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ON THE SIGNIFICANCE OF TEMPORALLY STRUCTURED ACTIVITY IN THE DORSAL LATERAL GENICULATE NUCLEUS (LGN)

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Abstract—Higher organisms perceive information about external or internal physical or chemical stimuli with specialized sensors that encode characteristics of that stimulus by a train of action potentials. Usually, the location and modality of the stimulus is represented by the location and specificity of the receptor and the intensity of the stimulus and its temporal modulation is thought to be encoded by the instantaneous firing rate. Recent studies have shown that, primarily in cortical structures, special features of a stimulus also are represented in the temporal pattern of spike activity. Typical attributes of this time structure are oscillatory patterns of activity and synchronous discharges in spatially distributed neurons that respond to inputs evoked by a coherent object. The origin and functional significance of this kind of activity is less clear. Cortical, subcortical and even very peripheral sources seem to be involved. Most of the relevant studies were devoted to the mammalian visual system and cortical findings on temporally structured activity were reviewed recently (Eckhorn, 1994, *Progr. Brain Res.*, Vol. 102, pp. 405–426; Singer and Gray, 1995, *Annu. Rev. Neurosci.*, Vol. 18, pp. 555–586). Therefore, this article is designed to give an overview, especially of those studies concerned with the temporal structure of visual activity in subcortical centers of the primary visual pathway, which are the retina and the dorsal lateral geniculate nucleus (LGN). We discuss the mechanisms that possibly contribute to the generation and modulation of the subcortical activity time structure and we try to relate to each other the subcortical and cortical patterns of sensory activity. © 1997 Elsevier Science Ltd

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ABBREVIATIONS

5-HT	5-Hydroxy tryptamine (serotonin)
A17	Area 17 of cat primary visual cortex
ARAS	Ascending reticular arousal system
AVG	Averaged (firing rate)
BICU	Bicuculline methiodide
DIR1	Direction 1
DIR2	Direction 2
EEG	Electroencephalogram
GABA	Gamma-aminobutyric acid
INTH	Interval histogram
ISI	Inter-spike interval
ISIH	Inter-spike interval histogram
JPSTH	Joint peri-stimulus–time histogram
K cell	Konio-type monkey LGN relay cell
L	Lateral
LOT	Left optic tract
LAT	Lateral sulcus
LFP	Local field potential
LGN (dorsal)	Lateral geniculate nucleus
LT	Low threshold (calcium spike)
M cell	Magnocellular monkey LGN relay cell
MUA	Multi-unit activity
n.s.	Not significant
NPP	Nucleus pretectalis posterior
nRT	Nucleus reticularis thalami
Off-cell	Off-center-type LGN relay cell or retinal ganglion cell
On-cell	On-center-type LGN relay cell or retinal ganglion cell
OT	Optic tract
P	Posterior
P cell	Parvocellular monkey LGN relay cell
PGN	Perigeniculate nucleus
PMLS	Posteriomedial lateral suprasylvian (sulcus)
PPS	Pulses per second
PST	Peri-stimulus-time
PSTH	Peri-stimulus–time histogram
PT	Pretectum
REM	Rapid eye movement (sleep)
RF	Receptive field
SUPS	Suprasylvian sulcus
VPL	Ventroposteriolateral nucleus of the thalamus
W-cell	W-type cat LGN relay cell
X-cell	X-type cat LGN relay cell
Y-cell	Y-type cat LGN relay cell

1. INTRODUCTION

The main intention of this article is to summarize experimental data that demonstrate a temporal structure in the visual activity of cat dorsal lateral geniculate relay cells (here abbreviated as LGN), to discuss the origin of such temporal patterns and to follow up with some reflections about the significance of temporally structured activity for higher level processing in the brain. Recent studies have shown that cortical networks, but also subcortical structures, exhibit a temporally structured activity during the presentation of specific visual stimuli that is characterized by correlated oscillatory activity in the gamma frequency range (cortex: Arieli *et al.*, 1995; Bressler, 1996; Doty and Kimura, 1963; Eckhorn *et al.*, 1988; Engel *et al.*, 1992; Gray and Singer, 1989; Jagadeesh *et al.*, 1992; Livingstone, 1996; Tallon *et al.*, 1995; but see Young *et al.*, 1992; LGN: Funke and Wörgötter, 1995; Ghose and Freeman, 1992; Neuenschwander and Singer, 1996; Podvigin *et al.*, 1992; Schroeder *et al.*, 1989; Wörgötter and Funke, 1995; retina: Adrian and Matthews, 1928; Ariel *et al.*, 1983; Doty and Kimura, 1963; Kuffler, 1953; Laufer and Verzeano, 1967; Przybyszewski *et al.*, 1993; Steinberg, 1966). Furthermore, these rhythmic activities become synchronized if the corresponding receptive fields are stimulated by the same object or if stimuli are used which share the same features and are part of a common object (e.g. coherent motion of two visual objects; for review see Eckhorn, 1994; Singer, 1993; Singer and Gray, 1995). The synchronous activity—whether oscillatory or not—of neurons responding to the same object was interpreted as one possible mechanism to solve the so-called "binding problem" (von der Malsburg, 1981, 1985; von der Malsburg and Schneider, 1986). Thus, a subset of cortical neurons or even an assembly of neurons crossing the boundaries of different hierarchical levels might use a temporal code instead of a rate code to represent single aspects of a visual scene (Abeles, 1991; von der Malsburg, 1981, 1985; Milner, 1974). Since receptors and primary afferents seem to use a rate code (firing frequency) to encode stimulus features like intensity or local contrast, there has to be one instance where this rate code is transformed into a temporal code. Our recent findings about the temporal structure of geniculate activity (Funke and Wörgötter, 1995) support the view that the main visual relay of the thalamus, the LGN may be involved in this process.

In the following, first we will summarize briefly some general aspects of peripheral sensory coding with special reference to the visual system. Then we continue to describe some basic properties of the electrical activity in the LGN and all those response characteristics that can be summarized under the aspect of temporal coding. This includes a discussion of the significance of different response components and firing modes which constitute the gross temporal waveform of the response—the waxing and waning of instantaneous firing frequency. Further attention is then given to significance of certain spike patterns and finally, also the response latency is discussed as one further encoding mechanism of sensory processing. The major part of this section is devoted to the temporal encoding of visual information by distinct inter-spike interval patterns in geniculate activity.

2. GENERAL ASPECTS OF PERIPHERAL SENSORY PROCESSING

Adequate behavioral responses to changes in our external world require a fast but detailed perception of various physical stimuli. For the visual system, the exact location, the intensity, the duration and the submodalities (i.e. the wavelength and hue of a

color) of a stimulus have to be perceived at the same time. Special—but often fundamental—features of a stimulus, like the orientation of a contrast border, the geometry of objects and the spatial and temporal relations between objects are stepwise extracted from this fundamental information at higher levels of the visual pathway. The visual system of humans and other mammalians is characterized by a remarkable efficiency for the recognition of single objects in a complex visual scene, still surpassing technical systems by far. This tremendous performance of the brain is based primarily on its high degree of parallelism in information processing. This principle is already established in the periphery, where sensory information is accumulated by numerous receptors specialized for distinct stimulus modalities. This way, information about the type and location of a stimulus can be transmitted in separate parallel channels at one time. The intensity of the stimulus is encoded in the number of action potentials (spikes) during a given time period—the firing frequency, and temporal changes in stimulus intensity are immediately followed by variations in firing frequency (see Perkel and Bullock, 1968). The highly parallel input stream however, demands for a fast and powerful mechanism that selects and integrates the incoming information in a way that the two-dimensional retinal projection of the visual scene is finally segmented into spatially arranged objects ("the binding problem"; von der Malsburg, 1981, 1985; von der Malsburg and Schneider, 1986; Milner, 1974). It has been proposed that one possible way to achieve this at sufficient speed would be the use of a temporally structured activity in addition to, or instead of, a rate code. Processing areas higher up in the hierarchy of the visual pathway might indeed mainly utilize a temporal code and perform their steps of analysis even without any analog scaling by firing frequency. Instead it seems that the temporal relationship between single spikes in a distributed neuronal network encodes a sensation or a program for a behavioral response (synfire-chains, Abeles *et al.*, 1993, 1994).

One general problem is to decide whether a subsystem in the brain uses a rate code, a temporal code or a combination of both. These problems were discussed in detail very recently by Theunissen and Miller (1995). Therefore, we add only few additional suggestions. If firing frequency is used by the brain to analyze the intensity of a stimulus, it has to be taken into account that firing frequency is calculated from the time interval between at least two spikes. Owing to the presence of noise at different levels in the system (stimulus transduction, transformation, synaptic transmission, postsynaptic integration times, etc.), the timing of a single spike is not accurate. Temporal averaging can be used as a means to obtain more reliable information about the firing frequency and there are at least two ways in a neural network of how to achieve this: (i) by integrating several consecutive spike intervals of a single input cell within an extended time window; or (ii) by averaging the spike intervals of simultaneously active cells in a short time window. A schematic illustration is given in Fig. 1. The disadvantage of the first method is a reduced temporal

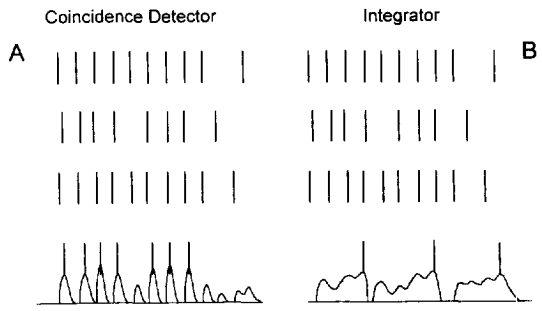

Fig. 1. Schematic diagram depicting the different output obtained from a coincidence detector neuron [(A), bottom] vs an integrator neuron [(B), bottom]. The input [(A) and (B), top] is assumed to be identical in both cases. The short time-constants in the coincidence detector neuron allow reproduction of the input firing pattern rather accurately, but such a neuron does not tolerate much variance in the input. As soon as one input spike is missing or arrives too late, the output neuron also fails to fire. An effect which becomes pronounced at the end of the spike train where the input pattern deteriorates in this example. The output spike-train of the integrate and fire neuron, on the other hand, is dissimilar to the input train but input inaccuracies are better tolerated.

resolution of the signal. If the spike train includes information about the stimulus contained in the temporal pattern of the spike sequence, this information is lost. With spatial averaging, however, the temporal resolution of the signal is preserved or could be even improved (as we will see later on, such an averaging principle can be used in a feedback loop to improve the correct timing of spikes in a sequence). The disadvantage of spatial integration is a possible loss of spatial resolution in the system. It is, however, a general feature of sensory systems that receptive fields increase in size when higher levels of the hierarchy are approached. This increase in receptive field size usually is accompanied by an increase in the specificity for certain aspects of stimuli. Since spatial convergence seems to be used to generate more specialized spatial receptive fields (e.g. orientation selectivity; Hubel and Wiesel, 1962), it would be advantageous to use the existing convergence at the same time also for the temporal averaging of activity. Furthermore, the presumed loss of spatial resolution seems to be compensated by an increase in the number of neurons in those areas where strong convergent connections are established. For example, for the retino-geniculate projection, the degree of di- and convergence seems to be low (see Orban, 1984) and the increase in the total number of neurons devoted to the same spatial aspect of the visual field is also low. However, the geniculo-cortical projection is characterized by a high level of di- and convergence and, accordingly, the number of neurons increases by a factor of 30–50.

Taking into account that a short time window of a couple of milliseconds is sufficient for spatially averaging the activity of several inputs, such a short time window would correspond to the "encoding time window" defined by Theunissen and Miller (1995) to analyze the temporal structure of afferent

activity. If a target cell integrates postsynaptic events only within such short time windows, the cell behaves like a coincidence detector, responding with a spike output only if a sufficient number of convergent activity arrives at the same time (König *et al.*, 1996). The logical consequence is that the temporal pattern of activity has to be very similar for most of the afferents to continuously drive the target cell (see Fig. 1). This way, the target cell would not only possess a spatially selective but also a temporally selective receptive field. The degree of selectivity concerning the temporal aspect may be allowed to vary with the length of the time window for encoding, or with the level of the membrane potential which determines the number of elements which have to be simultaneously active to push the membrane potential above spike threshold (see below). A short integration window bears the further advantage that the response latency is short and that any readout mechanism can follow fast changes in stimulus and firing patterns more efficiently.

3. THE PERIPHERAL VISUAL PATHWAY

This section describes in brevity the most important aspects of the peripheral part (retina, thalamus) of the visual system in mammals. Those readers who are familiar with this system should consider skipping this section.

In the retina, the process of transducing electromagnetic waves into electrical activity is performed by specialized photoreceptors. Long axoned ganglion cells transmit the visual information as a sequence of action potentials to the brain after several analog pre-processing steps have been performed in the intermediate cell layers of the retina (for details, see Boycott and Wässle, 1974; Masland, 1986; Wässle and Boycott, 1991). The horizontal intra-retinal network already performs spatial filtering of local illuminance contrast and wavelength via a center-surround antagonism implementing lateral inhibition. Very early in retinal processing, increments and decrements in light intensity are treated by separate channels, the On- and Off-subsystems (Schiller, 1995). On- and Off-bipolar cells depolarize in response to light increments or decrements, respectively. The corresponding On- and Off-ganglion cells, which follow in the vertical hierarchy of retinal connectivity, finally transform these graded depolarizations into sequences of action potentials, the firing frequency scaling which the amplitude of depolarization. This way, positive as well as negative deviations from a mean level of illumination can be encoded by a rate code with equally good resolution.

In the cat, three major classes of retinal ganglion cells can be distinguished by morphological and electrophysiological criteria (Boycott and Wässle, 1974). Alpha ganglion cells are characterized by their large cell bodies, their widespread dendritic trees and axons of large diameter. Beta cells have smaller somata, dendritic fields and axons. The diverse group of gamma cells has even smaller cell bodies and axons but, depending on the subclass, their dendritic fields are variable in shape and can exceed those of the alpha cells in size. According to the dendritic field dimensions, the smallest receptive fields (RF) are found in beta cells. Alpha and gamma cells exhibit a much larger RF, the latter with some specializations like spatial asymmetries and On/Off-subregions in their receptive field. Corresponding to their receptive field dimensions, beta cells show a significantly higher spatial resolution than alpha and gamma cells at a given eccentricity, but alpha cells display a higher contrast sensitivity and a better temporal resolution. In addition, the center-surround antagonism is stronger in beta than in alpha and gamma cells. Therefore, beta cells are thought to be specialized to detect fine details (patterns) in a visual scene, whereas alpha cells might encode large structures, like global changes in brightness and fast changing local illumination during flicker or object motion (for review, see also Casagrande and Norton, 1991). However, because of their high contrast sensitivity and resolution, small changes in illumination inside the receptive field, e.g. induced by a small image displacement, can be detected by alpha cells, a mechanism that induces high spatial contrast resolution also in this cell class (see Lee, 1993, for the analog M cells in monkey). Gamma cells show more specialized response features like On–Off responses to large stimuli and a directional bias for moving objects. These cells and their geniculate counterparts are not considered further in this review.

Some species, like monkeys and humans, developed color-sensitive ganglion cells which are classified as P cells (parvocellular) and exhibit at least some morphological analogies to the beta cells in cat. Correspondingly, the large color-insensitive M (magnocellular) cells of monkey are analog to the alpha cells of cat. Ganglion cells sharing some characteristics with cat gamma cells also are found in the primate retina. The trilogy of retinal cell types is continued by the Y (alpha), X (beta) and W (gamma) cells in cat LGN and the M, P and K (konio) cells in monkey LGN, respectively. These three afferent streams remain largely independent on their way to the primary visual cortex since excitatory convergence of these channels has been reported to be minimal if not absent in the LGN (Cleland *et al.*, 1971; Hamos *et al.*, 1987; Mastronarde, 1992). So far, only inhibitory interactions are known to take place between these channels at subcortical level. These include a strengthened center-surround antagonism in the LGN (Hubel and Wiesel, 1961; Sillito and Kemp, 1983) as well as new features like binocular (interocular) inhibition (Guido *et al.*, 1989; Schmielau and Singer, 1977) and long range lateral inhibition (Eysel and Ringeler, 1985) not found in the visual activity of the retina.

On the cat retinal surface, each location is covered by at least the dendritic tree of one alpha-On, one alpha-Off, one beta-On and one beta-Off ganglion cell and, correspondingly, in the LGN each point in the visual field is represented by at least one Y-On, one Y-Off, one X-On and one X-Off cell. In this way, the spatial location of a stimulus and its submodalities are transmitted by parallel fibers and

channels. Only the intensity of the stimulus submodality seems to be encoded by the firing rate.

Depending on the temporal characteristics of the photopic input, the visual responses of retinal and geniculate projection cells show a distinct temporal waveform. For instance, a sinusoidal modulation of the light intensity inside the receptive field is followed also by an almost sinusoidal change in firing frequency but with a phase difference which is depending on cell type and temporal frequency of the stimulus (Heggelund *et al.*, 1989; Hughes and Maffei, 1966; Lee *et al.*, 1981). On the other hand, a stepwise increment (for On-cells) or decrement (for Off-cells) in light intensity in the center of the receptive field creates a bimodal type of response. Initially, the firing rate abruptly increases (overshoot, or phasic response) but then it rapidly declines to a more or less constant level of activity as long as the stimulus remains unchanged (tonic response). In the LGN, the initial overshoot is often followed by a transient drop in firing rate below that of the following tonic response, usually called "the post-peak inhibition" and probably originating from intra- or peri-geniculate inhibitory interactions. During the tonic response to steady contrast, the firing rate slowly declines—mainly because of adaptational processes in the retina (Barlow and Levick, 1969). The X- and Y-cells differ slightly in their response dynamics. The Y-cells often were called "the phasic or transient cells" because they exhibit a stronger initial overshoot and a less prominent sustained tail of their response when compared to X-cells (tonic cells; see Bullier and Norton, 1979; Cleland *et al.*, 1971).

Firing frequency also is affected by the spatial extension (size) of the stimulus which can be attributed to the spatial organization of retinal and geniculate receptive fields. The receptive fields (RF) of retinal ganglion cells and LGN relay cells are almost circular, composed of an excitatory center (either of On- or Off-type) and an antagonistic (inhibitory) surround. According to RF plotting using a small spot of light, the RF surround is shaped like an annulus, but actually it extends throughout the area of the center component (Kuffler, 1953; Rodieck and Stone, 1965). The spatial sensitivity profiles of the center and the surround show a gaussian-like sensitivity profile with the highest sensitivity close to the center of gravity. The sensitivity profile of the compound RF is shaped like a "mexican hat", the algebraic sum of the gaussian profiles of center and surround. If a spot-like stimulus is stepwise increased up to the size of the excitatory center a response of increasing strength is evoked. Further increasing the size of the spot results now in a continuously declining response due to the action of the lateral inhibitory connections in retina and LGN. In the retina, lateral inhibition is primarily carried by the horizontal cells in the outer plexiform layer. In the LGN, lateral inhibition is conveyed by local interneurons with visual input from retinal ganglion cells situated in the antagonistic receptive field surround of the target cell.

Quite recently, it was hypothesized that the temporal waveform of the geniculate response might carry more information about the spatial composition of a stimulus pattern than could be transmitted simply by the mean firing rate (Funke and Wörgötter, 1995; McClurkin *et al.*, 1991b; Wörgötter and Funke, 1995). The studies of McClurkin and colleagues primarily focus on the temporal changes in instantaneous firing rate during the response (temporal waveform investigated by principal component analysis), those of Funke and Wörgötter describe the distributions and compositions of spike intervals.

4. SPECIAL PROPERTIES OF LGN ACTIVITY

Cat geniculate relay cells and the associated neurons of the perigeniculate nucleus (PGN) can generate a number of different activity patterns, which derive both from intrinsic characteristics related to specific ion conductances and from the properties of the local network. In the following, we will briefly summarize the predominant response patterns of geniculate cells without going too much into details. The LGN relay cells can, in principle, generate two different patterns of spontaneous activity: sequences of single action potentials at more or less irregular intervals corresponding to a mean firing frequency of 5–15 Hz (during the tonic or transmission mode), or groups of 2–7 action potentials (bursts) with intra-burst intervals generally shorter than 5 msec and inter-burst intervals of several hundred msec (the burst mode, see McCarley *et al.*, 1983; Steriade and Llinás, 1988). Burst and transmission mode are also found in the cells of the thalamic reticular nucleus (nRT) and its visual subdivision, the PGN. The bursts of these cells generally show a slower increase in firing rate and a longer tail of decreasing firing rate (Contreras *et al.*, 1993; Domich *et al.*, 1986; Hirsch *et al.*, 1982). The frequency of sustained (tonic) spontaneous activity in PGN and nRT cells can vary over a wide range (5–125 Hz) and is characterized further by a very constant firing, often preferring frequencies around 38, 65 and 100 Hz (Funke and Eysel, 1993; or 40 Hz, Pinault and Deschênes, 1992).

Due to the presence of voltage-dependent ion conductances, the preponderance of LGN relay cells for burst-firing or tonic activity is strictly related to the membrane potential. When the membrane potential is held close to the threshold for action potentials (between −60 and −55 mV), a single supra-threshold EPSP elicits a single action potential. Similarly, a constant depolarization of the cell membrane—induced by current injection—elicits a train of single action potentials with spike intervals shortening with increasing amplitude of the depolarization. The spike intervals are generally longer than 5–7 msec. At a more hyperpolarized level (−60 to −70 mV), a small subthreshold depolarization—which could be an EPSP or a release of inhibition—elicits a so-called "low threshold calcium spike" (LT calcium spike, Jahnsen and Llinás, 1984). The LT calcium spike is a large triangular shaped depolarization which finally elicits a high-frequency (200–500 Hz) "burst" of 2–7 action potentials. The LT calcium spike is carried by a voltage-dependent calcium current which is inactivated if the membrane is held at

potentials positive to −65 mV. The occurrence of bursts is not restricted to the spontaneous activity, also a retinal input can trigger an LT calcium spike and a subsequent burst if the cell membrane was sufficiently hyperpolarized before the arrival of the first retinal input spike (see Lo *et al.*, 1991; Lu *et al.*, 1992).

A frequent occurrence of spontaneous bursts is found during periods of synchronized sleep (deep sleep), where geniculate relay cells are generally more hyperpolarized (Steriade and Llinás, 1988) than during periods of wakefulness or desynchronized sleep (REM sleep). Repetitive spontaneous bursts preferentially occur either with a mean frequency of 0.3–3 Hz (delta rhythm) or in sequences with 7–14 Hz (alpha rhythm/sleep spindles, see Steriade *et al.*, 1993b). The thalamocortical projection cells of the LGN are able intrinsically to generate a burst rhythm at about 1 Hz (Curró Dossi *et al.*, 1992; Leresche *et al.*, 1991; McCormick and Pape, 1990a; Soltesz and Crunelli, 1992), and are therefore thought to be the generator of the delta rhythm found in EEG recordings. Recent studies also propose a contribution of reciprocal thalamocortical connections and intra-cortical networks to the generation of slow (delta) and ultra-slow EEG rhythms (< 1 Hz, Steriade *et al.*, 1993c). Thalamic oscillations in the alpha range show a waxing and waning appearance leading to short periods of repetitive burst activity, the so-called sleep spindles. Recent studies by von Krosigk, Bal and McCormick (von Krosigk *et al.*, 1993; Bal *et al.*, 1995) demonstrated that this rhythm is dependent on an intact reciprocal connectivity between thalamic relay nuclei and the nRT (or PGN in the case of LGN). The repetitive firing during a spindle is generated in the nRT-relay cell loop itself. The nRT (PGN) cells are excited by axon collaterals of thalamocortical relay cells and the latter are recurrently inhibited by the former. The pauses between spindles are thought to rely on adaptational processes in nRT neurons and on the reciprocal inhibitory interactions between themselves. On the basis of this thalamic connectivity and the diverse membrane conductances involved in the electrical responses of nRT and thalamocortical cells, Rinzel and coworkers (Golomb *et al.*, 1996; Wang *et al.*, 1995) could reproduce reliably these different patterns of thalamic oscillatory activity in a computer model.

