrelated activity comes from experiments with strabismic kittens (97). Raising kittens with artificially induced strabismus leads to changes in the connections between the two eyes and cortical neurons so that individual cortical neurons become connected to only one eye (77). Thus the population of cortical neurons splits into two subpopulations of about equal size, each responding rather selectively to stimulation of one eye only. This reorganization goes along with a modification of perceptual abilities. Strabismic subjects usually develop normal monocular vision in both eyes but they become unable to bind signals conveyed by different eyes into coherent percepts even if these signals are made retinotopically contiguous by optical compensation of the squint angle (160). This indicates that in strabismics, binding mechanisms are abnormal or missing between cells driven from different eyes. Recently, it was found that in strabismics, response synchronization does not occur between cell groups connected to different eyes, while it is normal between cell groups connected to the same eye (86). Moreover, it was found that cortico-cortical connections had reorganized and unlike in normal animals, no longer connected neurons receiving input from different eyes (97).

These results have several important implications. First, they corroborate the notion that tangential intracortical connections are the substrate for response synchronization. Second, they support the view that response synchronization serves perceptual binding. Third, they prove that the architecture of tangential connections is shaped by experience, and fourth, they suggest that this selection occurs according to a correlation rule in similar

ways as experience-dependent circuit selection at other levels of the visual system (for reviews see 138, 147).

RESPONSE SYNCHRONIZATION OUTSIDE VISUAL CORTEX

Apart from the studies in the visual cortex, which have been reviewed above, only few investigations have addressed the question of stimulation or context-dependent synchronization across spatially segregated groups of neurons. So far data are available only for the somatosensory and motor cortex (107), the acoustic and the frontal cortex (5, 157), and the pigeon optic tectum (S. Neuenschwander & F. Varela, in preparation). In every case, evidence has been obtained for transient interactions between simultaneously recorded neurons. As in the visual cortex, these episodes of manifest interactions were usually of short duration. In the acoustic and frontal cortex, the type of interaction was variable, in the optic tectum and the somato-motor cortex the interactions resembled those in the visual cortex, i.e. the cells synchronized their responses with zero-phase lag. Some indications are available that these episodes of coupled discharges and synchrony are correlated with behavior. Synchronization between units in somatosensory and motor cortex is particularly pronounced while the monkey tries to solve a difficult reaching task, but prolonged oscillations vanish once the task is learned and reaching is executed without difficulty (107). Synchronization between units in the frontal cortex has been reported to occur in contiguity with certain behavioral sequences in a complex delayed matching to sample task (5). Finally, there is the evidence for γ-range field oscillations during the P-300 event related potential. This potential is considered a correlate of cognitive processes related to attention (54). Its association with γ-oscillations might indicate therefore that synchronicity in the γ-frequency range is functionally relevant.

OSCILLATIONS, SYNCHRONY, AND THE PROBLEM OF EPIPHENOMENA

While these experimental results are all fully compatible with the hypothesis that response synchronization serves as a binding mechanism, the possibility needs to be considered that synchrony and oscillations are epiphenomena of a system's properties that have evolved for a completely different purpose.

Before discussing possible functional roles of oscillations and synchrony in a broader context, it needs to be emphasized that the two phenomena, while apparently often occurring together, do not necessarily depend on one another. Individual neurons can engage in oscillatory activity without necessarily being synchronized with other cells, likewise different cells can exhibit synchronous

discharges in the absence of narrow or broad band oscillations. One extreme case is that two cells always discharge simultaneously but at irregular intervals, which have a Poisson distribution. This condition is frequent for cells driven by common input, e.g. for neighboring cells in the lateral geniculate nucleus (8). Another case is the occurrence of simultaneous but nonrepetitive burst responses in several cells. This is seen, for example, during PGO waves (135).

