CONTEXTUAL EFFECTS IN THE PRIMARY VISUAL CORTEX OF ANESTHETIZED CATS

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2. **Biederlack, J.,** Castelo-Branco, M., Goebel, R., Singer, W. and Neuenschwander, S., (2000). Contextual effects in cat visual cortex differ for firing rates and neuronal synchrony. Forum of European Neuroscience, EJN 12 (Supp. 11):196.

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4. **Biederlack, J.,** Castelo-Branco, M., Goebel, R., Singer, W. and Neuenschwander, S., (2003). Dynamical formation of synchronous assemblies observed through simultaneous recordings from a large number of cells. Society for Neuroscience's 33rd Annual Meeting, New Orleans, November 08-12, 2003.

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Zusammenfassung

Im visuellen System der Katze können die Feuerraten individueller Neuronen bereits in sehr frühen Verarbeitungsstufen beeinflusst werden, wenn zusätzlich zur Stimulation des klassischen rezeptiven Feldes ein weiterer Stimulus außerhalb dieses Feldes präsentiert wird. Es wird vermutet, dass diese „kontextuellen Effekte“ für Verarbeitungsprozesse, die der Figur-Grund Unterscheidung und/oder der Objekt-Segregation zugrunde liegen, von Bedeutung sein könnten.

Das Hauptthema der vorliegenden Arbeit beschäftigt sich mit der Frage, ob der Kontext, in den ein visueller Reiz eingebettet ist, auch die synchrone Aktivität zwischen mehreren, zeitgleich abgeleiteten Zellen moduliert. Zu diesem Zweck wurden im primären visuellen Kortex von anästhesierten Katzen bis zu 32 Zellgruppen gleichzeitig abgeleitet. Die rezeptiven Felder aller abgeleiteten Neuronen wurden mit einem einzelnen sich bewegenden Vordergrundgitter stimuliert, welches die optimale Vorzugorientierung für die Mehrheit aller abgeleiteten Neuronen hatte. Dieses Vordergrundgitter wurde in ein zweites, sich bewegendes Hintergrundgitter eingebettet.

Die zwei wichtigsten Ergebnisse lauten wie folgt:
1. Je kleiner die Orientierungsdifferenz zwischen den Balken des Vordergrundgitters und denen des Hintergrundgitters ist, umso stärker wird die Feuerrate der abgeleiteten Neuronen durch das Hintergrundgitter inhibiert. Bei gleicher Orientierung von Vordergrund und Hintergrund beträgt der Grad der Inhibition nahezu 25% verglichen mit einer alleinigen Stimulation durch das Vordergrundgitter. Diese „Iso-Orientierungs-Inhibition“ wird schwächer mit zunehmender Orientierungsdifferenz zwischen Vordergrund und Hintergrund. Gleichzeitig ändert sich die Stärke der Synchronisation zwischen den Zellen nur geringfügig.

2. Vergrößert man bei gleicher Orientierung der Gitterbalken jedoch den Phasenwinkel zwischen Vordergrund- und Hintergrundgitter, hat dies keinen systematischen Einfluss auf die Feuerrate der abgeleiteten Neuronen. In diesem Fall konnte jedoch eine starke Zunahme der Korrelationsstärke zwischen den abgeleiteten Neuronen nachgewiesen werden. Bei maximalem Phasenwinkel von 180° war die Synchronisation zwischen den Zellen bis zu 38% stärker als bei einem Phasenwinkel von 0°.

Diese Ergebnisse lassen die Vermutung zu, dass bei der neuronalen Repräsentation von visuellen Reizen, neben der Kodierung durch eine Modulation der Feuerrate zusätzlich die Kodierung durch eine exakte zeitliche Strukturierung der einzelnen Aktionspotentiale genutzt wird.

Introduction

Cell assemblies and the binding problem

In the past three decades, research on the primary visual cortex has revealed an enormous organizational complexity (Livingstone and Hubel, 1988;Felleman and Van Essen, 1991;Maunsell and Newsome, 1987). Anatomical studies on connectivity patterns together with electrophysiological investigations on receptive field properties have led to the classification of more than 30 different areas being involved in the processing of visual information (Figure 1). This subdivision is assumed to reflect some kind of functional specialization because each area is characterized by neurons that are selective for a characteristic subset of stimulus features (Felleman and Van Essen, 1991). This selectivity is believed to emerge by the specific combinations of ascending, lateral and descending interactions (Hubel and Wiesel, 1962;Ferster and Jagadeesh, 1991;Bullier et al., 2001;Hupe et al., 1998;Galuske et al., 2002). While the classical feed forward model of the visual system is still valid for the first processing stage from the retina to the lateral geniculate nucleus (LGN), already the LGN receives almost 90% of its input via feedback connections from the cortex (Guillery, 1995). Each cortical visual area builds feed forward projections to and receives feedback projections from other brain areas and every stimulus evokes responses in multiple areas simultaneously. For example, a moving object activates neurons in areas that respond to motion parameters (V5 or MT) and at the same time it activates neurons in brain areas dedicated to form detection (IT).

Already in 1949, Donald Hebb formulated his hypothesis of a distributed representation. He proposed that the representation of the different visual aspects of one single object is distributed over many subdivisions of the visual cortex. A group of neurons that respond to the various features of an object, he named an *assembly*. Furthermore, he proposed, that for each feature dimension, for example the color of an object, a module (group of neurons) is set aside and that the neurons constituting this module are able to encode any possible value the object may take in this feature dimension. He believed that objects are represented as unique patterns of activation over all these modules. Such a distributed representation is very economical

because only a relatively small number of neurons is required to encode a large number of visual stimuli. Neurons that exhibit selectivity for a particular feature may participate in the representation of a large number of visual stimuli that contain this feature. An elegant property of such a distributed representation is that similar objects that differ only in a few feature domains evoke representational states that are more similar than objects that differ in more aspects.

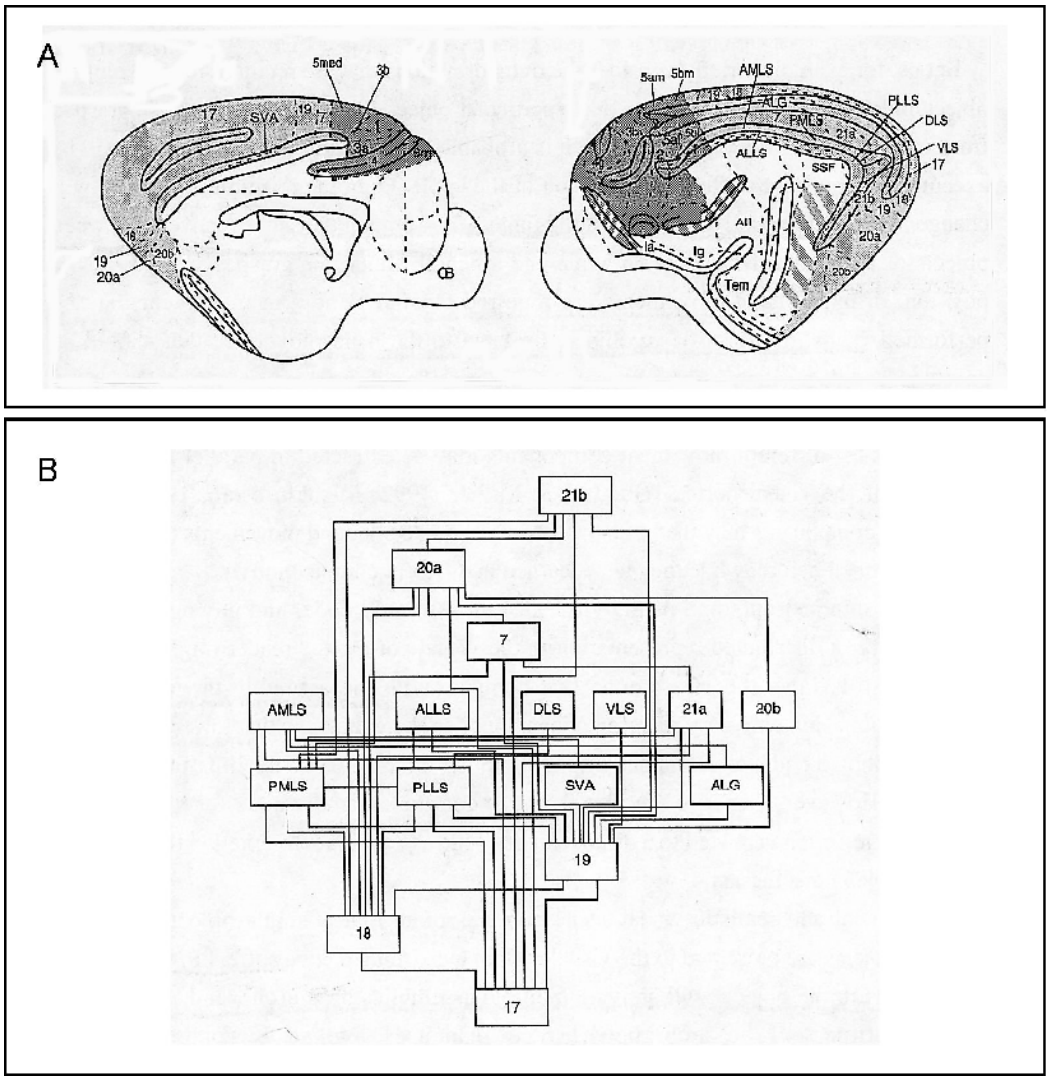


FIGURE 1: Organization of the visual cortex of the cat. (A) Medial (left) and lateral (right) views of the cat cerebral cortex. The visual areas are shown in light gray, areas of the somatosensory cortex and motor cortex in dark gray (from Scannell &Young, 1993). (B) Connections between visual areas. The areas have been arranged in eight hierarchical levels based on the laminar pattern of connections between them. In this scheme, higher visual areas occur at higher positions. ALG, anterolateral gyrus area; ALLS, anterolateral lateral suprasylvian; AMLS, anteromedial lateral suprasylvian; DLS, dorsolateral suprasylvian; PLLS, posterolateral lateral suprasylvian; PMLS, posteromedial lateral suprasylvian; SVA splenial visual area; VLS, ventrolateral suprasylvian (from Felleman & Van Essen, 1991)

Furthermore, novel objects may easily be accommodated as new patterns of activation over the existing modules. Contemporary representational theories share the view that lower visual areas use a distributed code, which is also supported by physiological evidence.

However, there are theories that do not assume a distributed code for higher visual areas. One argument is that any typical and realistic visual scene contains more than one single object. Thus, when multiple objects are presented to the visual system simultaneously, a distributed code suffers from the so called *"binding-problem"*. Multiple objects will activate multiple, even overlapping assemblies of neurons and the resulting representation will be ambiguous, because responses evoked by one object become indistinguishable from those evoked by another. This breakdown, called *the superposition catastrophe* (von der Malsburg, 1981), requires a mechanism that keeps track of responses that are evoked by one object and distinguishes them from responses evoked by another object.

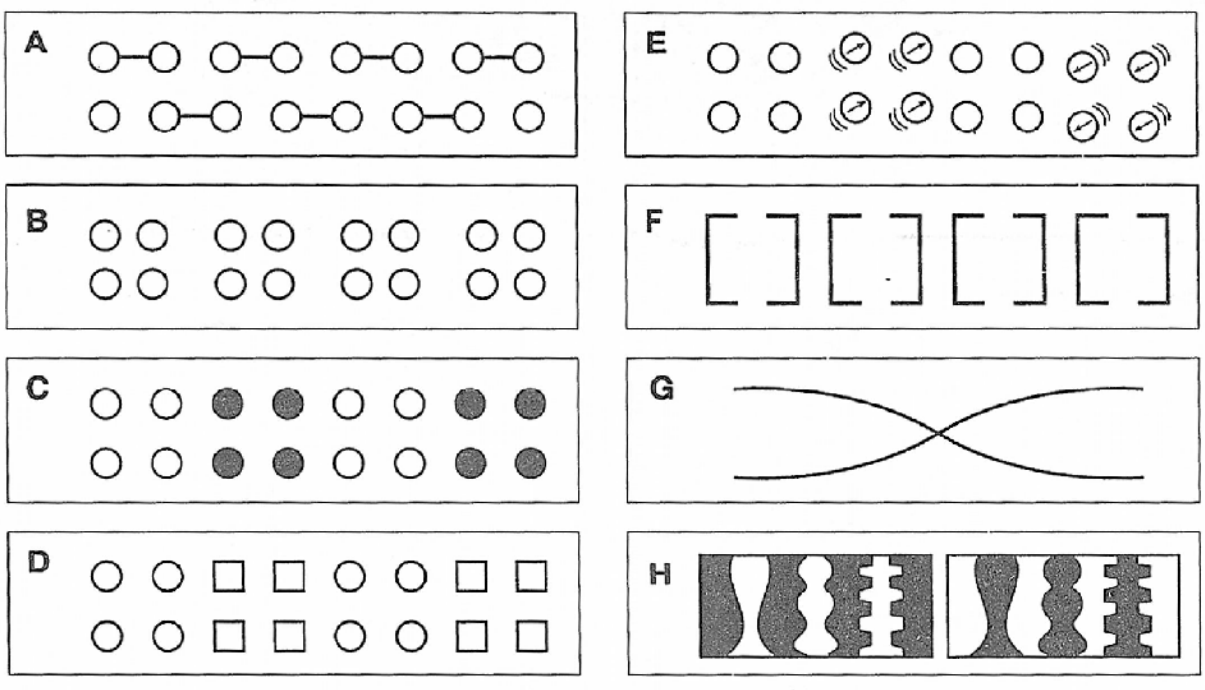


FIGURE 2: Gestalt laws of perceptual grouping. The visual system is likely to group image components that are connected (A), closely located (B) or have similar color (C) or shape (D). Further Gestalt rules include common fate (E), closure (F), good continuation (G) and symmetry (H). (Adapted from Rock & Palmer, 1990).

At the beginning of the last century, the Gestalt psychologists developed a theory of perceptual grouping (Rock and Palmer, 1990;Köhler, 1930;Wertheimer, 1923). They found that image components of similar shape or color are likely to be grouped together when they are closely located or when they move in the same direction (Figure 2).

It was proposed that these rules should guide the search for a neuronal mechanism that is able to distinguish responses originating from one single object from responses coming from different objects. One possibility for removing the ambiguities from the assembly representation is to provide the cortical network with binding units: neurons that are selective to the conjunction of features from different feature domains. These neurons should fire if a set of features – for example the color red and the shape of a square - are combined in one single object, but not if these features belong to different objects. This selectivity can be achieved by allowing only feature selective neurons with neighboring receptive fields to converge onto a binding unit, thus implementing the Gestalt rule of proximity. In a similar way the Gestalt rule of similarity of form or color could be hardwired by restricting the convergence to neurons with a preference for the same form or color.

An extreme version of this solution for the binding problem is the cardinal cell hypothesis (Barlow, 1972). This hypothesis assumes the existence of cells that are selective for very specific feature constellations. Cardinal cells are believed to reside in higher visual areas and they are assumed to acquire their high degree of selectivity by a convergence of neurons placed in lower visual areas. The highest degree of selectivity for complex features was found in neurons located in the inferotemporalcortex (IT) and in the anterior superior temporal sulcus. These neurons can be stimulated with complex and behaviorally relevant objects, such as for example faces or hands (Gross et al., 1972;Perrett et al., 1987;Perrett et al., 1987;Perrett et al., 1987;Rolls, 1992). However, when systematically simplifying such a complex object it is possible to isolate its critical parameters and it seems that a specific constellation of basic colors and forms rather than one specific object is crucial for the activation of these neurons (Tanaka et al., 1991;Tsunoda et al., 2001). Nevertheless, even though the cardinal cell hypothesis would resolve the binding problem it reintroduces problems that the representation by assemblies is well able to

handle. First of all, the cardinal cell strategy is very expensive in terms of the number of neurons required to encode all possible conjunctions of features which can easily outnumber the cells available in the entire brain. Secondly, the ability to represent one particular feature constellation is not necessarily associated with the ability to represent different combinations of the same features. And furthermore, to allow for the lifelong ability to learn and to acquire the representation of new feature combinations a certain percentage of neurons would have to be “reserved”.

An alternative solution for the binding problem consistent with a distributed representation focuses on the selection of a specific region of the visual field. From this specific region, the so called “window of attention”, responses are selected for further processing (Crick, 1984;Treisman and Gelade, 1980;Treisman and Sato, 1990). When the window of attention is positioned accurately and when only one single object is included, the binding problem can be avoided. However, it is necessary to position the window exactly around one single object which may be difficult especially when different objects are in close proximity. Thus, in these situations, the segmentation of the visual scene into objects and background is a prerequisite and not the result of appropriately positioning the attentional focus. A further limitation results from restricting the window to a single contiguous image region at a time. When objects are partially occluded by others, responses from non-contiguous parts of the visual field need to be integrated into a coherent percept. Furthermore, the representation of relations between different objects is difficult because as soon as more objects are included into the window of attention, the binding problem arises again.

A third option for solving the binding problem has been proposed by Abeles (Abeles, 1982), von der Malsburg (von der Malsburg and Schneider, 1986;von der Malsburg, 1981) and, in a preliminary form also by Milner (Milner, 1974). These authors suggested that ambiguities may be removed from a distributed representation by using the precise timing of action potentials as a mechanism for response selection. Neurons that respond to the different features of one single object should synchronize their discharges on a fine temporal scale, whereas neurons that respond to different objects should be desynchronized (Figure 3). This strategy for disambiguating the assembly representation allows for the simultaneous existence of

multiple assemblies that represent different objects. Furthermore, this mechanism is able to integrate responses from non-contiguous image regions into a coherent object. However, the binding of neuronal responses into coherent percepts requires the flexible definition of relations already in early stages of visual processing.

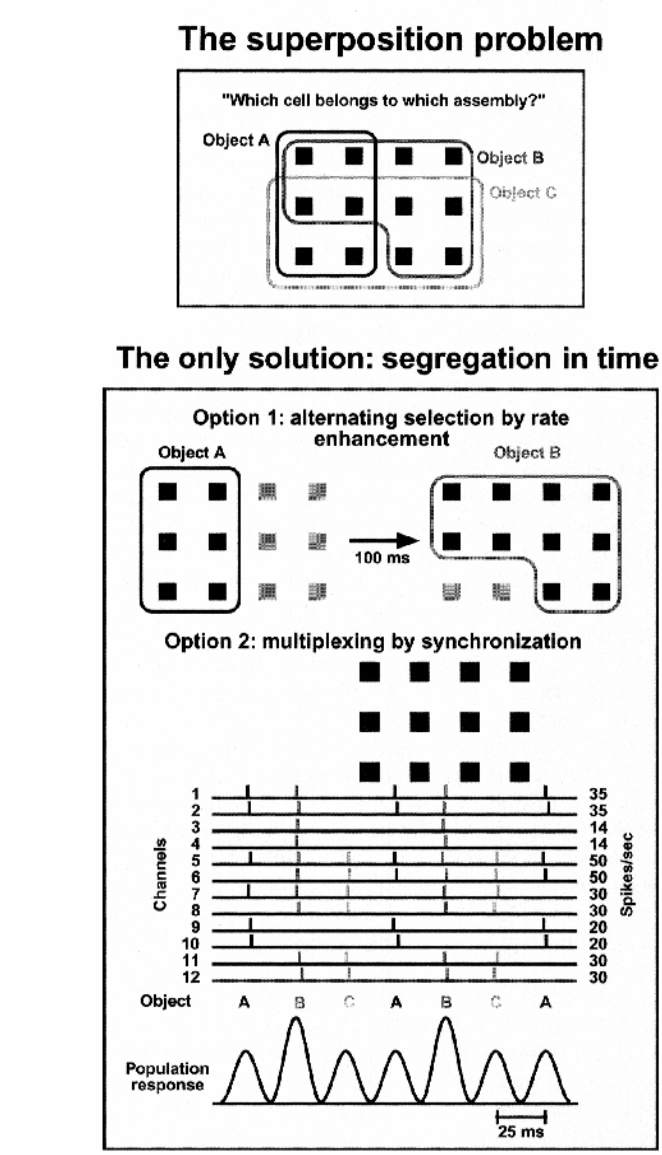


FIGURE 3:
The superposition problem. In the upper box three perceptual objects are represented by partially overlapping neuronal assemblies. This overlap causes the superposition problem because the different assemblies need to be segregated in time in order to avoid false conjunctions and to properly represent the corresponding object. One possibility for solving the superposition problem is to successively enhance the saliency of neuronal responses belonging to the same assembly (lower box, option 1). An alternative solution to selectively enhance the saliency of each assembly is to synchronize the discharges of the respective neurons with millisecond precision (option 2). This allows rapid multiplexing of different assemblies because coincident discharges can evolve within short time intervals and do not require temporal summation (from Singer, 2003)

If neural synchronization functions as a mechanism that binds distributed neuronal responses into a coherent percept, there is need for a mechanism that produces synchronization of only those responses that were evoked by a single object while synchronization between responses to different objects should be avoided. The network of connections between neurons that mediate their synchronization should be capable of grouping the appropriate cells into assemblies. This imposes huge constraints on the topology of these connections. It has been proposed that the architecture of synchronizing connections should comply with the Gestalt laws of perceptual grouping (Singer, 1993). Anatomical evidence indicates that the long-range tangential connections preferentially link columns that respond to common features and that tend to be grouped perceptually (Ts'o and Gilbert, 1988;Gilbert and Wiesel, 1989;Malach et al., 1993;Schmidt et al., 1997).

Experimental evidence for neuronal synchronization

Correlated activity between cell pairs has been observed in many different laboratories (Toyama et al., 1981b;Toyama et al., 1981a;Michalski et al., 1983;Ts'o et al., 1986;Hata et al., 1988;Kruger and Aiple, 1989;Schwarz and Bolz, 1991). Initially, the correlations observed in these experiments were not interpreted in the context of the temporal binding theory. Instead, centre peaks in cross-correlograms were interpreted solely as an indication for structural coupling between neurons. It was assumed that synchronization between two cells was caused by direct excitatory or inhibitory connections between these cells or by common input onto both cells. Therefore, synchrony was thought to simply reflect connectivity thus being independent of stimulus properties. The first experimental evidence for synchronized neuronal assemblies came with the discovery of strong 30-60Hz oscillations in the field potential of cat area 17 (Figure 4) by Gray and Singer (Gray and Singer, 1987;Gray et al., 1989;Gray and Singer, 1989). These authors also observed oscillations in recordings from several small cell groups (multi-units, MUAs) and found that multi-units can synchronize their discharges across the border of several columns. Synchrony between cells in different columns is an essential prerequisite for the temporal binding theory because relations between different properties, coded by cells from different columns, can be established.

In the past 15 years the temporal structure of neuronal discharges was explored in many different species and with a variety of methods on different scales of temporal and spatial resolution. Electrophysiological experiments on anaesthetized cats have revealed that neuronal synchronization can well extend beyond a single visual area.

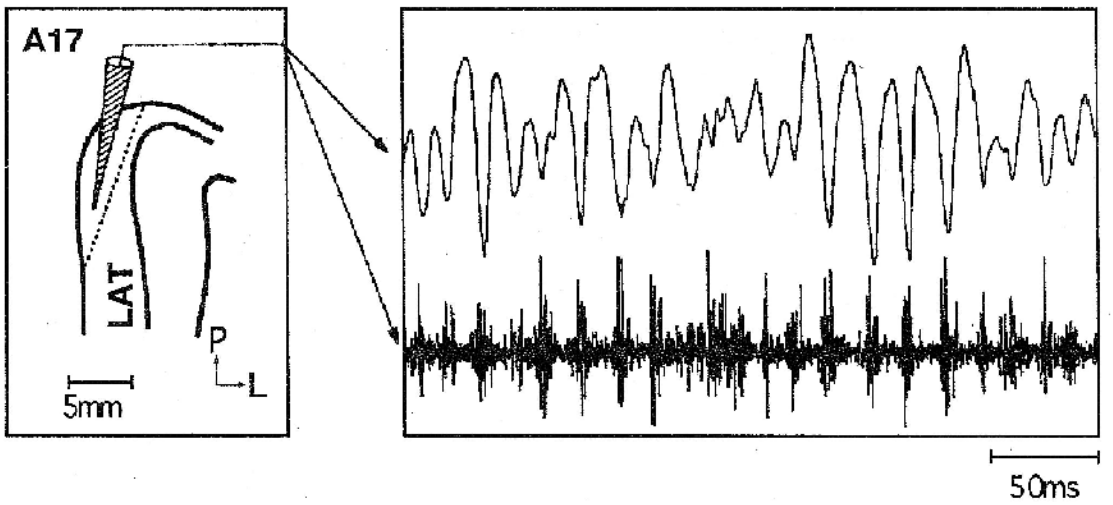


FIGURE 4:
Gamma oscillations in the visual cortex. (A) Position of the electrode in area 17 of the left hemisphere. (B) By filtering in different band passes, local field potential (top, positivity upward) and multi unit spike activity (bottom) are extracted from the raw electrode signal. As a light bar is passed through the cell's receptive field a clear oscillatory response is observed in the field potential, indicating that the neurons of the recorded cluster have engaged in a coherent and rhythmic firing pattern. Note the variability of both amplitude and frequency in this time series. The multi unit activity shows directly that different neurons (as indicated by spikes of different size) synchronized their discharges into a burst-and pause firing pattern. The spike bursts are in phase with the peak negativity of the field potential. Abbreviations: LAT, lateral gyrus; P, posterior; L, lateral (from Roelfsema, 1994).

For example, correlated firing has been observed between areas 17 and 18 (Eckhorn et al., 1988;Nelson et al., 1992) as well as between area 17 and the posteromedial area in the suprasylvian sulcus (PMLS) (Engel et al., 1991c).

These findings are of particular interest because interareal synchronization could mediate binding across different feature maps, which is required for the complete representation of visual scenes. Synchronization has also been observed between the primary visual cortex of the two hemispheres (Engel et al., 1991a). The primary visual cortex of each hemisphere contains a representation of the visual field restricted to the contralateral hemifield. Therefore, interhemispheric synchronization could be of importance for feature binding across the midline of the visual field. Interhemispheric synchronization was found to be abolished when the corpus

callosum - the massive fiber system that connects both hemispheres - was sectioned (Engel et al., 1991a). This suggests that synchronization of a millisecond precision is established at the cortical level and not mediated by a common driving input from subcortical structures.