When driven by the retinal input, geniculate activity can show a combination of bursts and tonic activity. For example, an On-type relay cell is excited by a bright stimulus projected into the center of its receptive field, but also actively inhibited by a dark stimulus. This so-called "reciprocal" or "push–pull" inhibition has been shown to evolve from reciprocal inhibitory interactions between topographically matched On- and Off-units (Singer *et al.*, 1972). Most probably this inhibition is mediated via the local geniculate interneurons. Inhibitory interactions of the push–pull type also have been postulated for the retinal network (Gaudiano, 1994). A periodical change of brightness in the RF center of an On-cell would cause an alternation between excitation and inhibition. If inhibition is strong enough to de-inactivate the LT calcium system, then the first retinal spike following this inhibition could elicit an LT calcium burst. Since hyperpolarization is terminated by the burst, the cell then switches to the transmission mode and the following retinal input spikes are now transferred in an almost one-to-one fashion, which means that one retinal EPSP elicits only one geniculate spike (Lo *et al.*, 1991).

5. THE TEMPORAL STRUCTURE OF CORTICAL ACTIVITY

Recent neurophysiological investigations have shown that sensory processing in primary and higher-order visual cortices is characterized by a distinct temporal pattern of spiking activity (reviewed in: Eckhorn, 1994; Singer, 1993; Singer and Gray, 1995). When activated by a visual stimulus (i.e. a moving light bar) cortical cells tend to fire in an oscillatory manner, preferring frequencies in the range of 30–90 Hz (see Fig. 2). Neurons simultaneously excited by the same stimulus *synchronize* their firing, so that oscillations become also visible in local field potentials (Bressler, 1996; Eckhorn *et al.*, 1988, 1993b; Engel *et al.*, 1991b; Gray and Singer, 1989; Kreiter and Singer, 1992, 1996; Livingstone, 1996). Synchronized oscillatory activity has been observed not only *within* one cell population but also *between* two separate cell groups when two separate stimuli were presented which could be parts of a common object, i.e. two bars moving along a common axis in the same direction and with the same velocity and the same contrast (see Fig. 3). If the same two bars move in opposite directions, each bar elicits synchronized oscillatory activity within a local cell assembly but between these assemblies no synchronization occurs. Both assemblies can fire with the same or a similar frequency, but there is either no temporal relation between the activity of the two assemblies or they fire with an almost constant phase shift. Synchronization can be achieved not only for the activity of cells located within the same or in different cortical columns of the same visual area (Brosch *et al.*, 1995; Eckhorn *et al.*, 1988; Engel *et al.*, 1990; Freiwald *et al.*, 1995; Gray and Singer, 1989; Gray *et al.*, 1989, 1990; Kreiter and Singer, 1996; Livingstone, 1996; Schwarz and Bolz, 1991), but also between cells of different, reciprocally connected, visual cortices (Bressler, 1996; Eckhorn *et al.*, 1988, 1992; Engel *et al.*, 1991b; Nelson *et al.*, 1992b) and even between the two hemispheres (Engel *et al.*, 1991a; Eckhorn *et al.*, 1992; Nelson *et al.*, 1992a). Stimulus-induced synchronous firing also can be observed without any oscillatory pattern of activity (Kreiter and Singer, 1996).

The synonym "synfire-chains" (see Abeles, 1991; Abeles *et al.*, 1993, 1994) has been created for synchronous firing patterns of arbitrary neuronal assemblies. The individual members of such an ensemble can be distributed throughout one or several cerebral areas. The characteristic response of a synfire-chain can be a very transient volley of synchronous activity, in some cases a single spike occurring almost simultaneously and repeatedly in the same assembly of cells. The described phenomenons were interpreted as one possible way to solve

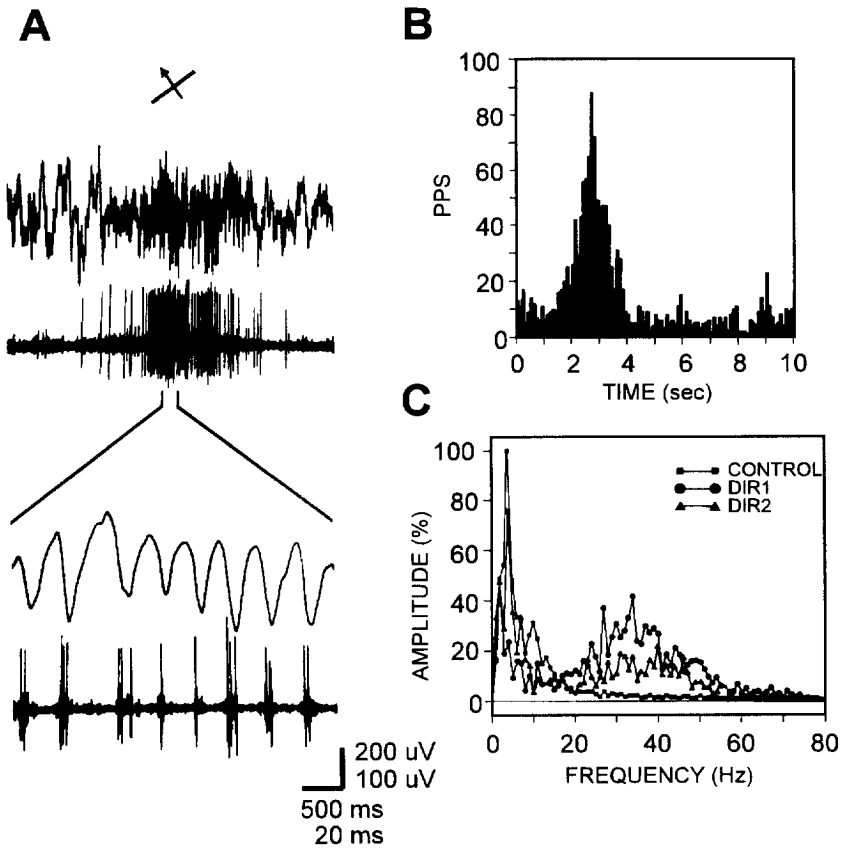

Fig. 2. Cortical oscillations (from Gray and Singer, 1989, Fig. 1). The following description is taken from these authors: "MUA (Multi-Unit-Activity) and LFP (Local-Field-Potential) responses recorded from area 17 in an adult cat to the presentation of an optimally oriented light bar moving across the receptive field. (A) Oscilloscope records of a single trial showing the response to the preferred direction of movement. In the upper two traces, at a slow time scale, the onset of the neuronal response is associated with an increase in high-frequency activity in the LFP. The lower two traces display the activity at the peak of the response at an expanded time scale. Note the presence of rhythmic oscillations in the LFP and MUA (35–45 Hz) that are correlated in phase with the peak negativity of the LFP. Upper and lower voltage scales are for the LFP and MUA, respectively. (B) Poststimulus time histogram of the MUA recorded over 10 trials illustrating a clear directional preference (PPS, pulses per second). (C) Average LFP frequency spectra computed from 1-sec data epochs (1024 points) over 10 trials at three separate latencies after the onset of each trial [control = 0 sec, direction 1 (DIR1) = 2.2 sec, direction 2 (DIR2) = 7.0 sec]. The LFP signals were digitally low-pass-filtered at 80 Hz. As the stimulus passes through the receptive field there is a simultaneous reduction of low frequencies and an increase in amplitude of high frequencies in the LFP that is more pronounced for the preferred direction of movement." Reprinted with kind permission of the authors.

the "binding problem" (von der Malsburg, 1981, 1985; von der Malsburg and Schneider, 1986). Parts of a visual scene that belong to a common object induce synchronous—or at least strictly correlated—activity at different cortical and subcortical levels. Those parts belonging to another object do the same: the induced activity is asynchronous to that elicited by the other object (for review, see Singer and Gray, 1995). This suggests that a temporally structured and/or spatio-temporally distributed activity is used by the brain to encode special features of a visual scene. A similar process can be assumed for the activity in motor and premotor cortical areas in association with changing behavior.

Recently, oscillatory activity in the gamma and beta range has been described for many cortical and subcortical areas including also non-mammalian higher visual centers: turtle visual cortex (Prechtl, 1994); human visual cortex (Lutzenberger *et al.*, 1995; Schürmann *et al.*, 1997; Tallon *et al.*, 1995); sensorimotor cortex (Bouyer *et al.*, 1981—cat; Ahissar and Vaadia, 1990; Lebedev and Nelson, 1995; Sanes and Donoghue, 1993—monkey); rat somatosensory and auditory cortex (MacDonald *et al.*, 1996); superior colliculus (Neuenschwander and Varela, 1993; Neuenschwander *et al.*, 1996—optic tectum of pigeon); somatosensory thalamus; VPL (Johnson and Alloway, 1994); LGN (Funke and Wörgötter, 1995; Ghose and Freeman, 1992; Neuenschwander and Singer, 1996; Podvigin *et al.*, 1992; Steriade *et al.*, 1991); nRT/PGN (Funke and Eysel, 1993; Pinault and Deschênes, 1992); intralaminar centrolateral nucleus of the thalamus (Steriade *et al.*, 1993a); retina (Adrian and

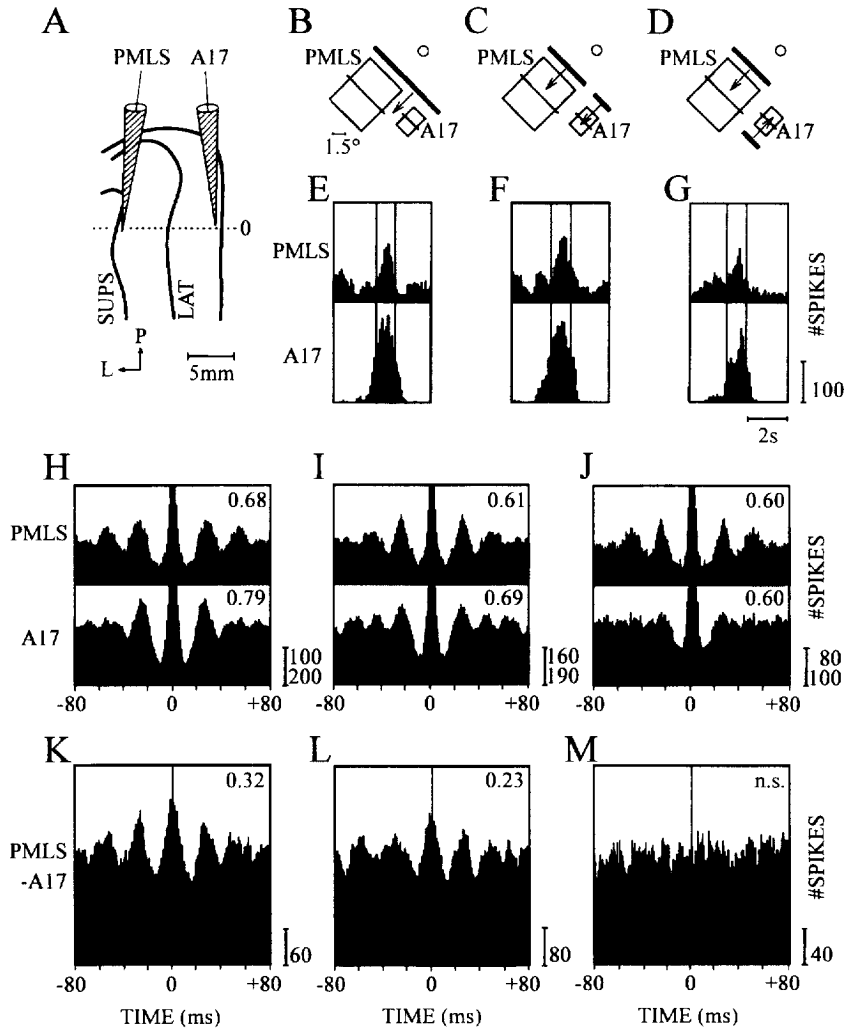

Fig. 3. Dependence of the synchronization between oscillating cortical units on the stimulus context (from Engel *et al.*, 1991b, Fig. 3). The following description is taken from these authors: "Interareal synchronization is sensitive to global stimulus features. (A) Position of the recording electrodes. A17, area 17; LAT, lateral sulcus; SUPS, suprasylvian sulcus; P, posterior; L, lateral. (B–D) Plots of the receptive fields of the PMLS and area 17 recording. The diagrams depict the three stimulus conditions tested. The circle indicates the visual field center. (E–G) Peristimulus time histograms for the three stimulus conditions. The vertical lines indicate 1-sec windows for which auto-correlograms were computed. The PMLS recording was directionally selective. Therefore, in (D) we reversed the direction of the bar stimulating the area 17 field. (H–J) Comparison of the auto-correlograms computed for the three stimulus paradigms. Note that the modulation amplitude of the correlograms is similar in all three cases (indicated by the number in the upper right corner). (K–M) Cross-correlograms computed for the three stimulus conditions. The number in the upper right corner represents the relative modulation amplitude of each correlogram. Note that the strongest correlogram modulation is obtained with the continuous stimulus. The cross-correlogram is less regular and has a lower modulation amplitude when two light bars are used as stimuli, and there is no significant modulation (n.s.) with two light bars moving in opposite direction." Reprinted with kind permission of the authors.

Matthews, 1928; Ariel *et al.*, 1983; Hashemiyoon and Chapin, 1993; Laufer and Verzeano, 1967; Neuenschwander and Singer, 1996; Przybyszewski *et al.*, 1993; Steinberg, 1966) and even for invertebrate neuronal systems (DeLaney *et al.*, 1994; Kirschfeld, 1992—mollusc olfactory lobe). Human studies and studies on wakeful monkeys and cats have shown that oscillatory activity in the gamma and beta range is most pronounced during attentive states and also occurs in relation to motor programs (Kristeva-Feige *et al.*, 1993; Pfurtscheller and Neuper, 1992; Pfurtscheller *et al.*, 1993—human motor cortex; Llinás and Ribary, 1993—REM sleep; Tiitinen *et al.*, 1993—40 Hz human auditory cortex; Tallon *et al.*, 1995—human visual cortex; Bouyer *et al.*, 1981—cat sensorimotor cortex; Rougeul-Buser, 1994—cat parietal area 5a; Ahissar and Vaadia, 1990—monkey somatosensory cortex; Sanes and Donoghue, 1993—monkey motor cortex). The studies on monkey and cat sensorimotor cortex

indicate that oscillatory activity is strongest during immobile attentive states (Bouyer *et al.*, 1981; Lebedev and Nelson, 1995; Rougeul-Buser, 1994) and that it is suppressed during tactile stimuli and voluntary movements. Since the oscillatory frequencies most frequently observed in the somatosensory cortex of awake monkey resemble the frequency tuning of mechanoreceptors of the finger tip, Ahissar and Vaadia (1990) postulated that one way to "measure" the input frequency of peripheral sensory activity may be by its interference with a central oscillator in a phase-locked loop. Such interactions of peripheral and central oscillatory activity could be achieved by recurrent activity in the cortico-thalamic feedback loop. Others have suggested that the cortical neurons which show oscillatory activity are interneurons of the inhibitory type (Llinás *et al.*, 1991), which during immobile and attentive states apply sustained inhibition to one population of neurons while others are gated (Lebedev and Nelson, 1995).

Some studies on visual oscillatory activity failed to find a systematic relation between oscillatory activity and relevant stimulus features (like coherence) in electrophysiological (Young *et al.*, 1992) and psychophysical (Kiper *et al.*, 1996) approaches. Accordingly, there is still an ongoing discussion, whether a temporally structured activity is important for information processing in the brain. In some studies a synchronous oscillatory activity was found only for distinct visual stimuli like the coherent motion of objects (Engel *et al.*, 1992); in others, a coherent oscillation was found also for rather simple visual stimuli, like flashes of light (Schürmann *et al.*, 1997). However, it has to be noticed that different stimuli also elicit different kinds of oscillatory activity. Oscillations in the gamma and also in the alpha range can either appear as stimulus-evoked or as stimulus-induced oscillations. Stimulus-evoked oscillations show a strong phase-coupling to stimulus onset and were found preferentially following short flash-like visual stimuli (Basar, 1980; Dinse *et al.*, 1990; Schürmann *et al.*, 1997), and somatosensory stimuli (taps—Schöner *et al.*, 1992). Evoked oscillations found in the gamma and alpha range usually last for a short period of 100–200 msec—sometimes up to 600 msec (Dinse *et al.*, 1990; Schöner *et al.*, 1992)—and often occur in association with distinct components of visual or auditory evoked potentials (Basar, 1980; Schürmann *et al.*, 1997; Tiitinen *et al.*, 1993). Stimulus-locked oscillations are sometimes followed by a period of stimulus-induced oscillations which show no clear phase relation to stimulus onset (Kruse and Eckhorn, 1996; Schöner *et al.*, 1992). The induced oscillations were primarily found with moving visual stimuli and often miss a preceding phase of stimulus-locked oscillation. Especially these late oscillations are thought to reflect processes contributing to feature linking (see Eckhorn, 1994; Singer and Gray, 1995; Singer, 1993).

Furthermore, it is not yet clear to what degree the generation of cortical oscillations and their synchronization is achieved by the cortical network itself. Afferents of subcortical origin also show oscillatory and synchronous discharges and therefore may contribute to the activity patterns observed in the cortex. Oscillatory activity in the 30–40 Hz range with intra-cortical and cortico-thalamic coherency also was described for spontaneous activity—without any specific sensory input—during activated brain states (low power of low frequencies in the EEG) and following electrical stimulation of the arousal centers of the brain stem (mesopontine cholinergic nuclei; see Steriade and Amzica, 1996; Steriade *et al.*, 1996).

Cortical studies about the temporal structure of spiking activity with special reference to oscillation and synchronization have been intensively reviewed in the near past (Abeles *et al.*, 1994; Eckhorn, 1994; Singer, 1993; Singer and Gray, 1995). This article therefore is designed to review preferentially the studies which are concerned with the temporal structure of the activity in those subcortical visual centers that provide the major afferent input to the visual cortex, like the retina and the dorsal lateral geniculate nucleus of the thalamus (LGN). Our recent studies were directed primarily to the question whether in cat geniculate visual activity some kind of temporal structure is encoded that could be involved in generating the spiking patterns described in the visual cortex. The LGN may be one key structure to transform the rate code of individual ganglion cells into a temporally structured activity which finally leads to spatio-temporally correlated population activity in the visual cortex. The LGN is not a simple "relay station" for retinal inputs. Cortically projecting LGN cells receive inhibitory inputs from local GABAergic interneurons, excitatory inputs from cortical back-projections, as well as numerous "modulatory" inputs from the brainstem, which either control the degree of excitability of LGN cells or switch the cell to different modes of operation (tonic vs burst mode, see Funke *et al.*, 1993; McCormick, 1992; McCormick and Pape, 1990b; Steriade and McCarley, 1990; Steriade, 1996). Therefore, the LGN is nowadays thought to be an "intelligent interface" between cortex and periphery, subserving multiple functions. In a state-dependent way, it contributes to the generation of different rhythmic activity patterns reflected in the EEG (alpha, delta, sleep spindles, see McCormick, 1992; Steriade *et al.*, 1993b; Steriade and Llinás, 1988), it controls the amount and type of sensory information transmitted to the cortex (Funke and Eysel, 1992; Kaplan *et al.*, 1993; Sherman, 1996) and it may also change the content and/or temporal structure of this information.

6. THE OVERALL TEMPORAL STRUCTURE OF GENICULATE VISUAL RESPONSES

Depending on the spatio-temporal characteristics of stimulation, geniculate relay cells show distinct dynamic changes in their firing frequency. A general response waveform can be established on a broad time scale (a couple of 100 msec in length) from the mean firing rate. This is achieved generally by plotting the temporally changing firing rate for a response in a peri-stimulus–time histogram (PSTH) by averaging several stimulus repetitions (Gerstein and

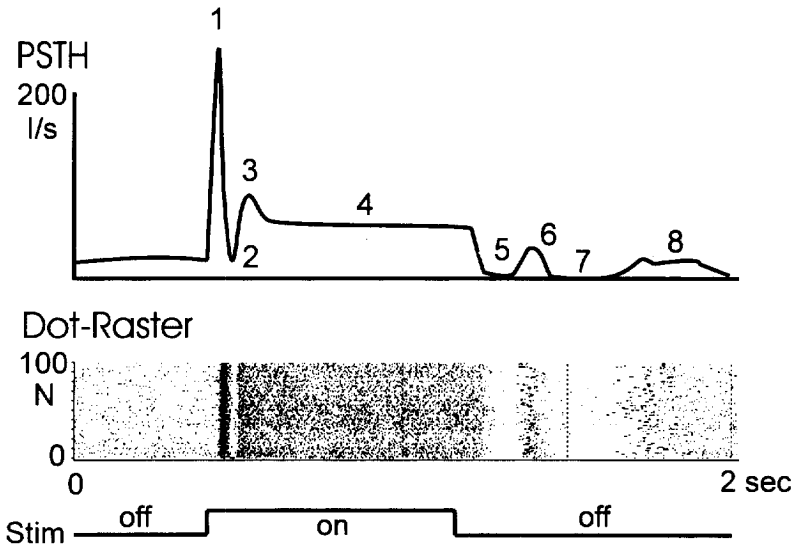

Fig. 4. Typical response of an LGN On-cell stimulated with a flashing light spot. The stimulus protocol is depicted on bottom. The dot-raster diagram shows the individual responses for 100 stimulus repetitions ("sweeps"). Every little dot represents the occurrence time of a single spike. The different response components can already be seen in the dot-raster diagram. In the peri-stimulus-time histogram (PSTH) on top, all 100 sweeps are averaged. The spikes initially were counted in 1 msec time windows ("bins") but, to depict the different response components more clearly, the PSTH is smoothed by low-pass filtering. The scaling is normalized with respect to the bin-size and the number of sweeps. Thus, it is given in "impulses per second". The different response phases (1–8) are explained in the text.

Kiang, 1960). The number of spikes occurring in equally long periods (bins of 1 or a few msec) before and after stimulus onset are counted as spikes per bin or are transformed to firing frequency with reference to the bin width and the number of responses averaged. The dot raster displayed in the lower part of Fig. 4 shows the individual visual responses of an LGN relay cell that were elicited by 100 repetitions of the same stimulus. Each dot in the diagram represents a single spike. The upper part of the figure shows the 100 responses collected in a PSTH which was smoothed to pronounce the different response components. The arbitrary selection of a bin size, however, introduces a problem. Wide bins (several msec) prevent accurate localization of the individual spikes, small bins ($\leq$1 msec), on the other hand, lead to many interruptions in the response waveform if the activity is only moderately strong or if too few responses can be averaged. One way to solve this problem is by smoothing the averaged data. A better way, however, is the calculation of the spike-density function (Richmond *et al.*, 1990): each spike in a train is replaced by a gaussian kernel and the resulting spike-density functions of each trial are averaged afterwards. The response waveform created in this way can be used to distinguish between different components of the sensory response or to search for periodic or aperiodic changes in firing rate that might correlate directly with stimulus features.