Oscillations as a Prerequisite for Synchrony

As reviewed in the introduction, oscillatory activity frequently appears to be associated with synchrony, which raises the question of whether and if so how oscillatory processes are related to synchronization. One possibility is that oscillatory activity favors the occurrence of synchrony. In oscillatory responses, the occurrence of a burst predicts with some probability the occurrence of the next. It has been argued that this predictability is a necessary prerequisite to synchronize remote cell groups with zero-phase lag, despite considerable conduction delays in the coupling connections (46). This view is supported by simulation studies that have shown that zero-phase lag synchronization can be achieved despite considerable conduction delays and variation of conduction times in the synchronizing connections if the coupled cell groups have a tendency to oscillate (89, 126, 129, 130). Another feature of networks with oscillatory properties is that network elements that are not linked directly can be synchronized via intermediate oscillators (89). This may be important, for instance, to establish relationships between cell groups lacking direct reciprocal connections, as is the case for remote cell groups within the same cortical area, or for cells distributed across cortical areas that process different sensory modalities. In both cases, linkages either via intermediate cortical relays or even via subcortical centers must be considered. The latter possibility is supported by the occurrence of gamma oscillations in a variety of thalamic nuclei (58, 59, 106, 145). These considerations suggest that oscillations, while not conveying any stimulus-specific information per se, may be instrumental for the establishment of synchrony over large distances and hence for the formation of temporally coded assemblies.

Synchronization is particularly easily achieved in networks that are sharply tuned to a single resonant frequency. If it is the role of oscillatory activity to facilitate synchronization, the question arises, why are the observed oscillations so irregular and cover such a broad frequency range? The reason for this could be that cell groups can be desynchronized more easily if their oscillations are broad-banded, and thus the network can be prevented from entering global states of synchrony that would be inappropriate for information processing. Furthermore, the number of assemblies that can coexist in the same cortical region is increased if the oscillation frequencies are variable because spurious correlations due to aliasing effects will be rare and only of

short duration. Thus a broad banded oscillatory signal appears as a reasonable compromise between several opposing constraints.

Why Should Oscillations Occur in the γ-Frequency Range?

The other question is why do the stimulus-induced synchronization events occur on the basis of oscillations in the γ-range and not on the basis of the more prominent low frequency oscillations? The following considerations suggest that there may be good reasons why mechanisms subserving perceptual grouping at low levels of visual processing should operate at such a rapid time scale.

Psychophysical studies show that segmentation of natural scenes can be accomplished within 100 to 200 ms (20, 25). If several simultaneously active assemblies have to be distinguished, a few successive synchronous bursts will have to be evaluated before such distinctions become possible. Thus oscillations in the α- and β-frequency range would be too slow to serve as carrier signal for binding at this level of processing. But much higher frequencies than those observed experimentally would not be tolerable because the conduction times of coupling connections do not allow establishment of synchrony at much higher frequencies. Simulation studies indicate that reciprocally coupled groups of neurons can only be synchronized if the coupling delays do not exceed about one third of the average period time. For much larger delays, temporal correlation with zero-phase lag cannot be established (89, 126, 129, 130). Transcallosal synchronization, for example, which has to cope with delays of at least 5 to 6 ms (79), requires a minimum period time of roughly 15 ms. Thus oscillatory activity in the γ-range appears as a good compromise between the opposing constraints to establish synchrony rapidly and with high temporal resolution on the one hand and over long distances on the other. The first requires rapid succession of short bursts, the latter sets an upper limit to the frequency of reverberation.

Oscillations as a Consequence of Synchrony

These considerations suggest that oscillatory activity might be instrumental for and causally related to synchrony. However, it is also conceivable that oscillations occur as a consequence of synchrony. Disregarding for a moment the difficult question of how an assembly of interconnected cells could reach a state where they emit a first synchronous burst, it is easy to see that once such a synchronous burst has occurred there will be a pause and most likely another synchronous burst, and so on. The reasons for the pause are twofold. First, a synchronous discharge in a population of cells generates strong and simultaneous inhibition in the same pool of cells due to recurrent inhibition (see e.g. 39). Second, the burst responses will activate Ca^{2+}-dependent K conductances, and these will contribute to the reduction of excitability (94, 95). Upon fading of these inhibitory events, firing probability will increase simultaneously for all cells and this, together with maintained excitatory input and nonlinear voltage-gated membrane conductances such as the low threshold Ca^{2+}-channels (95), will favor the occurrence of the next synchronous burst, and so on. Thus oscillations are a likely consequence of synchrony and it actually becomes an important issue to understand how cortical networks can be prevented from entering states of global oscillations and, if they do, how these can be terminated. This issue has recently been addressed in a number of simulation studies (72, 76, 87, 88, 127, 128, 142, 159).