Furthermore, it could be demonstrated in electrophysiological experiments that the impact of synchronized neuronal activity on target structures is much greater compared to activity that is dispersed in time. For example, in recordings of coupled neuron triplets in the thalamus and the primary visual cortex synchronized EPSPs within 2-3ms were more effective in driving the subsequent cortical neurons than EPSPs that were not synchronized in time (Alonso et al., 1996;Alonso and Martinez, 1998;Usrey and Reid, 1999). Data from multielectrode recordings in the visual cortex and retinotopically corresponding loci of the superior colliculus point in a similar direction. The impact of cortical neurons on their target structures in the colliculus is larger when the neuronal activity is synchronized compared to asynchronous activity (Brecht et al., 1998). Similarly, studies in amblyopic cats show a close correlation between the reduced synchrony in the primary visual cortex and reduced neuronal activity in higher visual areas (Roelfsema et al., 1994;Schroder et al., 2002).

The synchronous activity of a neuronal population and the associated simultaneous synaptic potentials results in a measurable field potential. Conversely, synaptic currents evoked by neurons that fire independently will average out (Abeles, 1982). Therefore, the presence of a measurable field potential in the visual cortex can be taken as an evidence for the synchronous activity of large clusters of cells. Many studies on EEG and magnetoencephalographic (MEG) gave evidence on the precise timing of neuronal synchronization during visual perception (Tallon-Baudry et al., 1996;Tallon et al., 1995) and other sensory modalities (Pantev et al., 1991) and species (Ravel et al., 2003). These investigations show that groups of neurons in the visual cortex of different species have the ability to synchronize their discharges over large distances, as it is postulated by the theory of temporal binding. However, although the hypothesis of von der Malsburg offers an attractive conceptual scheme for understanding the integration of distributed neuronal responses, the question to which degree the brain actually uses synchronization is still a matter of debate.

Functional correlates of synchrony

If neuronal synchronization labels responses that are evoked by one single object, the strength of synchronization should also depend on the different properties of a stimulus. This stimulus dependency of neuronal synchronization could be demonstrated in various experiments. Spatially separate cells in the visual cortex of cats and monkeys show strong synchronization only if they respond to the same visual stimulus (Gray et al., 1989;Engel et al., 1991c;Engel et al., 1991b;Kreiter and Singer, 1996) (Figure 5). If responding to two independent stimuli, the cells fire in a less correlated manner or even without a fixed temporal relationship. This suggests that the coherence of the stimulus is one critical parameter. These observations demonstrate that the Gestalt criteria of continuity and coherent motion are important for the occurrence of synchrony among neurons in the visual cortex. These latter experiments were performed in anesthetized cats but the stimulus dependency of synchronization could also be demonstrated in awake behaving cats and monkeys, indicating, that the observed phenomena were not due to artifacts caused by anesthesia (Kreiter et al., 1992;Frien et al., 1994;Maldonado et al., 2000;Friedman-Hill et al., 2000).

In an experiment on binocular rivalry performed in areas 17 and 18 of awake behaving cats, a close relation between synchrony and stimulus selection could be demonstrated (Fries et al., 1997;Fries et al., 2002). In this experiment, the two eyes of strabismic cats were stimulated with two moving gratings and the gratings could not be fused into one coherent percept. As a consequence, the perception always alternated between the two eyes. This phenomenon was used to investigate how neuronal responses to constant stimuli change, depending on if they are selected and perceived or if they are suppressed. The results of this experiment show that the amplitude of the neuronal response did not change, regardless whether the stimulus was perceived or not. Instead, a highly significant correlation could be observed between changes in synchronization strength and the perception of the stimulus. The responses of those cells that were driven by the “winning” eye, increased the synchronicity of their

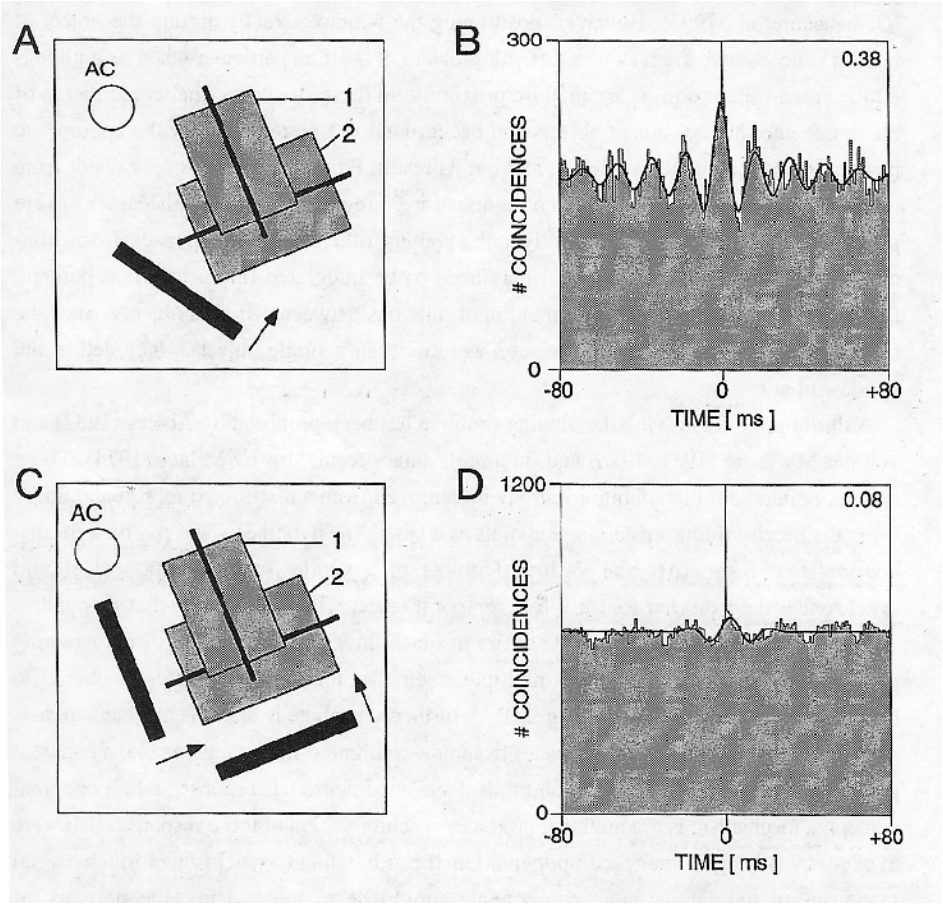


FIGURE 5:
Stimulus dependence of neuronal synchronization. Multi-unit activity was recorded from two recording sites of area 17 from the anaesthetized cat. The cell groups had overlapping receptive fields and orientation preferences of 22° (group1) and 157° (group 2) as indicated by the thick line drawn across the receptive fields in (A) and (C). (A, C) Two different stimulus configurations that were used to activate neurons at the two sites simultaneously. In (A) a light bar with an orientation of 55° was moved over the receptive fields. In (C) two light bars with the orientations 22° and 112° were used. (B) Cross-correlation function during the presentation of a single light bar. Note that the responses to this stimulus are strongly synchronized. The number in the upper right corner is the modulation amplitude, a measure of synchronization strength. (D) Correlation function during the presentation of two light bars with orientations that matched the orientation preferences at the two recording sites shown in (C). Synchronization between responses to different stimuli is much weaker. This indicates that the strength of synchronization depends on the configuration of the stimulus (from Engel, 1994)

discharges, while responses between cells that were driven by the suppressed eye became desynchronized. Experiments with awake behaving monkeys support these results (Sheinberg and Logothetis, 1997;Logothetis and Schall, 1989;Leopold and Logothetis, 1996). In these studies, the correlation between the perception of the stimulus and the strength of the neuronal response was very weak in early visual areas. In contrast, in higher visual areas perceptual suppression was always correlated with a loss of neuronal responses.

Another recently performed experiment showed a close relation between synchrony and perceptual binding (Castelo-Branco et al., 2000). Cells in area 18 and PLMS (posteromedial bank of the lateral suprasylvian sulcus) of anaesthetized cats were stimulated with two superimposed gratings that were moving in different directions (plaid stimuli) (Figure 6) The interesting aspect of this stimulus is that already small luminance changes at the intersections of the two gratings cause a binary switch in the perception of the stimulus. The two gratings are either perceived as two independently moving surfaces, one sliding on top of the other and both moving in different directions (component motion) or as a single pattern, moving in the intermediate direction (pattern motion). Cross-correlation analysis of neuronal responses revealed that cells synchronized their activity only when they responded to contours that were perceived as belonging to the same surface, while the cells did not engage in synchronous activity when they responded to different surfaces. These results strongly support the hypothesis that synchronization may enable response selection in a flexible and context dependent manner and could thus potentially serve to encode relations among simultaneously active neurons.

An important property of response synchronization is its state dependency. “State” in this context refers to different behavioral brain states and different brain states are known to be accompanied by characteristic parameters in the EEG. For example, states of sleep or drowsiness are dominated by high voltage activity in the lower frequency ranges (1–4 Hz) while states of alertness are dominated by lower voltage activity in the beta and gamma frequency range (20-60 Hz) (Figure 7). The low frequency high amplitude EEG patterns associated with resting states are commonly addressed as “synchronized EEG” because only the simultaneous activity of a huge number of neurons can summate to be measured in a surface recording. However, the stimulus dependent synchronization between spikes of cortical neurons is found during states of alertness when the EEG is “desynchronized”. This spike-synchronization occurs on a much finer time scale with a precision in the millisecond range. The transition between the different brain states is under the control of a number of modulatory brain systems, including the reticular formation of the mecencephalon (MRF) and the basal forebrain (for review, see (Steriade et al., 1990).

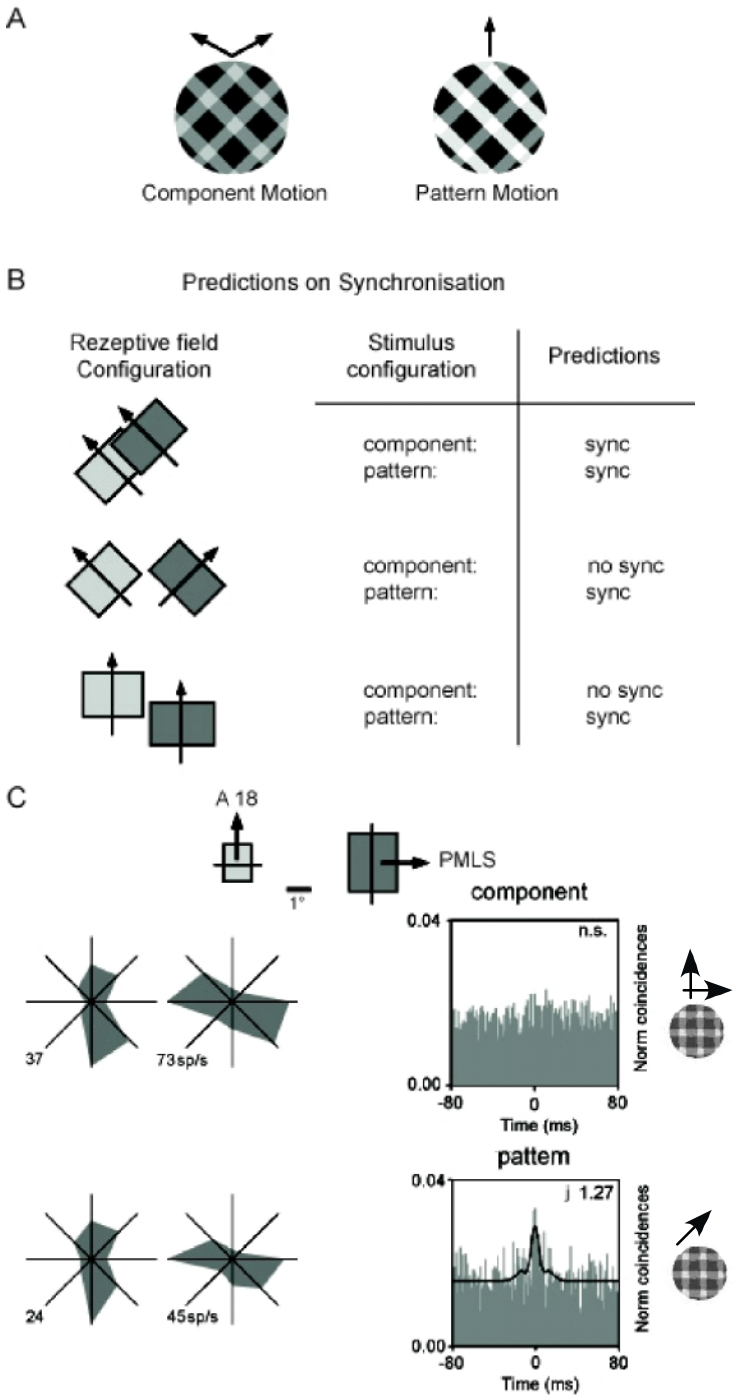


FIGURE 6:
(A) Two superimposed drifting gratings that differ in their orientation and move in different directions can be perceived either as two independent surfaces sliding above each other (component motion) or as one single pattern (pattern motion). Which of the two possibilities is perceived depends on the luminance conditions at the intersections of the two gratings. (B) Predictions on whether synchrony should be observed or not depend on the preferred orientation and the receptive field arrangement of the neurons as well as on the configuration of the stimulus. (C) Receptive field configuration of two simultaneously recorded neurons from areas 18 and PMLS (upper row). The tuning curves on the left side show that the two neurons preferred orthogonal orientations (left graphs). When the neurons were stimulated with a plaid pattern with component motion the cross-correlogram is flat (upper graph). In contrast, the neurons synchronize their activity when stimulated with a plaid under pattern motion condition (lower graph). (Adapted from Castelo-Branco et al. 2000)

Those studies, that reported a stimulus dependence of neuronal synchronization found that synchronization was mostly associated with local field potential oscillations that were dominated by higher frequencies in the beta and gamma range (Gray et al., 1989;Gray et al., 1990;Engel et al., 1992;Kreiter and Singer, 1992;Herculano-Houzel et al., 1999;Munk et al., 1996). Furthermore, it could be shown that oscillations in the gamma/beta frequency range are especially important for long-range synchronization (Engel et al., 1992) since synchrony over long distances breaks down when the EEG is dominated by low frequency oscillations.

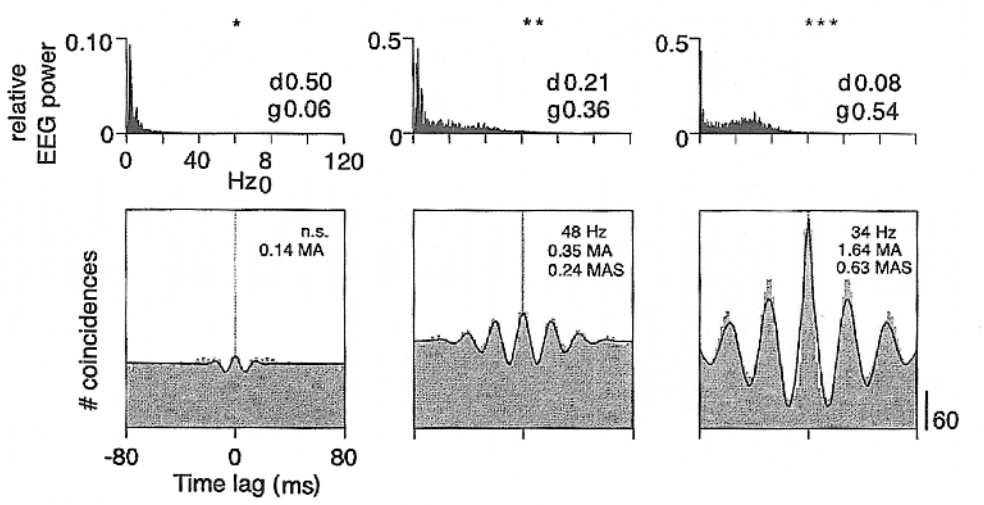


FIGURE 7:
State dependency of neuronal synchronization. The three graphs in the upper row show the power spectra of EEG recordings from three different episodes in an anaesthetized cat. The inserts give the relative power in the delta- and gamma-frequency range, indicating that the fraction in gamma-power increases from left to right. The cross-correlograms in the lower row are computed from two multi unit responses in area 17 recorded during the corresponding three episodes. Response synchronization is strongest when the EEG exhibits high power in the beta- and gamma-frequency range. The inserts in the cross-correlograms give the oscillation frequency (Hz), the relative modulation amplitude of the centre peak (MA) and the first side peak (MAS). (From Herculano-Houzel et al. 1999)

In an experiment in which cats were trained to perform a visually triggered motor response, cross-correlation analysis of field potentials revealed synchronized oscillatory activity in the beta-range between visual, association, somatosensory and motor areas when the animals focused their attention on the relevant stimulus. Once the task was performed and the cat rewarded, this coherent oscillatory pattern broke down and the field potential of the different cortical areas was dominated by much lower frequencies (Roelfsema et al., 1997;Fries et al., 2001). These findings suggest

a close relation between states of attention in the “working” brain and the occurrence of synchrony and support the functional role of neuronal synchronization in cortical processing.

Contextual modulation from beyond the classical receptive field

In order to segregate a figure from its background spatially distributed signals must be compared and assigned to either the figure or to the embedding background. The question how and to which degree synchronization *“tags”* the neuronal responses and establishes relations among them may, to a certain extent, be related to the processes underlying the modulation of neuronal responses by contextual stimuli. Already in early stages of processing, interesting spatial interactions between the receptive field and its surround can be observed. For example, responses of visual cortical neurons can be modulated by presenting stimuli that lie outside the classical receptive field (CRF). By definition, these additional stimuli never evoke a spiking response when they are presented alone. Although the function of contextual modulation is still not completely understood, mechanisms for local-global comparisons have been proposed (Knierim and Van Essen, 1992;Allman et al., 1985a). Such surround mechanisms could participate in many functions that require the integration of inputs over wide regions of visual space as for example the segmentation of the visual scenery into individual objects and the background. In the following paragraph a brief historical overview describing the modulatory influence of surround stimuli on neuronal responses shall be given.

Retina and corpus geniculatum laterale (LGN)

Already in 1953, Barlow systematically stimulated the apparently silent regions beyond the classical receptive field (Barlow, 1953). He found that he could suppress the response of a retinal ganglion cell by simultaneously presenting a spot of light within the receptive field of the cell and a second spot of light outside its receptive field. Around the same time Kuffler (KUFFLER, 1953) found, that the receptive fields of ganglion cells in the cat retina were divided into a centre and an antagonistic surround. When the cell responded to a spot of light in its receptive field centre, it also responded to turning off a spot of light in its surround. When the centre and the

surround were simultaneously stimulated, an excitatory response was evoked. Thus, centre and surround were termed as being parts of the central receptive field. Accordingly, the central receptive fields of neurons in the corpus geniculatum laterale (LGN) are composed of “on” and “off” regions (Hubel and Wiesel, 1961). Furthermore, it could be demonstrated that the responses of optic tract axons and LGN neurons were facilitated when, in addition to stimulating their receptive fields, a moving dark spot up to 90° away was presented (MCILWAIN, 1964). This so-called “periphery effect” was shown to be produced by mechanisms within the retina because the bilateral section of the optic tract did not reduce the effect and there are no back-projections from the thalamus to the retina, either.

Optic tectum

Also in the optic tectum evidence for modulatory influences of surround stimuli on neuronal responses has been found. Suppressive regions surrounding the CRF were found in the frog (Grusser-Cornehls et al., 1963), the ground squirrel (Michael, 1972), the cat (MCILWAIN and Buser, 1968) and the macaque monkey (Wurtz et al., 1980). The first indications for directional selectivity of responses to stimuli presented outside the receptive field were discovered in the late sixties (Sterling and Wickelgren, 1969) in the optic tectum of the cat. The response to a stimulus in the centre of the receptive field with a bar of optimal orientation and direction of movement was more suppressed when a bar in the surround had the same direction of movement as the bar in the centre compared to when the bar in the surround moved in the opposite direction. Another important discovery was made by Rizolatti (Rizzolatti et al., 1974). They presented a spot of light as far as 120° of visual angle away from the receptive field and still found suppressive effects in 90% of the investigated cells. Also, in the intermediate and deep layers of the optic tectum of pigeons, surround effects were directionally selective and more than 100° in diameter (Frost et al., 1981). Frost et al. stimulated the CRF with a moving spot and tested the effect of presenting different directions of movement of a random dot pattern in the background. Most of the cells were facilitated when the dot pattern in the background was moving in the opposite direction than the spot in the centre. Frost and Nakayama (Frost and Nakayama, 1983) showed that the surround effect in the pigeon depended on the direction of movement of the centre stimulus, such that the

direction of greatest suppression in the surround was the same as the direction of movement of the centre stimulus.

Visual Cortex

In the visual cortex, many experiments investigating influences from beyond the classical receptive field were already performed in the seventies. For example, in 1970 it was demonstrated that neuronal responses to optimally oriented bars could be either facilitated or inhibited by the presentation of a second bar (Jones, 1970).

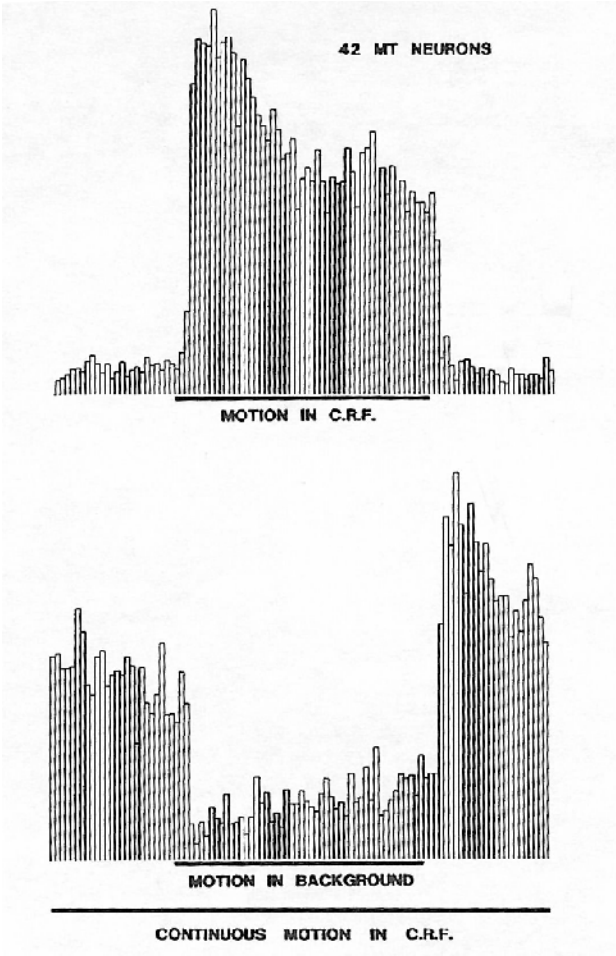


FIGURE 8:
The top histogram illustrates the combined responses of 42 middle temporal neurons to random dots moving for a 2 sec period in the preferred direction within their classical receptive fields (CRF), with the background stationary. The lower histogram, the same middle temporal neurons were stimulated continuously with random dots moving in the preferred direction within their CRF and then tested for a 2 sec period in which the random dot in the surrounding regions also moved in the same direction. Each bin represents 40msec. (From Allmann et al. 1985)

These modulatory effects could be evoked from distances up to 24° of visual angle, but more commonly from a distance of about 2° to 3° of visual angle. Another study (Blakemore and Tobin, 1972) described a complex cell with an orientation selective CRF and an antagonistic orientation selective surround. They found that the response of the cell to an optimally oriented bar was suppressed by presenting a grating of the same orientation and slightly facilitated by presenting an orthogonal grating in the surround. In complementary experiments with surrounding bars and gratings a wide range of contextual effects was demonstrated and inhibition as well as facilitation could be non-specific or any combination of orientation and direction specific (Maffei and Fiorentini, 1976;Fries et al., 1977;Nelson and Frost, 1978;Allman et al., 1985b).

Bishop et al (Bishop et al., 1973) continuously stimulated the CRF of simple cells in V1 and simultaneously presented test stimuli at different locations. Thereby, they could map inhibitory but non-orientation selective regions that extended 2° to 6° beyond the classical receptive field. In other studies, fascilitatory and inhibitory regions of both, simple and complex cells, were described (Maffei and Fiorentini, 1976). The fascilitatory surround regions were orientation selective, while the inhibitory regions were less selective for orientation. The authors showed that the fascilitatory and inhibitory surround regions were tuned to the spatial frequency of sine wave gratings and that the inhibition was strongest for the preferred spatial frequency. Several experiments analyzed surround interactions in the motion domain with random textured backgrounds. Supergranular (Hammond and Smith, 1982;Hammond and Smith, 1984) as well as deep layer complex cells (Gulyas et al., 1987;Orban et al., 1987) changed their preferred direction of movement when a background of moving dots was presented. Part of the population of cells preferred the direction of the centre motion opposite to the direction of background motion, and the other part of the population kept its direction selectivity for centre motion independently of the background motion. Similar observations were made in the orientation domain. The orientation preference of superficial layer complex cells in cats shifted away from the orientation of bars presented in the background (Gilbert and Wiesel, 1990;Gilbert and Wiesel, 1990). In monkeys, responses to a single bar within the receptive field of striate cortex neurons were inhibited by surrounding bars of the same orientation. This inhibition was less strong when the surrounding bars

were oriented orthogonal to the centre bar (Knierim and Van Essen, 1992). Kapadia et al. (Kapadia et al., 1995) combined electrophysiological and psychophysical experiments and explored the role of primary visual cortex in contour integration. They measured the contextual sensitivity of human contrast thresholds and compared it to contrast thresholds of superficial layer complex cells in monkey V1. An observer's contrast detection improved 40% by a second suprathreshold bar and this effect decreased when the two bars were either separated along their axis of orientation, were shifted in collinearity or had their relative orientation changed. Accordingly, recordings in monkey V1 showed that 42% of complex cells were facilitated when a second bar was presented outside their classical receptive field with a similar dependency on location and orientation as observed for humans. These effects were eliminated by adding an orthogonal line between the two iso-oriented lines.