6.1. The Different Response Components

A rather simple stimulus, like a spot of light flashed on and off inside the receptive field of an LGN cell, can elicit a sequence of several clearly separable response components, as shown in Fig. 4. In the case of the most frequently found "non-lagged" cell type (see Mastronarde, 1987), the onset of a spot-flash first initiates with a latency of 20–80 msec a high-frequency transient response (1) which then declines to a more or less constant firing level (4) during the following sustained response which continues as long as the stimulus is on. The transition from the phasic to the tonic response can be smooth, or interrupted by an inhibitory dip in between (2), which is often followed by a rebound of increased activity (3). Switching off the stimulus causes an inhibitory response (5) with about the same latency as the onset of the transient response. After a variable duration, this inhibitory period is often terminated by a so-called post-inhibitory rebound (6), in most cases a burst produced by a low-threshold calcium spike. Generally, a second more extended inhibitory period follows (7) before the activity returns to its final constant maintained firing rate (8). Also, this phase often is started with a second rebound burst. "Lagged cells" which are observed less frequently (Mastronarde, 1987) show a slightly different response characteristic (Saul and Humphrey, 1990), which is due primarily to a prolonged and obviously much more variable stimulus–response latency compared to non-lagged cells (Lu *et al.*, 1995). In this review, lagged cells will not be considered further, since there exist very few data concerning details of their temporal activity patterns.

So far, little is known about the significance of the different components of the visual response for higher level visual processing. The initial transient response evolves from fast changes of the luminance inside the receptive field which could be caused by

the sudden appearance/disappearance of an object. The phasic and the tonic excitatory light responses can be interpreted as two components which carry two different messages about the visual stimulus: the slope of changes in intensity is transmitted primarily by the initial phasic response, whereas the tonic part of the response carries information about the contrast between the new and the former stimulus intensity (Heggelund *et al.*, 1989; Troy and Enroth-Cugell, 1993). The initial phasic response persists when the EEG shows increased delta activity during drowsiness or sleep but the tonic response becomes largely suppressed (Funke and Eysel, 1992; Sawai *et al.*, 1988). The LGN relay cells are hyperpolarized during delta EEG, thereby impeding the transmission of the retinal input. However, the first retinal input spike is able to trigger a burst induced by an LT calcium spike after a sufficiently long (at least 100 msec) period of hyperpolarization (Lu *et al.*, 1992). Therefore, during synchronized EEG, the initial part of the visual response can be a burst of action potentials carried by the LT calcium spike. When the cell membrane potential occupies a more depolarized level both, the transient and the tonic response seem to follow more accurately the firing frequency of the retinal response, leading to a retino-geniculate transmission ratio of up to 1:1 for periods of attentive wakefulness (Coenen and Vendrik, 1972). It has been suggested that the transient response has an arousing function, elevating the general or focal attention in the visual system (see Funke and Eysel, 1992; Kaplan *et al.*, 1993). The tonic response of geniculate relay cells is often suppressed during an EEG pattern including delta waves. Therefore, it can be assumed that the tonic response carries information important for an attentive and more detailed evaluation of the visual scene but not needed during inattentive states and sleep. Primarily this part of the response has been found to exhibit a stimulus-dependent temporal waveform (McClurkin *et al.*, 1991b) and is composed of distinct spike interval patterns (Funke and Wörgötter, 1995; Wörgötter and Funke, 1995). Also cortical neurons have been shown to exhibit at least two response components which carry the major proportion of information, one at the very beginning and the other typically 100 msec later (Heller *et al.*, 1995). Both differ in type and amount of information transmitted. McClurkin and coworkers estimated that the temporal pattern of the response increases the amount of information carried by about 50% compared to a more simple code based solely on spike count (mean firing rate). Whether the rebound excitation which often follows the release of inhibition might contribute to visual processing is completely unclear. It has been suggested that the post-inhibitory rebound excitation might efficiently contribute to the synchronization of spiking activity in reciprocally connected cortical networks (Nischwitz and Glünder, 1995). Rebound bursts also could contribute to the generation of dampened after-oscillations, like those already observed in the retinal activity which is evoked by a flash of light (Creutzfeldt and Kuhnt, 1973; Grüsser and Grüsser-Cornehls, 1962; Steinberg, 1966). These dampened oscillations have been attributed to the phenomenon of after-images (Grüsser and Grüsser-Cornehls, 1962).

6.2. The Principal Components of Response Waveforms

In their triplet of papers in 1991, McClurkin and coworkers gave a detailed description of the response waveforms elicited in alert monkey X-type geniculate relay cells by so-called "Walsh patterns" projected onto the receptive field as shown in Fig. 5(A) and (B). Each pattern was positioned in a way that one of the central pixels was aligned with the RF center so as to evoke a pure On- or Off-response from the center. The remainder of the pattern covered the receptive field surround. As shown for one cell in Fig. 5(C), each pattern produced a characteristic response waveform which was clearly separable from those elicited by other patterns. Quantification of the temporal waveforms was achieved by calculating the principal components which when combined reconstruct the complete response waveform. Figure 5(D) gives examples for the first eight principal components (j_0–j_7) and the temporal course of the averaged firing rate (AVG) of all the response waveforms shown in Fig. 5(C). The first three principal components were found to contribute rather uniformly to the response waveforms of geniculate cells tested with a given stimulus and could, therefore, be used for a quantitative description of the stimulus specific temporal waveform. The very different waveforms elicited by individual stimulus patterns are thought to result from a different contribution of these components to the total response. Therefore, the power of each principal component was determined in a way similar to a Fourier transform, but using the principal components instead of a series of sine and cosine waves as basic functions. The power of the first component (j_0) was highly correlated with the averaged response strength (spike count, mean rate) and adds little information to the rate code itself. The next two principal components were not correlated to firing rate and could, therefore, increase the informational content of the spike train. A code including the first three principal components can transmit 0.64 bits of information per response compared to a code simply based on spike count, which transmits 0.47 bits. It now seems reasonable to ask what kind of information is transmitted by the temporal code? McClurkin and colleagues found that for the first principal component—reflecting mean spike rate—the bulk of information is dedicated simply to the mean luminance of the stimulus. Much smaller are the fractions including information about the stimulus pattern and local contrast. The second and third principal components, however, contribute much more to the encoding of the spatial distribution of contrast—the stimulus pattern.

The mean firing rate of an LGN relay is determined predominantly by the mean luminance in the classical RF, including excitatory center and antagonistic surround. McClurkin *et al.* (1991b) argue that the temporal structure of the response cannot be explained only on the basis of the rather simple spatial organization of the RF. They propose a

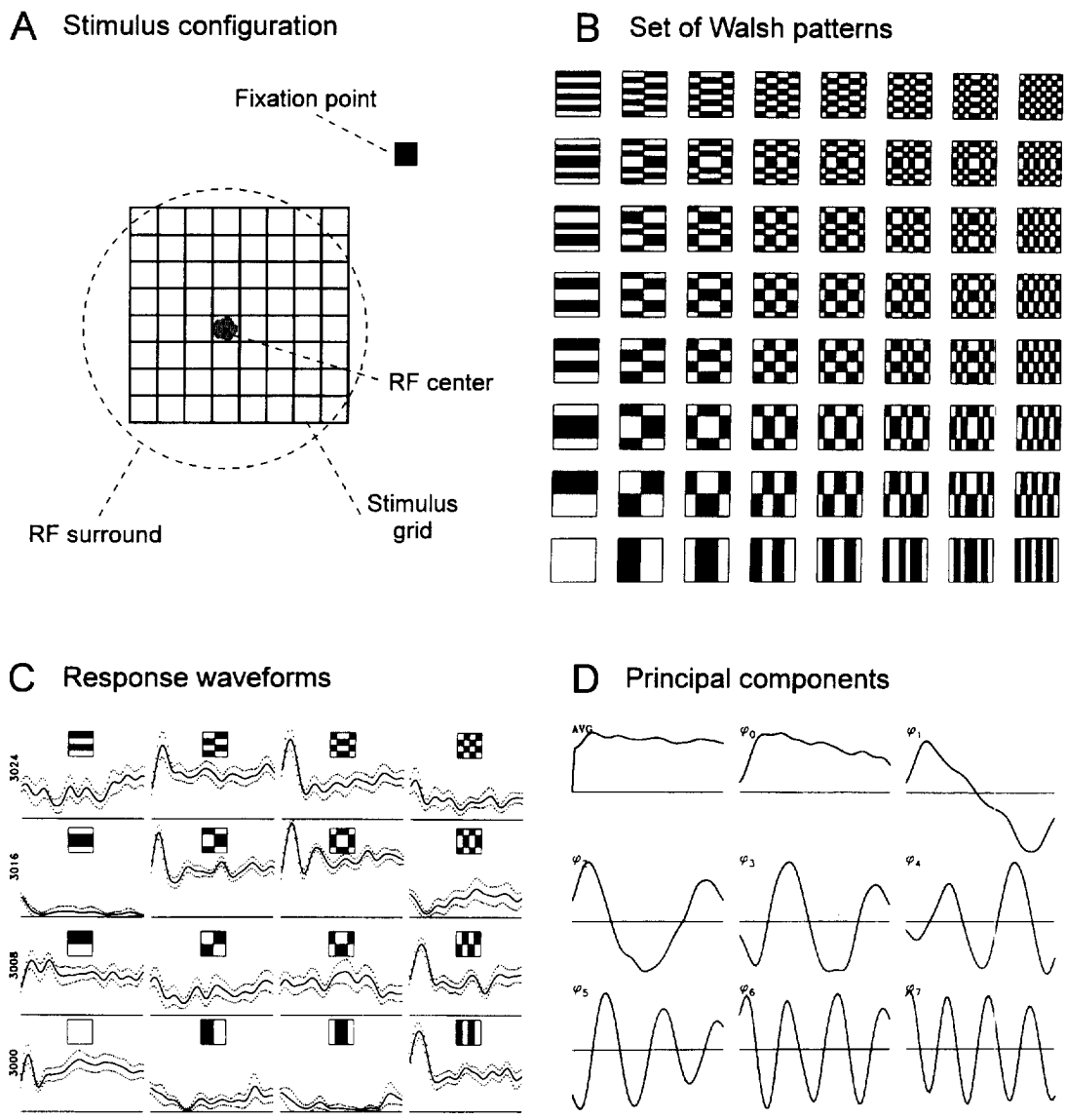

Fig. 5. Complex temporal waveforms observed in the visual responses of monkey LGN X-type relay cells (from McClurkin *et al.*, 1991a,b). The following description is slightly modified according to these authors: "(A) Relationship between the stimulus and the receptive field for stimuli that had a resolution of 1:8 pixels. A similar alignment was used for stimuli with a resolution of 1:4 pixel, i.e. the pixel just below and to the left of the center of the pattern was centered on the receptive field. Stimulus was placed off-center in this fashion so that the dividing line between pixels never bisected the receptive field center, thus avoiding null responses from X-like neurons. (B) Set of Walsh patterns used in these experiments. Contrast-reversed set was also used. (C) Response waveforms. These waveforms represent the mean probability of spike occurrence at any instant after the stimulus onset. Solid lines show the low-pass filtered responses of one neuron to 16 Walsh stimuli. Horizontal line below each waveform represents the zero level, and its length represents 256 msec. Dotted lines indicate standard error. Icon above each response shows the stimulus that elicited it. Temporal patterns as well as amplitudes of responses vary markedly across the stimulus set. The presence of this variability was the motivation for quantifying waveforms to determine whether or not this variability is determined by the stimulus pattern presented and contains stimulus-related information. (D). Principal components. The nine functions in this figure show the average (Avg) and the first eight principal components of all responses of the neuron shown in (C). Horizontal line in each plot represents the zero level. Each component spans 256 msec.".

more complex RF structure with a set of "spatial-to-temporal" filters that generate the principal components of the response, one filter for each principal component. The convergent output of the filters finally generates the desired response waveform in a single neuron. Alternatively, the RF could be composed of a set of Gabor functions (Daugman, 1985) with each individual filter resembling a subregion of

the RF like center, surround and far periphery. In addition, these filters could be equipped with different temporal characteristics resembling the different dynamics of inputs from RF subdivisions. Lateral inputs mediated by horizontal cells or amakrines are thought to lag behind the dominant center input (Enroth-Cugell and Lennie, 1975; Enroth-Cugell *et al.*, 1983; Fischer and Krüger, 1974). If we further assume a dampened oscillation in the responses of the single compartments, we end up with a set of waveforms which, when added up to a common output, may produce the observed response waveforms.

6.3. Repetitive and Oscillatory Responses

Thalamic relay cells have been demonstrated to exhibit a wide spectrum of oscillatory responses with and without excitatory drive from the sensory periphery (<0.1 to >100 Hz; see Steriade *et al.*, 1993b). The very slow oscillations in the delta (0.3–4.0 Hz), subdelta (<0.3 Hz) and alpha (7–15 Hz) range are characteristic for periods of reduced arousal like sleep and drowsiness, and are thought to be generated by reverberating waves of activity in a thalamocortical network. They occur without peripheral input and are controlled primarily by so-called modulatory inputs from the mesopontine brainstem (Steriade and McCarley, 1990; Steriade, 1996). The origin of oscillations with frequencies in the beta (15–30 Hz) and gamma (30–80 Hz) range is less well understood, although a couple of retinal and geniculate studies indicates that oscillations in the gamma and beta range may in part originate in peripheral sensory processes. Stimulus-dependent repetitive or periodic discharges in the LGN appear either as dampened oscillations after a briefly flashed stimulus, or as a continuing oscillation during prolonged presentation of a stimulus and are even existing in the dark without any stimulation. For these different periodic activities a wide range of frequencies has been reported. Light flashes of high intensity trigger oscillatory discharges with frequencies up to 100 Hz in anesthetized animals (Adrian and Matthews, 1928; Ariel *et al.*, 1983; Doty and Kimura, 1963; Laufer and Verzeano, 1967; Neuenschwander and Singer, 1996; Steinberg, 1966). In the awake monkey, Doty and Kimura (1963) found up to 160 Hz for optic tract (OT) fibers and up to 200 Hz in the visual cortex [see Fig. 6 part (I)]. With a short flash of light, the amplitude of the response usually declines rapidly and disappears after a couple of tens of msec, but can also reverberate a few times for 100–200 msec (Creutzfeldt and Kuhnt, 1973; Steinberg, 1966; Verzeano, 1973). These reverberations are thought to reflect the interaction of excitation and inhibition in the receptive field (Creutzfeldt and Kuhnt, 1973; Laufer and Verzeano, 1967; Steinberg, 1966) and may also account for the well-known after-images following flash stimuli (Grüsser and Grüsser-Cornehls, 1962). Long-lasting, almost continuous oscillations were found when large field light stimuli were applied for a longer time period [Laufer and Verzeano, 1967 see Fig. 6part (II)]. This ongoing oscillation appears shortly after the initial response, has a waxing and waning characteristic and its oscillatory frequency slowly decreases. For light-on, the frequency was clearly higher (60–70 Hz) than for light-off stimuli (30–40 Hz) both, in the optic tract and in the LGN. On the basis of recordings from retinal ganglion cells, such periodic activity has been questioned by others (e.g. Fuster *et al.*, 1965; Kuffler *et al.*, 1957). However, a periodic activity exists in many recordings of mass activity in OT and the activity of single ganglion cells or OT fibers seems to be correlated to the population activity but does not follow this pattern uninterruptedly (Laufer and Verzeano, 1967). At least the early oscillatory responses during the initial light response are stimulus-locked, since they are still visible in post-stimulus–time histograms obtained from several stimulus repetitions (Steinberg, 1966; Wörgötter and Funke, 1995). With intracellular recordings from cat retinal ganglion cells, Przybyszewski *et al.* (1993) found slow stimulus-locked as well as fast non-stimulus-locked oscillations of the membrane potential.

One prerequisite for ongoing oscillations seems to be the uniform stimulation of large parts of the retina (Adrian and Matthews, 1928; Laufer and Verzeano, 1967), the best stimulus being one that stimulates the receptive field surround while still eliciting a sufficiently strong response from the center (Ariel *et al.*, 1983). Also in the dark, retinal ganglion cells and OT fibers show ongoing oscillations but with a lower frequency (3–30 Hz) than observed with light stimuli (Doty and Kimura, 1963; Kuffler, 1953). In the rat, Hashemiyoon and Chapin (1993, 1994) demonstrated strong 10–40 Hz oscillations in the optic tract and the retino-recipient zones of the pretectum, the superior colliculus and the LGN. Since these oscillations showed the same frequency with a fixed phase shift, the authors suggested that the origin of these oscillations should be in the retina. Multi-electrode recordings further revealed that phase shifts were correlated positively with the retinal distance between the retinotopic sites of recording and stimulation, indicating the existence of traveling waves of oscillatory activity in the retina.

Oscillatory activity patterns were also described for cat LGN relay cells when more complex visual stimuli were used (Ghose and Freeman, 1992; Podvigin *et al.*, 1992). Podvigin and colleagues presented a photograph of a white cylinder at different spatial positions while recording action potentials from one LGN cell. Stimulus-locked oscillatory responses around 30 Hz were most relevant and with the highest degree of temporal correlation for those areas of the picture which were of adequate (e.g. bright for On-cells) and uniform contrast (within the object). While these studies promote the possible contribution of geniculate activity to cortical information processing by temporally structured activity, Ghose and Freeman (1992) came to a different conclusion. When using flashed light bars and moving gratings they found little correlation between stimulus conditions (optimal/non-optimal, etc.) and oscillatory activity in LGN and cortex. Indeed, the strength of oscillation in the LGN was highest during spontaneous activity. Therefore, these authors conclude that spontaneously generated oscillatory discharges of a subset of retinal ganglion cells are transferred via LGN to cortex and may

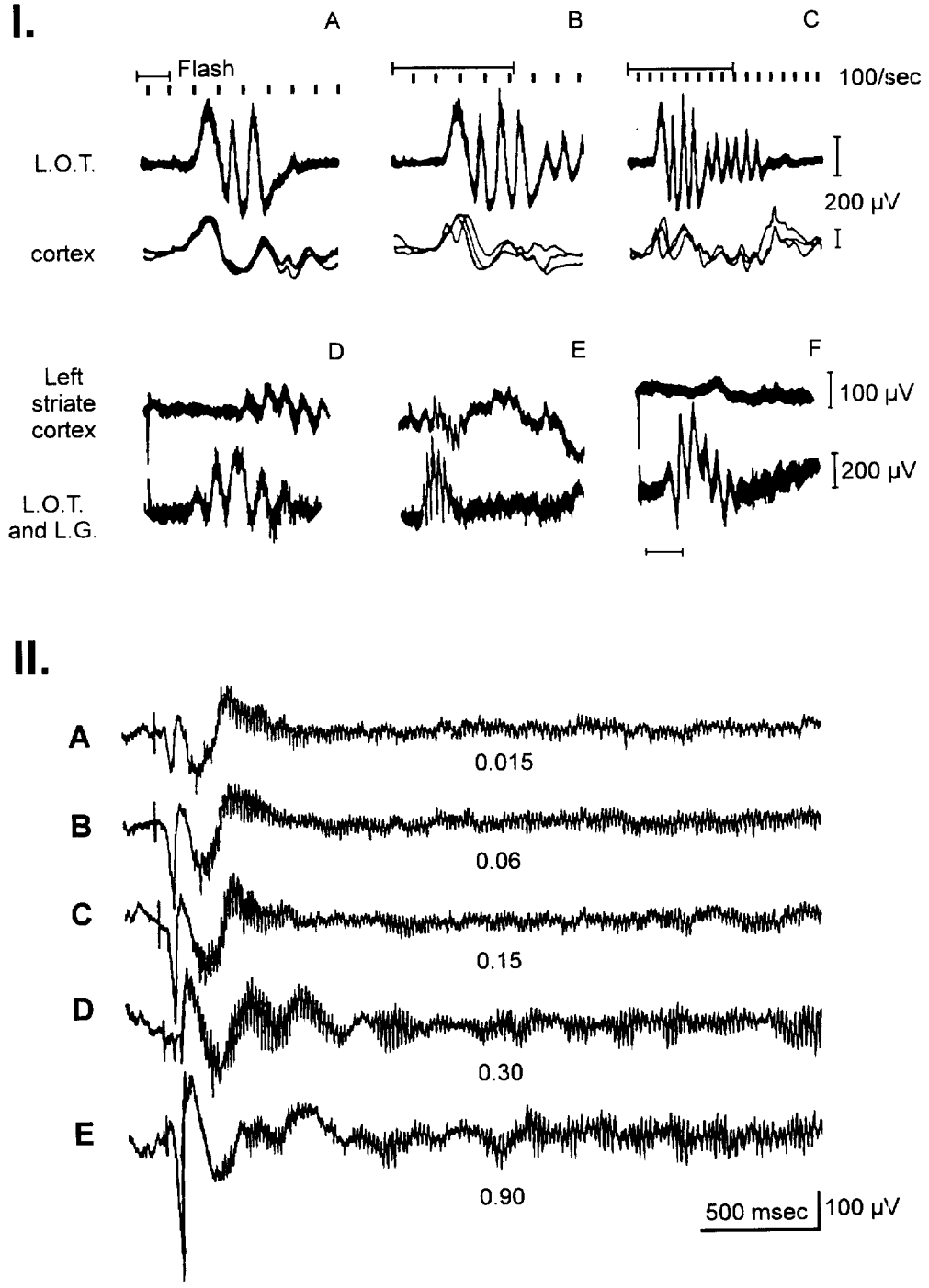

Fig. 6. Already older studies clearly showed oscillatory activity in different parts of the primary visual pathway. Part (I) is taken from Doty and Kimura (1963), part (II) from Laufer and Verzeano (1967). The following descriptions are taken from the original papers. "I) Relation of oscillations to cortical evoked potentials. Records (A–C): Cat C-89, mid-pontine pretrigeminal preparation, tungsten lamp, pre-amplifier filters set to eliminate frequencies below 80/sec for left optic tract (L.O.T). Flashes to right eye: (A) 12 msec; (B) 50 msec; (C) 90 msec. Latency 22 msec for 'on', same for cessation of oscillations at 'off'; oscillations 125/sec. Complex cortical response shows very limited relation to tract oscillations although it is obviously multiple. Records (D–F) Squirrel monkey 8, 18 days after implantation of electrodes. The pair for recording the upper trace was situated with one electrode at the edge of striate area 8 mm from the mid line and the other 3 mm anterior to it. Lower trace from electrodes at lateral edge of anterior pole of left lateral geniculate nucleus. Strobotron flash, pupils not dilated. Trace superimpositions (D) and (F). For (D) and (E) animal alert and free to close eyes or change direction of gaze; (F) at a surgical level of Nembutal anesthesia. In (D) and (E) cortical oscillations at 200/sec are faster than the same group at about 160/sec in tract. With anesthesia (F) the oscillatory frequency has fallen to 140/sec and the latency for tract response increased from about 11 msec (D) to 13 msec (F). Note lag of 15 msec between tract and cortical response in (D), about 20 msec in (F) with loss of cortical oscillations in the anesthetized state. Time marker: (A–C) 100/sec; (D) 10 msec; (E) 40 msec; (F) 20 msec. II) Oscillatory potentials recorded from the optic tract by means of a gross electrode in a dark adapted animal. Lights are turned on at the vertical bar in each tracing and maintained thereafter. Illumination given in lux, at the level of the eyes. Positivity downwards, in this figure." Reprinted from [part I] *Vision Research* **7**, M. Laufer and M. Verzeano, Periodic activity in the visual system of the cat, pp. 215–229, Copyright 1967, with kind permission from Elsevier Science Ltd, U.K.; [part II] *Journal of Physiology* **168**, R. W. Doty and D. S. Kimura, Oscillatory potentials in the visual system of cats and monkeys, pp. 205–218, Copyright 1963, with kind permission from the Physiological Society, London, U.K.

underlie cortical activity without any significance for visual information processing. However, in those LGN cells with strong oscillations during so-called "spontaneous" activity the mean rate of activity was quite high (20–40 Hz) and could well correspond to sustained activity induced by uniform stimulation of the retina (including dark discharges) as described in the previous studies (see above). During stimulation with a moving grating or bar or with repetitively flashed stimuli, clear oscillatory discharges may be difficult to detect since the mean firing rate undergoes dynamic changes as a consequence of the stimulation. Indeed, sudden accelerations of a pattern moving slowly at constant velocity have been shown to transiently interrupt ongoing oscillations (Kruse and Eckhorn, 1996; see also Section 9.1).