DETECTABILITY AND FUNCTIONAL SIGNIFICANCE OF γ OSCILLATIONS IN SINGLE UNIT RECORDINGS

Independent of the question of whether oscillatory activity is instrumental for the establishment of synchrony or whether it is just a consequence, oscillatory activity is interesting because it may serve as an indicator of synchrony. On the other hand, not observing oscillatory activity does not imply that there is no synchrony. This is particularly true for single unit recordings. The results from the visual cortex (61) and in particular from the olfactory bulb (52) clearly indicate that individual discharges of single units may be precisely time-locked with the oscillating field potential, which proves that these discharges occurred in synchrony with those of many other cells, without, however, showing any sign of oscillatory activity in their autocorrelation function. The reasons for this apparent paradox are sampling problems and non-stationarity of the time series. If the single cell does not discharge at every cycle and if the oscillation frequency is not perfectly constant over a period of time sufficiently long to sample enough discharges for an interpretable autocorrelation function, the oscillatory rhythm to which the cell is actually locked will not be disclosable. Thus the less active a cell and the more variable the oscillation frequency, the less is it legitimate to infer from non-periodically modulated autocorrelograms that a cell is not oscillating, or even less, not synchronized with other cells. This sampling problem becomes more and more accentuated as the frequency of the oscillations increases. This explains why γ-band oscillations have been observed first with macroelectrodes and remain difficult to observe with microelectrodes unless one can record from several coupled cells simultaneously.

Accordingly, while there are numerous field potential studies indicating the presence of γ-oscillations in many different cortical and subcortical areas (see introduction,) single unit analyses designed specifically for the search of γ-oscillations have failed to disclose them in a number of cortical areas or have led to controversial results. At present, all investigators agree that oscillating unit activity in the γ-range occurs in the primary visual cortex of

cats and monkeys, whether anesthetized or awake (40, 58, 59, 64, 65, 81, 121), in cat area 18 (40, 65), and in area PMLS of cat visual cortex (49). For area MT(V5) of the monkey visual cortex, there is one positive (91) and one negative report (164). No evidence was found in temporal visual areas of the monkey (149), but Nakamura et al (108) observed both low and high frequency oscillations associated with a recognition task in the temporal pole of macaca mulatta. High frequency oscillations in single cell activity have also been observed in somatosensory cortex where they were suppressed during sensory stimulation (6), and in the frontal cortex where they occurred in relation with particular behavioral sequences (5). Finally, oscillatory multi-unit responses similar to those occurring in the cat visual cortex have been observed in the optic tectum of awake pigeons (110). These data confirm that the single unit level the evidence from field potential and EEG recordings that oscillatory activity in the γ-range is a wide spread phenomenon.

However, it needs to be emphasized that the presence or absence of a regular oscillatory time structure in single cell responses neither proves nor disproves that spatially segregated cells discharge in synchrony. Oscillations per se are thus of little diagnostic value for the validation of the temporal coding concept. What really matters is synchrony and the dependence of synchronization probability on stimulus configuration. But these features can only be assessed by recording from several units simultaneously. Nevertheless, oscillations are of interest because they indicate organized activity and can be used to guide the search for synchronous events.

The Role of Synchrony in Signal Transmission and Synaptic Plasticity

While it is debatable whether response synchronization is of functional relevance in the context of binding, there can be no doubt that synchronization of neuronal discharges is of eminent functional importance for signal transmission and neuronal plasticity. Because neurons have a firing threshold and because synaptic potentials have a finite duration, signal transmission probability depends critically on the temporal structure of afferent input activity, synchronous input being the most effective of all possible constellations. This is particularly important for structures such as the neocortex, which are characterized by sparse connectivity. Statistical considerations on cortical connectivity indicate that a single neuron contacts a particular target cell with only a few synapses (1). Thus a cell will only be able to drive a follower cell if it is active in synchrony with many other cells that contact the same follower cell. Moreover, it becomes increasingly clear that synchronization is of outstanding importance for all processes of use-dependent synaptic plasticity. This holds both for the activity-dependent shaping of neuronal connectivity during development and use-dependent changes of synaptic gain in the mature