Obviously, contextual modulation appears to be a general phenomenon throughout the visual brain. In the past 50 years many different aspects of surround modulation have been investigated and the diversity of reported effects is large. One important reason for the different findings across studies may be due to the different measures of receptive field size. The classical method consists in measuring the region in the visual field that elicits an excitatory response when stimulated with a high contrast stimulus, such as a light bar, swept across the RF. The resultant region is called the minimum response field (mRf) (Barlow et al., 1967). More recently, reverse correlation methods have been developed that consist in briefly presenting a high contrast light or dark stimulus at random positions in the visual field and reconstructing the position of the bar at a given time before the occurrence of an action potential (DeAngelis et al., 1995). This method has the advantage of providing information about ON and OFF regions and about dynamical aspects of the centre response. A third method is to stimulate the cell with a moving high contrast sine wave grating with optimal parameters (velocity, spatial frequency and orientation) and to increase its size until the response of the cell starts to decrease (Levitt and Lund, 1997). This high contrast summation RF corresponds to the region of the visual field over which the cell summates its response. But even though different measures of RF size provide different estimates about the exact borders of the RF centre and its surround, which may partly explain the differing results on surround

effects, there exists an overall consensus about the predominant effect of surround modulation being suppression (Blakemore and Tobin, 1972;Nelson and Frost, 1978;Knierim and Van Essen, 1992;DeAngelis et al., 1994;Sengpiel et al., 1997;Walker et al., 2000). However, also facilitating effects have been described (Maffei and Fiorentini, 1976;Sillito et al., 1995;Jones et al., 2002), especially when the RF stimulus has low contrast (Sengpiel et al., 1997;Mizobe et al., 2001;Polat et al., 1998). It seems that the sign of the modulatory effect of surround stimulation primarily depends on the relationship among the parameters of stimuli inside and outside the CRF. A surround stimulus with the same stimulus parameters as the CRF stimulus usually exhibits the strongest suppressive effect (DeAngelis et al., 1994;Sengpiel et al., 1997;Walker et al., 2000;Sillito et al., 1995) and this suppression decreases when the difference in stimulus parameters between the RF and surround stimuli increases (e.g. orientation, lightness contrast or spatial frequency) (DeAngelis et al., 1994;Sengpiel et al., 1997;Walker et al., 2000;Sillito et al., 1995).

Contextual modulation requires the integration of visual signals beyond the receptive fields of single V1 neurons and cannot easily be explained by classical receptive field concepts. To identify the neural circuitry that underlies these long-distance interactions is crucial, because they may represent the neural substrate for feature grouping (Kapadia et al., 1995;Mizobe et al., 2001) and figure-ground segregation (Knierim and Van Essen, 1992;Nothdurft et al., 1999). While the properties of the classical receptive field are thought to arise from the cortical column and nearby regions of the cortex (within 500µm), the substrate for the surround effects are assumed to be long-range horizontal connections and/or feedback connections from extra striate areas (Gilbert, 1992;Gilbert, 1998). Long-range horizontal connections can extend up to several millimeters across the cortical surface which enables them to convey information from the far surround (Rockland and Lund, 1982;Gilbert and Wiesel, 1983;Martin and Whitteridge, 1984). These connections are reciprocal, intralaminar projections that arise from excitatory pyramidal neurons in layer 2/3, 4B/upper 4Cα, and 5/6 (Rockland and Lund, 1982;Gilbert and Wiesel, 1983;Gilbert and Wiesel, 1979;Kisvarday and Eysel, 1993). The nature of their connectivity suggests that the tangential connections could serve as a substrate for feature grouping because they show a periodic, patchy pattern of termination and

preferentially link cortical domains of similar functional properties (Ts'o et al., 1986;Gilbert and Wiesel, 1989;Ts'o and Gilbert, 1988;Malach et al., 1993;Schmidt et al., 1997) and thus could accomplish grouping according to criteria of similarity. Moreover, electrophysiological experiments demonstrated that the tangential connections modulate the amplitude of neuronal responses but not their feature selectivity, that they can synchronize the responses of cortical neurons in a context dependent way, and that they selectively enhance the saliency of responses without interfering with the feature selectivity of the neurons (Gray et al., 1989;Engel et al., 1991a;Singer, 1999b).

Aim of the study

So far, electrophysiological experiments on contextual influences have investigated primarily the modulation of firing rates and it was proposed that this modulation may underlie processes involved in perceptual pop-out or figure-ground segregation (Knierim and Van Essen, 1992;Akasaki et al., 2002;Walker et al., 2000;Jones et al., 2001;Sillito et al., 1995). Synchronization of neuronal discharges could serve a similar function as it also raises the saliency of neuronal responses (Brecht et al., 1998), is sensitive to context (Gray et al., 1989) and strongest among cells responding to features that tend to be bound perceptually (Singer, 1999a). However, most of the studies investigating the role of synchronization in neuronal processing manipulated directly the configuration of stimulus parameters covering the receptive fields of the respective neurons. Thus it is not clear whether and to which degree synchronization between neurons can be modulated by a surround that does not directly affect the stimulus that covers the CRF. According to the “coding by time” hypothesis, any increase in synchronization between neurons stimulated by a foreground stimulus should also increase the saliency of this stimulus even if firing rates do not change.

The primary goal of the present study is to investigate whether the stimulation of the receptive field surround modulates the synchronization between neurons that are stimulated by a foreground and how this modulation relates to the modulation of firing rates. To this end, simultaneous recordings from multiple neurons in cat primary visual cortex were performed and the effects of surround stimuli on both, the

amplitude and the synchrony of responses to RF stimuli were examined. The RFs of the neurons were stimulated with a drifting sinusoidal grating that was embedded in a larger grating of identical stimulus parameters (e.g. orientation, contrast, phase alignment) and perceptual pop-out between these stimuli was induced by changing the relation of one stimulus parameter at a time between both stimuli.

Materials and Methods

Electrophysiological experiments in the primary visual cortex were performed in 13 adult cats. The cats were raised in the colony of the Max-Planck-Institute for brain research. All experiments were performed as terminal experiments, meaning that the animals were anesthetized and surgery and electrophysiological recordings were performed only once. At the end of the experiment the animals were killed by an overdose of barbiturates without regaining consciousness. In order to investigate multi-unit neuronal responses to repeated presentation of visual stimuli, the neuronal activity from either 2-5 tungsten electrodes or from 2 simultaneously inserted 16-channel Michigan electrodes was recorded.

Anesthesia and surgery

Anesthesia was induced with i.m. injection of 0.1mg/kg Atropine, 10 mg/kg Ketamine and 2 mg/kg Rompun. Atropine, a parasympatholyticum, is a competitive antagonist at muscarinergic synapses. It stabilizes the cardiovascular system, prevents stenosis of the bronchi and reduces mucosal secretion in the respiratory tract. Ketamine belongs to dissociative anesthetics and induces sedation, immobility and analgesia. Xylacine works as a tranquilizer, causes muscle relaxation and furthermore potentates the effects of Ketamine.

Once corneal reflexes were absent, a tracheotomy was performed and a T-cannula was inserted into the trachea. During surgical intervention the wound was locally anaesthetized with Xylocaine, sutured and subsequently cleaned with 3% H_2O_2. The animal was then transported to a David Kopf stereotaxic table and artificial ventilation was immediately initiated with 70% N_20: 30% O_2 supplemented with 1% Halothane. The respiratory rate and the end tidal partial CO_2 pressure were monitored using an Ohmeda 4700 capnograph (Ohmeda, Louisville, U.S.A). The volume of the respiration pump (Harvard Apparatus, Southnatik, U.S.A) as well as the respiration frequency was adjusted to reach a maximal pressure of 7-10 mbar and the end-tidal CO_2 being between 3.0% - 3.5%, so that the cat was slightly hyperventilated in order to prevent either edema or lack of oxygen. In order to maintain the animals' internal temperature at 38°C, a rectal thermometer was inserted and connected to a unit that

controlled a heating pad placed under the cat. In addition, electrocardiographic leads were positioned and the hearts rate and the shape of the electrocardiogram (ECG) were continuously monitored. As soon as end-tidal CO_2 concentrations stabilized between 3.0 and 3.5% and ear bar insertion caused no acceleration of the heart rate, the animal was positioned in the stereotaxic frame using standard ear-, eye- and mouth bars. To prevent corneal desiccation the nictitating membranes were pierced with a fine surgical thread which was pulled backwards and then held the membranes extended over the eyes. To compensate for the loss of electrolytes and for parenteral nutrition an i.v. cannula was inserted into the radial vein and perfused with a solution of 2.5% glucose and 0.9% NaCl at a rate of 6ml/h.

The scalp was cleaned with an alcoholic solution, and an anterior posterior incision was made in the midline from about one centimeter above the eyes to the occipital crest. The exposed muscle and connective tissue attached to the skull was removed and the periosteum scraped away.

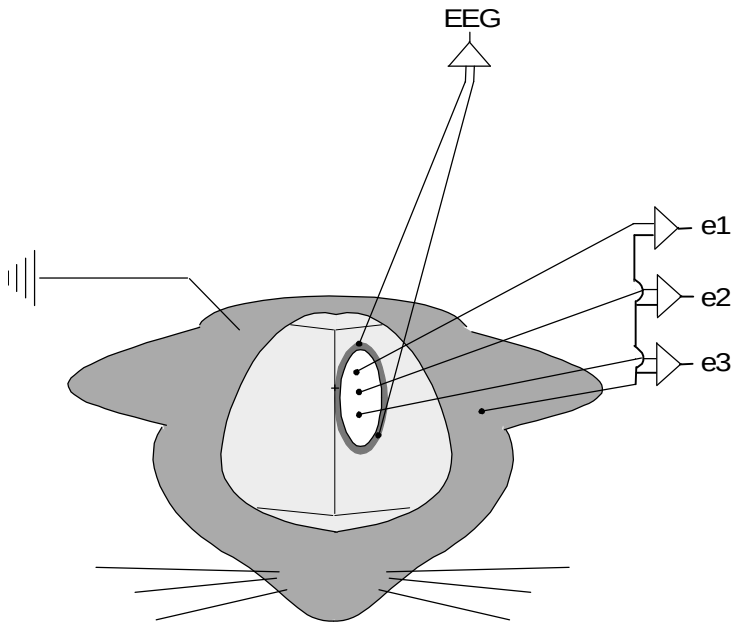


FIGURE 9a:
Experimental setup. The head of the anaesthetized cat was fixed to a holder by means of a screw cemented onto the skull. Spike activity was recorded with either tungsten electrodes or Michigan probes (e1-e3) positioned in Area 17, using an indifferent electrode inserted in the ear muscle as a reference. The EEG was recorded as a differential signal between two epidural silver balls positioned right above the dura mater. The schema illustrates the general position of the EEG electrodes relative to the tungsten electrodes/Michigan probes. A further electrode inserted into the muscle grounded the animal.

The skull was then cleaned with a 3% H_2O_2 solution. After the stereotaxic zero coordinate was marked according to Reinoso-Suárez (Reinoso-Suárez, 1961) the skull was opened from AP-coordinate A3 to P8 and about 4 mm paramedian (L0 to L4) in order to have access to Area 17 (Figure 9a).

To minimize vibration of the skull during craniotomy, the openings were drilled in 2 steps. The first bone layer was opened using a drill of 1.5 mm diameter and potential bleedings could be staunched with bone wax. In the second step the inner bone layer was removed with a drill not larger than 0.5 mm. The exposed dura mater was cleaned of blood and debris and maintained moist with 0.9% saline solution. Subsequently, a recording chamber was built from dental acrylic (Paladur, Kulzer&Co GmbH, Wertheim) and filled with saline. Now the dura mater could be opened using a small hook and surgical scissors, which entirely exposed the cortical surface that was visible through the recording chamber. In order to remove eye and ear bars the head of the animal had to be fixated on the stereotaxic frame. To this end, four small screws were inserted into the frontal bone for support and covered with a thin layer of dental acrylic for electrical isolation. A head holder was positioned in the stereotaxic frame and the attached head bolt fixed with dental acrylic onto the skull. Eye and ear bars were then removed and electrodes for ground- and reference potential were inserted into the muscle of the upper arm or leg. After all surgical procedures were finished the animals were paralyzed with pancuronium bromide (0,6 mg/kg/h, Pancuronium, CuraMed Pharma GmbH, Karlsruhe) in order to prevent eye movements during recording. To enlarge pupils a few drops of 1% atropine solution (B. Braun, Melsungen) and for retraction of the nictitating membrane one drop of phenylephrine (Neosynephrin, Ursapharm, Saarbrücken) were put into the eyes. Contact lenses with a pupil window of 3 mm were inserted into the cats' eyes and the visual acuity of the cat was measured with a refractometer (PR50 Rodenstock, Munich) and if necessary, corrected with appropriate contact lenses to focus on the stimulation screen at a distance of 57cm. With the aid of a fundus camera (Zeiss, Jena), the position of the fovea as well as the blind spot was then plotted on the computer screen used for stimulation. During the experiment the contact lenses were taken off at regular intervals, the eyes were rinsed with 0.9% saline solution and closed with the nictitating membranes to prevent corneal opacity.

Recording sessions

Surgical procedures and positioning of the electrodes usually took the most part of the first day of the experiments. Thus, recording sessions usually started on the second experimental day, which also ensured that the Ketamine injected for induction of anesthesia had already been metabolized by the time recording started.

EEG recording

The electroencephalogram (EEG) was recorded between two epidural silver ball electrodes that were placed over posterior visual cortex in the same hemisphere and with a spacing of 3-5 mm. The EEG signal was amplified 1000x and filtered between 0.1 and 1000 Hz.

Intracortical recordings with tungsten electrodes

In 12 cats (cos 01-12) multi-unit activity (MUA) was recorded with tungsten electrodes. In each of these experiments, two to five tungsten electrodes (1.0-2.0 MΩ impedance at 1000 Hz) were inserted into area 17 in a region close to the area centralis (0° to 12° eccentricity). The electrodes were manufactured from tungsten wires with a diameter of 125 µm. They had been electrolytically sharpened, such that the tip diameter was about 25 µm and were subsequently isolated with varnish. Two electrodes at a time were mounted in a stainless metal guide tube (inner diameter 600 µm, 7 mm length) in order to restrict lateral scattering of the electrodes during the insertion into the cortex. Each pair of electrodes was attached to a micro-drive (SPI Mikro-Triebe), with which the electrodes could be moved up and down pair-wise and independently from the other pairs. The electrodes were positioned directly above the cortex with a distance of about 1-2 mm to each other. The penetration angle was adjusted such that they would enter the cortex approximately perpendicular to the surface. The recording chamber was filled with Agar (2.5%) and sealed with melted bone wax to prevent cortical movements and drying out. By advancing the electrodes in steps of about 50 µm perpendicular through the cortex responses from all cortical layers were sampled. The signals from each channel were fed into a 16-channel head stage with an amplification factor of 10x (custom made at

our workshop) and subsequently brought into the main amplifier (Tektronix, Beaverton, Oregon, U.S.A) where they were differentially amplified 1000x and band pass filtered between 300 Hz and 3 kHz. Signals were then thresholded using custom made window discriminators with the threshold being twice the noise level. The resulting TTL pulses for each action potential were digitized by a PDP-11 based data acquisition system sampling at a conversion rate of 10 kHz. In addition, signals were fed into an audio system and an oscilloscope, for auditory feedback and visual monitoring.

Intracortical recordings with Michigan probes

In one cat multi unit activity was recorded with two silicium based multielectrode arrays (16-channels per electrode) supplied by the Centre for Neural Communication Technology at the University of Michigan. These electrodes gave the chance to record from up to 32 multi units simultaneously. Each multielectrode array consisted of four 3 mm long shanks (Figure 9b) that were separated by 200 µm and contained four electrode contacts each (177 µm diameter, 0.3-0.5 MΩ impedance at 1000 Hz, inter-electrode distance 200 µm). The electrode contacts were inlayed with iridium oxide for interfacing to the tissue. Before the insertion, the electrode arrays were positioned directly above the cortex and about 2 mm apart from each other. Due to the increased resistance for penetration that was caused by the relatively large size of the electrodes, it was necessary to insert them in very small steps into the cortex in order to minimize damage of cortical fibers. Furthermore, it was necessary to continuously control the insertion through the microscope and to fill the recording chamber with a very firm agar in order to avoid any bending of the electrodes. After all electrode contacts were inserted into the brain, which usually required about two to three hours, the recording chamber was sealed with melted bone wax. Each individual Michigan probe allowed simultaneous recording from neurons with overlapping RFs at different cortical depths and along an axis tangential to the cortical surface, spanning a distance of about 700 µm in both directions.

The electrodes were connected to a 64-channel custom made headstage where the signals were amplified by a factor of 10. Subsequently signals were fed into the main amplifier with an integrated filtering system (MCP-Plus, Alpha-Omega Engineering),

amplified by a factor of 1000 and filtered between 500 Hz and 3,5 kHz for MUA and between 0.1 Hz and 120 Hz for LFP's. All signals were then sent to an analog-to-digital converter and after the detection of spikes by means of a thresholding process stored in computer memory. The spike detection and data acquisition software package *NeuroSync* was developed by Sergio Neuenschwander in LabView (National Instruments, Austin, TX). *NeuroSync* consists of the *SpikeFinder* module, an on-line amplitude discriminator and the data acquisition software. *SpikeFinder* monitors the raw signal and the spike shapes and it is possible to compute online real-time autocorrelation functions of each channel in order to obtain an immediate insight into the temporal structure of the ongoing neuronal activity. For AD conversion LFPs were sampled at a frequency of 5 kHz and MUA was sampled at a rate of 32 kHz.

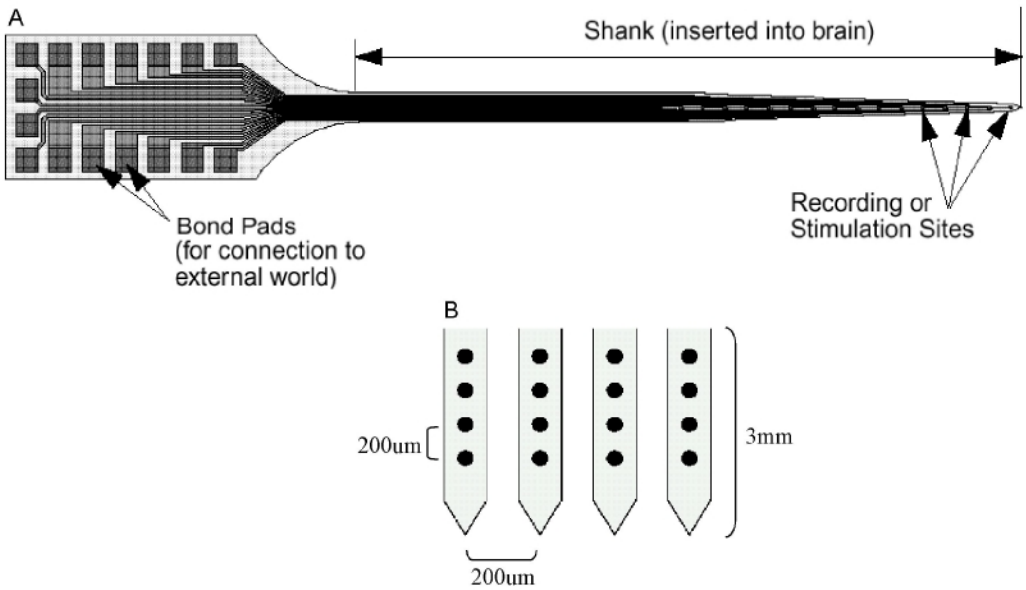


FIGURE 9b:
A) Schematic drawing of a single shank acute probe. The back-end contains bond pads for connection to the pre-amplifier. The shank is inserted into the brain and the sixteen conductive sites are organized along the shank. Data presented in this thesis were collected with four shank probes **(B)**. Here, electrode openings are organized along a four by four matrix.

Mapping the receptive fields of cells

In search of neuronal responses, the electrodes were moved down in steps of 5 µm while simultaneously moving light bars over the computer screen. For mapping the receptive field of each MUA a software package that was developed by Sergio Neuenschwander in LabView was used. This software allows the presentation of stimuli in form of bars, dots or gratings of different velocity, orientation and color and free-hand movement of these stimuli by the control of a computer mouse.

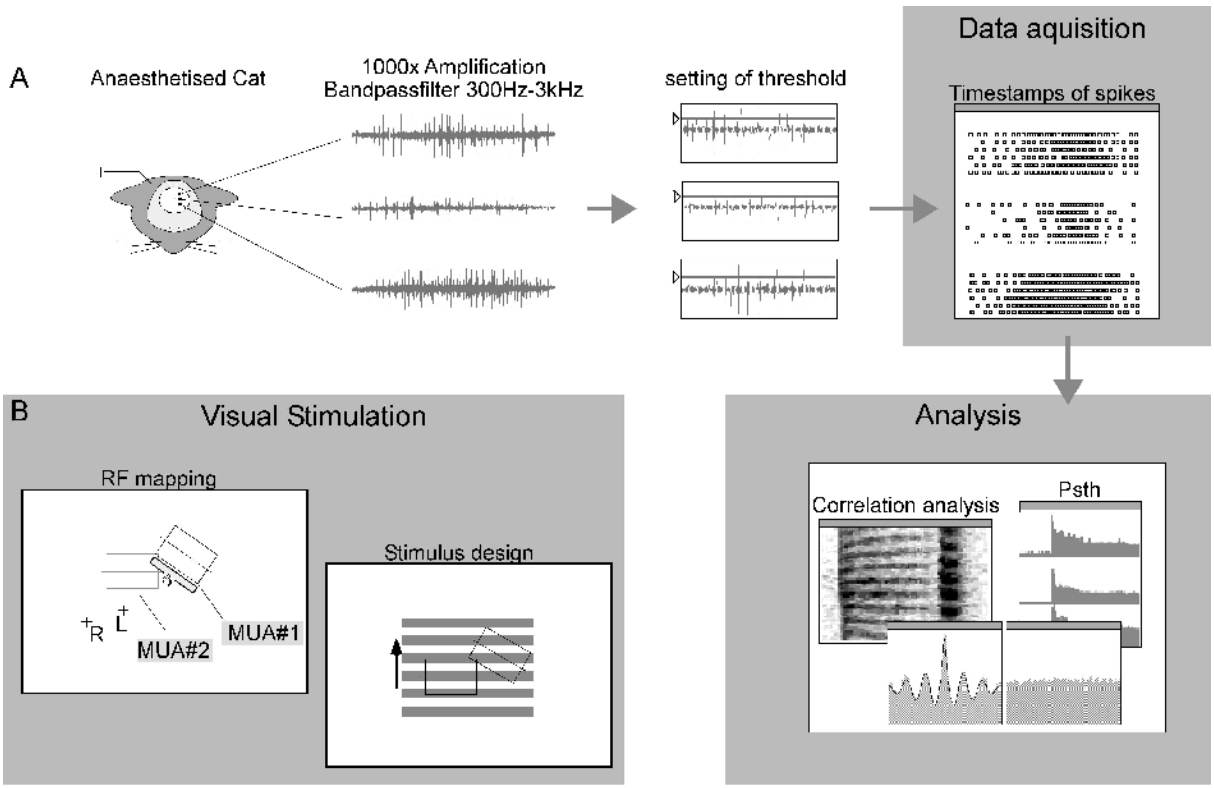


FIGURE 10:
Schematic drawing of an experimental session. (A) Each of the three electrodes records the activity of a multi-unit (MU) from the left hemisphere of a cat visual cortex. Subsequently, the signals are amplified, filtered and after the setting of the threshold, the timestamps of the action potentials are sent to the data acquisition system and stored in a PC for further analysis. (B) Mapping of receptive fields. With the aid of a light bar that can be moved over the screen by the computer mouse (left upper panel, light bar indicated by hand) it is possible to locate and identify the receptive fields of the neurons under investigation. R and L refer to the projection of the fovea of the eyes. Two receptive fields of two MUAs are illustrated (MUA#1 and MUA#2). Their location and preferred orientation is initially identified manually through auditory feedback. The right panel illustrates the design of a visual stimulus covering both receptive fields.

The software was used to characterize the receptive fields of the recorded multi-units (Figure 10). As soon as neuronal responses to visual stimulation were detected the response properties of the neurons with regard to size, orientation and position of their receptive fields were qualitatively investigated by auditory and visual feedback from loudspeaker and oscilloscope. Furthermore, in order to stimulate the neurons binocularly the optical axes of the two eyes were aligned by positioning a prism in front of one eye. The receptive fields, determined by stimulating each eye independently, were aligned by adjusting the azimuth and the elevation of the prism so that both receptive fields perfectly overlapped on the computer screen.

Visual stimulation and Data acquisition

Stimuli were presented on a 21" computer screen (HITACHI CM813ET) with a refresh rate of 100 Hz. In the experiments with tungsten electrodes, a DOS based stimulus generation program written by Rainer Goebel (University of Maastricht, Netherlands) was used which could be fed with individually selected stimulus parameters through a second program, written in LabView by Sergio Neuenschwander.

In the experiments where data were collected with Michigan Probes, the software for visual stimulation was a combination of custom-made programs and a commercially available stimulation tool, ActiveSTIM developed in our laboratory by Danko Nikolić (www.ActiveSTIM.com). This program allows the presentation of bitmap files and films with high temporal precision. The bitmap images in our study included drifting sinusoidal gratings and moving bars.

In order to guide the choice of stimulus to be used to activate the neurons optimally, orientation tuning curves for each MUA (Figure 11) were obtained in the beginning of each recording session by presenting either moving light bars or drifting sinusoidal gratings in twelve different directions with steps of 30°. Light bars and drifting gratings had a spatial frequency of 0.2 – 1.2 cycles/degree and moved with a velocity of 1 – 3 degrees/second. The direction of movement was always orthogonal to the orientation of the stimulus and the stimulation was always binocular.