In a recent study, Neuenschwander and Singer (1996) could demonstrate very strong and long-lasting oscillatory activities for cat LGN relay cells (38–125 Hz, mean 81 Hz) and retinal ganglion cells (61–114 Hz, mean 88 Hz) when large uniform stimuli were flashed on and off, or when large gratings were set into slow motion. The oscillatory activity was highly synchronous for those LGN relay cells receiving afferent input from the same retina and for ganglion cells of the same retina separated up to 20° in visual space. Synchronous firing also was observed between LGN relay cells and those retinal ganglion cells that provide input the corresponding LGN layer when in all cases the receptive fields were stimulated by a common object. Synchronization was minimal or absent if two spatially separate receptive fields were stimulated simultaneously by two identical objects forming a gap in between. These result indicate that the high-frequency oscillations originate in the retina and that they synchronize between those areas which are stimulated almost in the same way, e.g. by an object of rather uniform illumination. In the case of two separate but identical objects, the gap of unstimulated retina prevents phase-coupling between the oscillatory activity for the two stimulated populations.

In the behaving cat, oscillatory activity in the beta range (16–24 Hz) has been reported by Wrobel *et al.* (1994) to occur synchronously in LGN and visual cortex. The amplitude of the oscillatory activity was found to be attention-dependent. During a task requiring visual attention, the power in the beta range was remarkably stronger than during an inattentive period or when attention was directed to acoustic stimuli.

In summary, these studies demonstrate that an oscillatory kind of activity is visible at different stages of the visual system, from the very beginning in the retina up to the cortical visual centers. Large and more or less uniform stimuli, flashed or presented for some time, seem to be necessary to induce a synchronous oscillatory activity in populations of retinal and thalamic cells.

7. THE TEMPORAL FINE STRUCTURE OF GENICULATE SPIKE TRAINS

The temporal structure of sensory responses also can be described at the level of single spikes or spike trains using a finer time scale in the range of milliseconds with sub-millisecond resolution. The analysis of single spikes or spike patterns is complicated because of the high variability of sensory responses to identical stimuli (Levick, 1973; Lu *et al.*, 1995) and because of noise which affects transmission and integration times, leading to an unavoidable jitter in the time of spike occurrence. Nevertheless, highly precise groupings of spikes (triplets, quadruples) have been found to occur repeatedly in the spontaneous and visually driven activity of cat (Lestienne, 1996) and monkey (Lestienne and Strehler, 1988) cortical cells. These replicated triplets also were reported to occur in the cat LGN (Beaux *et al.*, 1992). However, it has to be taken into account that in LGN and cortex most of the replicated triplets were composed of spike intervals that fall into the range of burst intervals (2–7 msec). These bursts of spikes are, in part, generated by the LT calcium mechanism in LGN relay cells (and some cortex cells) and, therefore, the individual spikes are not triggered by independent inputs from a network but by a mechanism intrinsic to the single cells. Nevertheless, some of these very precisely replicated patterns seem not to be based on burst discharges, since they also include longer intervals and may be a property of the neuronal network. For synaptically driven spikes, the time of occurrence should increasingly deteriorate with each step of integration in a hierarchical system, unless there exist mechanisms that reduce jitter and thereby improve the temporal accuracy of spike timing. Spatio-temporal integration of temporally structured activity and feedback circuits may be one way to achieve an improved timing of individual spikes as demonstrated for LGN relay cells with reversible inactivation of the cortico-geniculate feedback (Beaux *et al.*, 1992; Funke *et al.*, 1996; see also Section 9.2).

Nevertheless, noise is an important problem for the analysis of the temporal structure of spike trains. To bypass this problem it is suitable to first look for more general characteristics of spike trains, e.g. the frequency and distribution of interspike intervals (ISI histogram), the periodicity of spikes in a sequence (auto-correlogram) or the temporal relations between individual spikes of two different cells (cross-correlogram). This way it has been shown that many different brain regions of different species are able to generate oscillatory and often synchronized activity (for review, see Singer and Gray, 1995). If the temporal composition of spikes changes over time, i.e. when passing through different components of the response, it seems to be most appropriate to separately analyze short consecutive periods of the response. If one is interested in the correlation between spikes of two different cells, this can be achieved by the joint response diagrams of Aertsen *et al.* (1989) (Palm *et al.*, 1988, see Fig. 7 here). In a two-dimensional matrix, the activity of one cell is plotted vs the activity of a second cell. Along both axes the activity of each of the two cells is displayed individually as conventional peri-stimulus–time histograms (PSTH). The central area of the diagram shows the amount of correlated activity by comparing the number of spikes occurring at a

distinct time during the response of cell 1 (one bin of the PSTH of cell 1) with any other time window (bin) of the activity of cell 2. This way, this special kind of cross-correlation analysis not only shows the overall degree of correlation in the activity of two cells, but also displays the temporal dynamics of correlation. In a similar way, temporally changing inter-spike interval distributions resulting from dynamically changing response rates can be visualized if spike interval distributions are

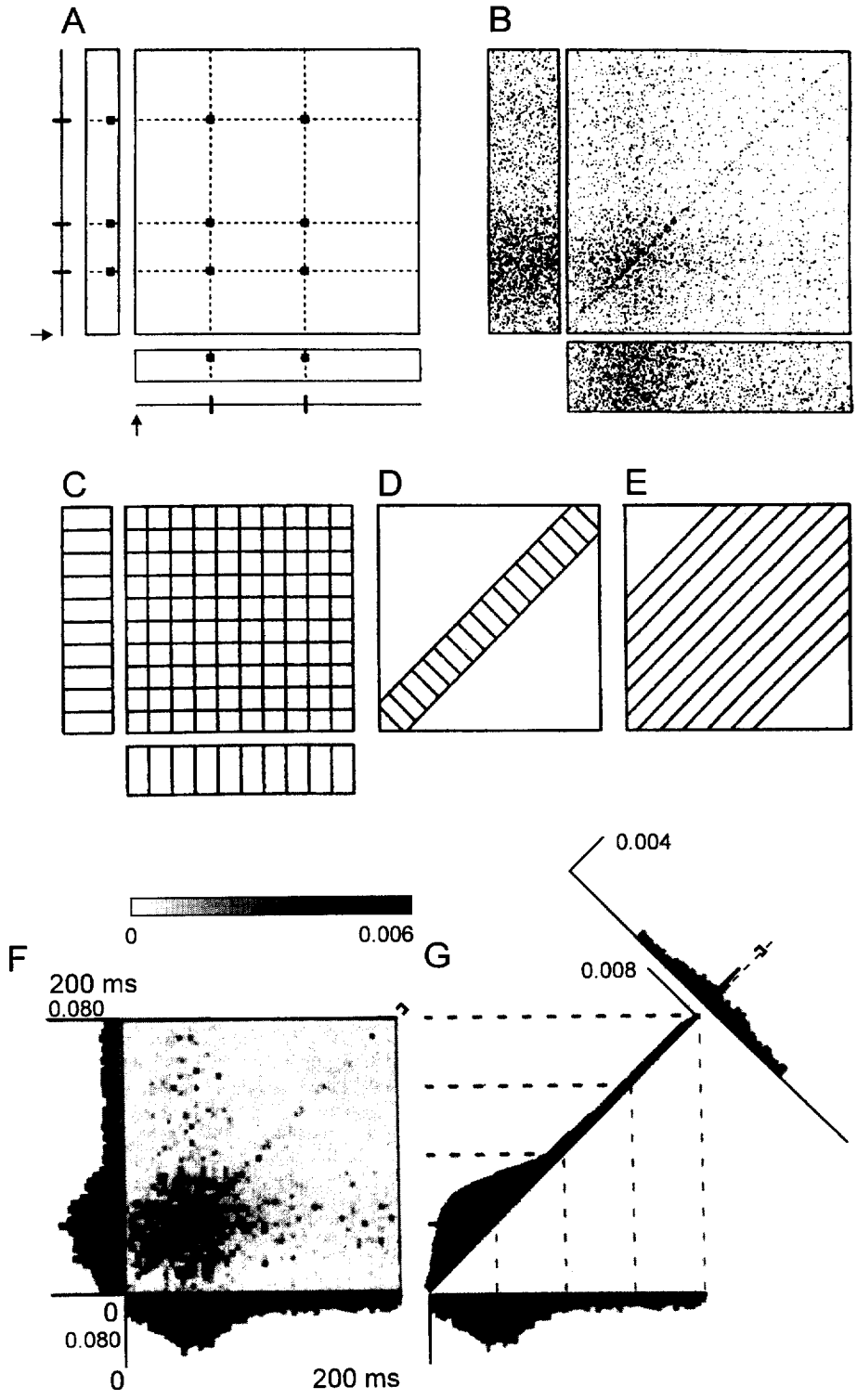

Fig. 7 (*caption on facing page*).

calculated for consecutive time windows, the intervalogram (Funke and Wörgötter, 1995).

7.1. The Temporally Local Spike Interval Analysis—the Intervalogram

The intervalogram is designed to show the temporal variations in the spike interval distribution during the time course of a sensory response. The analysis takes into account that spike interval distributions may change when the firing rate changes in response to varying response phases. Therefore, a spike interval distribution is not calculated for the whole period of stimulus presentation, but for numerous, temporally successive, short time windows (usually 100 msec in length). This procedure makes it possible to demonstrate the spike interval distribution at different times before, during and after the sensory response. In our analyses, we used a sliding time window technique as shown in Fig. 8. In the intervalogram, the time axis runs from top to bottom. A conventional peri-stimulus–time histogram (PSTH) calculated for 50–100 stimulus repetitions (sweeps) is plotted along this axis. The individual time window interval distributions are plotted as horizontal pixel lines perpendicular to the time axis [see Fig. 8(A)]. For every time window of 100 msec, the frequency of spike intervals is determined for intervals between 1 and 100 msec length and with a temporal resolution (bin-width) of 1 msec. The number of intervals in each bin (pixel) is encoded by a gray-scaling. Starting at the origin of the time axis, the first interval distribution is calculated from the first 100 msec (from 0 to 100 msec) of each sweep. The time window then is shifted along the time axis by usually 10 msec and the second interval distribution is calculated for the next 100 msec (from 10 to 110 msec), which results in an overlap of 90 msec to the first time window. This process is repeated until the end of the vertical time axis is reached. In this way, 200 successive interval distributions are computed for sweeps of 2 sec length. On top of the horizontal axis, a conventional inter-spike interval histogram (summed INTH) shows the interval distribution averaged from all time windows, which corresponds to the overall interval distribution during the entire visual response, including the stimulus-off periods at the beginning and end of each sweep.

Part (B) of Fig. 8 gives an example for the dynamic changes in the spike interval distribution during the course of the visual response of an X-On cell. At stimulus onset, the visual response starts with a transient high frequency burst which is then followed by sustained (tonic) firing for the entire duration of the stimulus presentation (see PSTH to the left). The initial transient response is characterized by the presence of very short spike intervals in the range of 1–5 msec. More interestingly, the sustained part of the visual response exhibits a bi-modal spike interval distribution, which appears as a banded structure in the intervalogram. Note that this bi-modal distribution is nearly invisible in the conventional inter-spike interval histogram (summed INTH) on top. The sliding time window analysis of inter-spike intervals by mean of an intervalogram has the advantage that it can show preferred spike intervals also for continuously changing firing frequencies. The same principle can also be applied to auto- and cross-correlation functions (see Aertsen *et al.*, 1989).

Fig. 7. Two-dimensional cross-correlation method (from Aertsen *et al.*, 1989). The following description is slightly modified according to these authors: "Stimulus-locked dynamic correlation of neuronal firing. (A) Principle of generation of a two-dimensional scatter diagram of the firing of two neurons relative to each stimulus onset (indicated by an arrow on horizontal and vertical axis): each dot in the scatter diagram represents a (delayed) coincidence of the two spike trains during one stimulus period. The spike trains and their contributions to the single-unit dot displays are indicated along the x- and y-axes. (B) As this process is carried out for many repetitions of the same stimulus, we build up the joint peri-stimulus-time (PST) scatter diagram and, along the axes, the single-unit dot displays. Spike trains used for Fig. 2 were obtained from a neuronal simulator. (C–E) Different binning schemes for estimation of dot densities in the scatter diagram and the single-unit dot displays. (C) Cartesian grid of bins over which tallies are made results in the joint-PST histogram (JPSTH) and the two ordinary PST histograms. (D) Tallies over a (para-) diagonal arrangement of bins lead to a histogram of the time-locked near-coincident firings; the PST coincidence histogram. (E) Tallies over the set of (long) para-diagonal bins, suitably normalized for the different length of each bin, estimate the time average of near-coincident firing as a function of relative delay: the ordinary cross-correlation histogram. (F) Joint-PST histogram (JPSTH matrix) and the two ordinary PST histograms along its x- and y-axis (bin-width: 4 msec). Values in the JPSTH matrix are displayed by using gray levels: the higher the value, the darker the gray, as indicated in the gray wedge with the associated values. The tick mark above the gray wedge corresponds to the value zero. All counts were divided by the number of stimulus presentations. (G) PST coincidence histogram (running from lower left to upper right) and the ordinary cross-correlation histogram (running from upper left to lower right). The PST coincidence histogram was smoothed using a gaussian with s of four bins; this particular value (gs4), as well as the location and width of the selected diagonal band, are indicated in (F) and (G). The position of true coincidence (zero delay) in the cross-correlogram coincides with the intersection point of the PST coincidence histogram and the cross-correlogram; it is indicated by a tick mark near the diagonal band marker above the correlogram." Reprinted from the *Journal of Neurophysiology* **61,** A. M. H. J. Aersten, G. L. Gerstein, M. K. Habib and G. Palm, Dynamics of neuronal firing correlation: Modulation of effective connectivity, pp. 900–917, Copyright 1989, with kind permission from the American Physiological Society, 9650 Rockvelle Pike, Bethesda, MD 20814-3991, U.S.A.

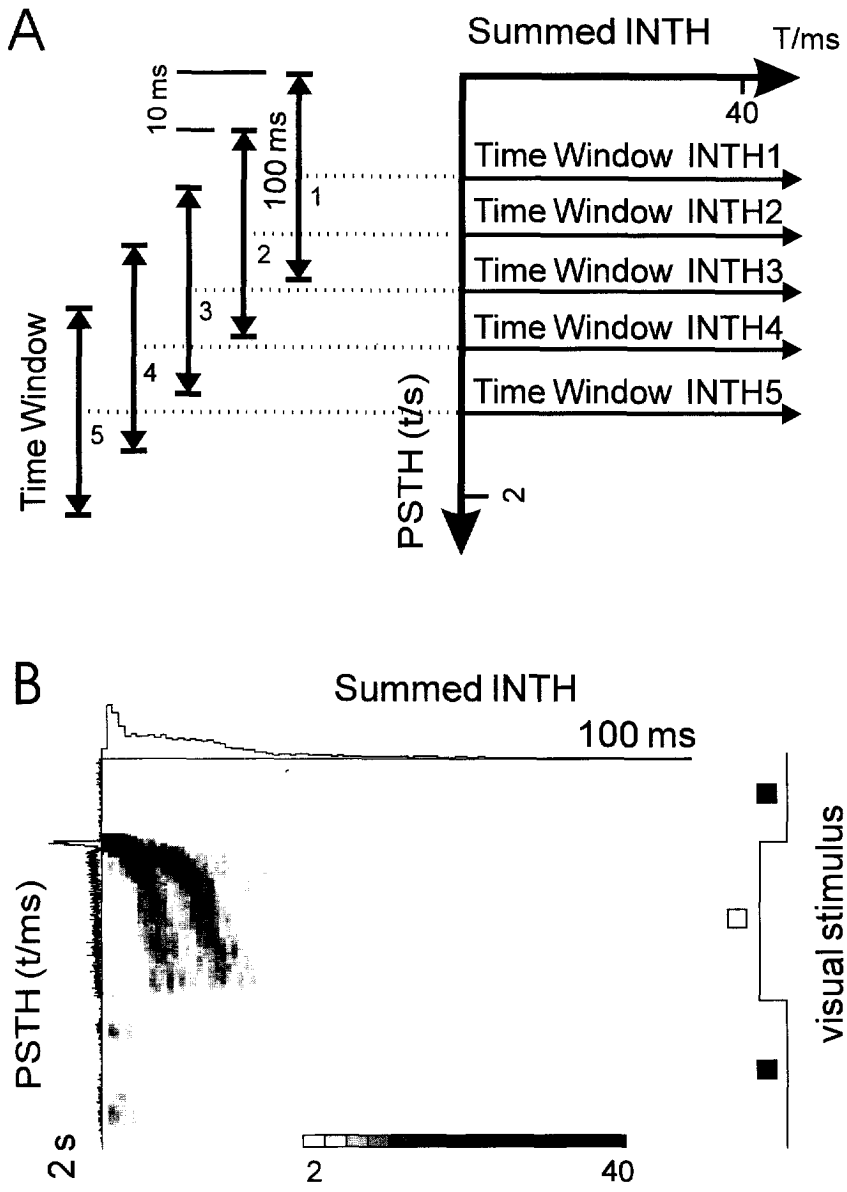

Fig. 8. (A) Schematic; and (B) original drawing of an intervalogram. The intervalogram demonstrates the dynamic changes in the distribution of spike intervals during a visual response elicited by a spot of light projected into the center of a geniculate receptive field. A conventional peri-stimulus–time histogram (PSTH) is plotted along the vertical time axis and shows the mean firing rate during the visual response. For a small time window of 100 msec, an interval distribution is computed and plotted as a gray-scaled horizontal pixel line centered with respect to the time window. Then, the time window is shifted by 10 msec along the time axis and a new interval distribution is plotted as the next pixel line. The regular interval histogram on top (summed INTH) represents the sum of all pixel lines. The temporal resolution of the time-axis (vertical axis) is 10 msec, that of the INTH horizontal axis is 1 msec. As demonstrated in (B), the interval distribution during the tonic part of the light response is often not a continuous poisson- or gamma-like distribution but a multi-modal distribution (in this case a bimodal distribution), which appears as banded structure in the intervalogram.

7.2. The Interval Distributions of Geniculate Visual Activity

A more or less constant mean firing rate, as found during the sustained light response, could, in principle, be generated by three different types of firing patterns: it could derive from a single almost constant firing frequency, from randomly varying spike intervals (poisson-distribution), or from the mixture of a limited number of different firing frequencies, which leads to a multi-modal spike interval distribution. All three spiking patterns have been found in the visual activity of cat LGN relay cells (Bishop *et al.*, 1964; Frishman and Levine, 1983; Herz *et al.*, 1964; Levick and Williams, 1964; Munemori *et al.*, 1984). According to the intervalogram analysis of

Funke and Wörgötter (1995), the frequency and distribution of spike intervals during the tonic part of the visual response generally depends on the type of relay cell and on the characteristics of the visual stimulus. A clear multi-modal interval distribution with sharp interval peaks (or bands) like the one shown in Fig. 8(B) was found for the majority (75%) of On-center relay cells [see also Fig. 9(A)]. Uni-modal distributions with a single sharp band could also be found for On-center cells. Off-center cells primarily exhibited a more widespread, poisson-like, distribution which rarely developed more than one interval mode [Fig. 9(B)]. According to this, the following analyses of the temporal structure of spike trains were primarily done with On-cells which exhibited multi-modal spike interval distributions.

Compared to the X-cells, the interval distributions of Y-cells were generally less sharp, leading to a partial overlap of interval modes. Depending on stimulus features and internal states a multi-modal distribution in the intervalogram could be composed of up to four, rarely up to eight, interval bands. An analysis of numerous interval distributions yielded that the higher interval modes (those to the right in the diagram) are generally multiples of a fundamental interval which is given by the leftmost band in the intervalogram at around 5–10 msec. In some cases, a tiny interval peak is visible close to the *y*-axis at spike intervals of about 2–5 msec. This peak corresponds to burst discharges, does not produce any intervals of multiple length and were not considered as one of the preferred spike intervals during the tonic light response. The multi-modal distributions of the preferred spike intervals of cat LGN relay cells are obviously caused by a fundamental firing frequency (fundamental spike interval) which, by an integer-division, generates the multiple intervals and is not produced by a mixture of different, independent firing frequencies. Lateron, we will see that this multi-modal pattern is generated by the interaction of excitatory retinal inputs with local inhibition in the LGN.

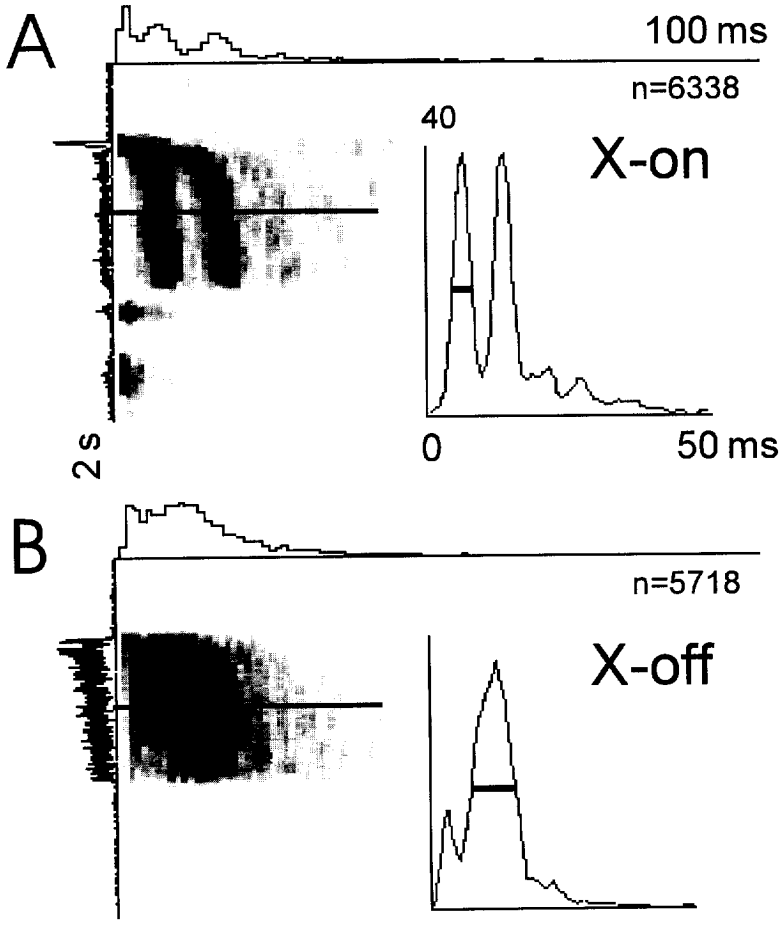

Fig. 9. Intervalograms typical for X-On and X-Off geniculate relay cells. Insets show conventional INTHs calculated from the averaged values of five adjacent pixel lines from the tonic response at position 800 msec on the time axis (indicated by the horizontal line). In general, X-On cells (A) very often show two or more separate interval bands or peaks while X-Off cells (B) generate only broad and unimodal interval distributions. At one-half the height of the maximum interval peak, horizontal bars illustrate the width of the corresponding peak. The value of *n* indicates the total number of intervals included in the intervalogram.