brain (for review see 32). The reason is that the processes that lead to modifications in synaptic connectivity and in synaptic gain have thresholds that are voltage-dependent. Thus it has been shown that experience-dependent modifications of connections in the developing visual cortex occur only if the target cells of the modifiable connections are activated beyond a critical threshold (66), and it was possible to relate this threshold with the activation of NMDA-receptor-gated Ca^{2+}-conductances (29, 31, 84, for review of the extensive literature see 138). For synaptic gain changes in the mature cortex, two thresholds have been identified. If neurons are driven above a first threshold, modifiable synapses undergo a long-term depression (LTD) and when a second threshold is reached, they undergo long-term potentiation (LTP) of their efficacy (9, 74). The first threshold appears to be related to the activation threshold of voltage-gated Ca^{2+}-channels (9, 23), while the second is related to the activation of NMDA-receptor-gated conductances (10, 11). Rather similar conditions are found for synaptic modifications in the hippocampus and a variety of other brain structures (for review see 71). Thus the probability of occurrence of a synaptic modification and its direction, increase or decrease of efficacy, depend on the level of postsynaptic depolarization and hence directly on the synchrony of discharges in the afferents converging onto a particular neuron. Synchronously active inputs are likely to become enhanced, while inputs that are active out-of-phase with other synchronous inputs are likely to undergo depression (see e.g. 144). Finally, if there is no synchrony between any of the converging afferents, modifications are unlikely to occur because the relatively high modification thresholds will not be reached. It follows from this that the temporal coordination of distributed neuronal responses is crucial not only for signal transmission, but also for synaptic plasticity.

The Role of Oscillations in Synaptic Plasticity

The fact that the temporal correlation between converging inputs to a cell is a criticial variable in use-dependent plasticity adds a further aspect to the putative functional significance of an oscillatory time structure in neuronal discharge patterns. The responses of neurons are usually rather long, extending over several 100 ms. Thus most of the responses evoked by a visual scene in the visual cortex are overlapping in time. According to the established synaptic modification rules, this would in the long run increase the gain of most of the coupling connections in the visual cortex and hence lead to unselective and meaningless association of neurons. This superposition problem can be avoided if the responses of the connected neurons have an oscillatory time structure. In that case, the membrane potential alternates rapidly between de- and hyperpolarizing phases (81). As a consequence, only those of the simultaneously active, oscillating inputs will have a chance to improve

synaptic gain, which oscillate in precise synchrony with the target cell. Only then will the active synapses be able to activate voltage-sensitive NMDA-receptor-gated conductances (102, 113), which has been identified as a necessary prerequisite for homosynaptic potentiation of synaptic transmission in hippocampus (30) and neocortex (10, 11). Inputs whose oscillatory responses are out of phase with the oscillatory activity of the postsynaptic cell, or exhibit a fixed phase shift, will either become depressed or remain unchanged depending on their phase relation with the cell's activity. Direct support for this prediction comes from results obtained in the hippocampus (144). The coincidence criterion for synaptic gain changes is then determined by the frequency of the oscillation of a response rather than by the overall duration of a response. For oscillations in the γ-frequency range, this implies that the temporal window for cooperative interactions between converging inputs narrows down to 10 ms and less. Thus imposing an oscillatory burst and pause modulation on neuronal responses improves by an order of magnitude the temporal precision with which mechanisms that rely on coincidence detection and cooperativity can operate.

In a sense the functional role of temporally structured responses in synaptic plasticity is the same as that proposed for assembly coding. It serves to resolve superposition problems by providing a fine grain temporal code to express relations. Thus considerations on assembly coding and on synaptic plasticity both lead to the same postulate of a temporal code that relies on synchrony at a millisecond time scale. This convergence is, of course, not unexpected because both the formation of assemblies and use-dependent synaptic modifications are intimately related. In order to assure that a particular constellation of features always leads to the emergence of the same assembly of coherently active neurons, an architecture of synchronizing connections has to be developed that assures preferential coupling between the neurons constituting this assembly. Hence, connections between cells that have repeatedly been part of an assembly should strengthen and consolidate. According to the concept of temporal coding, the signature for cells belonging to an assembly is the synchronization of their temporally structured responses. As synchrony between pre- and postsynaptic activation is at the same time the condition that favors strengthening of synaptic connections, the same temporal code that serves to distinguish the neurons of an assembly can thus be used to distinguish the connections that need to be reinforced to stabilize an assembly.