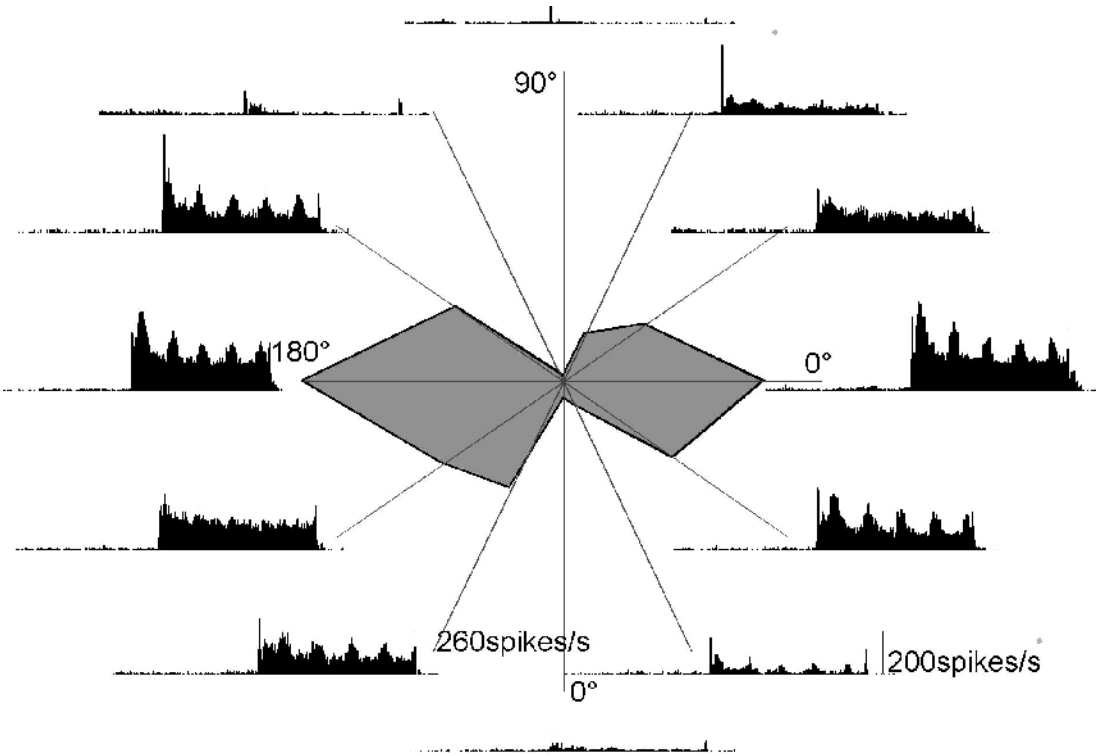


FIGURE 11:
Orientation tuning curve of a multi-unit (MU) recorded with one tungsten electrode in response to drifting gratings. Each line of the inner polar plot refers to one of the twelve directions in which the grating moved. The gray area corresponds to the firing rate of the MU. The outer plots illustrate the neuronal responses to each stimulus condition (each direction of movement of the grating) in form of peri-stimulus-time-histograms (PSTHs).

The stimuli that were used to investigate surround effects consisted of a drifting grating placed in the foreground (figure) that was centered over the receptive fields of the investigated neurons and a grating in the surround (background) that had identical spatial frequency and drifting velocity as the foreground.

The luminance contrast $(L_{max}-L_{min})/(L_{max}+L_{min})$ was in the range of 0.83 - 0.97 with a mean luminance of 31.4 cd m^{-2}. In the first set of experiments (cos01-cos12) in which neuronal responses were recorded with tungsten electrodes, the foreground and background stimuli consisted of square wave gratings of quadratic shape (not shown). In the experiments with Michigan probes, gratings were of circular shape

and sinusoidally modulated. The contrast between the foreground grating and the background grating was induced by manipulating one of the following parameters:

1. Introduction of an annulus between the foreground and an iso-oriented background (Figure 12, A). The area of the annulus exceeded the size of the foreground either by **a**: 10%, **b**: 35%, **c**: 65%, **d**: 95% and had the same average luminance contrast as the background of the screen. In addition three control conditions were presented: the foreground alone, the background alone and a gray patch superimposed on the background to ensure that the background did not cover the receptive fields of the recorded neurons. These controls were presented in all five protocols.
2. Manipulation of the luminance contrast of either the foreground or the background (Figure 12, B). In this stimulus configuration either the centre grating was held at high luminance contrast (0.8) and the background grating was presented at luminance in one of the three categories (**a:** 0.2; **b**: 0.4; **c**: 0.6) or vice versa, meaning the background was kept at high luminance and the contrast of the foreground was varied in the same manner.
3. Changes in the orientation contrast between the foreground and the background grating (Figure 12, C). The orientation of the background was manipulated in four steps of 30° ranging from complete alignment between foreground and background (0° orientation contrast) to an orthogonal orientation between foreground and background. (90° orientation contrast).
4. Changes in the phase alignment (phase contrast) of foreground and background (Figure 12, D). In all experiments with tungsten electrodes, differences in spatial phase between foreground and background were subdivided into four categories, ranging from 0° to 90° phase contrast in steps of 30°. In the experiment with Michigan probes, the spatial phase angle between foreground and background was manipulated in 30° steps from 0° to 330° (12 categories).

The orientation and the direction of movement as well as spatial frequency and stimulus velocity of the figure grating were adjusted to activate a maximal number of cells and were kept constant in each recording session. Spatial frequency ranged between 0.5-1.2 cycles/degree and velocity between 1.0 - 3.0 degrees/second to

match the preferences of area 17 neurons (Bisti et al., 1985;McLean et al., 1994). In each trial, stimuli were presented for 4-6 seconds in a randomized order and each recording session included 20 repetitions.

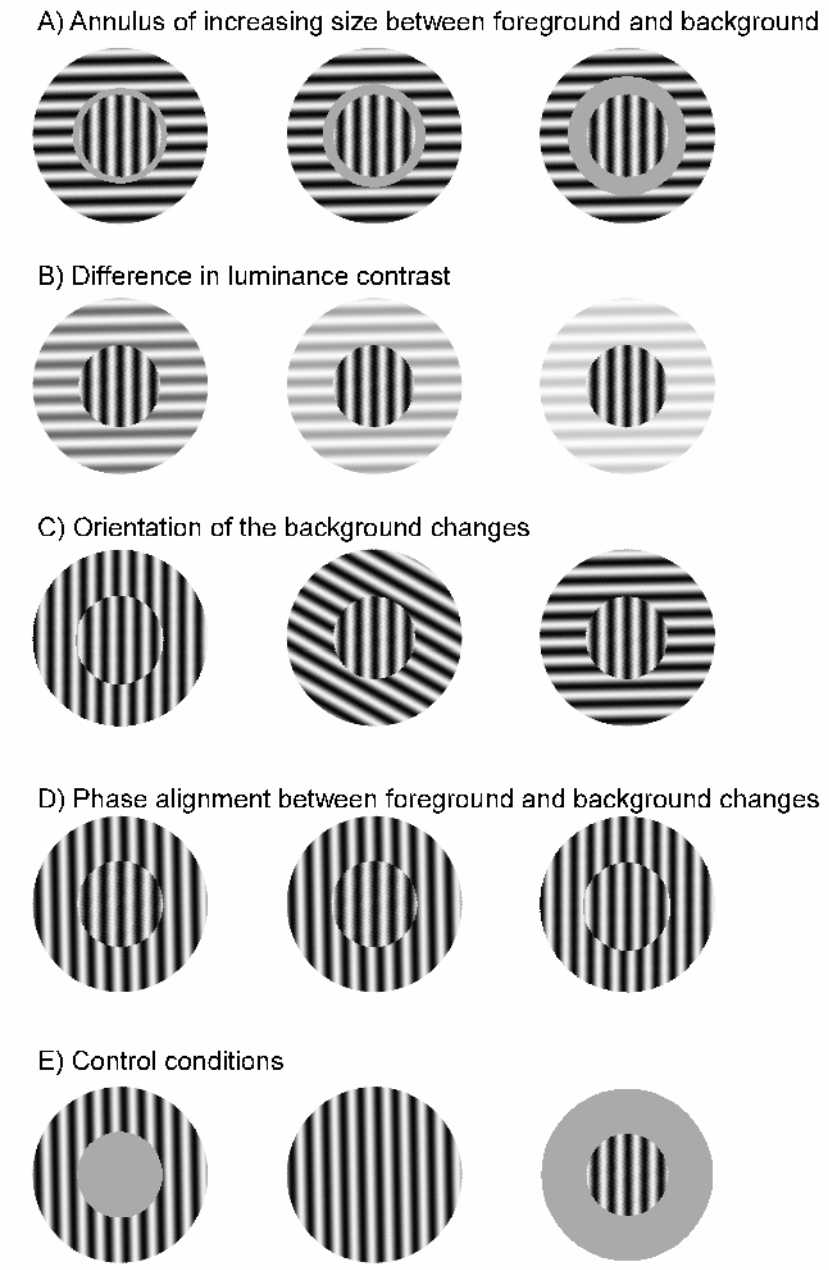


FIGURE 12.
Design of visual stimuli. Note that for each stimulus protocol only a few examples are shown. Receptive fields were usually always covered by the foreground unless noted otherwise. The contrast between foreground and background was induced by the following parameters: A) Introduction of an annulus between foreground and background. Shown are three of four area dimensions of the gray annulus. B) The luminance contrast of either the background or the foreground was varied in four steps. C) The orientation of the background changed from iso-oriented to orthogonal. D) The relative spatial phase angle between foreground and background was manipulated from perfect phase alignment to 180° phase-offset. Stimuli shown under (E) were used as control conditions.

Data analysis

First of all, peri-stimulus-time-histograms (PSTHs) for each multi-unit over a time window of 1-3 seconds length and with a bin width of 25ms were computed. In a PSTH, all action potentials of the recorded neurons are counted relative to the time of the response and thus it is possible to determine the character of the neuronal response.

Correlation analysis

The oscillatory modulation and synchronization of neuronal responses was analyzed by computing auto- and cross-correlation functions. Cross-correlation functions provide information on the probability of the simultaneous occurrence of two events, i.e. in a time series of action potentials of two neurons the number of synchronously occurring spikes is calculated. Any modulation or peak in the correlogram points to a temporal dependency between both neurons, indicating at which point in time the occurrence of a spike of neuron **A** correlates with the occurrence of a spike from neuron **B** (Figure 13). It is possible to investigate the specific character of the coupling between both neurons, for example, whether the coupling is shifted in time or if the temporal structure is modulated in an oscillatory manner. Evenly filled (flat) correlograms indicate a lack of temporal relation between the two neurons. In addition, shift-predictors were computed. The shift predictor, a cross correlation between responses of two units from different trials provides the fraction in the cross-correlogram caused by the frequency of action potentials and its stimulus induced variations. Therefore, a shift-predictor evaluates the nature of the temporal relationship between two neurons as it distinguishes between stimulus locked and internally generated correlations (Perkel et al., 1967). If the modulation of the shift predictor is identical to the modulation of the cross-correlogram, the correlation between the two neurons is time locked to the external stimulus. If the shift predictor is not modulated, the cross-correlogram does not contain stimulus-locked temporal structures but internally generated synchronization.

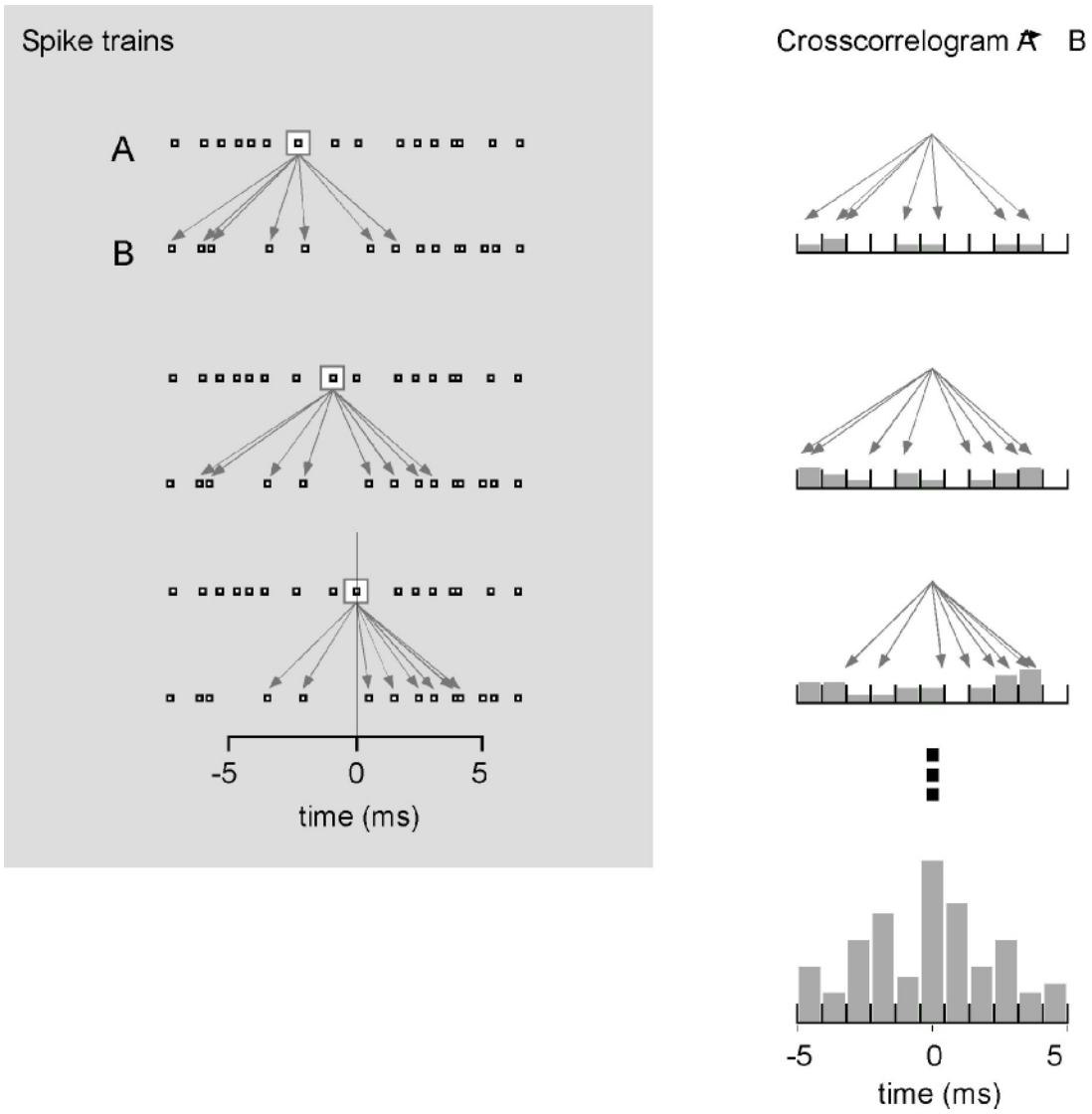
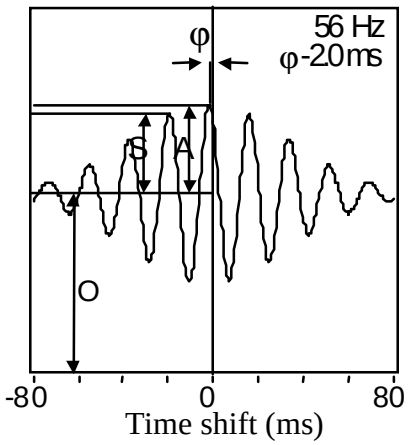


FIGURE 13:
Schematic drawing of computing a cross-correlogram. (A) A and B refer to two neurons and their response pattern shown as a sequence of action potentials. Each square represents one action potential. One spike of neuron A (surrounded by a white frame) illustrates the reference action potential. The timestamps of those action potentials marked with an arrow are plotted relative to the reference spike in the cross-correlogram in (B). If two neurons fire synchronously in a millisecond range, a peak will occur at time point 0. To detect coupled but phase-delayed events it is important to include into analysis not only simultaneous but all action potentials in a certain window around the reference spike (in example from –5 ms to 5 ms). If neuron B fires about 1.8 ms after neuron A, the peak in the cross-correlogram will arise 1.8 ms shifted to the right.

For the quantitative analysis of the correlograms, a 2-*3 s* analysis window (depending on the length of stimulus presentation) was chosen to cover most of the response epoch. The analysis window always started about 100 ms after visual stimulus onset in order to avoid the initial transient, stimulus-locked component of the responses. Auto- and cross-correlation functions were computed from individual trials for time shifts of ± 80 ms with a resolution of 1.0 ms and averaged over 20 presentations of the same stimulus. In order to quantify the strength of synchronization, a damped cosine function (Gabor function) was fitted to the correlogram by using the Levenberg-Marquardt-Algorithm (König, 1994). This algorithm is a non-linear, iterative procedure in which, by minimizing χ^2 individual parameters of the function are adjusted such that the function reflects the modulations of the cross-correlogram as precisely as possible. The gabor function has the following formula:

$$f(t)= A*e\ -(\text{Abbott et al., 1997})^{l}\ *\cos(2pn(t-j)) + e\ -(\text{Abbott et al., 1997})^{l} + \mathbf{O}$$



In detail the variables have the following meaning: λ refers to the variable exponent of the exponential-function, A is the amplitude, τ the slope, ν the frequency, φ the phase angle and o refers to the offset. f (t) describes the sum of three terms: the first term refers to a generalized gabor function, the second term is a gauss-function and the third term reflects the constant fraction of the function.

The strength of neuronal synchronization was estimated by the modulation amplitude (MA). The MA was computed from the height of the amplitude relative to the offset of the fitted function (MA = *A/(o+A)*).

The function was inspected visually in each particular correlogram and was satisfying in most cases. However, in several cases, especially when firing rates were low, the height of the amplitude was either over- or underestimated, and the function did not describe the correlogram correctly. For this reason the peak and the offset of each correlogram were additionally measured by positioning lines for the peak and offset on the bases of subjective estimation (Figure 14).

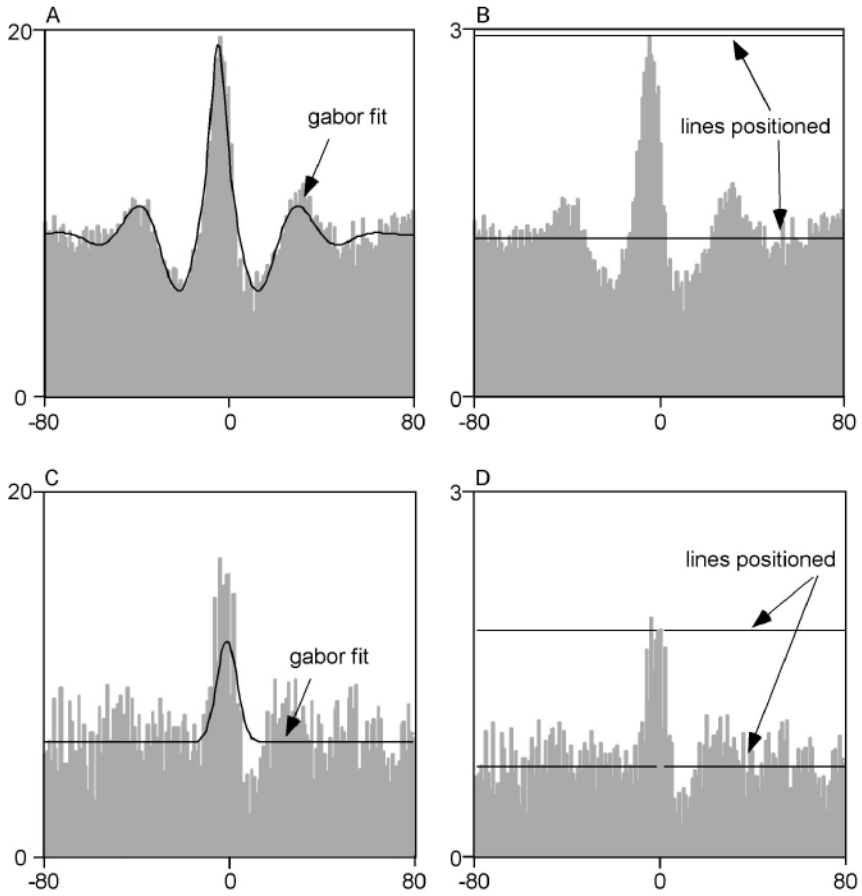


FIGURE 14:
To quantify the strength of synchrony the height of the centre peak was estimated by fitting a Gabor function to the correlogram (A). In some cases, especially when firing rates were low, the fit was not satisfying because it either over- or under estimated the height of the amplitude (C). In these cases lines were positioned manually to the top of the peak and the offset of the raw correlogram on the bases of subjective estimation (B,D).

Figure 15 compares both methods and the correlation between the two is high (0.914). However, when neurons had low firing rates the function rarely described the correlogram precisely and the algorithm gave a high estimation of errors. The outliners in Figure 15 always correspond to such cases, in which at least one partner of the neuronal pair had a low firing rate. In these cases synchronization strength was estimated from the raw correlogram. Correlation functions were quantified directly, i.e. without subtraction of the shift predictor (Perkel et al., 1967) once it was ascertained that this was flat.

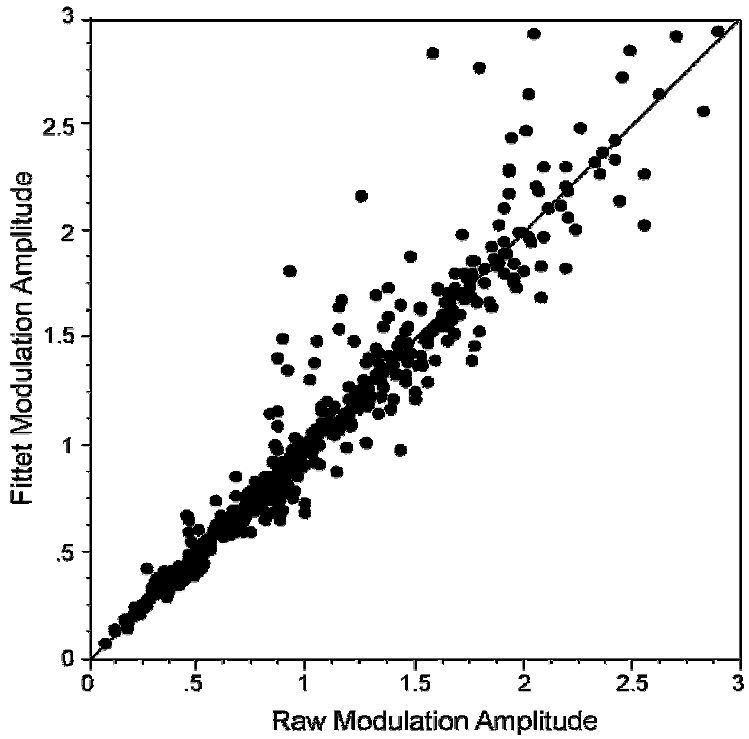


FIGURE 15:
Raw modulation amplitude plotted against the fitted modulation amplitude. (Correlation = 0.914). Outliners are always pairs in which at least one of the two neurons had very low firing rates.

Normalization

Prior to analyzing the average population responses firing rates for each particular recording site and the measures of MA for each particular cell pair were normalized relative to the largest value observed for the respective site (pair) across all

stimulation conditions. Therefore, all measures were transformed to a scale ranging from 0 to 1, where 1 corresponds to the strongest response. Normalized values of firing rates and MA were used in all analyses except for the spike-field coherence. For the present data set, the overall firing rate responses were on average 69.9 spikes/second (sd = 46.6, range 0.2 to 214 spikes/second) and the MA was on average 0.76 (sd = 0.87, range 0.1 to 12). All statistical tests were based on two-tailed p-values for rejecting null-hypotheses.

Effect size

In order to compare the degree of surround modulation for firing rates and synchronization effect sizes were computed. The measure of effect size provides information different from the information provided by statistical significance. Significance indicates the probability that two populations differ in their means and this probability depends on the sample size. In contrast, effect size is independent of the sample size and indicates the degree to which an independent variable affects the dependent variable relative to the variability in the population. The measure of effect size provides information similar to the Pearson's correlation coefficient. A measure for effect size known as Cohen's *d* (Cohen, 1988) was used. According to Cohen the effect can be considered large if *d* is larger than 0.8 and should be considered small if *d* is smaller than 0.2. The effect size, "standardized mean difference" (Cohen's *d*), was calculated from the unpaired t-test according to the following formula (see below). In order to avoid an artificial boost of effect sizes due to correlation between variables in the repeated measure design, we also used the unpaired t-values in repeated measures (Dunlop et al., 1996). To compute Cohen's *d* from the t-values the following formula was used if the two groups had the same sample sizes:

$$d = \frac{2t}{\sqrt{df}}$$

And in the cases in which two groups had different sample sizes the following formula was used:

$$d = \frac{t(n_1 + n_2)}{\sqrt{df}\sqrt{n_1 n_2}}$$

where n_1 and n_2 are the sample sizes of each group, *df* represent the degrees of freedom and *t* is the t-value of a Students' test.

Spike triggered average and spike field coherence

For the calculation of the spike triggered averages (STAs), the LFP of one electrode was averaged within a window of ±128 msec and centreed on each trigger spike recorded by a second electrode (Gray and Singer, 1989).The response epochs were identical with those described above that were used to compute the cross-correlations. In order to obtain a measure of synchronization between MUAs and LFPs that was independent of the power spectrum of the LFP, the spike field coherence (SFC) was calculated. This allowed to distinguish between changes in synchronization and changes in the regularity of oscillatory patterning, the latter enhancing the power of the field potential in the respective frequency band. For each of the LFP segments used for the computation of STAs, the power spectrum was calculated and by averaging these spectra, the spike-triggered power spectrum was obtained. The SFC was then computed as the ratio of the power spectrum of the STA over the spike-triggered power spectrum.