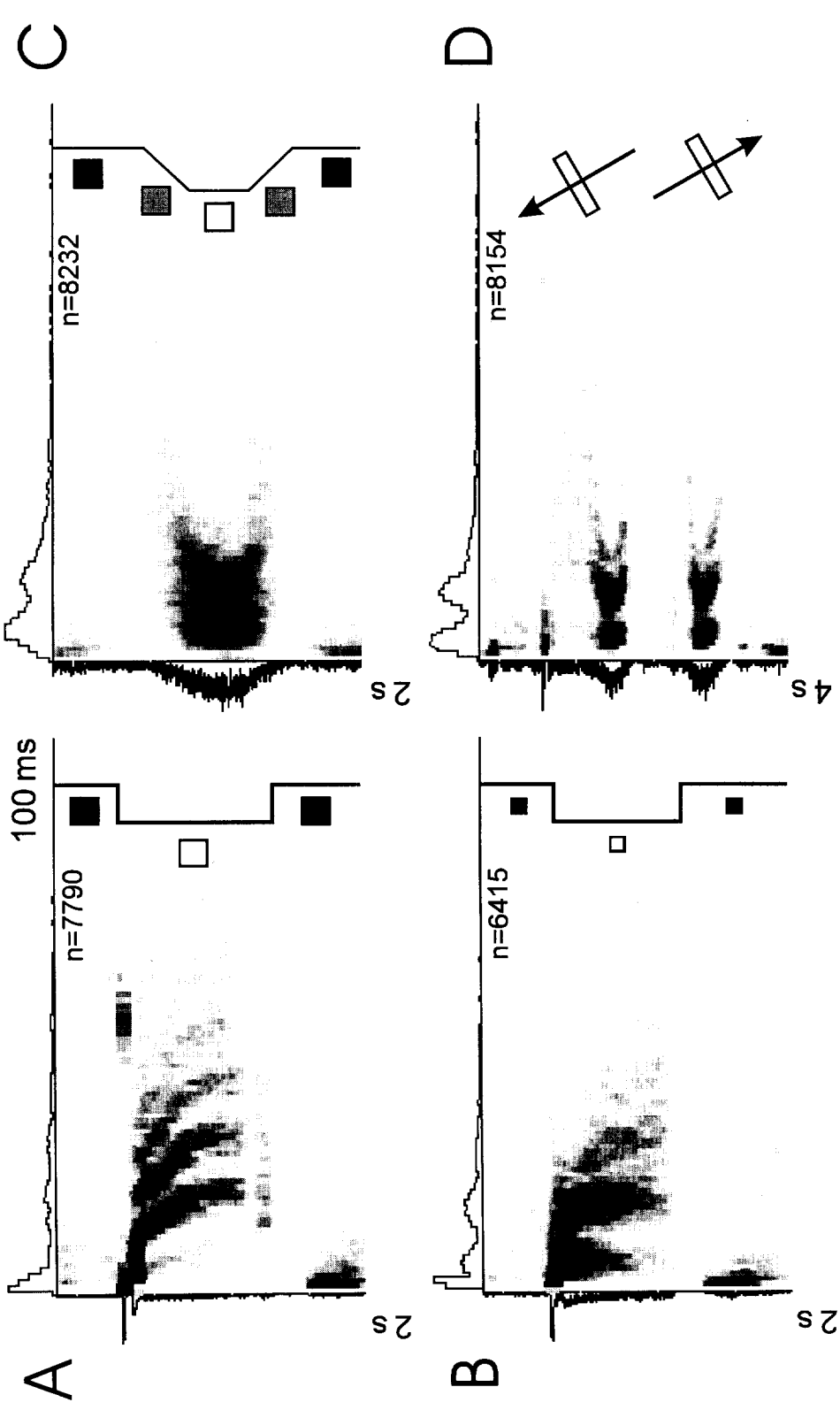

Fig. 10. Intervalograms obtained from an X-On cell during four different stimulus presentations: rectangular modulation of light intensity (flash) of (A) a large; or (B) a small spot; (C) ramp-like changing intensity of a light spot; and (D) movement of a light bar across the receptive field. All stimulus presentations with almost 100% contrast modulation. Multi-modal interval distributions are obtained with all stimulus types. The moving bar (D) causes dynamic changes in the interval distribution very similar to those obtained with ramp-like modulation of light intensity inside the receptive field (C). The value of *n* indicates the total number of intervals included in the intervalogram. Reprinted from the *Journal of Physiology* **485**, K. Funke and F. Wörgötter, Temporal structure in the light response of relay cells in the dorsal lateral geniculate nucleus of the cat, pp. 715–737, Copyright 1995, with kind permission from the Physiological Society, London, U.K.

7.3. The Dependence of LGN Interval Structure on Stimulus Features

For a geniculate relay cell, a multi-modal spike interval distribution can be found if the illumination throughout its receptive field is held constant or if it is varied slowly. The latter can be achieved by ramp-like modulation of the brightness of a stationary stimulus or by slowly moving the stimulus across the receptive field. Figure 10 gives four examples for multi-modal interval distributions obtained from the same cell but with different visual stimuli. Parts (A) and (B) demonstrate that small, dot-like stimuli flashed centrally into the receptive field produce multi-modal distributions if the stimulus is presented long enough to generate a sustained, elevated activity succeeding the initial transient response. The size and brightness of the spot affects

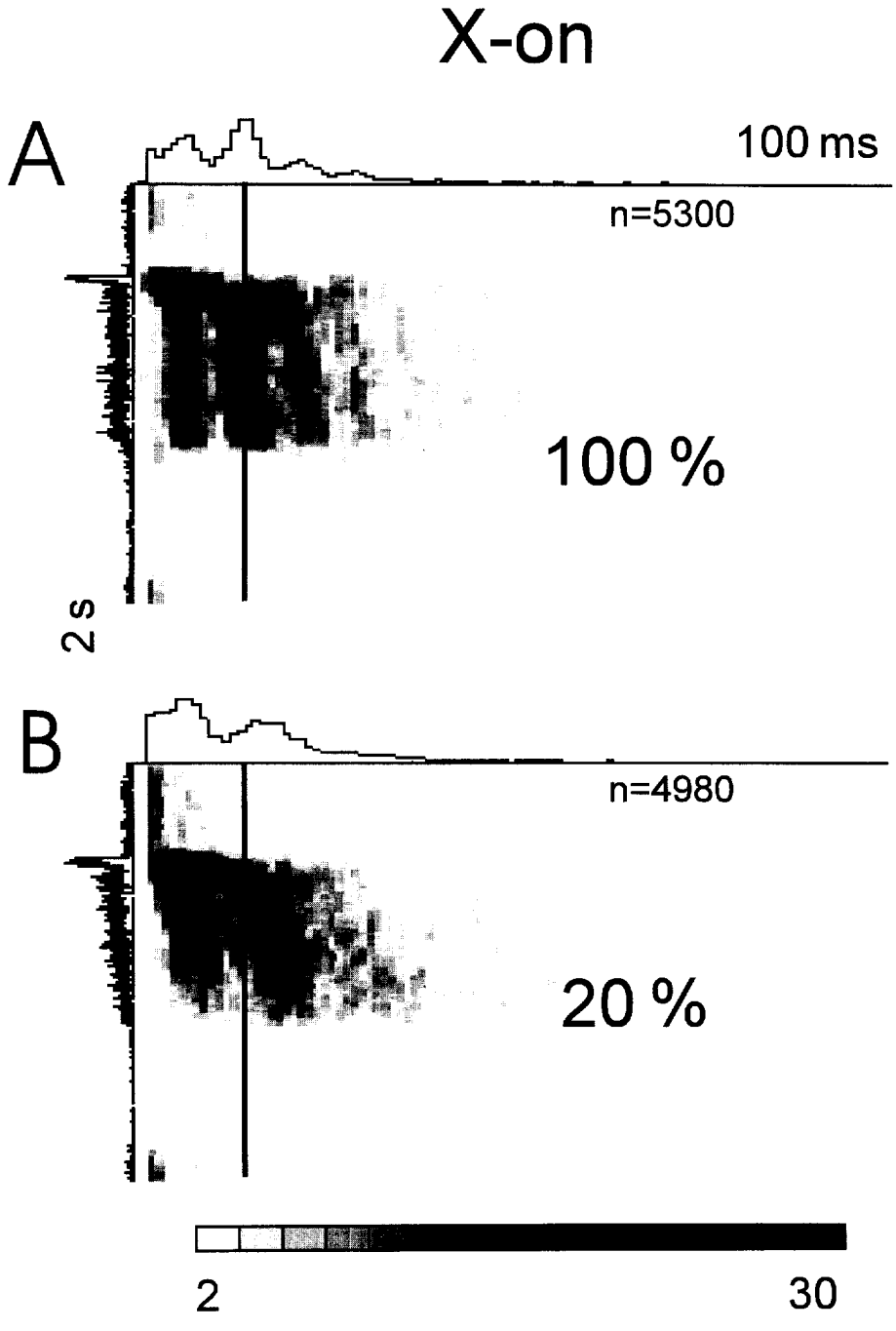

Fig. 11. The effect of a changing stimulus contrast is shown for an X-On cell. A reduction of the stimulus contrast from 100 to 20% causes not only a general reduction in activity but also a shift of the interval bands to the right (compare with location of the vertical reference line) without a significant redistribution of intervals to the rightmost higher-order bands.

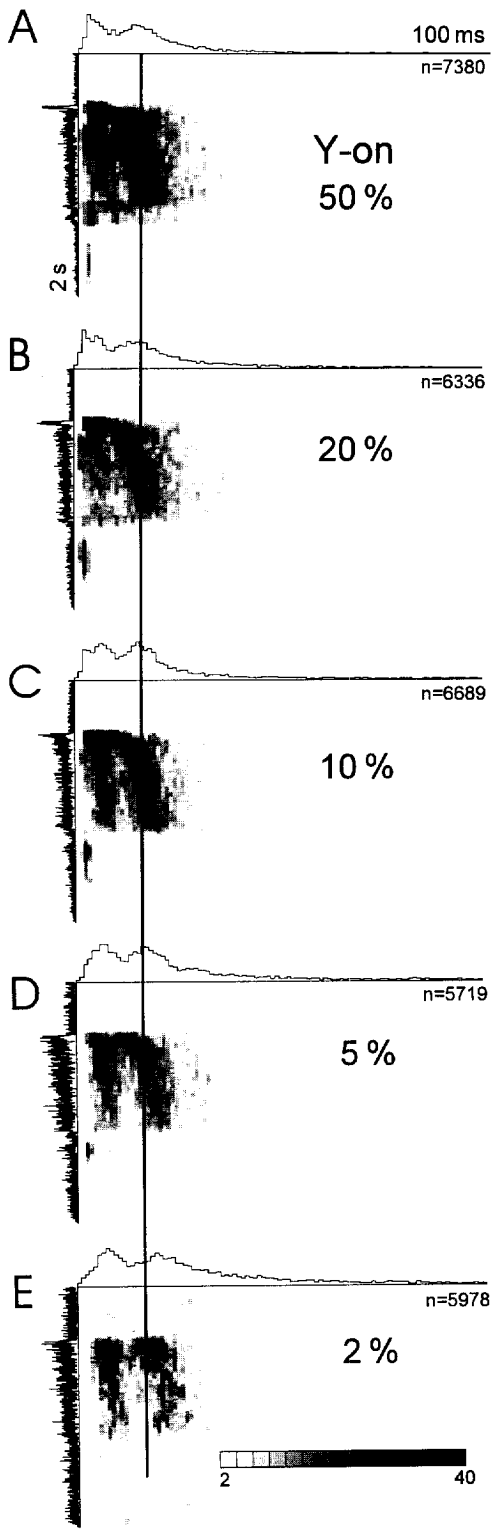

Fig. 12. Effect of changing stimulus contrast in a Y-On cell. For this cell, the stimulus contrast could be varied widely. The rightward shift of the interval bands (compare Fig. 11) becomes obvious only below 10% contrast. Above this contrast, the cell was probably driven at saturation level.

the number, position and height of the modes (see below). The interval bands are often tilted, which is caused by a progressive increase of the fundamental interval. The increase in the fundamental interval (decrease in fundamental firing frequency) is correlated with the decreasing mean firing rate during the tonic light response as can be seen in the PSTH to the left. Adaptational processes to steady-state illumination may account for this decline in activity.

A ramp-like modulation of stimulus intensity (C) causes a different but also a multi-modal interval distribution. Because of the rising and falling firing rates during incremental and decremental changes of stimulus luminance/contrast, the interval bands appear as crescent-like structures. A bright bar moving across the receptive field of the On-center cell (D) elicits an interval distribution very similar to that evoked with the ramp-like change in illumination. When slowly moving into the receptive field, or when leaving it, the stimulus also causes a continuous change of the total brightness in the receptive field. If the stimulus is moved too fast, only a phasic response is elicited and no interval bands appear.

The length of the fundamental spike interval, which seems to be of retinal origin (see below), is obviously determined by the stimulus intensity or the stimulus contrast. This dependence of the fundamental interval length on the stimulus contrast is evident from the ramp-like modulation of stimulus brightness in Fig. 10(C). The varying length of the fundamental interval here directly parallels the change in mean firing rate. The contrast-dependent change of the fundamental interval length is further demonstrated in Figs 11 and 12, using light spots of constant size but different contrast. With decreasing contrast the length of the fundamental interval progressively increases and the interval bands (those of the fundamental and the multiple intervals) shift to the right.

The multi-modal pattern of these spike interval distributions suggests the existence of a process that divides the basic firing frequency into lower-order harmonics (or higher-order intervals). One possible mechanism could be the intra-geniculate inhibition that modifies the retinal input frequency. It can be assumed that the dominant retinal input to an LGN relay cell generates EPSPs large enough to reach the threshold for action potentials, as long as they are not diminished by simultaneously active inhibitory inputs. Cleland *et al.* (1971) and more recently Mastronarde (1987) and Kaplan and Shapley (1984) could demonstrate that one retinal spike usually generates only one geniculate spike, some retinal spikes fail to do this but very rarely a geniculate spike is elicited without preceding retinal activity with the exception of bursts generated by a LT calcium spike. The so-called transfer ratio for retinal spikes depends on the actual state of arousal. It can be close to 100% during wakefulness and declines to less than 50% during sleep or drowsiness (Coenen and Vendrik, 1972). A reason for the reduced retino-geniculate transfer ratio could be a strengthened inhibitory activity during delta wave sleep (see Funke *et al.*, 1993; Steriade and Llinás, 1988). One way to test the involvement of intra-geniculate inhibition in the generation of interval multiples is by

trying to experimentally change the strength of the inhibitory input. In a natural way, this can be achieved by driving the inhibitory units through activation of the antagonistic surround of the receptive field. Alternatively, a pharmacological manipulation of the inhibitory mechanisms can be achieved via the iontophoretical administration of specific neuroactive substances.

7.3.1. *The Influence of the Center-surround Antagonism*

In the LGN, the inhibitory action of the antagonistic receptive field surround was found to be considerably stronger than that found in the retinal ganglion cells (Cleland and Lee, 1985; Hubel and Wiesel, 1961; Sillito and Kemp, 1983). The additional suppressive surround in the LGN is established by a classical type of lateral inhibition: retinal ganglion cells located in the area of the LGN RF surround of the target cell project to local GABAergic LGN interneurons which exert inhibition. Thus, as demonstrated in the scheme of Fig. 13, a large stimulus which activates the center and the surround of the receptive field should induce a higher level of activity in the inhibitory units than a small stimulus which excites only the RF center. Coincidence of inhibitory activity with excitatory retinal input then prevents the generation of geniculate spikes. If the following retinal input is not affected, a spike interval of double length compared to the fundamental interval will be the result. Therefore, we would expect that, using a large stimulus, the number of fundamental intervals should be smaller and the number of intervals of double or triple length should be higher as compared to a stimulation with a small spot. The examples in Fig. 14 demonstrate that this was exactly the case for On-cells. With the smallest stimulus, the band of the fundamental intervals (the leftmost band) dominates, or is as strong as, the second band. With increasing spot size, the first band becomes smaller, the second band dominates and additional bands of the orders 3 and 4 appear. It should also be noted that the interval bands occupy almost the same position irrespective of the spot size (see reference lines). The fundamental firing rate is obviously the same for stimuli of different size, but the relative number of single and multiple intervals is changed.

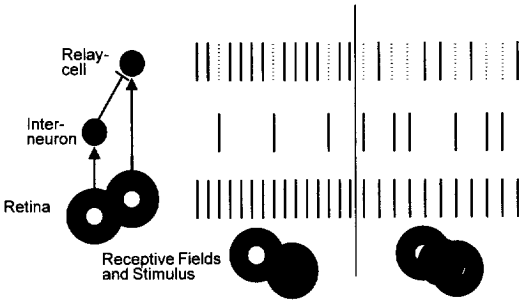

Fig. 13. Simple qualitative model of a retinogeniculate connection scheme (to the left) that is sufficient to produce multiple interval bands in a geniculate relay cell. Receptive fields (RF) of retinal ganglion cells are drawn as disks with a white center and a gray surround. Sustained stimulation with a light spot (black disks) induces a very regular firing in that retinal ganglion cell that is directly linked to the relay cell (bottom row, black bars represent single spikes). The mean firing rate of the ganglion cell changes little with increasing stimulus size (compare spike trains right and middle). Without inhibition, a one-to-one transmission by the LGN relay cell is assumed (top row). During an inhibitory input (middle row), individual spikes are blanked out (dashed lines in top row) and multiples of the fundamental interval are obtained. The number of fundamental intervals is strongly reduced and the number of multiples dominates when the inhibitory input is increased by stimulation of the ganglion cell that belongs to the inhibitory surround of the geniculate RF. The scheme to the left gives an example for a feed-forward inhibition, a feedback inhibitory connection would lead to the same results.

7.3.2. *Pharmacological Modulation of the Strength of Inhibition*

A pharmacological manipulation of the intra-geniculate inhibition can, in principle, be achieved in two ways: by blocking the inhibition or by enhancing it. The most elegant way would be a selective activation or blockade of the inhibitory interneurons itself. So far, however, there seems to be only one substance that affects solely the GABAergic cells when applied by local micro-iontophoresis *in vivo*. Serotonin (5-HT) was found to excite the GABAergic neurons of the PGN (Funke and Eysel, 1993; McCormick and Wang, 1991) and probably also the intra-geniculate interneurons (Funke and Eysel, 1995b; Pape and McCormick, 1995) obviously without directly acting on the relay cells. Local 5-HT application to the cat LGN was found to strongly inhibit spontaneous and induced activity in relay cells (Phillis *et al.*, 1967) and this inhibition could be blocked with the $GABA_A$-receptor antagonist bicuculline (BICU; Funke and Eysel, 1995b). Therefore, Funke and Eysel suggested that the strong inhibition of LGN relay cells by 5-HT is primarily based on the excitatory action of 5-HT on GABAergic interneurons. Figure 15 demonstrates the opposite actions of BICU and 5-HT on the visual response and the underlying spike interval distribution for an X-On cell. Due to the common stimulation of receptive field center and antagonistic surround, the tonic response is composed of interval multiples leading to a strong second and third band (A). The first band is missing but appears during application of BICU (B). The weakening of inhibition by BICU also reduces the number of intervals in the second and third band. After termination of BICU application the response returns to the pattern seen before BICU application (C). Part (D) of the figure demonstrates the strong suppressive action of serotonin. The two leftmost bands disappear completely, only a rudimentary part of band 3 remains, and a faint forth and fifth band appear (the latter being smeared because of the weak activity in these high-order modes). The additional application of BICU (E) cancels the 5-HT effect, leading to an interval distribution intermediate to that of the control (A) and the BICU (B) measurement. During the final recovery (F) the long-lasting 5-HT effect is still visible by the reduced second and enhanced forth

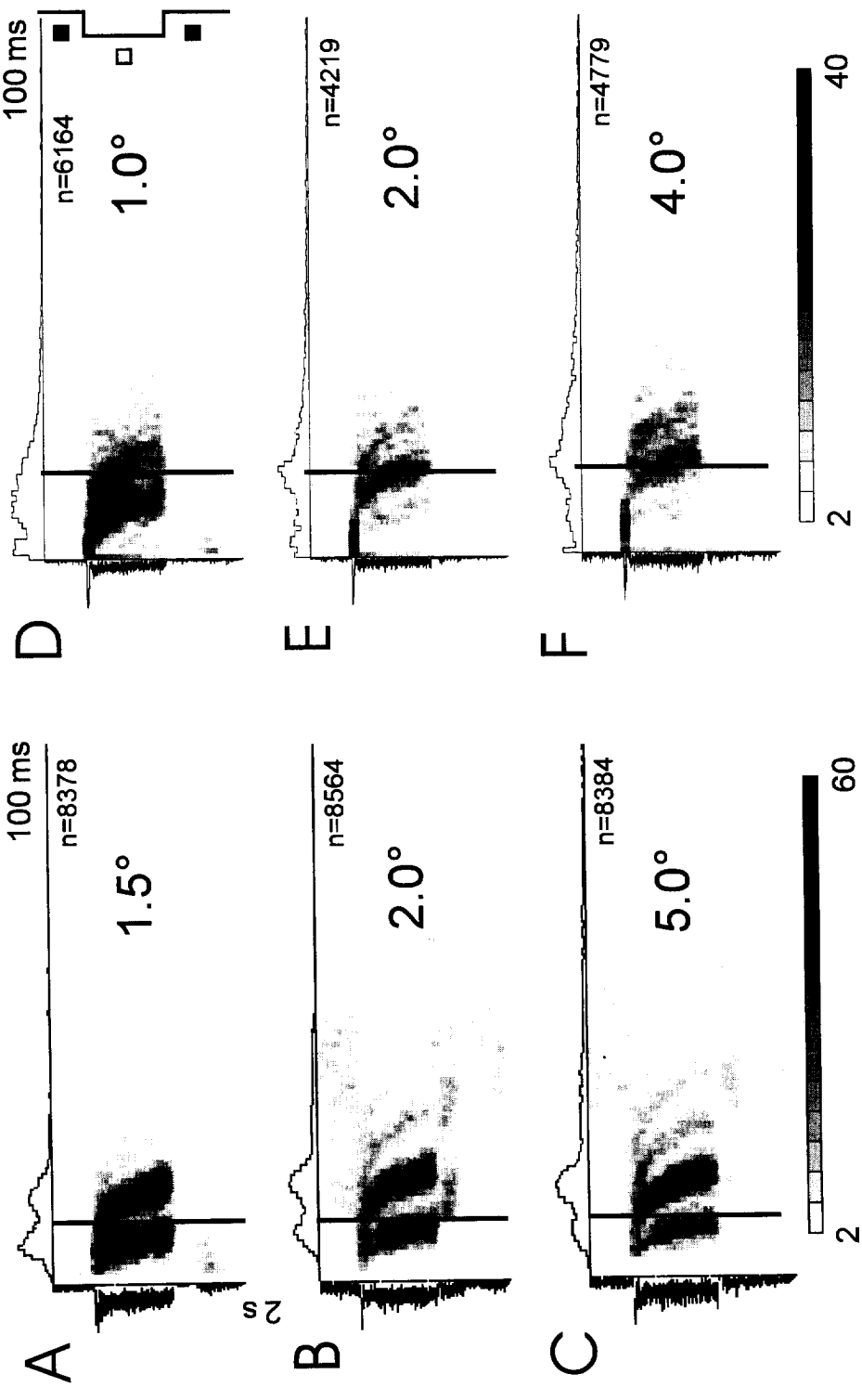

Fig. 14. Effect of increasing stimulus size on the interval distribution shown for an X-On and a Y-On cell. In both cases, the number of events in the first (fundamental) interval band decreases with increasing spot size and additional bands occur. The absolute location of the bands changes very little as can easily be estimated by the reference line.