In conclusion, several independent lines of argument concerning the nature of neuronal representations, the constraints for signal transmission, and conditions of use-dependent synaptic plasticity all lead to the postulate of a temporal code. All emphasize the significance of synchrony at a millisecond time scale. This in turn requires a temporal structure in neuronal responses that allows first for the distinction of synchronous from asynchronous states

with high temporal resolution, and second for the establishment of synchrony over large distances. Both of these requirements appear to be met best by oscillatory discharge patterns in which bursts and pauses follow one another with a certain degree of regularity that should be neither too high nor too low. The fact that such rhythmic, synchronous activities are ubiquituous in the brain suggests that temporal codes may indeed be of similar importance as position and amplitude codes. The evidence that the average frequency of these rhythms changes in a state-dependent way and differs in different brain structures would then indicate that different states and different functions require integration at different temporal and spatial scales. As the rhythm slows down, the temporal window during which events can be distinguished as synchronous or asynchronous broadens, temporal discrimination becomes less precise, but binding by synchrony can be achieved over larger distances and between more cells. The consistent observation that the amplitude of field potential oscillations increases as oscillation frequency decreases underlines this inverse relation between oscillation frequency and size of synchronously active cell assemblies.

OUTLOOK

In order to obtain direct evidence in support of or against the hypothesis that response synchronization serves as a code for neuronal processing, experiments are needed in which causal relation can be established between the occurrence of response synchronization in defined subgroups of neurons and particular functions that need to be assessed at the behavioral level. This will require simultaneously recording from several selected areas in the brain of awake behaving animals with techniques that enable assessment of response synchronization with high temporal resolution. With the techniques that are currently available, the number of recording sites that can be examined simultaneously is bound to remain small. This poses a severe sampling problem. For the brain, one or two bursts may be a highly significant event if they occur simultaneously in a large number of cells. Hence, for non-ambiguous conditions, the episodes characterized by synchronization can be kept very short and in extremis can be restricted to one or two bursts. For the experimenter, however, who can only look at a few cells, such brief events of synchrony may pass undetected, and may be deemed significant only if they recur. Thus until new techniques become available, the relationship between synchronization and behavior will be detectable only for conditions where synchronization is maintained long enough to be observed, even if only a few cells can be looked at simultaneously. This may confine the behavioral conditions suitable for such analyses to problem-solving tasks that are difficult, fraught with ambiguity, and require long periods of sustained, focused

attention. It might be rewarding in this context to reconsult the EEG literature for the identification of behavioral states that are likely to be associated with response synchronization in the γ-frequency band.

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THE MECHANISM OF EXPRESSION OF LONG-TERM ENHANCEMENT OF HIPPOCAMPAL SYNAPSES: Current Issues and Theoretical Implications

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INTRODUCTION AND HISTORICAL OVERVIEW

At least since the time of Hebb (49) it has been an act of faith within the psychological, neuroscience, and theoretical neural network communities that some persistent form of synaptic modification must underlie memory. The principal reason for this faith is simply that other proposals (e.g. molecular storage, altered threshold, etc) have led to a theoretical impasse when confronted with the problems posed by both capacity requirements and associative recall. The theory of how information can be associatively stored and retrieved through a variety of hypothetical synaptic "weight"-change rules is now well developed. With such rules, rather remarkable results have been obtained in the fields of cognitive science and artificial neural networks, both in capturing essential features of human or animal psychological data, and in solving intractable problems involving complex, nonlinear input-output mappings (for review see 50). These modification rules have one element in common: the involvement of the postsynaptic neuron as an essential locus of control.

Beginning in the late 1950s and continuing through the 1960s, a few

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