Results

The present results were obtained in electrophysiological experiments in the visual cortex (area 17) of anaesthetized cats. The data presented in the first part of this chapter were obtained in experiments with tungsten electrodes and the data reported in the last part are based on highly parallel recordings with multiple 16-channel Michigan probes.

The entire dataset obtained with tungsten electrodes results from experiments in 12 cats in which multi-unit activity (MUA) was recorded from two to five electrodes simultaneously in regions close to the representation of the area centralis. In these experiments, neuronal responses to a centre grating were modulated by an additional grating that completely surrounded the centre grating and thus stimulated the area outside the classical receptive fields. In four different sets of stimulus configurations, perceptual segregation between the centre grating and the surround grating was manipulated and the effects that these manipulations produced on neuronal responses were investigated. In the first set of stimulus configurations segregation was induced by adding an annulus of increasing size between the centre and an iso-oriented surround grating. In the following three stimulus sets the two gratings were perceptually segregated either by manipulating the luminance contrast between the centre and the surround, by changing the orientation of the surround grating relative to the orientation of the centre or by varying the phase alignment between both gratings in conditions when they were iso-oriented.

The results obtained with Michigan probes originate from experiments performed in one cat. Two 16-channels probes were inserted simultaneously and thus the activity of 32 channels was recorded in parallel. This dataset consists of three recordings, in which the findings obtained with tungsten electrodes (surround modulation by phase offsets between two iso-oriented gratings) were replicated in a more adapted approach with multiple instead of only two different phase angles between centre and surround. The last part of this dataset goes beyond investigating the modulation of responses to the centre and investigates also responses of cells stimulated directly by the surround. This last part is restricted to one recording from two Michigan probes.

Synchronization strength is modulated by stimuli that are placed in the surround

First of all it was investigated whether the presentation of a visual stimulus outside the classical receptive field had any modulatory influence on the precise timing of neuronal action potentials and, thus, on the correlation pattern between the stimulated neurons. To this end the activity from 37 MUAs in two cats was recorded. In order to select the optimal orientation and direction of movement of the foreground grating, the tuning properties of each individual MUA were determined by presenting a single grating that moved in 12 different directions (see methods). The neuronal responses to each direction of the grating were then used to calculate orientation tuning curves for every MUA. Besides characterizing the orientation preferences and the tuning width of the respective neurons, responses to the tuning curve stimulus served to select those MUAs that would be investigated by surround modulation. A MUA was selected only if it synchronized its response with at least one other multi-unit in any of the twelve directions of the tuning curve. After having specified the exact location, size and the preferred orientation of all neurons under investigation the foreground grating was placed such that it covered all receptive fields and such that it had an orientation nearly optimal for all recorded neurons. In order to then modulate the neuronal responses to the foreground an additional grating was presented in the surround that either moved orthogonal (90°) or anti-directional (180°) to the direction of the foreground grating.

An example is illustrated in Figure 17. Two MUAs with similarly oriented and overlapping receptive fields were stimulated with a single grating moving in 90° direction. The PSTH reveals that both channels enhance their firing rates with stimulus onset. This enhancement lasts during the 2 seconds of stimulus presentation. In addition, the discharge rates of both channels are weakly synchronized as indicated by the peak in the cross-correlogram calculated between both units. The strength of this synchronization was quantified the height of the centre peak relative to the offset of the cross correlogram (MA, see material and methods). In the second stimulus condition, a grating that surrounded the centre grating and moved orthogonal to it was presented. This additional stimulation of the

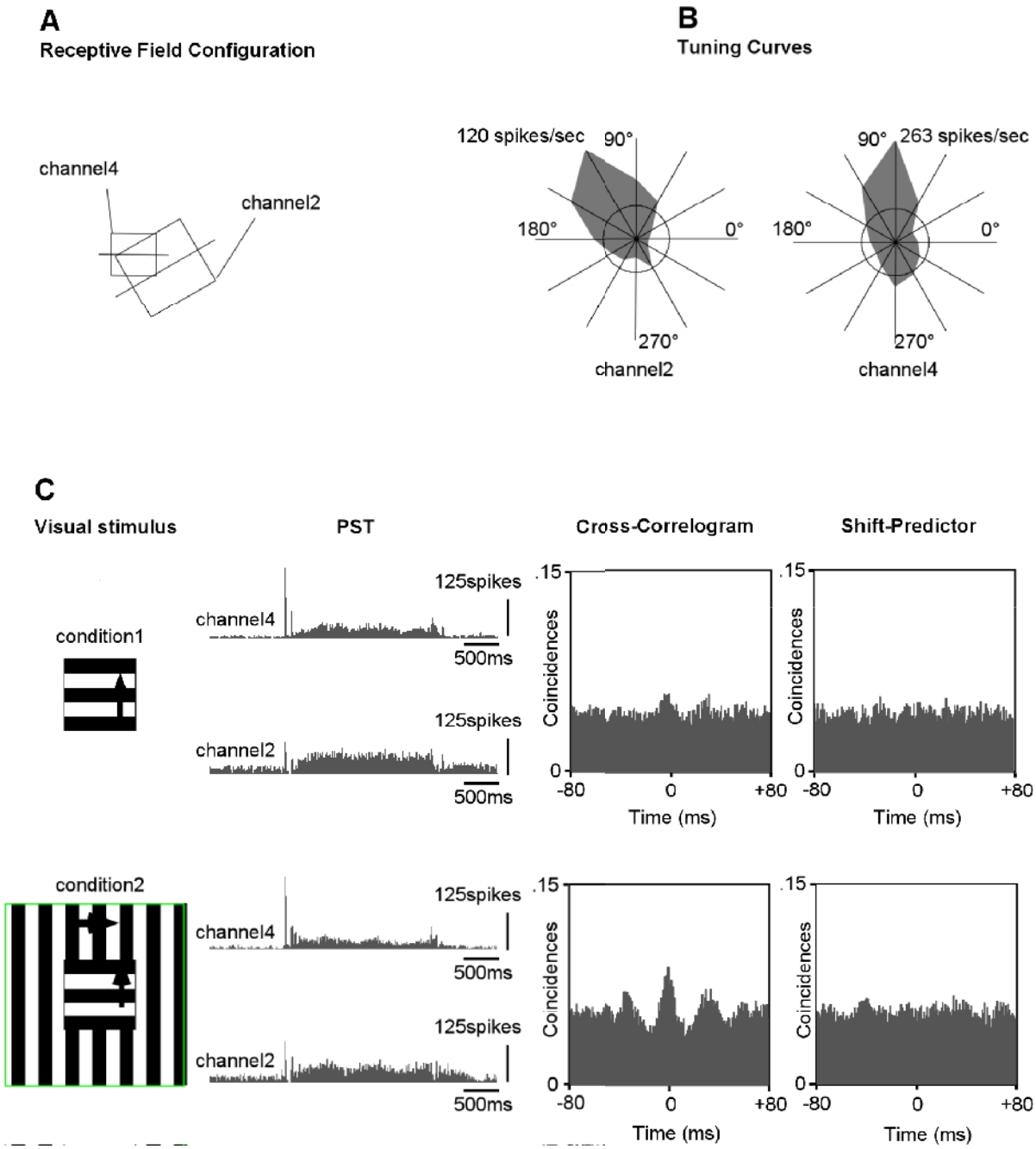


FIGURE 17:
Context dependent changes in correlation strength. (A) The receptive fields of both multi units are overlapping. (B) The polar plot indicates that the orientation preference of both multi units is similar. Each line of the grid in the polar plot represents the direction of movement of a grating from 0° to 330°, in steps of 30°. The black colored area corresponds to the neuronal responses. (C) A single drifting grating moving in 90° activates both multi units but the synchronization strength between both channels is weak. When a background grating moving in the orthogonal direction of the foreground grating is presented, synchronization strength increases.

surround resulted in a slight suppression of the neuronal responses and this inhibition was accompanied by an increase in synchronization strength and a weak oscillation of 28 Hz.

A second example is illustrated in Figure 18. Again, the receptive fields of both multi units were overlapping, even though to a smaller degree compared to the first example. Both channels were bi-directional and had similar orientation preferences. The presentation of a single grating moving in the preferred direction of both channels produced a strong oscillation with a frequency of 37 Hz and a centre peak with the relative height of 0.33. In contrast to the first example, firing rates as well as synchronization strength decreased when a second grating was presented in the surround (MA = .26). These two examples illustrate that stimuli presented outside the classical receptive field may modulate not solely the amplitude of the neuronal responses but also the precise temporal pattern of action potentials between neurons.

Out of the entire population of 37 investigated cell pairs, correlation strength was modulated in 23 cell pairs (62%) by the introduction of a background grating. 78% showed an increase in correlation strength, in some cases (6 pairs) accompanied with increased oscillatory modulation. In 22% correlation strength decreased with the presentation of the background grating. All cell pairs that did not show any contextual modulation (14 pairs, 38% of the entire population) had non-overlapping receptive fields with inter-receptive field distances larger than 2 degrees of visual angle. Among the 23 cell pairs that showed contextual modulation of synchronization, 19 pairs had overlapping receptive fields and 4 pairs had non-overlapping receptive fields with inter-receptive field distances of less than 1 degree of visual angle. This finding motivated the following experiments.

Sample Size = **37 MUAs**

	Number of Cell Pairs	Modulation of Synchrony
Overlapping RFs	19	19
Non Overlapping RFs	18	4

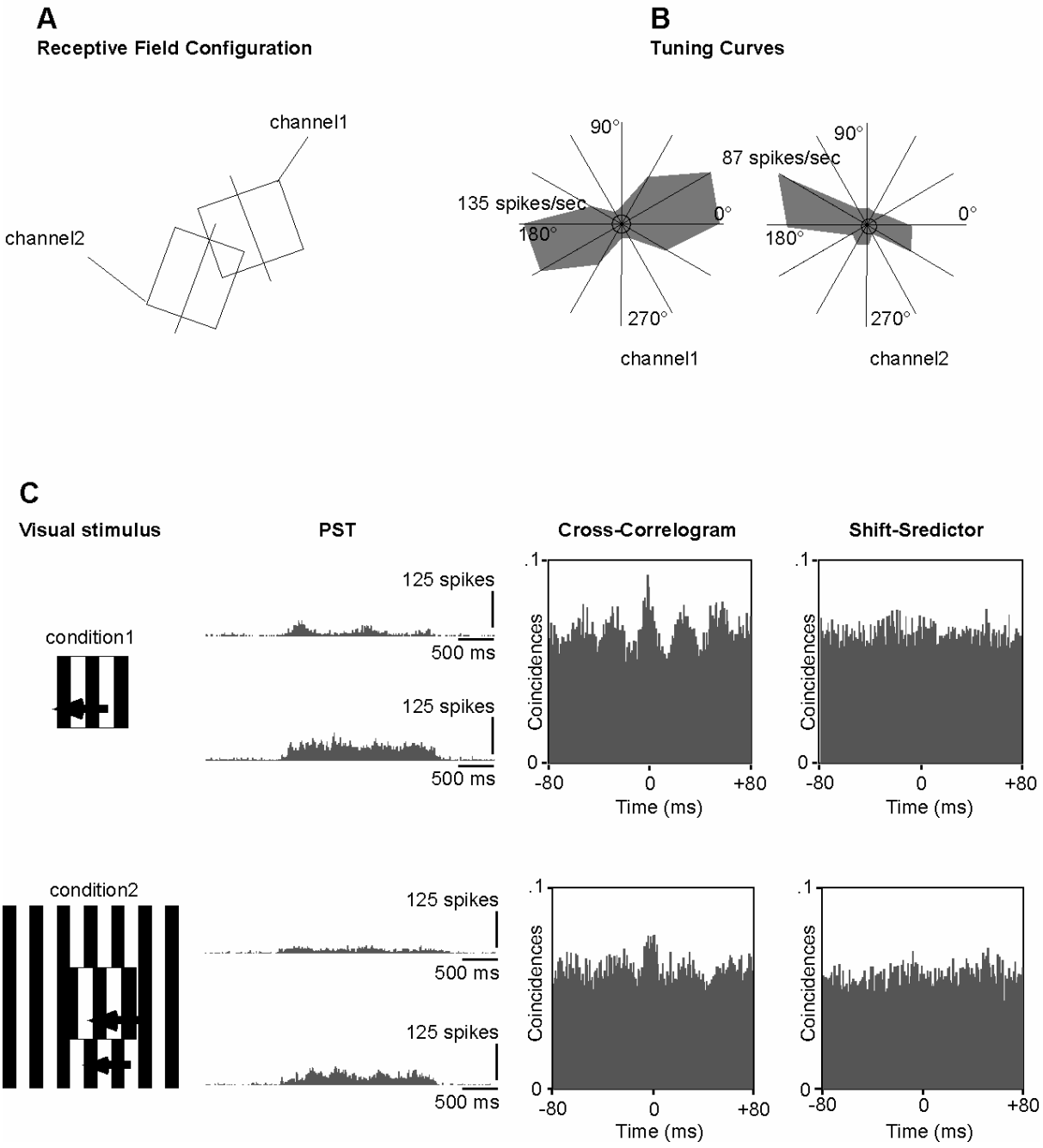


FIGURE 18:
Dependence of correlation strength on the presence of a background grating. (A, B) The receptive fields of both multi units are partly overlapping and their orientation preferences are similar. Compared to the first example both multi units are bi-directional. (C) A single drifting grating produced an enhanced firing rate in both multi-units and the cross-correlogram shows a 37 Hz oscillation. Both synchrony and this oscillation strength are reduced when a background grating is presented.

Introduction of an annulus between centre and surround

In order to get a deeper insight into the dynamics underlying contextual modulation the relationship between different parameters of the foreground grating and the background grating were systematically manipulated.

In the first set of stimulus conditions the relation between the spatial characteristics of surround suppression and synchronization strength were investigated by varying the inner boundaries of the background while holding the dimensions of the foreground constant. This generated an annulus of different size between foreground and background that had the same parameters in luminance and contrast as the background of the computer screen (see methods). Four categories of annulus size (a: 10%, b: 35%, c: 65%, d: 95% of the size of the foreground) were presented together with two control conditions. These consisted of the foreground stimulus alone and the background stimulus presented alone, both moving in the preferred orientation of the recorded neurons. The data result from experiments in 2 cats. As described in the previous paragraph, selection criteria of MUAs were based on the evaluation of responses to the tuning curve protocol and this procedure led to 31 MUAs and 23 cell pairs. The unbalanced number between MUAs and cell pairs results from the fact that some recordings were performed with two electrodes simultaneously and others with three or four. When simultaneously recording from more than two electrodes, not every site necessarily synchronizes its activity with all the other sites and therefore it is not possible to conclude on the number of pairs by summing up the numbers of MUAs. For better understanding, the exact number of electrodes per recording and the total number of multi units and pairs is illustrated in the table below (table1).

The effect of increasing the annulus between foreground and background on average firing rates and synchronization strength is shown in Fig. 19. Both measures are normalized for their dynamical ranges of change prior to averaging (see methods). In contrast to the foreground grating, the surround stimulus presented alone was not efficient in evoking action potentials or synchronization. This stimulus condition served as a control because it indicated that the surround stimulus did not invade the

receptive fields of the recorded neurons. Rate responses to the foreground decreased on average by 32% with the addition of an iso-oriented background. As the size of the annulus increased, suppression of firing rates decreased continuously (22.4% less suppression than to the uniform grating) and this effect was highly significant (one-way ANOVA, $F(4, 457) = 4.4$, $p = 0.001$). Additionally, a measure of effect size was used to compare the degree to which the surround stimulus modulated firing rates on the one hand and synchronization strength on the other hand (see methods). Suppression of the firing rates due to the increase of annulus area produced an effect size of $d = 0.5$. This gradual and continuous release of suppression may indicate that the processes driving surround suppression are expressed evenly throughout the surrounding area of visual space rather than originating from locally defined and distinct regions of the surround. Changes in the strength of synchronization between different stimulus conditions do not reflect any correlation with changes in stimulus parameters. Both, the analysis of variance ($F(4, 197) = 1.2$, $p = 0.3$) as well as the size of the effect ($d = 0.2$) indicate that the strength of synchronization is not modulated by the exact dimensions of the area between foreground and background covered by the annulus.

In all four stimulus conditions with different annulus sizes, phase shifts between the iso-oriented centre and surround gratings were presented randomized. Therefore, the dataset includes conditions in which centre and surround were phase aligned as well as conditions in which both gratings had different phase offsets. For the analysis of phase contrast effects responses were sorted post-hoc into two categories – the first category includes the data recorded with perfect phase alignment between centre and surround (**category 1:** no phase contrast) and the second category includes different degrees of phase offset between centre and surround (**category 2:** phase contrast). This post-hoc categorization resulted in relatively low and unequal sample sizes across different stimulus conditions as illustrated in Table 2. Consequently, the structure of this dataset does not allow computing a one-way analysis of variance across the different stimulus conditions. However, to obtain an impression of how the introduction of an annulus relates to the phase-alignment

	Recording	Nr. of electrodes (MUAs)	Nr. of MUAs used in analysis	Nr. of pairs
Cat #1	1	4	2	1
	2	3	2	1
	3	4	2	1
	4	4	3	3
	5	3	3	3
	6	2	2	1
	7	4	3	3
Cat #2	1	4	2	1
	2	4	3	3
	3	3	3	3
	4	3	2	1
	5	4	2	1
	6	4	2	1
	Total of:	**46**	**31**	**23**

Table1:

Numbers of recording sites, electrodes and cell pairs that were used to investigate the effect that different annulus sizes between centre and surround produce on neuronal responses. The second column, named “recording”, refers to different recordings performed at different cortical depths. The cortical distance between individual recordings ranges from 20 to 100µm. For example the first recording in cat#1 was performed with four electrodes. However, only two of these electrodes were used for further analysis. Electrodes were excluded from analysis either due to bad tuning properties or due to lack of synchronization with one of the other channels in at least one orientation of the tuning curve protocol (see methods). This resulted in one cell pair for the investigation of synchronization strength.

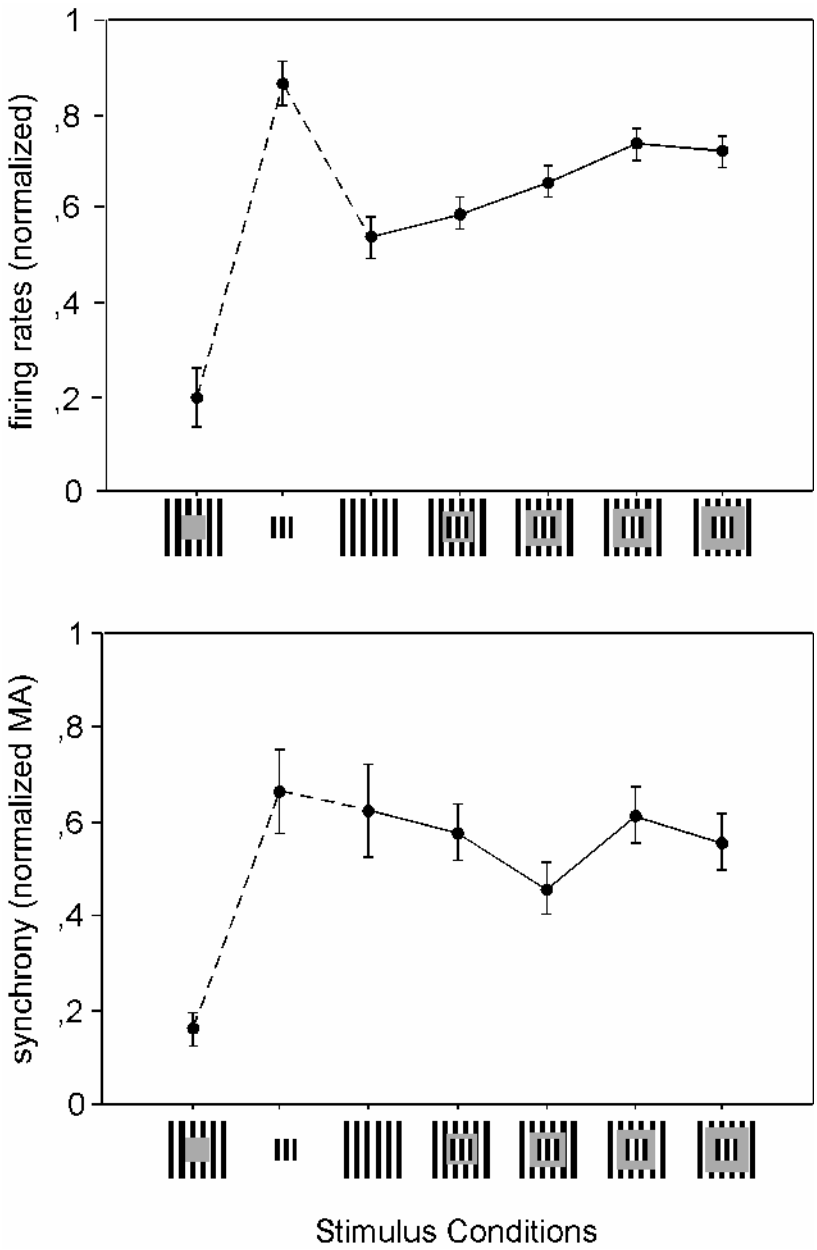


FIGURE 19:
Context dependent modulations of rate responses and synchronization strength. The stimulus configurations are depicted on the horizontal axis of both graphs. The average measures of rate responses (upper graph) and synchrony (lower graph) are shown on the vertical axis. Surround suppression of the response amplitude shows a clear correlation with the size of the annulus while correlation strength seems to be independent of annulus size. Error bars indicate ±1 standard error (SE).

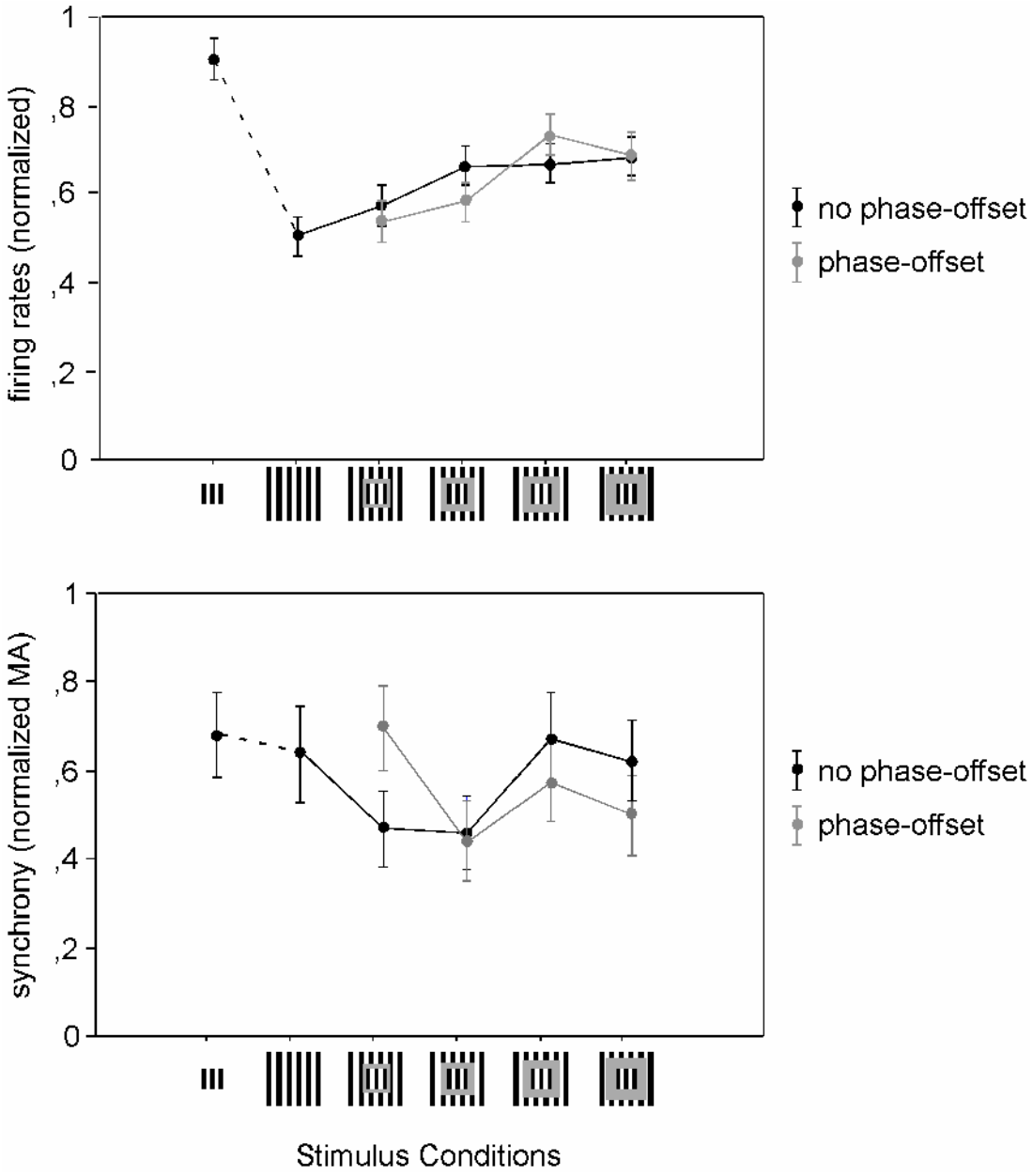


Figure 20:

Modulation of firing rates and synchrony due to different phase-relations between centre and surround when both gratings are separated by annulus of increasing area. Firing rates increase continuously when the size of the annulus increases, regardless of the phase alignment between centre and surround. When the annulus has its smallest size, synchronization strength is stronger when centre and surround are not phase aligned (not significant). With increasing annulus size this effect is reversed.

between the centre and the surround t-tests were computed for each of the two categories (Table 2). Results are plotted in Figure 20. For firing rates, the release of suppression due to increasing annulus size was equally strong for conditions with and without phase offset. This increase in rates was statistically significant in both categories (ANOVA for category with no phase offset: $p = 0.04$; ANOVA for category with phase offset: $p = 0.006$). Nevertheless, within each individual group of annulus size, no statistically significant differences between the two categories of phase alignment were found (Table 2).