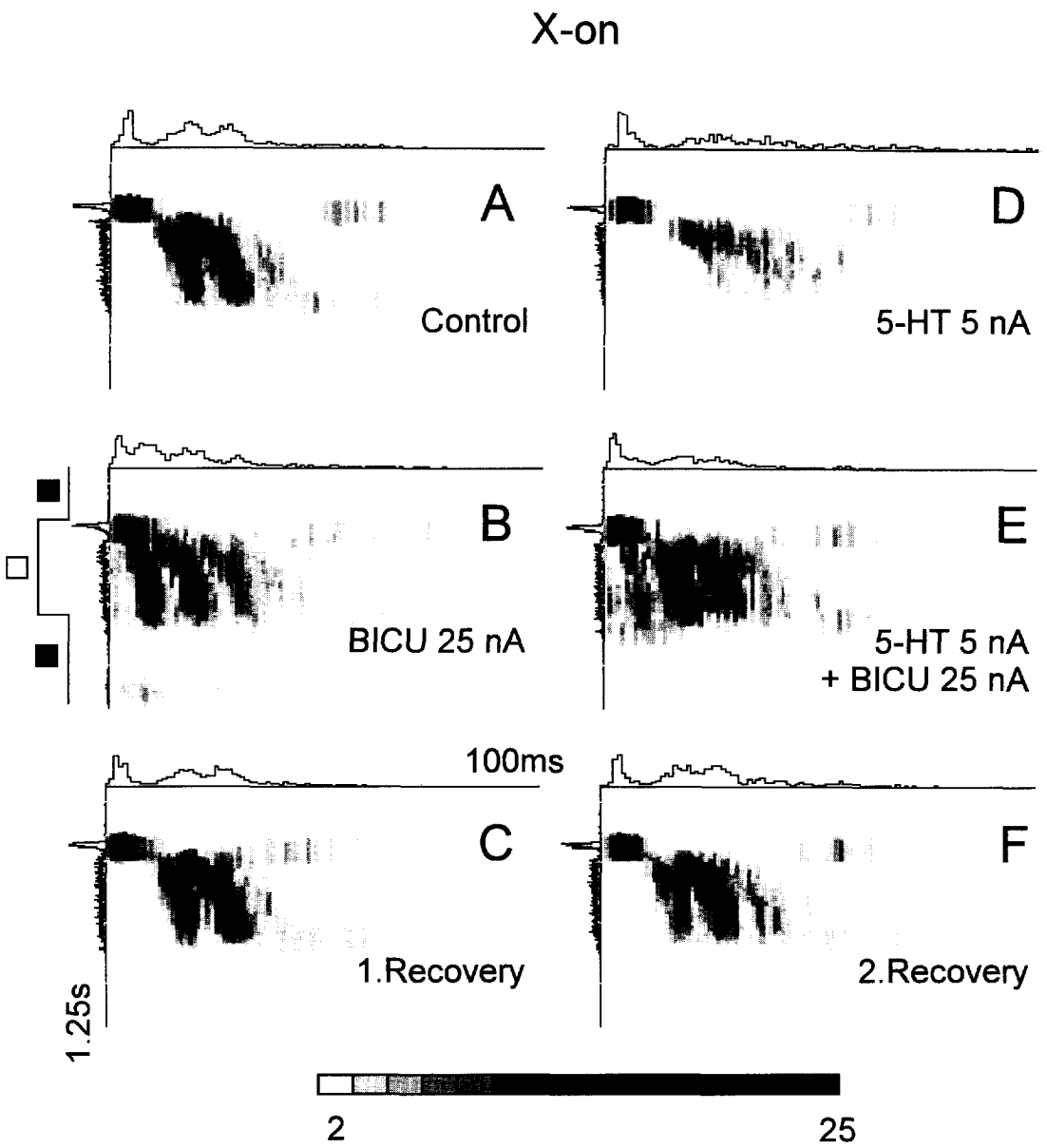

Fig. 15. Intervalograms of the activity of an X-On cell during application of bicuculline (BICU), 5-hydroxy-tryptamine (5-HT, serotonin) or a combination of both substances. The disinhibitory action of BICU (B) leads to an increase in activity which is accompanied by a redistribution of the preferred spike intervals. The leftmost band resembling the intervals of the fundamental intervals was totally absent during the control recording (A), but is now the dominating mode. The second and third band is clearly reduced. After termination of the BICU application, the activity returns to control level within a few minutes (C). Application of 5-HT causes a strong inhibition of LGN activity leaving only a faint remainder of the third and fourth band (D). The additional application of BICU during the continuing 5-HT delivery (E) induces an interval pattern intermediate between control and pure BICU level. The inhibitory action of 5-HT is antagonized, but the basic level of inhibition is not fully abolished as found during application of only BICU. The total recovery from the action of BICU and 5-HT is approached after a couple of minutes (5–15 min).

band. These results show that the number of fundamental and multiple intervals critically depends on the strength of intra-geniculate inhibitory input.

The amount of inhibition acting on an LGN relay cell can also be modulated by local application of agonists and antagonists of the GABA receptors. Figure 16 gives another example for the effect of the $GABA_A$ receptor antagonist BICU in comparison with the effect of GABA, the natural inhibitory neurotransmitter in the LGN. The GABA directly applied to the cell probably induces a more general form of inhibition which is less specific in terms of its temporal patterns as compared to the action of the inhibitory interneurons but the effect of the drug application is very similar. A typical dominance of the intervals of multiple length is induced if GABA

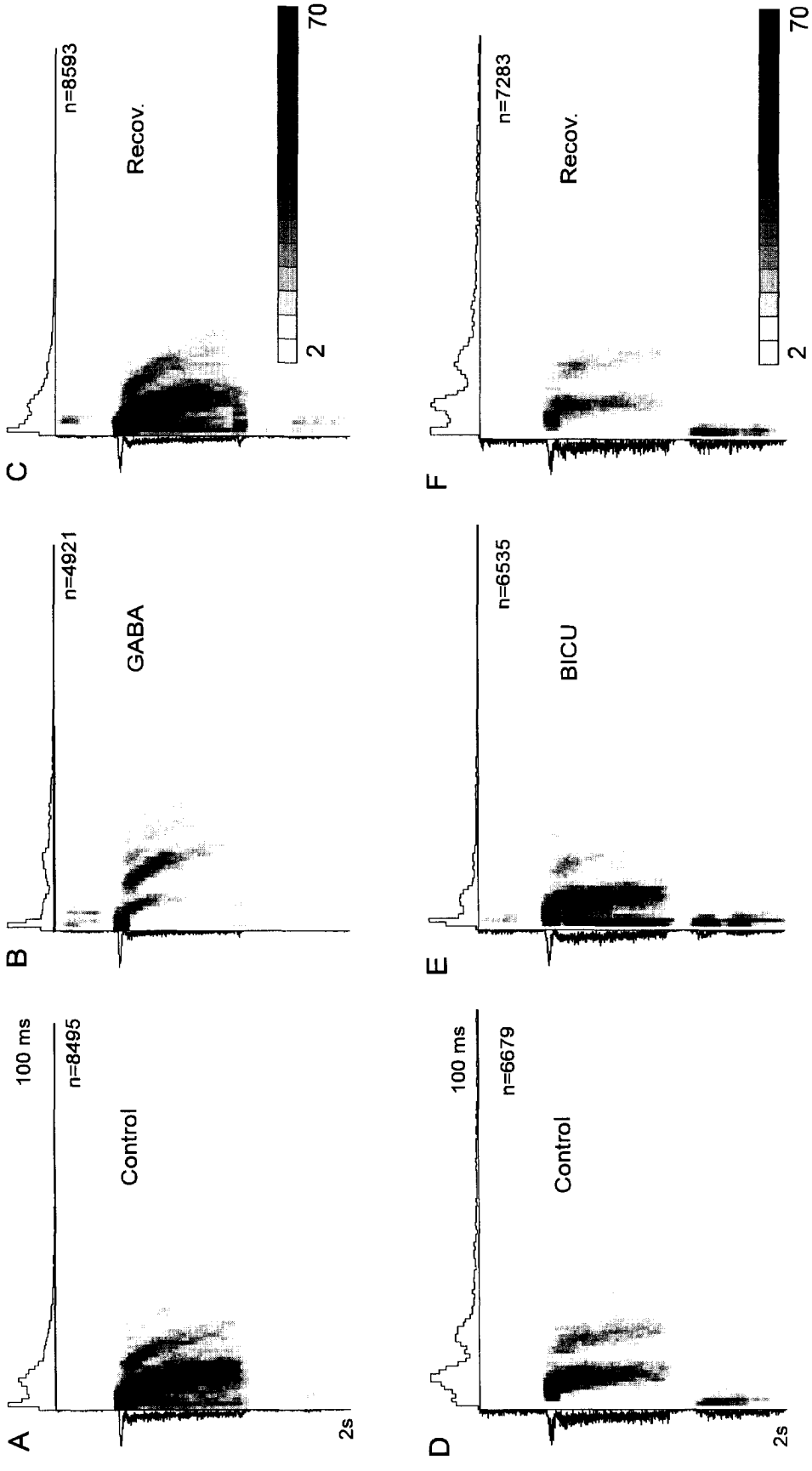

Fig. 16. Intervalograms of two X-On cells recorded during gamma-aminobutyric acid (GABA) and bicuculline (BICU) application in the LGN. The GABA induces an inhibitory effect at the LGN cell, activity is decreased and the intervals are redistributed into the higher order bands. BICU, on the other hand, leads to a redistribution of the intervals into the first band. During BICU more bursts (high frequency group discharges with 2–4 msec inter-spike intervals) can be observed.

reduces but not totally blocks the activity of the LGN relay cell. In the example shown in the Fig. 16(A)–(C) GABA caused an almost complete disappearance of the fundamental intervals, a dominating second band and the appearance of a weak third and faint fourth interval band. The BICU, on the other hand, induces the opposite effect. Reduced inhibition following application of BICU is expressed by an almost total disappearance of the higher-order intervals. The second band visible in Fig. 16(D) is erased in Fig. 16(E), but reappears after termination of BICU application (F). In particular during BICU application, but also during periods of strong activity, an additional band of intervals of very short length (2–4 msec) is visible close to the vertical axis to the left. These short spike intervals may correspond to so-called "high-threshold" burst discharges which can be observed also during tonic activity when LGN relay cells are strongly depolarized (see Lo *et al.*, 1991; Lu *et al.*, 1992).

7.3.3. *Retinal or Geniculate Origin of Interval Multiples?*

The results obtained by manipulation of the strength of intra-geniculate inhibition are a good indication but not an ultimate proof for a geniculate origin of interval multiples. It cannot be excluded that interval harmonics are already present in the retinal input. Furthermore, it is also possible that the fundamental firing frequency is generated by mechanisms intrinsic to LGN relay cells or by the input of an external pacemaker. The simultaneous registration of LGN output and corresponding retinal input should lead to additional evidence. So-called pre- or S-potentials precede the geniculate spike by a constant time between 0.5 and 1.0 msec and have been attributed to the afferent input activity of the dominant retinal cell that drives the LGN cell (Kaplan and Shapley, 1984; Mastronarde, 1987). The S-potentials can be recorded simultaneously with the geniculate spike when a high impedance tungsten-in-glass electrode (Wörgötter and Eysel, 1988) is used. There is anatomical and physiological evidence that most LGN cells, especially the X-cells, receive only one predominant retinal input (Kaplan *et al.*, 1987; Mastronarde, 1987, 1992). Figure 17 shows two examples for simultaneously recorded geniculate (X-On) spikes and corresponding retinal pre-potentials. The inset cross-correlograms demonstrate the strong coupling between these two events with a delay of less than 1 msec. The raster plots of Fig. 17(G) and (H) demonstrate this strong coupling at the single spike level. Ten spike sequences during the tonic part of the response are taken from the pair stimulated with a flashing spot (G from A + C) and another 10 from the response to ramp-like contrast modulation in B + D (H). In the 20 double traces, each line in the upper trace represents a retinal pre-potential, each line in the lower traces indicates the occurrence of an LGN spike.

A clear multi-modal interval distribution is visible only for the intervalograms of the geniculate spike activity, the intervalograms of the pre-potentials show only one interval band. The raster-plots show that each LGN spike is preceded by a retinal pre-potential within 1 msec, that not every pre-potential is followed by an LGN spike and that LGN spikes not preceded by a pre-potential are rare in Fig. 17(G) and almost missing in Fig. 17(H). Interval histograms for the spiking activity of retinal ganglion cells have also been shown by Troy and Robson (1992). Different from the experimental protocol of Funke and Wörgötter (1995), these authors used a uniform field of constant luminance or a stationary sinusoidal grating for visual stimulation. Correspondingly, the mean firing rate obtained by these stimuli was considerably lower and the interval peaks were broader than those found during stimulation of the receptive field with a flashing spot of high contrast. Nevertheless, the retinal interval distributions shown by Troy and Robson (1992) (see also Frishman and Levine, 1983) also exhibit only one interval peak. Therefore, it can be assumed that clear multi-modal distributions are first generated in the LGN. As already mentioned above, Off-relay cells of the LGN often exhibit a more diffuse interval distribution which lacks a multi-modal structure. In this case the interval distributions of LGN spikes and retinal pre-potentials were similar but due to a transmission rate less than 100% the number of LGN spikes was smaller than the number of retinal pre-potentials. A similar difference in the interval distributions of On- and Off-cells has also been shown by Troy and Robson (1992). Both X- and Y-ganglion cells of the Off-type were found to generate more widespread interval distribution than their On-type counterparts.

The strong coupling between the pre-potential and the LGN spike and the finding that the retinal interval band occupies the same X-position in the diagrams as the leftmost LGN interval band indicates that the fundamental firing frequency is indeed generated by the retinal ganglion cell, whereas multiples arise as the consequence of intra-LGN inhibition.

7.4. Simulation of the Generation of Multi-modal Interval Patterns

Earlier studies of the sixties (Bishop *et al.*, 1964) have already mentioned a multi-modal interval distribution in the LGN and the theoretical studies of Ten Hoopen (1966a,b) were designed to analyze the possible mechanisms that produce these patterns. Ten Hoopen found that a gamma-like distributed excitatory input results in a multi-modal output if it interacts with a poisson-distributed inhibitory input. These multi-modal distribution always showed a monotone decay of the modes with the first peak being the largest. However, in the distributions obtained from cat LGN relay cells (Funke and Wörgötter, 1995), often the second or third peak dominates. This difference can be explained in part by the fact that Ten Hoopen treated the inputs as restricted points in the time domain (point processes). For neurons, this is unrealistic since integration at the postsynaptic membrane is performed by excitatory and inhibitory potentials of a distinct duration. Therefore, we tested the interaction of the

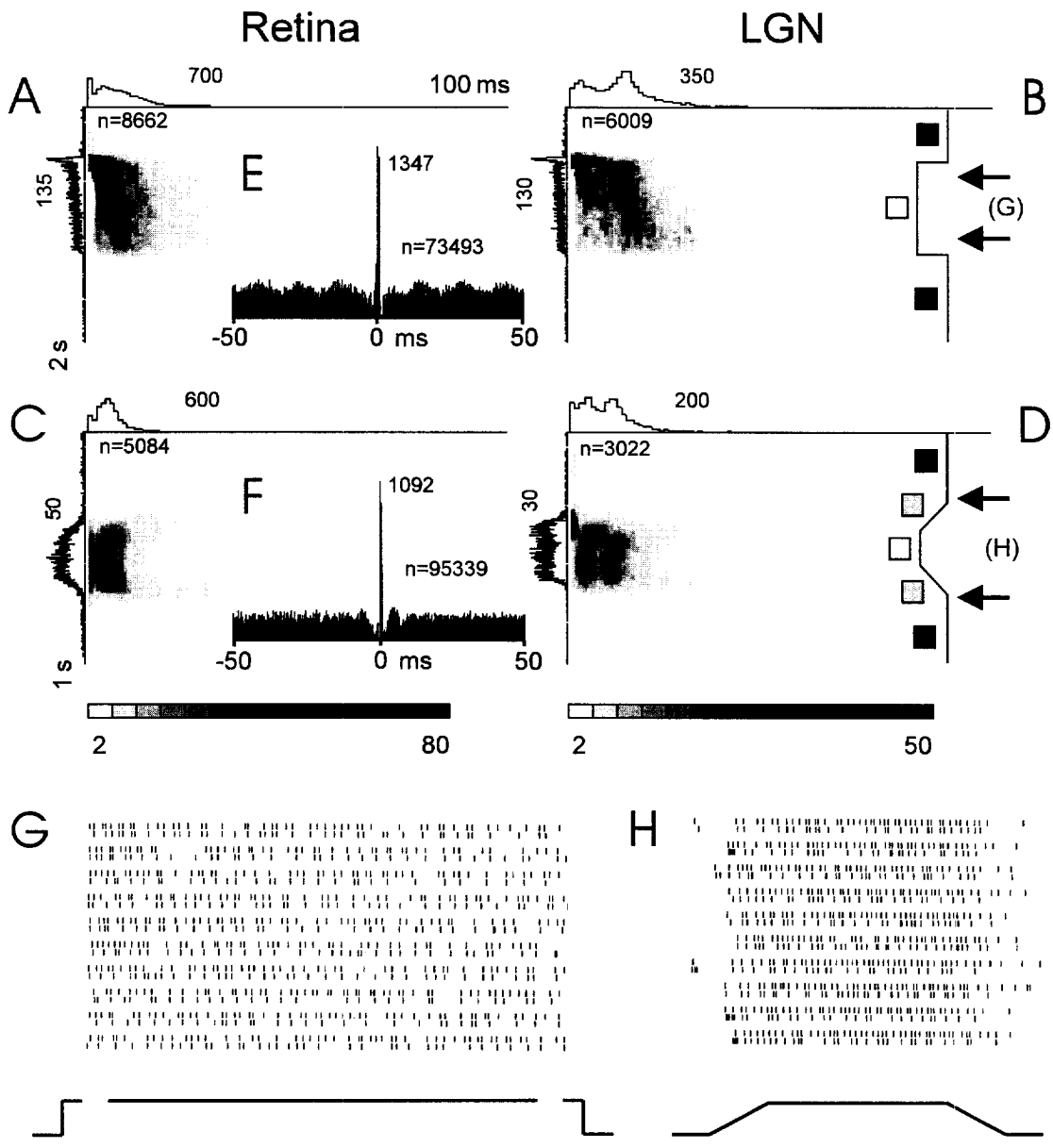

Fig. 17. Intervalograms obtained from two different geniculate X-On cells [(B) and (D)] and from simultaneously recorded retinal prepotentials [(A) and (C)] together with raster plots of the prepotential and LGN spike trains [(G) and (H)]. (A) and (B) In the upper case, the visual stimulus was a flashing spot. (C) and (D) In the lower case, a ramp-like modulation of light intensity was used. In both cases, only the geniculate relay cells exhibit multiple interval bands, the retinal input generates only one band at the fundamental interval length. (E) and (F) The cross-correlograms demonstrate the direct link between the retinal prepotential and the LGN cell (1 msec bins, n = number of spike correlations performed). (G) and (H) Raster plots show for 10 sweeps the prepotential activity and the corresponding LGN cell activity with the former plotted on top of the latter. The period of the record from which the 10 activity sequences were taken is indicated by the arrows in the stimulus timing diagrams to the right of (B) and (D). Not every prepotential elicits an LGN spike, while LGN spikes without prepotentials occur only very rarely. Reprinted from the *Journal of Physiology* **485**, K. Funke and F. Wörgötter, Temporal structure in the light response of relay cells in the dorsal lateral geniculate nucleus of the cat, pp. 715–737, Copyright 1995, with kind permission from the Physiological Society, London, U.K. .

retinal input with local geniculate inhibition in a biophysically more realistic model which simulates the integration of postsynaptic potentials as changes of the membrane potential. We varied the interspike intervals for the retinal inputs and for the inhibitory inputs within physiological ranges and added some noisy inputs. In addition, we systematically varied the duration and strength of the postsynaptic potentials. In this way, we could reproduce reliably the experimentally obtained interval distri-

butions (see Fig. 18). Similar to Ten Hoopen's results, in our simulations a single poisson-like distributed inhibitory input caused in most cases an exponential decay of the interval peaks. However, a dominance of higher-order modes could only be achieved if the inhibitory input itself was distributed in a gamma-like fashion or when there was a convergence of several inhibitory units. The most realistic interval distributions were obtained when the inhibitory units were coupled in a reciprocal fashion as is the case for the PGN neurons involved in the negative feedback loop to the LGN.