Again, the evaluation of cross-correlograms revealed that synchrony among the respective pairs of recording sites was not correlated with annulus size, independent of whether the centre and the surround were in- or out-of-phase (ANOVA for category with no phase offset: $p = 0.3$; ANOVA for category with phase offset: $p = 0.2$). When the annulus has its smallest size, synchrony is stronger in cases when centre and surround are presented with phase offset, even though this effect does not reach statistical significance ($p = 0.07$). This lack of significance may result from the small sample size because the effect size in that respective category is considerably high ($d = 0.8$). As the annulus size increases, this effect disappears and even tends to be reversed, although neither reaching statistical significance nor strong effect sizes. Altogether, neither firing rates nor synchrony show consistent response modulation regarding the effect of phase offset when centre and surround are separated by an annulus. This suggests that the potential effect of a phase offset between the centre and the surround is cancelled out when an annulus is introduced. Similar results were recently obtained in psychophysical experiments (Yu et al., 2001) (see Discussion).

Luminance contrast between centre and surround

In the next set of stimulus conditions perceptual segregation between centre and surround was induced by varying the luminance contrast between the centre and the surround grating. The data reported on in this section were obtained from two cats.

	Count for "no phase contrast" (MUAs/Pairs)	**Count for phase contrast** (MUAs/Pairs)	**p-value** (Firing Rates/ Synchrony)	**Effect Size** (Firing Rates/ Synchrony)
Annulus a	12/ 9	19/ 14	0.8/ 0.07	0.04/ 0.8
Annulus b	12/ 9	19/ 14	0.1/ 0.7	0.4/0.1
Annulus c	12/ 9	19/ 14	0.3/ 0.5	0.3/0.3
Annulus d	12/ 9	19/ 14	0.9/ 0.3	0.4/0.01

Table 2:
Effect of phase-alignment between centre and surround when centre and surround are separated by an annulus of increasing size. The size of the annulus increases from a to d.

Responses were recorded from 32 multi units which resulted in 36 pairs of multi units for investigating the modulation of synchronization and firing rates. The centre grating was presented either at high contrast (0.8) and the luminance contrast of the background was reduced in three steps (0.6, 0.4 and 0.2) or the background was presented at high contrast and the contrast of the foreground was reduced stepwise in the same manner. Additionally, three control conditions were presented: the foreground alone, the background alone and a single large grating. All three control conditions were presented at high contrast (0.8). This resulted in nine different stimulus conditions in total.

Similar to the previous experiment, strongest rate responses were evoked by a small and optimally oriented grating that covered the classical receptive fields. Any stimulation of the surround produced rate suppression. This suppression was strongest when foreground and background were iso-oriented and iso-luminant and gradually decreased when the luminance of the background was reduced (37% in total). The effect was highly significant (one-way ANOVA, $F(6, 389) = 19{,}8$, $p < 0.0001$, Figure 21) and also the size of the effect was large ($d = 0{,}8$). When the

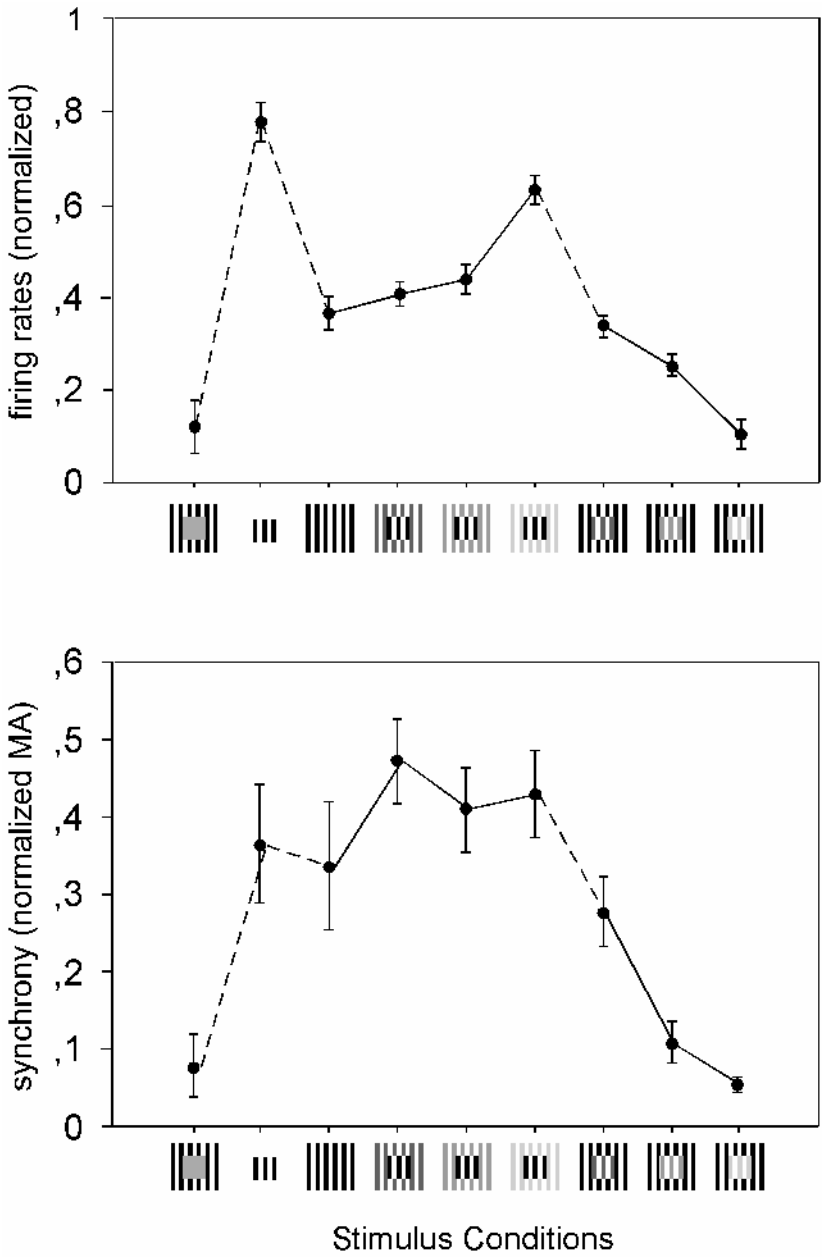


FIGURE 21:
Changes in luminance contrast of background and foreground modulate firing rates and synchrony. When the luminance of the background is reduced, surround suppression is reduced but synchronization strength is not affected. When the luminance contrast of the foreground is reduced, firing rates and synchrony decrease.

luminance contrast of the foreground was reduced while keeping the contrast of the background high, rate responses decreased even further.

The modulation of synchronization strength due to reduction of luminance contrast of the background grating was not consistent and the variance was high. Consequently, analysis of variance revealed no significant differences across the different stimulus conditions ($F(3, 98) = 0.6$, $p = 0.6$) and also the effect size was very small ($d = 0.1$). The decrease of luminance contrast of the foreground grating resulted in a rapid decrease in synchronization strength (97% in total). This effect was highly significant (ANOVA, $F(3, 99) = 11.3$, $p < 0.0001$) and the effect size was large ($d = 1.5$). This strong decrease in synchronization strength was correlated with the strong decrease of the discharge rates (correlation = 0.9).

Orientation contrast between centre and surround

In the third set of stimulus conditions contrast between centre and surround was induced by changes in the orientation of the background grating. The data presented in this paragraph were collected in experiments in 10 cats and selection criteria of multi units led to a total of 168 multi units and 172 pairs for investigating the modulation of firing rates and synchronization strength, respectively. The orientation of the background grating was manipulated in steps of 30°, ranging from iso-orientation with the foreground (0° contrast) to the orientation that is orthogonal to the foreground (90° contrast). The iso-oriented background was always phase offset to the foreground and therefore the two components of the stimulus were perceptually segregated. As controls, a single large grating, the foreground stimulus alone and the background stimulus alone were presented. The direction of movement of the three control gratings was identical to the direction of the foreground grating and thus matched the preferred orientation and direction of the recorded neurons.

The average rate responses and the strength of synchronization obtained during the six stimulus conditions are shown in Figure 22. Again, the weak responses to the background presented alone indicated that the surround stimulus was placed correctly and did not invade the receptive fields of the recorded neurons. The discharge rates to the foreground alone decreased on average by 27% when the iso-

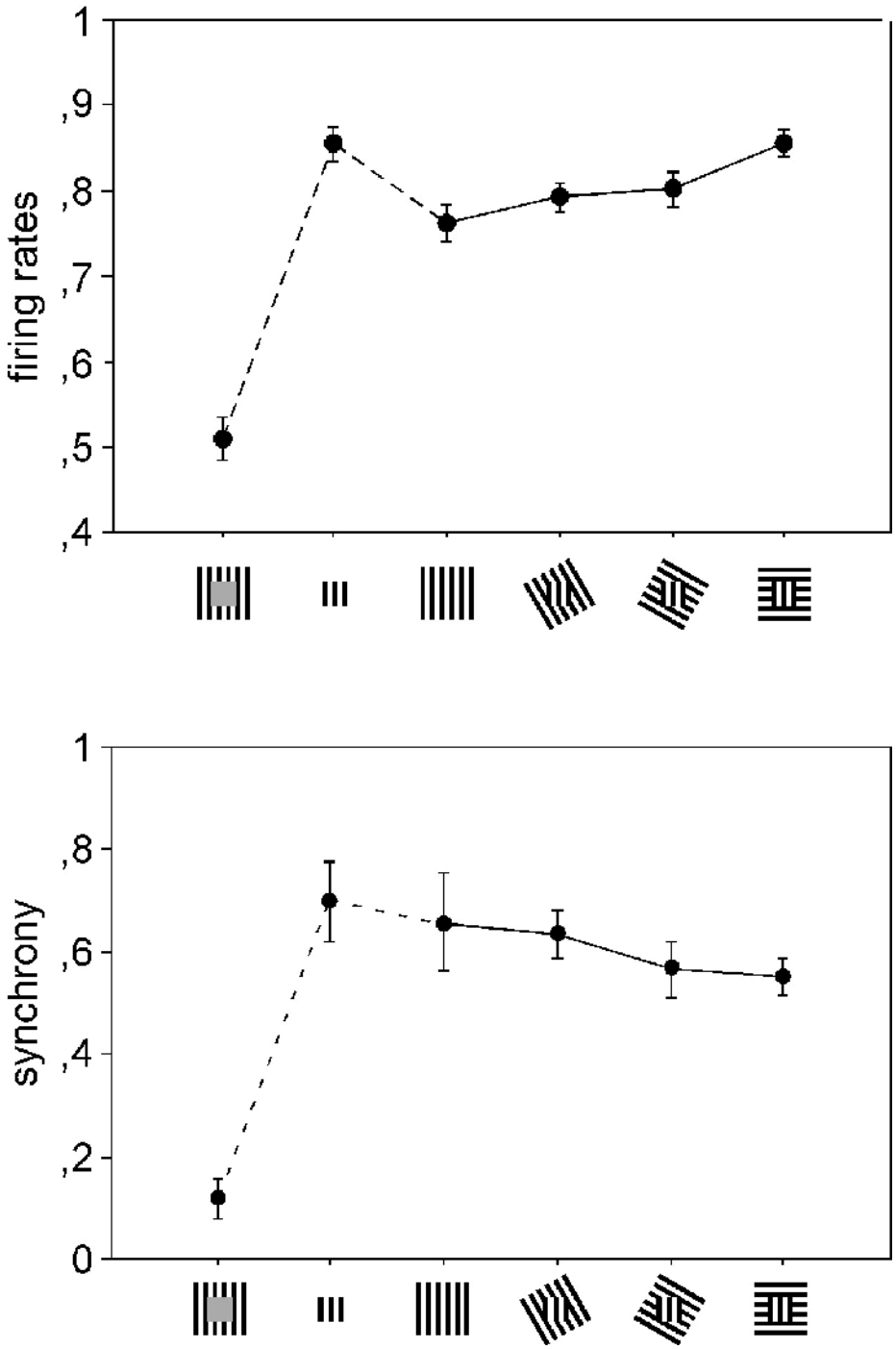


FIGURE 22:
Changes in orientation contrast modulate firing rates and synchrony. The strongest rate responses were evoked by a small grating covering the classical receptive fields of the recorded neurons. The addition of a superimposed background grating produced a suppression of about 25%. The magnitude of surround suppression was highly dependent on the orientation difference between centre and surround. Suppression progressively decreased with increasing difference in orientation. In contrast, synchrony tended to decrease with increasing orientation offset, but the changes were not significant.

oriented background was presented (Figure 22 and also Figure 24 for scatter plots between extreme conditions). The degree of suppression to the iso-oriented surround was similar to the amount of suppression in the two previous experiments. This suppression progressively decreased with increasing orientation difference between the two components of the stimulus and the differences were statistically significant (one-way ANOVA, $F(3, 471) = 5.1$, $p = 0.001$, Figure 22). The finding that an iso-oriented surround produces stronger suppression of firing rates than an orthogonal surround is in perfect agreement with previous reports (DeAngelis et al., 1994;Sengpiel et al., 1997;Sillito et al., 1995;Walker et al., 2000). However, in contrast to firing rates, synchronization strength tended to decrease with the increase in orientation contrast by a maximum 8% and ANOVA computed between the four stimulus conditions failed to reach significance ($F(3, 490) = 0.2$, $p = 0.2703$). The change of the background from minimum to maximum orientation contrast (0° to 90°) produced an effect of medium size on the average rate responses ($d = .49$) and a considerably smaller effect on synchronization strength ($d = 0.03$). Therefore, even if the changes in synchrony reached significance, the small effect size suggests that in this stimulus configuration, modulation of synchrony is not likely to play a major role in information processing. In addition, the trend of changes in synchronization strength is in the opposite direction to what would be required for an increase in the saliency to code for a stimulus that is segregated from the background.

So far these findings indicate that changes in size, luminance and in the orientation of the surround modulate primarily firing rates and not synchrony and therefore, only firing rates would have the potential to play a role in processes underlying perceptual segregation under these stimulus conditions.

Phase contrast between centre and surround

In this last set of stimulus conditions segregation between centre and surround was induced by manipulating the phase alignment between the black and the white bars of the two gratings. Rate responses were analyzed from 124 recording sites which resulted in 130 pairs of multi units for investigating synchronization strength. The phase-shifts were presented randomly. For the analysis of phase contrast effects the responses were sorted post-hoc into four groups, according to the degree of phase

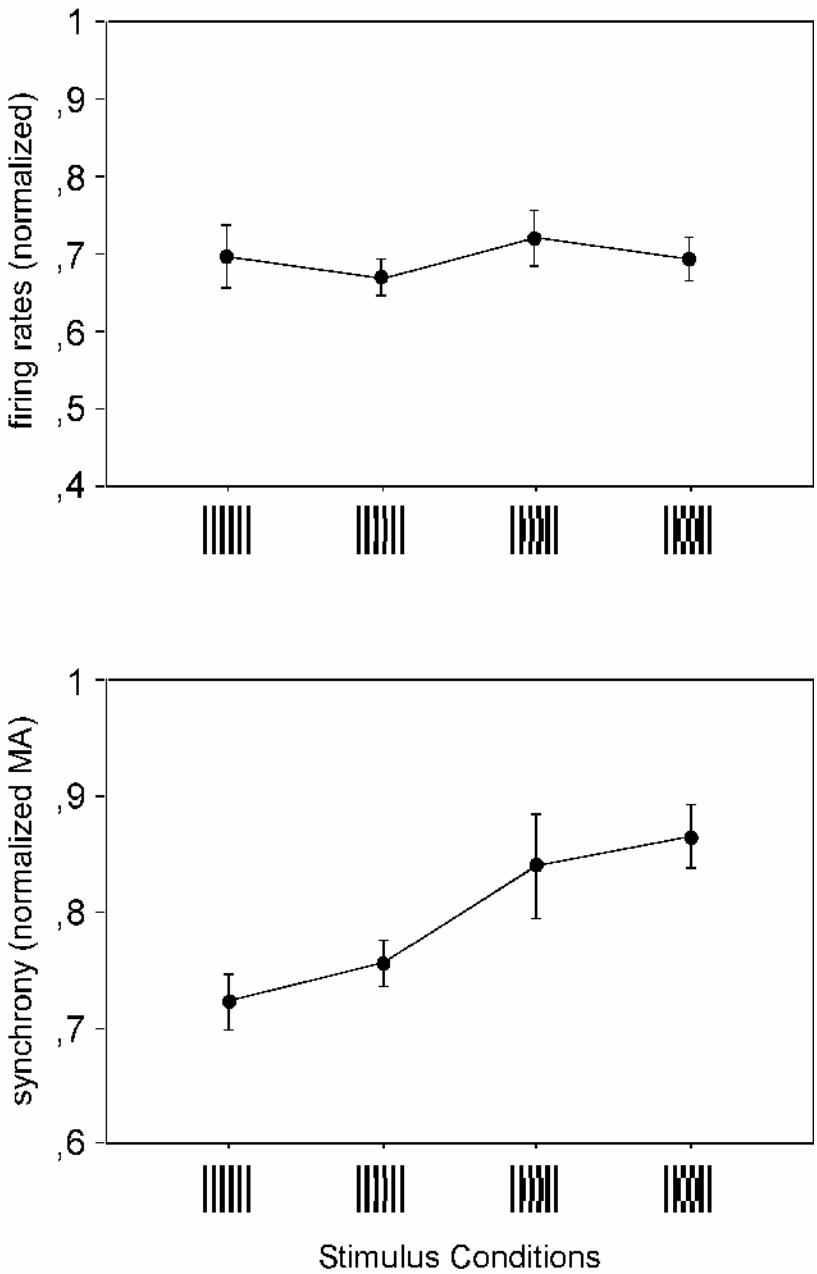


FIGURE 23:
Synchrony was strongly modulated by changes in the relative spatial phase between foreground and background. With increasing phase angle, synchronization between neurons stimulated by the foreground grating gradually increased. On the other hand, firing rates showed no detectable effect to changes in the relative spatial phase between foreground and background.

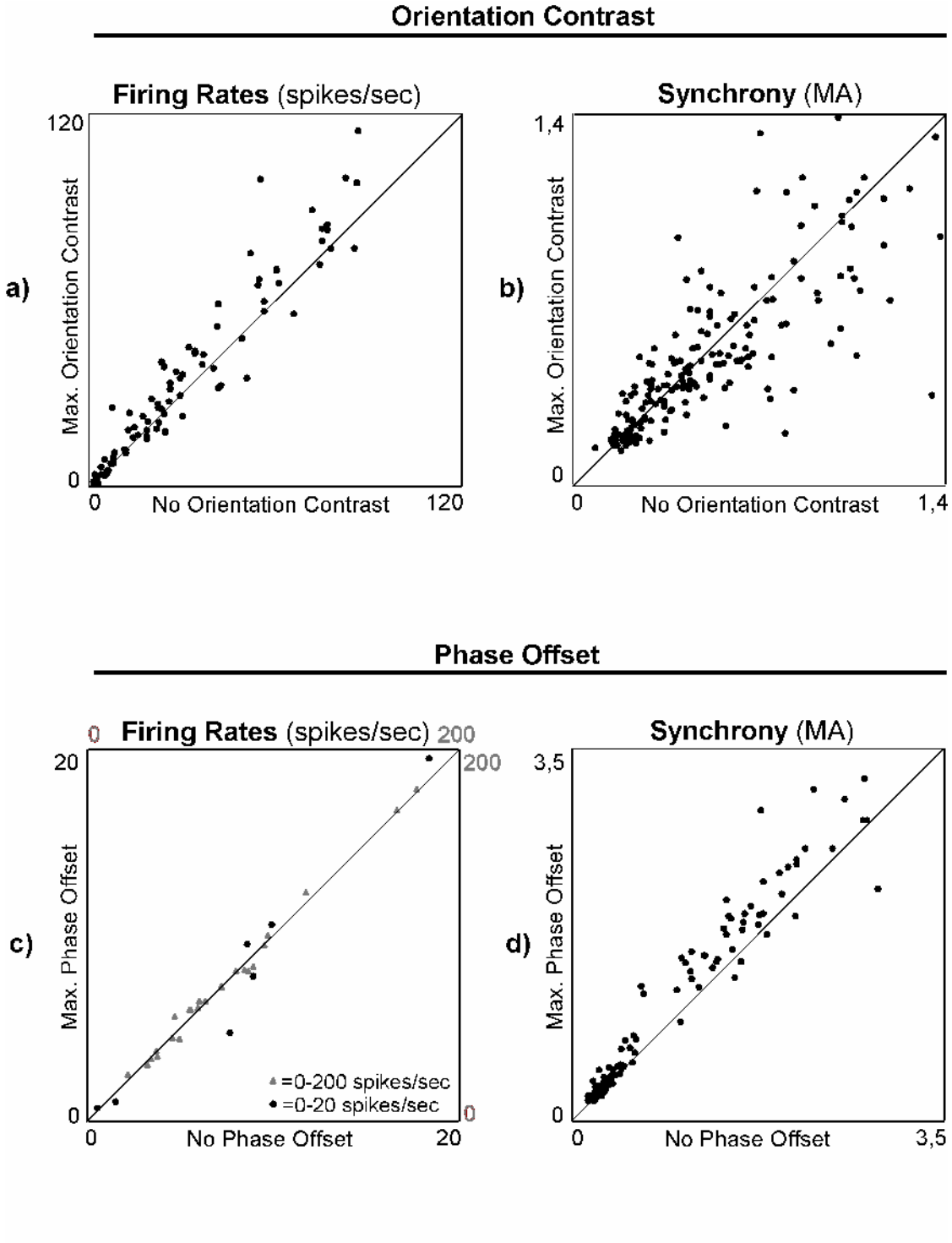


FIGURE 24
Responses at individual recording sites to extreme stimulation conditions. Responses to zero orientation contrast (0°) are plotted against responses to maximum orientation contrast (90°) for firing rates **(a)** and synchrony **(b). c)** and **d):** responses to minimum (0°) and maximum (180°) phase offsets for firing rates and synchrony, respectively. Note that due to large differences in the number of cells composing a multi unit, raw firing rates are presented at two scales for clearer presentation.

alignment (phase offsets: 0°, n = 34; 1°-30°, n = 45; 31°-60°, n = 30; 61°-90°, n = 57). The group with zero degree phase offset was based on the responses to a single large grating that was initially used as a control stimulus (see methods).

Average firing rates did not change significantly across different phase offsets (ANOVA, $F(3, 298) = 1.358$, $p = 0.2558$) and there was no observable trend of change (Figure 22). This finding is in agreement with other reports (DeAngelis et al., 1994;Tanaka et al., 1987). By contrast, synchronization between the cells stimulated by the foreground increased consistently with increasing relative phase shift between foreground and background (16% of modulation, Figure 23). Accordingly, ANOVA indicated significant differences in synchronization between the four groups ($F (3, 327) = 5.893$, $p = 0.0006$). The effect sizes that phase offsets produced on rate responses were also different from those on synchronization. The effect size for rates between minimum and maximum phase offset (0° and 90°) was small ($d = 0.02$) whereas effect size between the same groups was much larger for synchrony ($d = 0.66$). These findings suggest that the effects, which phase contrast produces on synchrony are reversed compared to the effect observed for orientation contrast. When a foreground stimulus is perceptually segregated from an iso-oriented background by an offset in phase angle, synchrony is modulated strongly and firing rates are not.

Recordings with Michigan Probes

In order to substantiate the finding that synchrony is modulated by the phase contrast between two gratings the activity of a larger number of neurons was recorded in parallel with multi-channel electrodes (Michigan Probes) to replicate the finding in an additional approach.

In the following experiment, the activity from 32 multi units was recorded in parallel in area 17 of one hemisphere. Two probes were positioned such that they would enter the cortex approximately perpendicular to the surface. The spatial arrangement of the recording sites allowed to simultaneously record from neurons at different cortical depths and along an axis tangential to the cortical surface. The distance between the

probes on the cortical surface was about 2 mm. Penetrations were adjusted such that the receptive fields of the neurons were overlapping and had sufficiently similar orientation preferences (± 30°, Figure 25 A) to permit simultaneous activation of the majority of cells. Fore- and background gratings always had the same orientation and the relative phase was changed in 12 steps of 30°, ranging from 0° to 330°. Again, the tuning properties of the recorded neurons were determined prior to investigation of surround effects. In contrast to the previous experiments recording sites were not pre-selected according to synchronization strength, but only channels that showed orientation selective responses were included into the analysis in order to exclude contribution from thalamic afferents. In total, the responses from 47 multi unit sites were evaluated (n_1 = 19, n_2 = 17, and n_3 = 12 in each session) and correlograms were computed from 325 pairs of recording sites (n_1 = 149, n_2 = 119, and n_3 = 57), resulting in 4008 cross-correlogram functions.

Figure 25 illustrates an example of a tuning curve protocol during one recording session shown for all 16 recording sites of one Michigan probe. The receptive fields of one probe were always overlapping and the orientation preferences of most channels were similar. In line with the results from previous studies the chance to observe correlated activity between neurons with overlapping receptive fields and similar orientation preferences is very high. In this example, 80% of the multi units synchronized their activity in at least one stimulus condition of the tuning curve protocol.

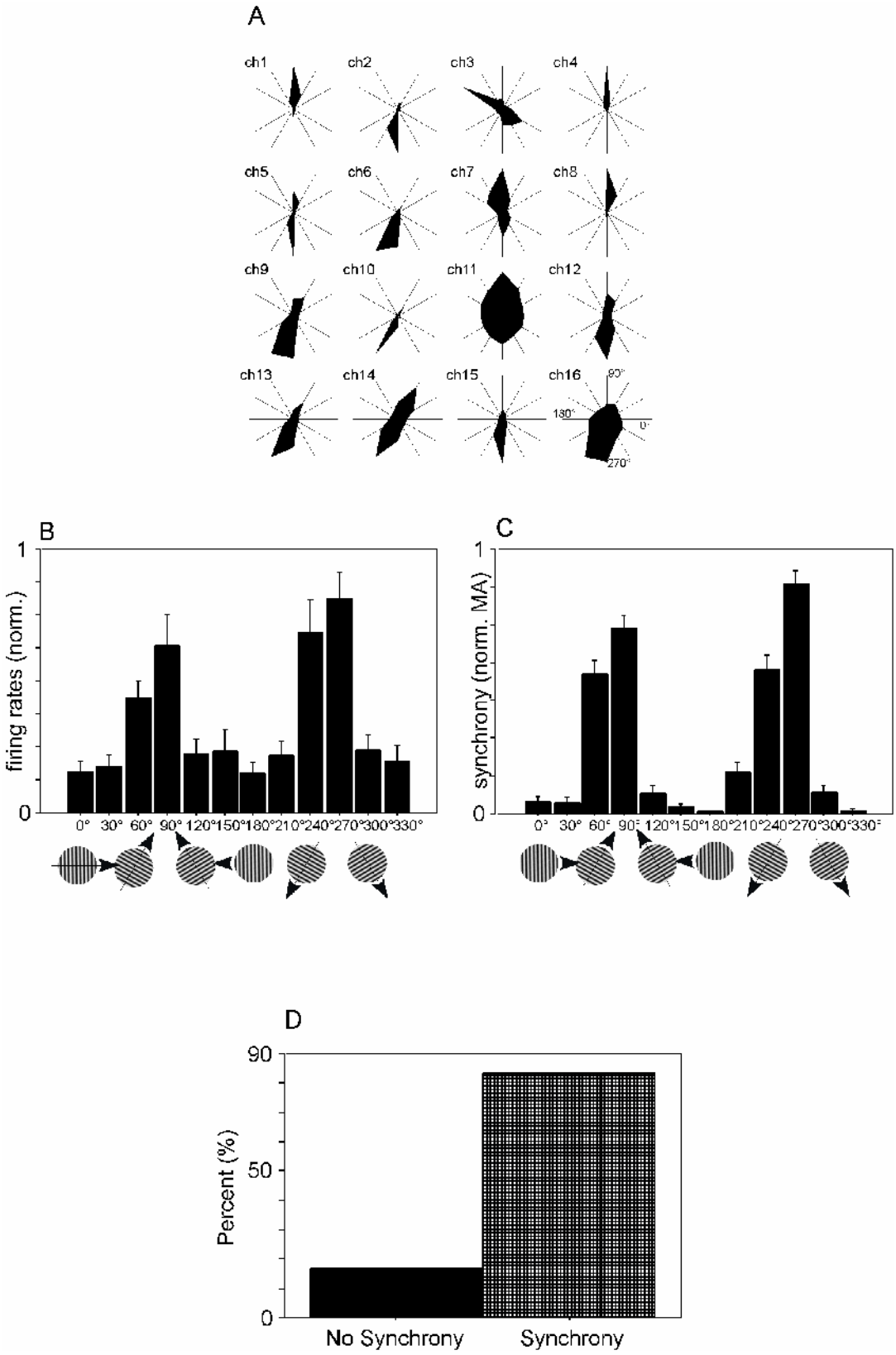


FIGURE 25
Example for the tuning curves 16 MUAs recorded with one Michigan probe. (A) All 16 channels show similar orientation preferences (± 30°) and all receptive fields are overlapping (not shown). (B, C) Modulations of firing rates and synchrony are correlated and highest in the preferred stimulus orientations. (D) More than 80% of multi-units show correlated activity in at least one stimulus condition.

The results presented in the following paragraph are based on recordings obtained from one cat and include three different recording sessions with two probes. Two of the three recordings were obtained during one insertion at two different cortical depths (300 µm difference between recording positions), thereby recording responses from partially overlapping regions of cortical tissue. For the third recording another insertion in the same hemisphere was made.

The last section of this paragraph goes beyond investigating the modulation of responses to the centre and additionally investigates responses of cells stimulated directly by the surround. This last dataset is restricted to one recording from two Michigan probes.

Phase contrast between centre and surround with Michigan Probes

The main findings obtained with tungsten electrodes were replicated. Synchronization strength between neurons stimulated by the foreground increased with the increase in phase offset (ANOVA, $F(11, 3455) = 40.7$, $p < 0.0001$, Fig. 26). This dependence was similar in all three recording sessions, i.e. with different electrode positions (Fig. 27), and the differences between conditions were also significant in all three sessions (ANOVA, all F-values > 13.3 and all p-values < 0.0001, degrees of freedom within groups ranging from 538 to 1567). The effect sizes between minimum and maximum phase offset were large (between $d = 1.06$ and $d = 1.5$) and about 44% larger compared to the experiment with tungsten electrodes. This increase in effect size was only partly due to stronger modulation (on average 7% increase). It is also a consequence of the decrease in variability due to highly parallel recordings (on average 27% decrease) because sequential recordings at different times necessarily include responses obtained during different cortical activation states.

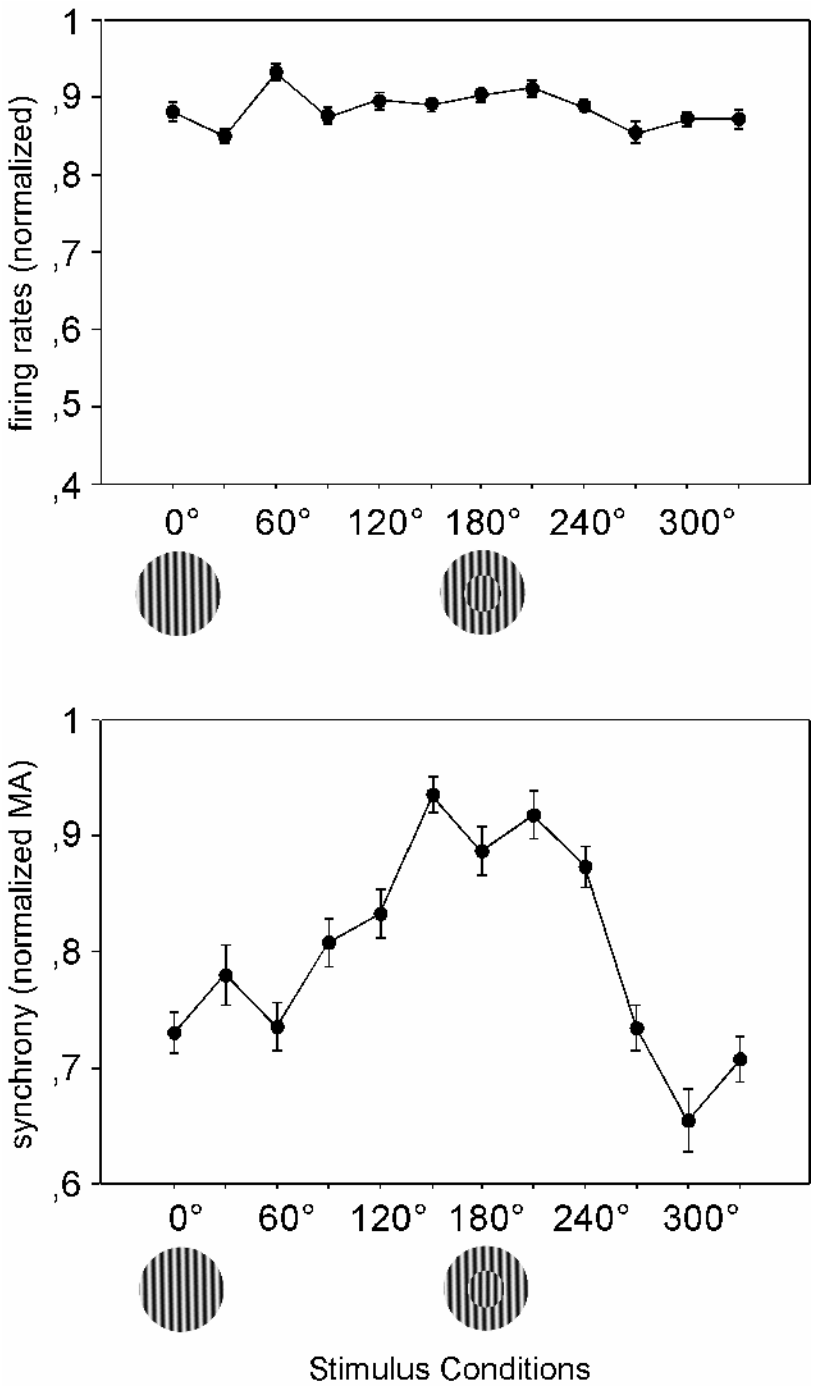


FIGURE 26:
Phase Contrast: Data shown in this plot were collected with Michigan Probes. In this experiment the main findings illustrated in Figure 22 are replicated: Synchronization strength increased with increasing relative spatial phase angle between foreground and background, while firing rates again were not consistently affected.

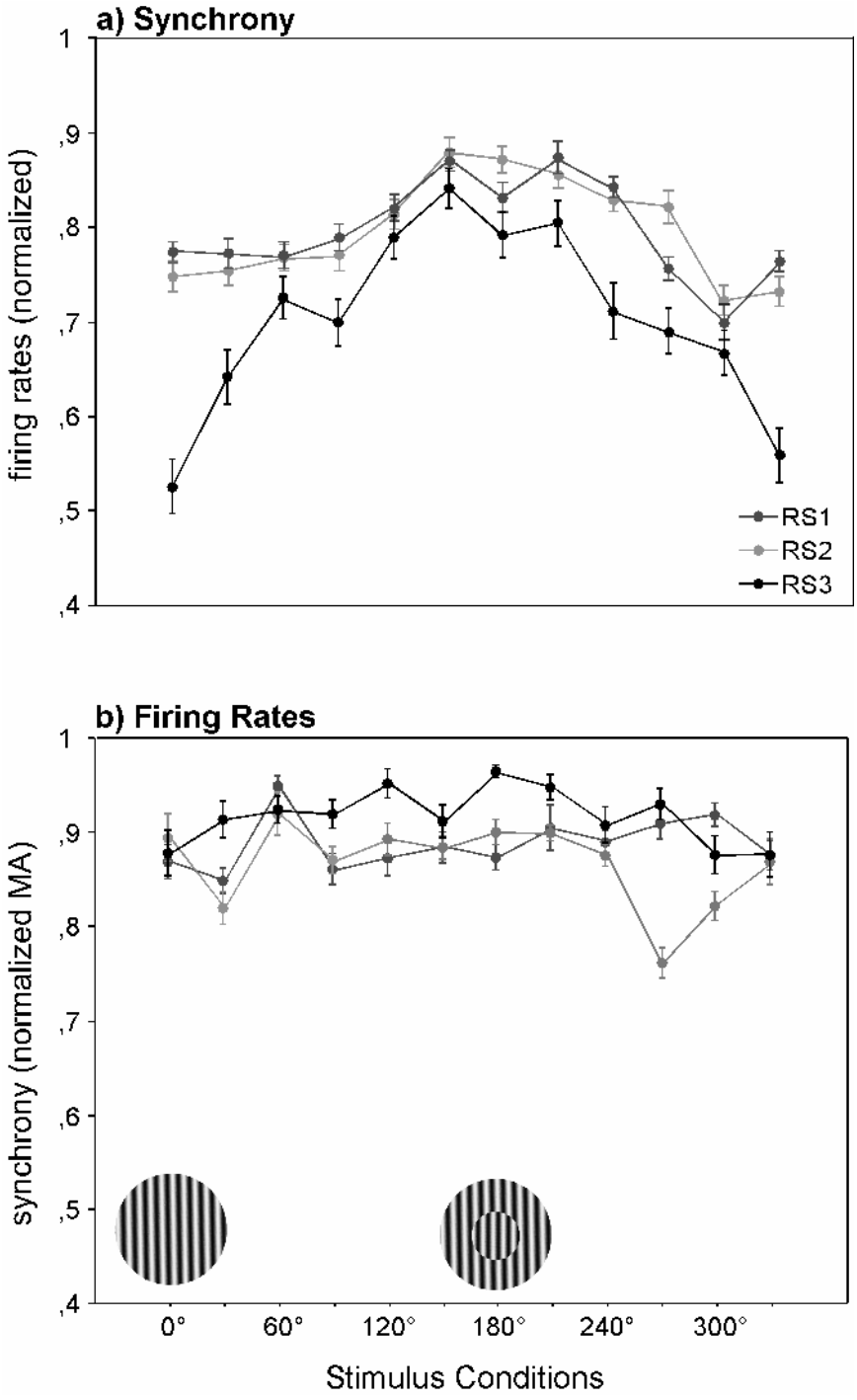


FIGURE 27

Changes of synchrony and firing rates due to changes in spatial phase for individual recording sessions. **Modulation of synchrony**: Each curve represents one single recording session. In each recording session the effect was highly significant (all p-values < .0001). **3b) Modulation of firing rates:** In all three recording session there were significant differences in at least one condition. These differences were neither consistent nor did they systematically correlate with the perceptual organization of the stimulus.

The curves in Figure 27 show different dynamical ranges of change in synchronization strength. The two curves with lower dynamical range of change (on average 16% modulation, in red) were computed on the basis of responses that include both, short-distance synchronization between channels of the same probe and synchronization over longer distances between the channels of different probes. In contrast, the curve showing the largest dynamical range (38% modulation, in blue) is based solely on short-distance synchronization obtained from a single probe. Therefore, one explanation for the difference in the dynamical range of modulation between the curves is that synchrony between distant neurons is usually weaker (Engel et al., 1990;Konig et al., 1995) which in the present case, resulted in a smaller dynamical range of changes (Figure 28).

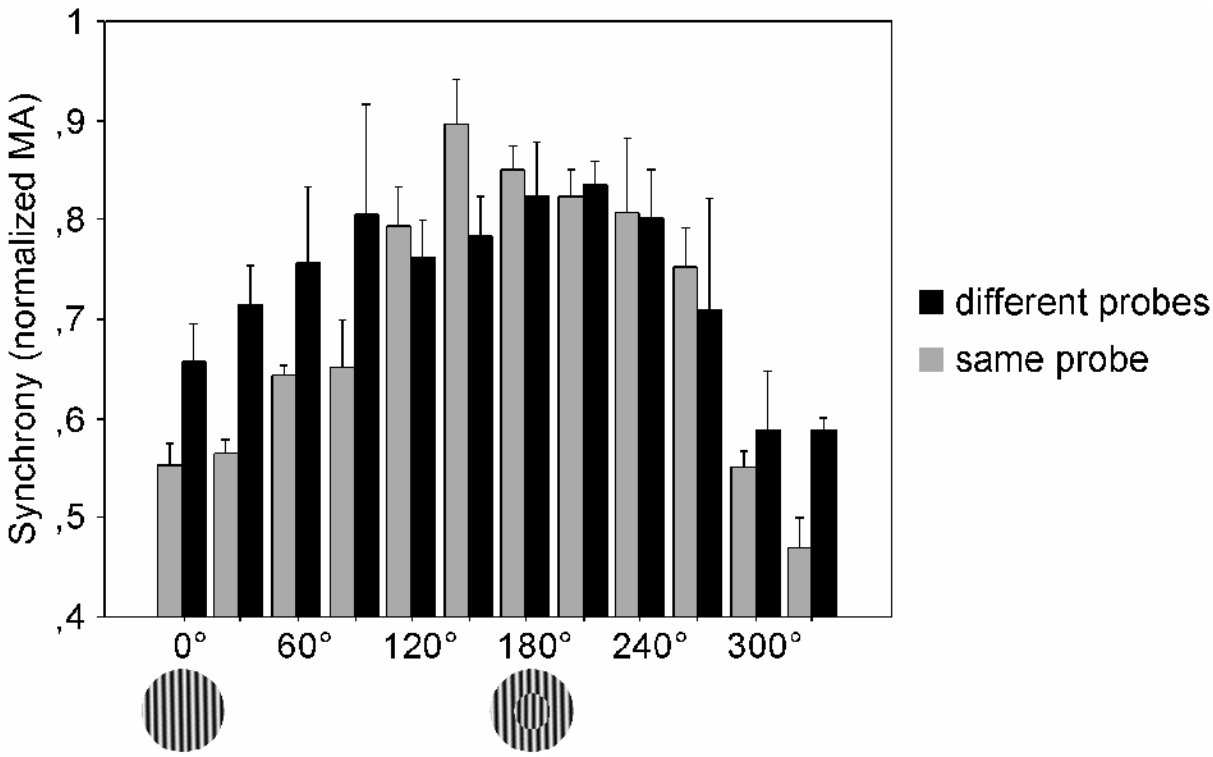


FIGURE 28
Synchrony between recording sites of two different probes (in black) show a lower dynamical range of change in synchronization strength between the different stimulus conditions than synchrony between recording sites of the same probe (in gray).

In contrast to the first experiment, firing rates also changed significantly across different stimulus conditions (ANOVA, $F(11, 948) = 4.9$, $p < 0.0001$). These

differences sometimes also showed large effect sizes (up to d = 1.2). However, the differences were not systematically related to phase changes nor were they consistent across the recording sessions (Fig. 27). Thus, in agreement with the previous experiment, there was no evidence that firing rate modulation contains reliable information about the degree of phase offset between the centre and the surround grating.

The phase effect on synchrony observed in this experiment with Michigan probes was much stronger compared to the experiment with tungsten electrodes. One reason for this is presumably the decrease in variability of responses due to the use of highly parallel recordings. Therefore, the present results support the hypothesis that synchrony may enhance the saliency of a centre stimulus that is segregated from an iso-oriented surround by an offset in phase.

Synchronicity across the centre-surround border

Responses to one stimulus condition can be defined as salient only if they are related to responses evoked by another stimulus condition. Thus, the increase in the strength of synchronization between neurons stimulated by a foreground stimulus can be interpreted as a phase-dependent enhancement in saliency only under the following condition: the synchronization between responses to the foreground stimulus and responses to the surround stimulus must not change in the same way. Otherwise, the observed phenomenon would simply reflect an overall change in synchronization strength that could not assist the detection of phase shifts. Similarly, if the increase in synchronization strength between neurons responding to the centre is contingent with an increase in the synchrony between neurons responding to the surround, the relative saliencies of responses to the two components of the stimuli would not change. Thus, the present results need to be complemented with an investigation of the dynamics in the temporal structure of neuronal activity that includes responses to the surround. This requires simultaneous recordings of responses to the centre and surround. The recording sites must be positioned such that the receptive fields of the neurons are sufficiently separated and at the same time prefer similar directions of the stimulus. In addition, evidence suggests that the long-range tangential connections extend in particular between neurons that have a

collinear arrangement of receptive fields (Schmidt et al., 1997). Therefore, it would be preferable that the receptive fields of two probes are also collinear. In one recording session these conditions were satisfied. The clusters of receptive fields associated with each of the probes were separated about four degrees of visual angle. Responses at 11 sites of one probe were selective for the orientation that was sufficiently close to the orientation at the two sites of the other probe. Thus, the stimulus could be positioned such that both groups of neurons were stimulated optimally and one group was activated by the centre and the other group by the surround. The cluster of receptive fields with the larger number of appropriately oriented channels was chosen to be covered by the surround. Due to the large distance between recording sites synchronization of discharges was not sufficiently strong to permit evaluation of conventional cross-correlation functions. The lack of long-distance synchronization can be explained by the relatively low level of cortical activation in this recording session in respect to the presence of oscillatory activity in the cortex (Konig et al., 1995;Herculano-Houzel et al., 1999). Therefore the analysis was opted for the more sensitive method of spike-field coherence to detect changes in the temporal structure of neuronal discharges. Action potentials at one site were correlated with the local-field potentials (LFPs) recorded at the other site and these spike-triggered averages were normalized for the LFP power in the various frequency bands (see methods). This analysis was confined to the frequency range between 20 and 80 Hz. Spike field coherence was determined for 22 pairs of recording sites distributed across the figure-ground border, for 55 pairs responding to the background and for one pair activated by the figure.

Coherence across the figure-ground border decreased continuously with increasing phase offset between fore- and background grating (Figure 29a). These changes were highly significant (ANOVA, $F(11, 252) = 14.5$, $p < 0.0001$) and the effect size between minimum and maximum phase offset was also strong ($d = 2.4$). These results were similar across three different frequency ranges (20-30 Hz, 33-60 Hz and 60-80 Hz). Reversing the LFP-spike assignment gave the same result. This finding is

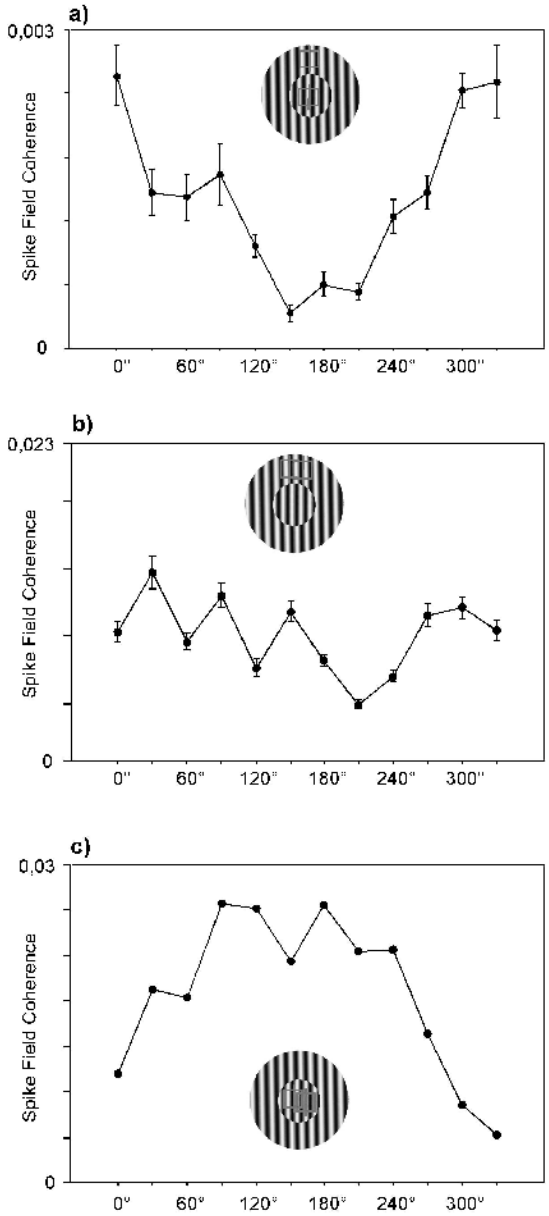


FIGURE 29

Temporal coding between neuronal responses to the foreground and the background. (a) The spike field coherence (SFC) between neurons stimulated by the foreground (spikes) and neurons stimulated by the background (local field potential) gradually decreases as the foreground segregates from the background. Note that with zero phase offset (0°) between foreground and background, neurons are activated by one coherent grating. Both populations are stimulated by different gratings when the phase angle between foreground and background is different. (b) The correlation between neurons activated by the background seem to be independent from the phase relation between foreground and background while the SFC between neurons stimulated by the foreground (c) show the same dependency and synchrony on a millisecond timescale.

similar to that of a recent study in V1 of monkeys by Gail (Gail et al., 2000), who found a decrease of coherence between LFP responses to gratings that were not phase aligned.

Unexpectedly, spike-field coherence computed between recording sites activated by the background grating also changed significantly with changes in phase offset (ANOVA, $F(11, 339) = 22.2$, $p < 0.0001$; Figure 29b). However, these changes were not systematically related to the amount of phase offset. Accordingly, the effect size between minimum and maximum phase offset was relatively low ($d = 0.3$). Also this result was similar for the three frequency ranges analyzed separately. By contrast, the spike field coherence between the two recording sites corresponding to the figure increased systematically with increasing phase offset (Figure 29c). The latter agrees with the changes of the cross-correlation functions computed from neuronal discharges in experiments 2 and 3, underlining the similarity of the two measures. The discharge rates of the neurons responding to the surround stimulus were not affected by the phase offset (ANOVA, $F(11, 120) = 0.01$, $p = 0.9$; d between 0° and 180° phase offset = 0.02; Figure 30).

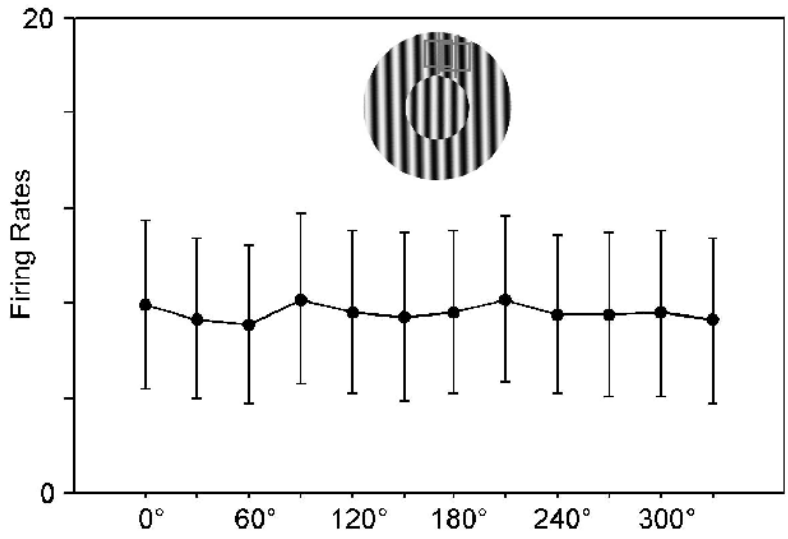


FIGURE 30

Firing rates of neurons responding to the background are not correlated with the phase relationship between the foreground and the background. Firing rates are not normalized.

The analysis of the dataset of this last paragraph suggests that the modulation of synchrony in the previous experiment did not reflect global changes in the strength of synchronization. Instead, synchrony across the border separating foreground and background decreases with phase offset, indicating that neuronal assemblies segregate according to the perceptual organization of the stimulus. Furthermore, synchrony between neurons stimulated by the background does not change across different conditions, which indicates that the foreground can have a different saliency than the background.