7.5. The Modulation of Geniculate Time Structure

The number of retinal inputs to LGN relay cells is quite small (10–15%; Guillery, 1971) compared to the so-called "modulatory" inputs which derive from different regions of the brain. The projections from the visual cortices back to the LGN constitute about 40% of the synaptic terminals, the local inhibitory connections and those from the PGN neurons amount to roughly 25% and the remainder is made by projection from a couple of different brainstem regions. The last group of connections can be further subdivided in two different functional entities. One originates in the mesopontine reticular formation and belongs to the ascending reticular arousal system (ARAS) which includes widespread cortical and subcortical projections of cholinergic, noradrenergic and serotonergic fibers (see Hobson, 1989; Jouvet, 1972; Steriade, 1996). The second group is made of projections from mesencephalic regions associated with the control of eye movements (superior colliculus, pretectum). The global state of the whole system is thought to be controlled by the ARAS and is reflected by periodic changes in arousal (sleep and wakefulness) which are associated with variations in the pattern of global electroencephalographic activity (EEG). During an EEG dominated by low frequencies (1–10 Hz), which is typical for drowsiness and sleep, LGN relay cells show spontaneous, often rhythmical burst discharges (from two to seven spikes at 300–500 Hz, Domich *et al.*, 1986; McCarley *et al.*, 1983). Incoming retinal activity is not transmitted faithfully by geniculate relay cells: the first retinal spike often elicits a burst discharge and the following sustained retinal input is suppressed, leading to phasic visual responses in the LGN (Funke and Eysel, 1992; Sawai *et al.*, 1988). Thus, retino-geniculate transmission is very different from periods of arousal which are accompanied by a predominance of higher EEG frequencies (15–80 Hz). In this state, LGN relay cells exhibit phasic–tonic visual responses similar to their retinal input and their spontaneous activity is largely free of high-frequency burst discharges. For more details regarding the modulation of retino-geniculate transmission, see Singer (1977), Sherman and Koch (1986), Casagrande and Norton (1991), Sillito and Murphy (1988) and Steriade and McCarley (1990). Changes in the EEG pattern also affect the spike interval distribution in the LGN. The occurrence of delta waves in the EEG causes a strong reduction of short spike intervals during the tonic light response and a relative increase in the number of higher-order intervals [see Fig. 19(A)–(C)]. In many cases with strong delta waves [see Fig. 19(C)], the fundamental intervals are totally erased and only spike intervals of the third or higher orders appear or the tonic response is completely suppressed.

A similar effect on the LGN response dynamic and interval structure can be achieved with inactivation of the cortico-geniculate feedback [Fig. 19(D)–(F)]. In general, the corticofugal system seems to facilitate retino-geniculate transmission since reversible inactivation of the visual cortex reduces the tonic visual response in the LGN (Funke and Eysel, 1992). This reduction of the tonic response is also accompanied by a change in the spike interval distribution. The number of fundamental intervals is decreased and the distribution is dominated by higher-order intervals [Fig. 19(E)]. Figure 19(F) demonstrates that the effects of cortical inactivation (either by cortical cooling or by microiontophoretical application of GABA, see Funke *et al.*, 1996) is fully reversible. In addition, the corticofugal feedback also influences the timing of the individual LGN spikes, an aspect which is discussed in more detail in Section 9.2.

Further control of retino-geniculate transmission derives from the oculomotor centers of the tectum and pretectum. Modulatory influences on cat LGN activity with different effects on the X- and Y-channel have been demonstrated with reversible inactivation of the superior colliculus (Xue *et al.*, 1994) and the pretectum (Funke and Eysel, 1995a). Subdivisions of the pretectum (nucleus of the optic tract, NOT; nucleus pretectalis posterior, NPP) send off direct projections to the LGN (Cucchiaro *et al.*, 1991; Kubota *et al.*, 1987, 1988; Schmidt and Hoffmann, 1992; Wahle *et al.*, 1994) and PGN (Funke *et al.*, 1995), the influence arising from the superior colliculus is thought to be mediated in part via the central nuclei of the thalamus (Lo and Xie, 1987). The pretectal projection to the cat LGN has been shown to affect not only the strength of geniculate visual responses but also the composition of spike intervals (Funke and Eysel, 1995a). In a control situation, the geniculate receptive field was stimulated by a flashing (0.5 Hz) spot of light which was either presented on a stationary or on a slowly moving (5–10°/sec) grating. The response to the flashing spot obtained from X-type relay cells with the moving grating in the background was considerably reduced compared to that obtained with the stationary grating in the background, accompanied by a relative increase in the number of spike interval multiples. Figure 19(G) shows the situation with the moving grating in the background. Inhibition of the visual responses of LGN X-cells during motion of the background grating could be mediated by pretectal cells since these have been shown to respond preferentially to the motion of large textured stimuli (Schmidt and Hoffmann, 1992). The stationary grating in the background does not stimulate the pretectal cells efficiently. For the experimental verification of this assumption, the pretectum (PT; including NOT and NPP) was reversibly inactivated by micro-iontophoretical application of the inhibitory transmitter GABA. During PT-inactivation the inhibition of the visual response by the moving

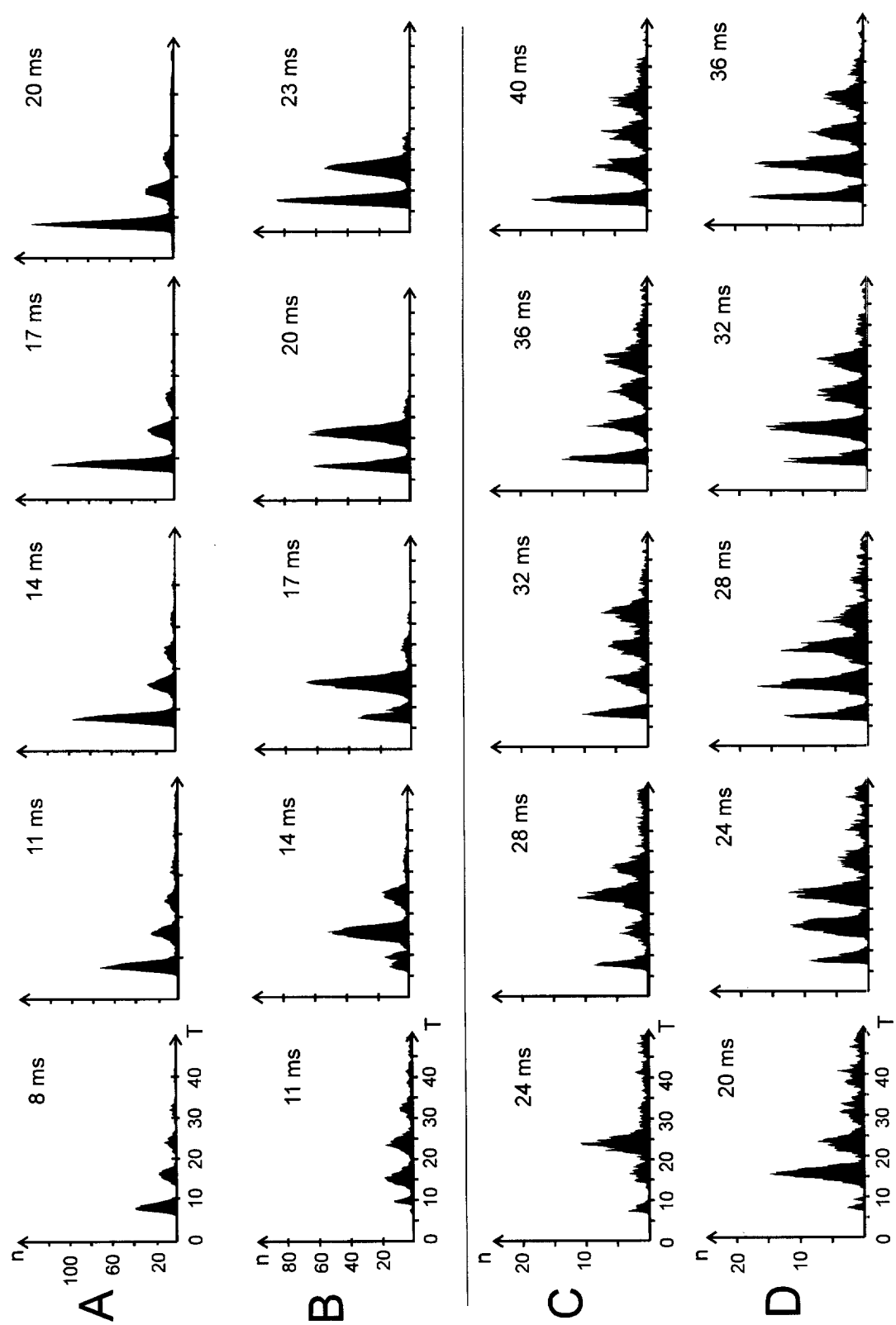

Fig. 18. (*caption on facing page*)

grating was significantly reduced and the number of lower order intervals (modes 1 and 2) considerably increased for the tonic component of the visual response [compare Fig. 19(H) with (G)]. The PT-inactivation with the stationary background, however, had nearly no effect, which supports the notion that a stationary grating does not stimulate the PT cells (not shown, see Funke and Eysel, 1995a). Figure 19(I) demonstrates that the procedure was reversible.

A common effect for all these modulatory influences is a change in the ratio of fundamental to higher-order intervals with no effect on the fundamental firing frequency and without adding "new" spike intervals which are not multiples of the fundamental interval. This finding indicates that these modulatory inputs either act by weak, clearly subthreshold postsynaptic mechanisms or by driving the inhibitory network in the LGN or PGN. Regulating the activity of the inhibitory inputs would be the most likely way to adjust the ratio of fundamental to higher-order intervals without affecting the fundamental interval length. Furthermore, one could assume that regulation of the ratio of short to long intervals could be a general principle to control the flow of visual information to the cortex. A spike train composed of only long intervals might be a signal of much lower priority for cortical processing than a pattern including stretches of short spike intervals. Or, in other words, the switch from short interval trains to those composed of longer intervals might reduce the "cortical attention" to this input line. Such a mechanism could be used to control the focal attention in one system, to switch attention from one to another system or, to generally increase the threshold for the transmission of afferent visual signals during deep sleep or as saccadic suppression.

7.6. The Statistics of Distinct Spike Patterns

In principle, distinct sequences of spike intervals could be used like a neuronal alphabet to create "words" and to transmit information exceeding that included in the mean firing rate. The nearly unlimited number of possible combinations of spike intervals normally prevents any statistical analysis of the frequency of distinct spike interval sequences. However, the limited number of preferred spike intervals (fundamentals and integer multiples) found in the visual activity of many LGN relay cells reduces the number of possible combinations in a spike train and makes this kind of activity accessible to a statistical analysis of spike patterns. The analysis performed by us (Wörgötter and Funke, 1995) is schematically shown in Fig. 20(A). In a first step, the spike intervals occurring during the tonic light response were labeled "1", "2" or "3" when their length fit to the corresponding range of one of the first three interval modes or were labeled "0" in the case where the length of the interval was out of the range of all three interval modes. At the first branches of the tree shown in Fig. 20(A) (level 1) the number of these intervals is indicated, the origin of the tree (level 0) includes all intervals counted, including also those labeled with "0". In a second step, the number of possible interval patterns resulting from combinations of these three intervals were determined. At level 2, all the nine possible patterns resulting from the combination of two intervals are shown, level 3 includes 27 cases for trains of three intervals and finally, level 5 represents 243 (3^5) possible combinations of five intervals.

However, the *absolute* numbers of these cases are less meaningful because these counts critically depend on the total interval count. For example, if only the interval 1 would exist, the probability two find stretches of interval 1 would be *a priori* high, but the probability to find patterns including the interval 2 or 3 would be zero. Therefore, for each new pattern we calculated the *a priori* probability (i.e. if it would occur randomly) as it results from the absolute number of the pattern from which it originates combined with the absolute number of the interval which has been added to build the new pattern. Each branch at levels 2–5 then was labeled

Fig. 18. This figure shows the result of different models for the generation of multiple peaks in the ISIH of an LGN relay neuron, which receives excitatory retinal input and inhibitory input, mediated by interneurons. In all cases, the excitatory afferent input is modeled by a truncated gaussian in the ISIH ($T = 8$ msec, $\sigma = 2$ msec, characterized by a uni-modal ISIH). The inhibitory input, which is much more difficult to ascertain experimentally, is varied according to a set of different models. In the top part, we show the resulting ISIH of the relay neuron, when the intervals of a single inhibitory input are (A) poisson-distributed; or (B) gaussian-distributed. Within one row, the strength of the inhibition (average firing frequency) has been reduced, for the poisson-inhibition from 125 Hz (8 msec) to 50 Hz (20 msec) in steps of 3 msec and for the gaussian case from $T = 11$ to 23 msec (standard deviation always 3 msec). For the case of poisson-distributed inhibition, we always observe a monotone decrease of the peak heights with increasing interval length. The resulting ISIHs are, however, generally not in accordance with the experimental findings. For inhibition shaped according to a truncated gaussian, we observe already fairly realistic ISIHs for various parameter settings. In the lower part of the figure, there is a convergence of several inhibitory cells onto the relay neuron. The temporal structure of each inhibitory cell is again described by a truncated gaussian. Row (C) shows the ISIH of the relay neuron, that receives converging input from four inhibitory interneurons, each with a gaussian-shaped ISIH of standard deviation $\sigma = 4$ msec and mean interval length 24, 28, ..., 40 msec. Row (D) shows the ISIH of the relay neuron, when the inhibitory interneurons are inhibitorily coupled with their nearest neighbors. Even though this introduces an additional temporal structure on the overall inhibitory input to the relay neuron, realistically looking ISIHs are obtained. The panels show the ISIH for a variation of the average inter-spike interval of each inhibitory cell from 20 to 36 msec, for a standard deviation of 4 msec. This result shows that the spatial and temporal fine structure of the inhibitory input is not crucial for the generation of realistic multi-modal ISIHs.

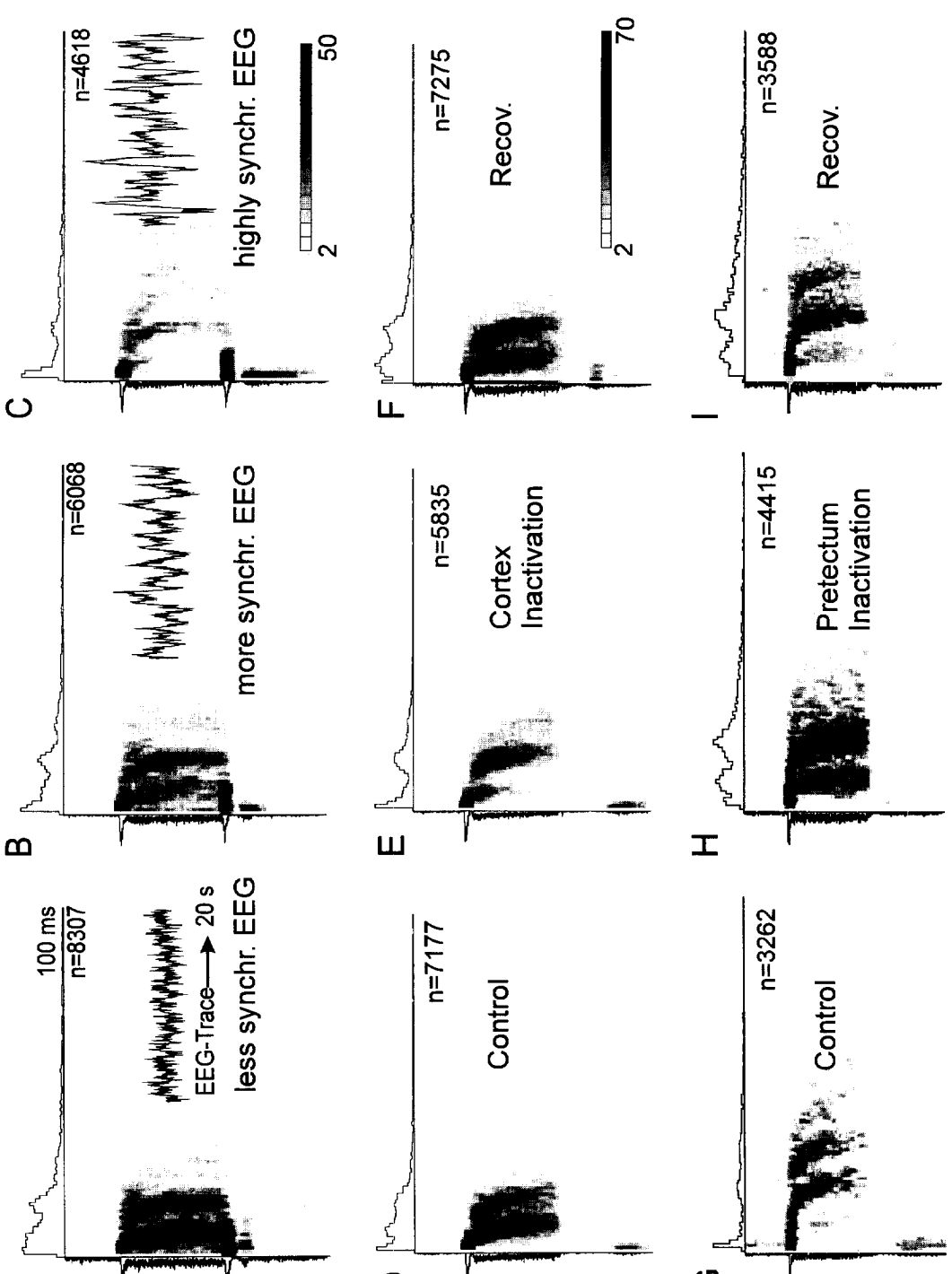

Fig. 19. Changing patterns of interval distributions observed under different conditions for three different LGN X-On cells stimulated with flashing dots. (A)–(C) During a spontaneous change of the EEG from a desynchronized to a highly synchronized state, the lower order bands fade and the higher-order bands prevail. A similar but less strong effect can be observed during cortical inactivation by cooling (D)–(F), while the reverse effect occurs during pretectum inactivation by GABA application (G)–(I). For further explanation, see text.

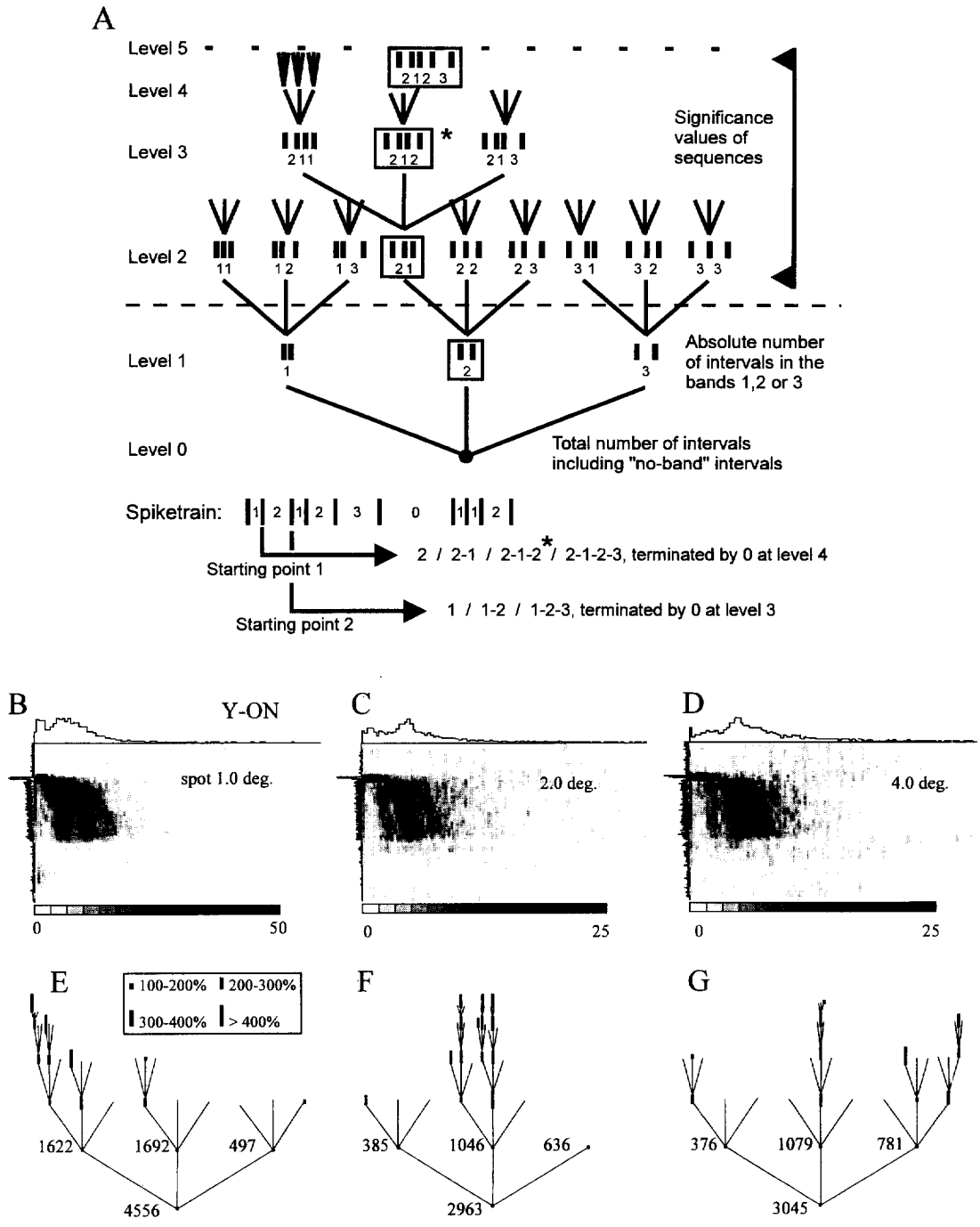

Fig. 20. Interval tree analysis. (A) Schematic drawing of a tree diagram depicting either absolute numbers of single inter-spike intervals taken from the first three bands in the intervalograms (levels 0 and 1) or so-called "significance values" (levels 2–5) of interval sequences. Above level 2, only a part of the tree is shown. Actually, at level 5, the tree has $3^5 = 243$ branches. Below the tree, one example for a spike train and the resulting interval sequences for two different starting points of the analysis are shown. For starting point 1, the boxes in the interval tree label the interval sequences up to level 4. Interval sequences are terminated if a "no-band" interval (0) occurs. In addition, one interval sequence is indicated by the asterisk in the spike train and the tree. For further explanation, see text. (B)–(D) Intervalograms; and (E)–(G) tree diagrams for an Y-On cell stimulated with light spots of increasing size and a contrast of about 50%. Absolute numbers of intervals are given for the two bottom levels of the trees, significant deviations from chance are coded by narrow bars in the levels above. The bar length indicates by how much an individual branch of the tree exceeds the maximally tolerated deviation from the expectation value. Scale bars are given in the inset (E). As expected, the most frequent intervals are redistributed from the fundamental to the higher-order bands with increasing stimulus size. At the same time, the branching pattern of the trees also shifts to the right. Thus, similar intervals tend to follow each other more often than statistically expected. The total numbers of intervals included in the intervalograms are (B) 6164; (C) 4219; and (D) 4779.