Discussion

Methodological Considerations

Influence of anesthesia

The experiments in the present study were performed under general anesthesia. Therefore, it is important to discuss the potential effects anesthetics on response properties of cortical neurons. For several anesthetics, their specific molecular and cellular mechanisms of action are not very well understood. Unlike anesthetics which block or activate certain neurotransmitter receptors, such as benzodiazepines or ketamine, the effects of halothane, a volatile anesthetic which was used in all experiments described here, is not clearly confined to a single site of action. There is evidence that it blocks electrical synapses (He and Burt, 2000). Other studies indicate that halothane interferes with the cholinergic system by inhibiting the uptake of choline into cortical synaptosomes (Griffiths et al., 1994) and this uptake is known to be the limiting factor in the resynthesis of acetylcholine. In the present study, the concentration of halothane was in the range of 1.0% on the first experimental day and in the range of 0.6% on the following days of the experiment. This concentration level is 1/6 of the concentration level used in the experiments by Griffiths and, thus, is presumably too low to exert these effects. However, volatile anesthetics such as isoflurane or halothane are also known to work as agonists at inhibitory neurotransmitter receptors (mainly $GABA_A$), resulting in the amplification of inhibitory currents (Greenblatt and Meng, 2001). This could, at least to some degree, account for the weaker oscillations observed in anaesthetized animals because comparative electrophysiological studies in awake and anaesthetized animals in fact showed that the strength of cortical oscillations is slightly weaker under anesthesia (Gray and Viana, 1997).

The local receptive field properties of primary visual cortical neurons such as their preferred orientation, spatial frequency tuning or direction selectivity seem not to be affected by halothane (Lamme et al., 1998). Controversial results were obtained for the effects of anesthesia on global field properties such as the integration of information from beyond the classical receptive field. Even though contextual effects

of various kinds have been reported in anesthetized animals (Allman et al., 1985b;Gulyas et al., 1987;Gilbert and Wiesel, 1990;Sillito and Jones, 1996), some authors found contextual modulation to be completely suppressed in V1 neurons of anesthetized monkeys (Lamme et al., 1998). However, in another study, the same authors found modulatory effects when the monkey was slightly anesthetized with fentantyl even though surround effects were much smaller compared to when the monkey was awake (Zipser et al., 1997). An important difference to other studies may be that the authors did not put much emphasis on matching the stimulus on the RF with its tuning properties and typically used fine grain textures that stimulated the receptive fields only suboptimally (Lamme et al., 1998). The differences in results regarding contextual modulation under anesthesia might gradually depend on the depth of anesthesia as well as on differences in the experimental paradigm, visual stimulation and the experimental animal. Therefore, the ongoing debate in how far the results from anesthetized animals are comparable to the situation in the awake brain remains controversial.

However, the first results on oscillations and synchronous firing patterns in relation to stimulus properties were gained in anaesthetized cats (Gray and Singer, 1989) and could subsequently be confirmed by studies in awake cats (Fries et al., 1997) and monkeys (Kreiter and Singer, 1996). Therefore, it is likely that we are dealing here with very basic aspects of neuronal processing which are quite resistant to anesthesia. Given this, and also the observation that primary cortical areas are less affected by anesthesia than higher areas (Lamme et al., 1998), it is likely that the observations in the present study on synchronization phenomena in the primary visual cortex are highly relevant for processing mechanisms in the awake brain.

Extracellular recordings

The data in the present study were recorded with extracellular electrodes. While intracellular recordings establish the possibility to precisely relate the recorded neuronal activity to one single cell, extracellular recordings are more an indirect measure of the simultaneous activity of a cluster of neurons. Consequently, the properties of the mapped receptive field do not correspond to one single neuron but instead reflect the superimposed properties of all recorded neurons at that respective

recording site. However, given the vertical columnar organization of the visual cortex where neurons with similar functional properties (as for example receptive field location, ocular dominance, orientation selectivity and spatial frequency tuning) are grouped together, the recorded activity of adjacent neurons within the same MUA should exhibit similar functional properties. Even though this has proven to be true in most instances, some studies (Freiwald, 1998) using stereotrodes and spike sorting techniques could demonstrate that individual neurons within a MUA may also drastically differ from each other in their respective field properties. These observations are most likely due to recordings made close to so called singularities or “pin-wheel centers”. Near “pin-wheels centers”, all possible orientation preferences are represented in extremely close vicinity and neurons with individually well defined RF properties are lumped together and thus produce a very broad group tuning (Maldonado et al., 1997). In order to ensure that the tuning properties of the entire multi-unit matched approximately the individual properties of the respective single-units, the present analysis includes only multi-units, who’s summed orientation preference was not broader than 60°.

Another important problem with extra-cellular recordings arises when two electrodes are positioned too close to each other. In this situation it is possible that the activity of the same cell is recorded by both electrodes simultaneously. Such a case should present itself by showing a cross-correlogram with a very narrow peak exactly at time point zero - similar to an autocorrelation function - and this narrow peak should occur independently of the coherence of the stimulus. As this could not be observed in the present study, such a double recording of the same neuron can be ruled out.

The first part of the present dataset was recorded with conventional tungsten electrodes while the second part was collected with multi-electrode arrays. One of the most evident advantages of using multi-electrode arrays lies in their possibility to record a large and defined number of neurons in parallel. Whereas the maximal number of simultaneous recorded multi units was 7 when using tungsten electrodes, this number could be increased to the sevenfold (48 multi-units in parallel) by using Michigan probes. Such highly parallel recordings are nowadays indispensable in order to gain deeper insight into the temporal structure of distributed neuronal processes underlying object perception. A further advantage in using multi-site

recording techniques is that the variability in neuronal responses due to changes in cortical states can be reduced enormously. Often, and even during anesthesia, the processing state of the brain changes considerably. Therefore, performing sequential recordings may lead to variances which are independent of changes in stimulus properties but are rather based on changes in cortical processing conditions. As several studies suggest (Worgotter et al., 1998;Herculano-Houzel et al., 1999) RF properties and temporal characteristics of cortical responses may fluctuate over time. Therefore, the pooling of neuronal responses over long time stretches will either lead to substantial variances beyond the stimulus induced response changes or result in the exclusion of a considerable amount of data when sorting and grouping the data post-hoc according to cortical states being reflected in the EEG.

Therefore, recordings with multi-electrode arrays provide more reliable results compared to the averaged responses over individual electrodes from different recording epochs. Moreover, to simultaneously record from many neurons in parallel establishes the possibility to correlate the differences in responses between repeated recordings to the associated cortical states and to learn more about the related processing changes.

Discussion of results

Links between physiology and perception

In the past three decades, several studies investigated contextual modulation from beyond the classical receptive field. These studies described the phenomenon mainly on the level of single recording site responses in primary visual areas and, thus, from a physiological rather than from a perceptual point of view. However, the growing bond between psychology and basic neurosciences has led to remarkable new discoveries regarding the role of context for the neuronal basis of perception. The systematic variation of contextual cues established neuronal-perceptual links which revealed how the visual system uses these cues in order to extract the properties of complex visual scenes.

Nevertheless, there exists an important difference between the definitions of context as it has been applied in neurophysiology and the definition adopted in psychophysics. The neuronal definition is based on the spatial interaction in the RF, i.e. contextual information from the surround modulates the neuronal responses to the classical receptive field stimulus. The perceptual definition of context, however, is based on the ability of contextual information to segregate a sensory stimulus out of the environment it is embedded in. As it will be discussed in the following paragraphs, part of the data gathered in the present study can accord with both definitions of context as they indicate that surround modulation can serve perceptual disambiguation.

Contextual modulation of firing rates

Orientation contrast between centre and surround

Confirming previous studies, the results of the present work show that the discharge rates of neuronal responses to a centre grating are modulated by the presence of a surround. The surround produced strongest inhibition when it was iso-oriented to the central stimulus and this inhibition gradually decreased with increasing orientation difference to the central grating. In other words, increasing the orientation contrast between the centre and surround enhances the neuronal responses to the centre. This orientation dependent suppression suggests that the network of long-range tangential connections is involved in the suppressive modulation by the surround stimulus for the following reasons: first, the horizontal connections extend up to several millimeters across the cortical surface which enables them to convey information over a wide range of the visual field (Rockland and Lund, 1982;Gilbert and Wiesel, 1983;Martin and Whitteridge, 1984). Second, the long-range connections show a periodic and patchy pattern of termination and preferentially link cortical domains of similar functional properties (Ts'o et al., 1986;Gilbert and Wiesel, 1989;Ts'o and Gilbert, 1988;Malach et al., 1993;Schmidt et al., 1997). This pattern of connectivity makes the horizontal connections the perfect candidate to be involved in the observed orientation selective surround modulation. Even though these connections arise almost exclusively from excitatory neurons (Rockland and Lund, 1982;Gilbert and Wiesel, 1983) and make ~80% of their synapses onto excitatory

neurons (Kisvarday et al., 1986;McGuire et al., 1991) experiments, in which surround stimuli were added to a strong central stimulus indicated also a suppressive role for long-range inputs (Blakemore and Tobin, 1972;Nelson and Frost, 1978;Gulyas et al., 1987;Knierim and Van Essen, 1992;Grinvald et al., 1994).

This orientation dependent surround suppression corresponds well with psychophysical experiments investigating brightness perception. Experiments with human observers demonstrated that the perceived brightness and the contrast of a centre stimulus are influenced by stimuli presented in the surround (Agostini and Galmonte, 2002;Yu et al., 2001;Huang et al., 2002;Cannon and Fullenkamp, 1991). When a high contrast sinusoidal grating is surrounded by another grating of high contrast, the orientation of the surround is crucial for the quality of the perception of the centre grating. The perceived brightness is minimal when centre and surround are iso-oriented and maximal when they are cross-oriented because the perceived brightness of the white bars of the grating increases with increasing orientation contrast. This change in perception and its correlation with changes in neuronal firing rates in the present study and in previous studies (Jones et al., 2001;Sillito et al., 1995;Blakemore and Tobin, 1972;DeAngelis et al., 1994;Walker et al., 2000;Knierim and Van Essen, 1992;Nelson and Frost, 1978;Sengpiel et al., 1997) may be a direct indication for a neuronal-perceptual link.

Although the absolute magnitude of orientation dependent surround modulation in the present study (12%) corresponds well to the magnitude of contrast enhancement in psychophysical experiments (e.g., 6% – 12% across subjects (Yu et al., 2001) it was weaker than the modulation observed in other electrophysiological recordings (up to 70% suppression for iso-oriented centre-surround gratings) (Jones et al., 2001). This is probably due to the fact that in the present study central stimuli were much larger. The reason is that they had to cover multiple RF fields simultaneously. This could have exerted attenuating effects on surround inhibition: first, the large centre stimulus already induced some surround inhibition itself, because its size exceeded the size of the classical RFs of the recorded neurons and, therefore, acted like an iso-oriented surround by itself. Second, due to this large centre stimulus, the distance between the classical RFs and the actual surround stimulus was increased.

Hence, the surround stimuli reduced the responses to the centre by no more than 50%.

Segregation between centre and surround by an annulus

The presentation of an annulus of increasing size between the centre grating and the surround grating gradually releases surround suppression. This finding does not correspond with results from psychophysical experiments. In these studies it was shown that iso-orientation surround suppression is eliminated already by the introduction of a thin line between centre and surround (Yu et al., 2001). Further increasing the area of the annulus did not improve contrast detection thresholds in human subjects. In contrast, the data obtained in the present study show that the suppression of the firing rates declines slowly and linearly as the annulus size increases. This indicates that the processes driving surround suppression seem to be expressed homogeneously throughout the surrounding area instead of originating from locally defined regions of the surround. Otherwise it could be expected that the release of suppression with increasing annulus size was not as even and uniform as observed in the present data. Nevertheless, other studies showed that the suppressive influence may indeed be limited to a distinct local area outside the classical receptive field (Walker et al., 1999;Walker et al., 2002). This was shown in experiments in which neuronal firing rates were suppressed with an iso-oriented centre-surround stimulus, similar to the one used in the experiments of the present work. In addition, a small masking stimulus was positioned at different locally defined areas in the surround, which led to a reversal of the suppressive effect (Walker et al., 2002). This disinhibition could restore the response of the cell to the level obtained with optimal stimulation with the centre stimulus alone. These results are difficult to interpret because the masking stimulus consisted of a patch of grating with an orientation that was orthogonal to the centre grating. There is evidence that such a stimulus configuration induces “cross-orientation-facilitation” (Jones et al., 2001;Sillito et al., 1995) However, it is difficult to unequivocally differentiate between cross-orientation-facilitation and the release of suppression. It may well be that the disinhibition observed in the study by Walker et al. (2002) was rather cross-orientation facilitation. However, to decisively answer this question it is

necessary to repeat the experiments performed in the present study with much finer steps of increasing annulus size.

Luminance contrast between centre and surround

The changes in neuronal firing rates in response to luminance changes between centre and surround grating suggest that the inhibitory circuit driving surround inhibition is, at least to some degree, contrast dependent. When the luminance of the foreground is reduced while keeping the luminance of the background maximal, rate responses decrease to a level just above spontaneous activity. This finding does not correspond to results observed in psychophysical studies in which facilitation of the centre stimulus was found in cases when a low contrast centre grating was surrounded by a high contrast background grating Ejima. In comparable electrophysiological studies it has been shown that the contrast of the centre stimulus determines whether long-range inputs will produce facilitative or suppressive effects: the same surround stimulus facilitates responses when the centre contrast is low, but suppresses responses when the centre contrast is high (Polat et al., 1998;Sengpiel et al., 1997). Also in-vitro preparations showed that electrical stimulation of long range inputs induced inhibitory post-synaptic potentials (PSPs) in cases when the local circuitry was strongly activated (Hirsch and Gilbert, 1991;Weliky et al., 1995). This suppression decreased as the level of activation of the centre was reduced. The mechanism which underlies these contrast-dependent changes remains unclear. Modeling studies have suggested that the level of activity of the receptive field centre could determine the sign of the response, favoring inhibition at high levels of activity and facilitation at low levels (Somers et al., 1998;Stemmler et al., 1995). However, in the present study firing rates were not facilitated when the centre grating was presented at low contrast together with a high contrast surround grating. In this case, rates rather decreased compared to when the centre grating had the same high contrast as the surround. A reason for this difference in results may be the difference in stimulus size. Since the present study investigated primarily synchronization between neurons responding to a foreground stimulus, the foreground always had to cover several receptive fields simultaneously and therefore was much larger compared to other studies. This, in turn, could have important implications for the character of the neuronal response

observed. In a recent study by Jones et al. (2002) it was shown that especially the location of stimulus borders with respect to the classical receptive field borders strongly affects the sign of V1 responses and whether facilitation or inhibition is induced. In that study, the effect of orientation contrast between a centre and a surround grating was investigated in single unit responses. The location of the border of the centre stimulus with respect to the receptive field could markedly influence both, the magnitude and also the nature of the response since a given cell sometimes showed different effects for different border locations. It is possible that this does not only hold for orientation contrast effects but also for luminance contrast effects.

Phase offset between centre and surround

Furthermore, the present results confirm the finding that the degree of phase alignment between a centre grating and an iso-oriented surround grating does not modulate the amplitude of the firing rate responses to the centre stimulus (DeAngelis et al., 1994;Tanaka et al., 1987). However, unlike the experiments with tungsten electrodes, the experiment with Michigan probes revealed significant changes in rate responses across different stimulus conditions, even though these occurred only in one of the three separate recordings. But as these changes did not systematically depend on the magnitude of the phase offset it is unlikely that firing rate modulation contains reliable information about the degree of phase offset between the centre and the surround grating.

Contextual modulation of response synchronization

Orientation contrast between centre and surround

Firing rates were suppressed by an iso-oriented centre surround stimulus and facilitated when the orientation of the background changed to being orthogonal to the centre. However, different results were obtained for changes in response synchronization. Changing the orientation of the surround grating had no significant effect on the synchronization of responses between neurons stimulated by the centre grating. There was a trend towards a decrease of synchrony with larger orientation contrast that amounted to a change of about 10%. However, the perceptual changes associated with this specific stimulus configuration correlate with the changes in firing rates and not with changes in synchronization strength: the perceived contrast of the centre stimulus increases with increasing orientation offset and, in parallel, firing rates increase with increasing orientation contrast. If the observed changes in synchronization strength (the decrease of synchrony with larger orientation contrast) were significant one would expect a reduction rather than an enhancement of perceived brightness in psychophysical experiments. This, however, is not the case. Thus, it is more likely that the reduction in synchrony with larger orientation difference simply reflects the underlying network of horizontal connections which was shown to link primarily cortical domains of similar orientation preference (Ts'o et al., 1986;Gilbert and Wiesel, 1989;Ts'o and Gilbert, 1988;Malach et al., 1993;Schmidt et al., 1997).

Phase offset between centre and surround

Both, the introduction of an annulus of increasing size as well as changes in the luminance contrast between the centre and the surround grating do not seem to systematically affect response synchronization nor does synchronization strength correlate with the perceptual changes of the stimulus. In contrast, changing the phase relation between centre and surround grating had a large, systematic and highly significant effect on the strength of response synchronization. Synchronization steadily increased with increasing phase offset and peaked at the maximum offset of 180°. These changes amounted to nearly 20% and depended approximately linearly

on phase offset. Qualitatively, the changes in synchrony among responses to the centre grating were similar regardless of whether the distance between recording sites was small or large. However, the short-distance synchrony was modulated more strongly than long-distance synchrony (the respective averages were 18% and 12%).

These results are closely correlated with results obtained in psychophysical experiments on perceived brightness using identical stimulus configurations. In these experiments the enhancement in perceived brightness of the centre grating was induced by phase offsets between the centre and the surround grating (Yu et al., 2001;Cannon and Fullenkamp, 1991;Ejima and Takahashi, 1985). As the phase offset between centre and surround increases the perceived brightness of the centre grating increases. The magnitude of changes in response synchronization observed in the present study corresponds very well to the magnitude of changes in perceived brightness (8% - 24% across subjects (Yu et al., 2001)). Furthermore, the present and also previous studies demonstrate that under this condition the discharge rates of neurons in early visual areas do not correlate with the perceived brightness. Instead, rate responses remain equally inhibited by the surround grating regardless of its phase relation to the centre grating (DeAngelis et al., 1994;Tanaka et al., 1987). Interestingly, it was shown that the brightness induction effect is eliminated as soon as a small annulus is added between the centre and the surround (Yu et al., 2001). This suggests that the effect of brightness induction is due to the local contrast produced at the border of the two phase-offset gratings which then spreads across the entire centre stimulus. As soon as the local border contrast is removed by introducing an annulus between centre and surround the brightness induction effect disappears. In the present study, the majority of recording sites investigated with an annulus had the centre and surround grating perfectly phase aligned. However, in a small fraction both gratings were not phase aligned, even though here the sample size is too small for statistical evaluation. Nevertheless, when the annulus between centre and surround is small and the two gratings are not in-phase, synchronization strength behaves similar to the situation without an annulus: Synchronization strength increases with phase offset (Figure 20). However, when the area of the annulus increases, response synchronization fails to differentiate between phase angles and even decreases slightly when the annulus reaches its maximum size. To

really discuss and compare these results with the psychophysical data, the sample size needs to be increased and more experiments are required. But still, so far the results are motivating because they correspond with the psychophysical experiments (Yu et al., 2001;Ejima and Takahashi, 1985) showing that an annulus between centre and surround abolishes the brightness induction effect.

It is possible that the increase in response synchronization to the centre grating reflects processes underlying figure-ground segregation instead of changes in perceived contrast. In order to distinguish between these possibilities one needs to know the corresponding psychophysical functions because in previous studies the perception of phase offset gratings was investigated only for extreme cases of either perfect phase alignment or 180° phase offset (Yu et al., 2001;Cannon and Fullenkamp, 1991). For this reason, psychophysical experiments with humans on identical stimulus configurations as those in the present study (Figure 12) were performed in our laboratory. These experiments showed that the perceived contrast of the centre grating increased monotonically with the phase offset and peaked at the maximum of 180°. These changes closely match the changes in the strength of synchronization in cat area 17. Figure-ground segregation as measured by the accuracy with which subjects identified one of two different sizes of the centre grating, however, did not correspond to the changes in synchrony. Subjects reached the plateau of 100% accuracy already with phase shifts as small as 5°, the 'just noticeable difference' (JND). This suggests that any increase in the phase offset beyond about 5° does not contribute to the ability to segregate the foreground from the background stimulus. Therefore, the changes in the strength of synchronization correlate closely with the perceived contrast of the centre stimuli but not with the segregation of the centre from the surround.

Another interesting aspect is that the enhancement of perceived brightness by phase offset is associated with increased BOLD (Blood oxygen level dependent) responses in human V1 (Williams et al., 2003). This suggests that the brightness enhancement caused by phase offset is due to mechanisms that operate in early visual areas. As recent evidence suggests that BOLD responses correlate not only with neuronal discharge rates but also with synchronization (Niessing et al., 2003) this might serve

as further indication of brightness induction by phase offset being associated with the observed increase in response synchronization to the centre grating.

The exact mechanism that underlies these results is unclear. It is possible that the local border contrasts are translated into enhanced synchrony which propagates across all responses to the centre stimulus. A likely substrate for this filling-in process is the network of tangential connections or feedback projections from higher cortical areas. The fact that the effects are present despite anesthesia excludes the participation of attention dependent processes and favors the involvement of low-level computations.

Coherence across the contour boundary

In order to investigate whether the changes in synchrony induced by phase offsets were global or confined to responses to the centre grating, synchrony changes were also measured between recording sites activated by the centre and recording sites activated by the surround. To this end, the RFs of one Michigan Probe were covered by the centre grating and the RFs of the second Michigan Probe were covered by the surround. The analysis was confined to pairs whose RFs shared the same orientation and were aligned collinearly. The reason is that this allows the analysis of long-range interactions because cells with such properties are connected particularly tightly by long-range tangential connections (Gilbert and Wiesel, 1989;Kisvarday et al., 1986;Schmidt et al., 1997) Therefore, they synchronize better than cells with differing orientation preferences (Engel et al., 1990). Long distance synchrony was assessed by determining the spike field coherence (SFC). This method is a more sensitive measure for synchronization than cross-correlations computed from neuronal discharges. The SFC assesses the extent to which the discharges of a cell are synchronized with the activity of a larger cell population by quantifying the precision of the correlation between action potentials at one site with fluctuations of the local field potential at another site (Fries et al., 1997).

In the present study the SFC between responses from one single Michigan probe (“short-distance” SFC) was about five times stronger than the SFC between the two different probes (“long-distance” SFC) (~0.01 vs. ~0.002, respectively). Nevertheless,

the long-distance coherence between sites responding to the centre and the surround grating was sensitive to the different stimulus conditions and changed significantly as a function of phase offset. SFC decreased continuously with increasing phase offset and reached minimal values with the maximum offset of 180°. These changes in SFC occurred mainly in two gamma frequency bands (33–60 Hz & 60-80 Hz). They were highly consistent and associated with large effect sizes (2.03 & 1.7, respectively). The changes in coherence in the beta range (20–30 Hz) were much less systematic and associated with a much lower effect size (d = 0.3). A similar decrease in gamma band synchrony across the border of two phase-offset gratings has been observed in V1 of awake monkeys (Gail et al., 2000). Thus, phase offset affects also long-distance synchrony across the centre-surround border. Here synchrony changes were in a direction opposite to the changes in synchrony among neurons stimulated by the centre grating. A possible explanation for this phase-offset dependent reduction of synchrony between the responses to centre and surround may be the selectivity of long-range tangential connections. The development of these connections is susceptible to experience dependent modifications and leads to selective stabilization of connections between neurons whose activity exhibits a high degree of correlation (Lowel and Singer, 1992). Thus, it is conceivable that the pattern of tangential connections reflects the temporal coherence of discharges which is produced by continuous contours. In the mature system these connections are then responsible for the strong synchronization of responses to continuous or collinear contours (Gray et al., 1989). Such a selectivity of synchronizing connections could explain the finding that a violation of colinearity reduces synchronization among neurons activated by iso-oriented but phase-offset contours.

In conclusion, the present findings indicate that surround stimuli modulate not only the firing rates of neurons responding to centre stimuli but also their response synchronization. Both variables are sensitive to different properties of the stimulus. Rates are modulated primarily by changes in the orientation of the surround which implies the involvement of orientation selective inhibitory mechanisms. By contrast, synchrony is modulated by changes in the phase alignment between centre and surround, implying involvement of additional mechanisms which are not yet understood. Traditionally, changes in firing rates have been considered as the only candidate mechanism to explain perceptual changes in vision. The present findings

suggest that synchronization could have a similar function, in particular because changes in response synchronization correlate well with perception in conditions in which discharge rates remain unchanged. Since it was suggested that cortical neurons may act as coincidence detectors and are sensitive to increases of synchronous firing in the millisecond time range (Usrey et al., 1998;Konig et al., 1995), an increase in synchronization may enhance the saliency of neuronal responses to a similar degree as an increase in discharge rates (Abeles, 1982;Konig et al., 1996). Therefore, the present results suggest that the modulation of discharge rates and synchrony may act as complementary mechanisms in adjusting the saliency of neuronal signals. This conclusion is also supported by recent findings on orientation discrimination in visual cortical neurons (Samonds et al., 2003;Samonds et al., 2004). This study clearly demonstrated that rates are not the only signaling modality in cat area 17 and that, especially when fine orientation differences need to be discriminated, synchrony between cells is much more efficient and reliable compared to rate code. However, the discrimination of coarser angles was achieved by the modulation of firing rates and therefore, rates and synchrony seem to be two coding mechanisms, processing different aspects of visual information.

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Ehrenwörtliche Erklärung

Hiermit erkläre ich ehrenwörtlich, dass ich die in dem Fachbereich Zoologie der Technischen Universität Darmstadt eingereichte Dissertation mit dem Titel:

„Contextual effects in the primary visual cortex of anesthetized cats“

im Max-Planck-Institut für Hirnforschung unter der Leitung und Betreuung von Herrn Prof. Singer und Herrn Prof. Galuske ohne Hilfe selbst durchgeführt habe und keine anderen als die in der Dissertation aufgeführten Hilfsmittel benutzt habe.

Ich habe bisher an keiner in- und ausländischen Naturwissenschaftlichen Fakultät bzw. Fachbereich ein Gesuch zur Zulassung zur Promotion eingereicht, noch die vorliegende Arbeit als Dissertation eingereicht.

Köln, den 7. Juli 2006

Julia Biederlack