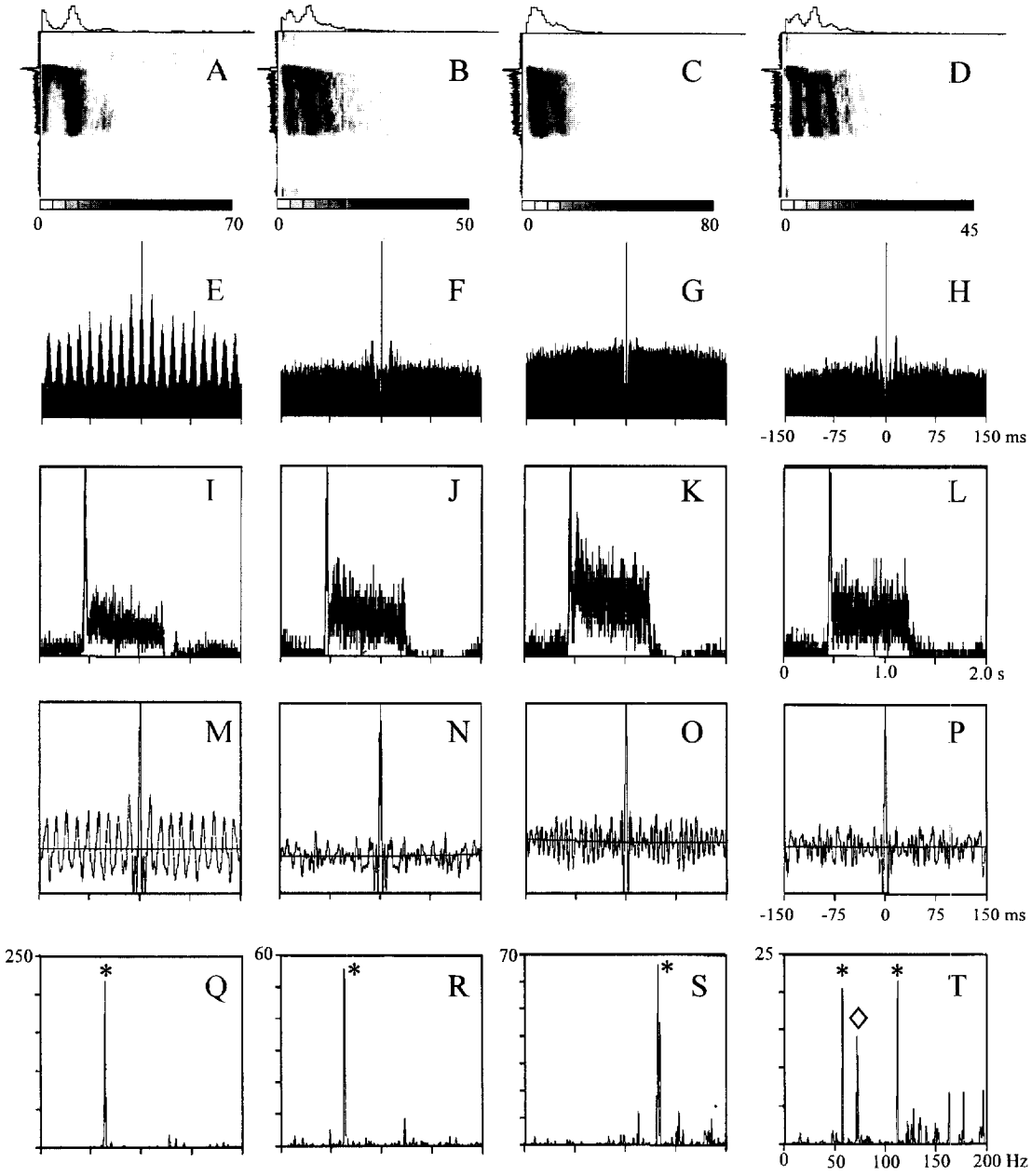

Fig. 21. (A)–(D) Intervalograms; (E)–(H) conventional ("spike-by-spike") auto-correlograms; (I)–(L) PSTHs; (M)–(P) auto-correlograms of the tonic response in the PSTHs; and (Q)–(T) power spectra computed from the PSTHs of four different cells. (For explanation, see text.).

with a value representing the percentage by which the number of the corresponding pattern exceeds the *a priori* occurrence. In the example shown in the lower part of the figure (B) the determined values (between 100 and >400%) are encoded by the length of the bars placed at each of the branches of the tree. A value of 100% indicates that the corresponding pattern was found twice than expected by chance; 400% resembles five times more frequent than expected.

The spike trains were sequentially scanned for these patterns in a way depicted in the lower part of Fig. 20(A). Starting with the first spike, the pattern was stepwise lengthened until it included five intervals or until an interval labeled "0" occurred. The patterns resulting from the first search are labeled by the boxes in the tree. The process was then repeated starting with the second spike in the train, and so on.

Figure 20(B)–(D) show the intervalograms and the interval trees that were obtained from the visual responses of one Y-On cell for three different spot stimuli. It is clearly obvious that the interval trees differ for light spots of different size. The smallest

stimulus (1.0°) leads to a dominance of the leftmost branches of the tree, indicating that sequences composed of intervals of the length 1 were found more frequently than any other interval pattern. It has to be noted that even a pattern of five consecutive intervals of length 1 was found five times more frequently (>400%) than expected. This result was not depending on the absolute number of intervals "1", since it (1622) was even a bit smaller than that of interval "2" (1692). A larger spot caused either a dominance of only the middle branches (2.0°, C) or of the middle and right branches (4.0°, D). The straight branch in the middle indicates that patterns existed that were composed only of intervals "2" and the rightmost branch corresponds to sequences exclusively made of intervals "3".

In summary, these findings indicate that geniculate relay cells do not use a highly sophisticated spike interval code like a morse code to transmit visual information. On the other hand, we found long stretches (at least six spikes) of identical intervals for short (1) but also for longer (two or three) spike intervals. These stretches could by themselves be used to encode different stimulus situations like spots of different size, but the capacity for carrying visual information would be limited and would barely exceed that of a rate code. The situation is different if we assume that these interval stretches occur at distinct times during the visual response in a stimulus-locked fashion. Higher-order intervals (two or three or higher) are shown to be generated by the action of inhibitory inputs at the LGN relay cell. Therefore, the overall temporal waveform of visual responses and the intrinsic structure of individual spike trains could well be controlled by the activity of intra-geniculate and perigeniculate inhibitory neurons which all exhibit different response characteristics and intrinsic properties (Contreras *et al.*, 1993; Destexhe *et al.*, 1994; Dubin and Cleland, 1977; Funke and Eysel, 1993; Pape and McCormick, 1995).

The concept of a temporal code can be extended further if we consider that distinct spike interval patterns repeatedly occur at the same position during the response thereby shaping the averaged response waveform. If this assumption holds, we would expect to find some temporal pattern reflecting the spike interval structure also in the averaged visual responses. In addition, one could expect to find groups of spike trains that bear some degree of similarity. One has, however, to keep in mind that stimuli repeated a couple of times will not always lead to identical responses since intrinsic encephalic modulatory influences fluctuate over time. Some of these influences are clearly visible as changes in the pattern of the EEG and have been shown to strongly affect the response strength (Funke and Eysel, 1992; Sawai *et al.*, 1988) and pattern (this study) of geniculate visual responses. Consequently, one can expect to find several groups of different response patterns during the repetition of 100 identical stimuli but within one group the pattern of individual responses may be similar.

Figure 21 demonstrates for four different cells (the four columns) a different relationship between the expression of oscillations in the auto-correlograms and the expression of distinct bands. Although, in all cases, the intervalograms show clear and sharp interval bands (first row, A–D) only for the leftmost cell the auto-correlogram (second row, E–H) shows a strong periodic pattern. This result indicates that the predominance of one interval and its multiples leads (not ultimately) to a clear oscillatory pattern of activity. One reason for a rather flat auto-correlation could be a strong jitter of the interval or a steadily changing length due to adaptational processes. These two factors, however, cannot explain the huge difference between the shape of the left and the three right auto-correlograms, since the bands show about the same width and the tilt due to adaptation is moderate. A more critical factor seems to be the length of stretches composed of intervals of the fundamental length. Frequent disruption by higher-order multiples or spike intervals that are not an integer multiple can disrupt the continuity or increase the jitter. These examples show that in some cases the spike interval analysis might be a more sensitive and robust method than the auto-correlation and is at least a useful supplement.

Quite surprisingly, the auto-correlograms (fourth row, M–P) and power spectra (bottom row, Q–T) calculated from the tonic response components of the PSTHs (third row, I–L, 1 msec bin width), and not from the spike train as usual, display frequency components that resemble the dominating spike interval (asterisks in the power spectra). The fact that the averaged signal shows a periodicity that is based on the dominating spike interval pattern indicates that most of the individual responses are built on spike trains which are highly stimulus-locked. The averaging process of the PSTH seems to weaken the disturbing effect of spike interval jitter or missing spikes which prevent the detection of a clear periodicity at the single spike train level. In most cases, the power spectra of the PSTHs contain more than one peak. Some of these (asterisks) seem to be the result of harmonics of the fundamental interval length, others do not resemble a dominating spike interval.

Multiple peaks in the power spectra also could result from a changing internal structure of the visual response itself, since retino-geniculate transmission is affected by a couple of modulatory influences (global arousal system, oculomotor and corticofugal influences, see Sillito and Murphy, 1988; Singer, 1977). Accordingly, a PSTH averaged from 100 responses could represent a mixture of different response variants and it would be useful to classify groups of different response variants prior to averaging. The sorting process (here not described in detail, see Wörgötter and Funke, 1995) is based on an evaluation of the similarity (or dissimilarity) of single spike trains. Figure 22 shows one result of this sorting process for an X-On cell stimulated with light spots of three different sizes (0.3, 1.0 and 1.5°). The 100 responses obtained for each spot size were subdivided into groups of similar responses, the responses were averaged and a power spectrum was calculated for the resulting PSTH. The responses to the smallest stimulus (left column) could be divided into two groups of 44 and 17 re-

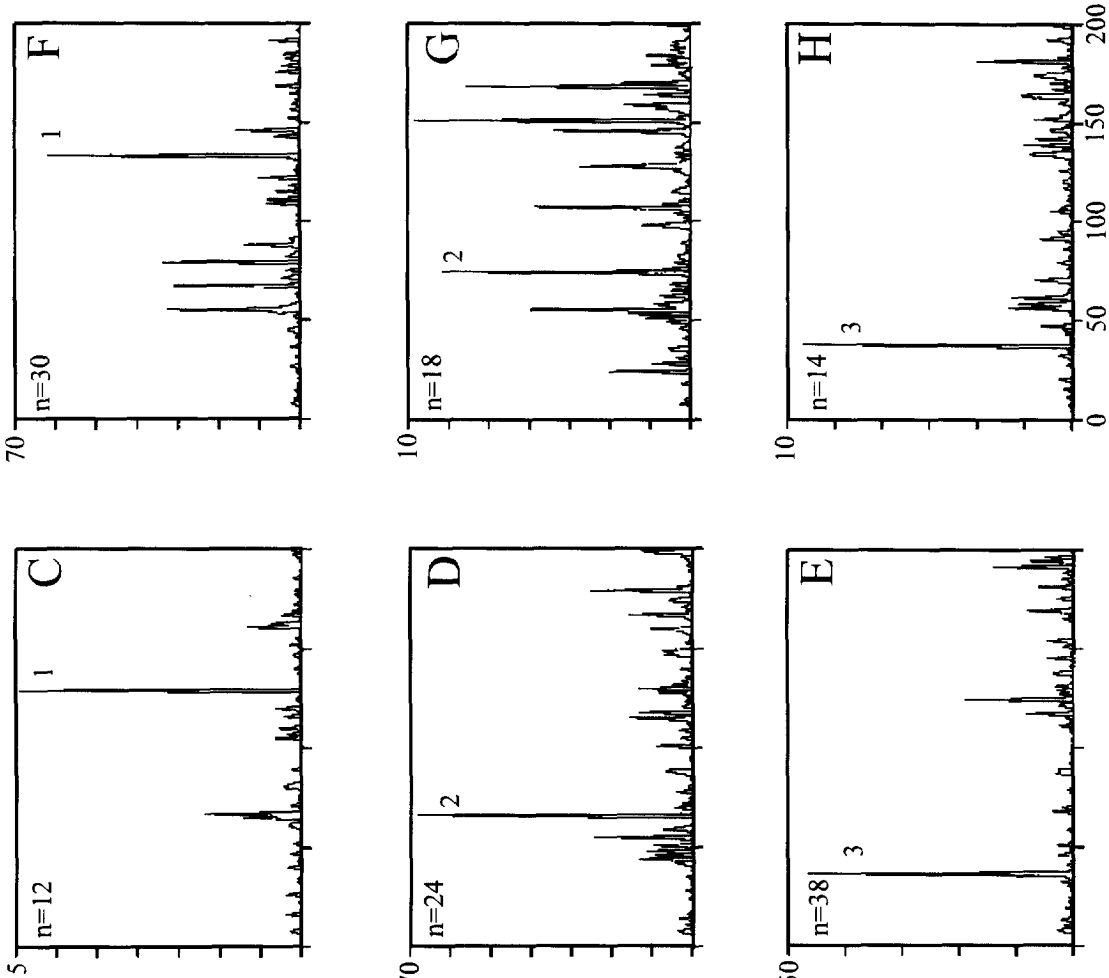

Fig. 22. Power spectra computed from groups of similar sweeps for an X-On cell stimulated with light spots of different size [(A) and (B) 0.3°; (C)–(E) 1.0°; (F–H) 1.5°]. The total number of sweeps in each record obtained for a given spot size was 100. The largest peaks in the power spectra (labeled by numbers) are always associated with the frequencies represented in the dominating bands of the corresponding intervalograms (not shown). Reprinted from *Visual Neuroscience* **12**, F. Wörgötter and K. Funke, Fine structure analysis of temporal patterns in the light response of cells in the lateral geniculate nucleus of the cat, pp. 469–484, Copyright 1995, with kind permission from Cambridge University Press, New York, U.S.A.

sponses of sufficient similarity, the remaining 39 responses could not be subdivided into groups containing more than 10 members and were therefore omitted. The PSTHs calculated from the single groups do not give any indication of a different response pattern. However, the power spectra clearly show differences which are based on the spike patterns. For example, a prominent peak close to 150 Hz is present in the upper of the two spectra of the left column, but at the corresponding position in the lower diagram a much smaller peak is visible. On the other hand, the lower spectrum shows a strong peak at about 75 Hz which is absent in the upper case. The responses to the medium (1.0°, middle column) and large (1.5°, right-hand column) spot could each be divided into three response groups exhibiting differing spike patterns and power spectra. It should be noted that peaks at 75 and 37 Hz are associated with larger stimuli.

The results described above justify two major conclusions: (i) responses to identical stimuli can vary considerably but still show a distinct intrinsic response pattern and obviously a limited number of response types; and (ii) responses may show some degree of stimulus-locking without which an establishment of groups of similar response patterns would have been unlikely. If spike sequences show a distinct and reproducible stimulus-dependent pattern, and if they are furthermore locked to the stimulus onset, then they may build the basis for stimulus-characteristic response waveforms like those described for the visual responses of geniculate relay cells in monkeys (McClurkin *et al.*, 1991b). In the study of McClurkin and coworkers, the response waveforms were derived from spike-density functions, with the spike density probably reflecting the relation of the number of fundamental and higher-order intervals. Since the variability of response patterns (conclusion 1) could be a reflection of a changing corticofugal activity, the variability can be expected to be reduced if the corticofugal feedback is permanently abolished. This, indeed, has been demonstrated by McClurkin *et al.* (1994): monkey geniculate relay cells lost the power and variability of the higher principal components of the response waveforms when the cortico-geniculate feedback was inactive.

The results summarized under the aspect of the fine temporal structure of geniculate visual activity indicate that stimulus-dependent variations of spiking activity in the retino-cortical pathway are not simply a reflection of the changes in firing rate. Spontaneous discharges and stimulus-induced responses bear a couple of different spiking patterns, most of them being oscillatory or at least periodical. Oscillatory activity prevails during stimulation with large objects and this obviously holds also for the visual cortex (Bauer *et al.*, 1995). When light is flashed on and off, an oscillation is clearly visible in the gross response due to the highly stimulus-locked synchronization of activity. With smaller stimuli both, oscillation and synchronization seems to be less prominent and more variable but can still be demonstrated when small time windows are used for analysis. Long-lasting patterns of synchronous oscillatory activity which are not phase-locked to stimulus onset are also evident during steady stimulus conditions, e.g. during standing contrast or a continuously moving pattern. Following stimulus onset, the oscillatory frequency declines, it is generally higher for On than for Off stimuli and is also present in the spontaneous activity as the "dark discharge" but with a clearly lower oscillatory frequency than during a period directly following a change in contrast. In the LGN, the oscillatory pattern of activity is not simply based on a constant firing frequency: the spike trains are composed of multiples of a fundamental interval and the ratio of higher- to lower-order multiples is related to stimulus characteristics (e.g. size). The content of information transmitted by a spike train composed of different spike intervals could, therefore, be higher than that carried by only a constant oscillatory firing frequency.

8. USING RESPONSE LATENCY FOR TEMPORAL CODING

The latency between stimulus onset and the onset of the visual response can be considered as a further aspect of temporal coding since it is affected by the spatial distribution of contrast throughout the receptive field. Response latency is shorter for intense stimuli than for weak stimuli and most often shorter for large as compared to small stimuli [at least in Y-cells, Bolz *et al.*, 1982; Dinse and Krüger, 1994; Sestokas *et al.*, 1987; see Fig. 23 for retinal (A) and geniculate (B) data]. The higher the amount of light energy, which hits the receptive field of a ganglion cell, the stronger and steeper is the change of the corresponding membrane potential so that the firing threshold is reached faster. Furthermore, it has to be considered that the different sub-divisions of the receptive field generate excitatory or inhibitory responses with different latencies (Enroth-Cugell and Lennie, 1975; Enroth-Cugell *et al.*, 1983; Rodieck and Stone, 1965). If the receptive field center, the antagonistic surround and the far periphery are stimulated simultaneously by a flash of light, the excitatory input to a ganglion cell which comes from the center precedes the inhibition from the surround by a few milliseconds (Enroth-Cugell and Lennie, 1975). Additional excitatory—or possibly also inhibitory—inputs from the far periphery (periphery effect or shift effect, Fischer and Krüger, 1974) are even slower. The joint response which results from the convergence of center, surround and periphery responses may, therefore, exhibit a distinct temporal waveform which is determined by the spatial distribution of bright and dark elements throughout the receptive field (see Fig. 24). This mechanism could be one way to produce the different temporal waveforms of visual responses to Walsh patterns projected into the receptive field of alert monkey geniculate relay cells (McClurkin *et al.*, 1991b). In the last paper of this series (Gawne *et al.*, 1991), the authors suggest a couple of different parallel spatial-to-temporal filters to produce the individual principal components of the response waveform. These filters might correspond to the different RF-subregions (center, surround, far periphery). An

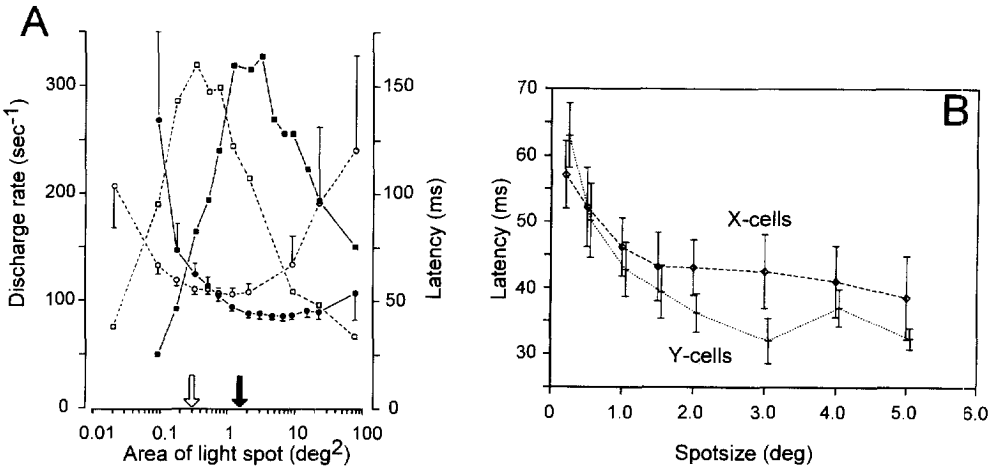

Fig. 23. Dependence of the visual latency in retina (A) and LGN (B) on the size of the stimulus. (A) This is recompiled from Fig. 7 of Bolz *et al.* (1982) and shows the response of a brisk-sustained X-cell (open symbols) and an adjacent brisk-transient Y-cell (filled symbols) to concentric light spots of increasing size. The size of the receptive field center of the brisk-sustained (X) unit is indicated by the open arrow, that of the brisk-transient (Y) unit by the filled arrow. The discharge rate was highest and the latency shortest for stimuli having the size of the receptive field center. (B) Shows a similar observation for samples of X- (n = 21) and Y-cells (n = 8) in the LGN (the mean latency of Y-cell responses to a spot size of 4° is based on only two measurements).

alternative origin for the geniculate response waveforms could be the timing of intrinsic inhibition in the LGN. Lateral inhibition in the LGN is strengthened by inhibitory inputs from the local interneurons and by the GABAergic inputs from the PGN neurons which transmit the activity of retinal ganglion cells located in near or far antagonistic surround, respectively (Eysel and Ringeler, 1985; Eysel, 1986; Hubel and Wiesel, 1961; Sillito and Kemp, 1983). This way, the different response latencies of the RF subunits and the delays generated by the associated network might produce a temporal waveform of activity that could be used to transmit information about the spatial distribution of light throughout the receptive field.

As mentioned above, onset-latency of the light response is largely depending on the amount of light energy accumulated inside the receptive field and should, therefore, vary according to local contrast. It is conceivable that a contrast profile (e.g. a shading or a border) also causes a response latency profile within the retinal ganglion cell layer. Transmitted to the cortical network, this latency profile might support the mechanisms of object segmentation. A similar hypothesis for the recognition of stimulus patterns by the timing of action potentials has been put forward by Hopfield (1995). Each possible stimulus pattern elicits a different spatial pattern of activity in the afferent pathway. The activity differs not only in the mean firing rate of each

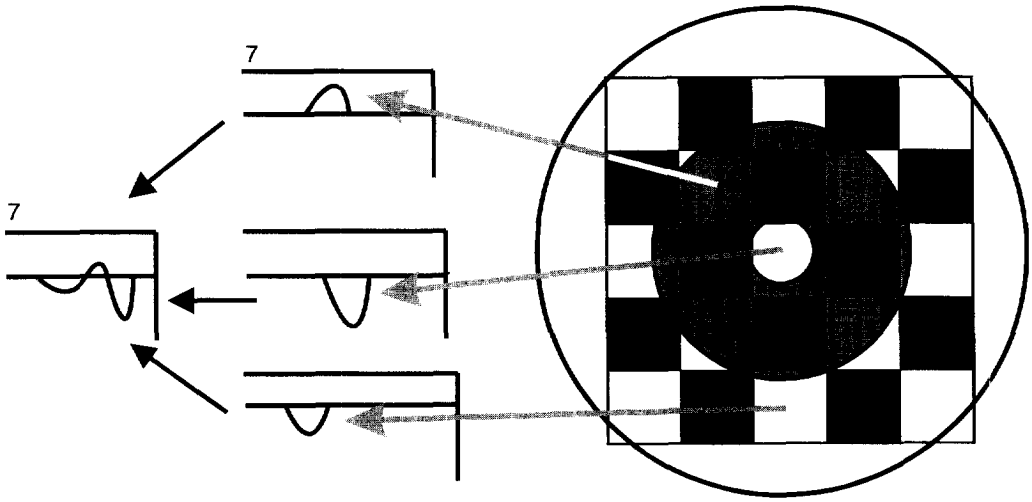

Fig. 24. Schematic diagram of how to compose a complex wave-form from individual response components of a cell which are elicited from different parts of the receptive field with a different latency. For further explanation, see text.

member but also by the distribution of response latencies. Neurons acting as coincidence detectors may be able to distinguish and recognize such latency arrays. Responses to stimuli of the same brightness propagate through the network simultaneously but are temporally displaced from responses to brighter or darker stimuli. This contrast-dependent response latency was also used by Wörgötter *et al.* (1996) and Opara and Wörgötter (1996) to improve a mechanism of object binding by synchronous (oscillatory) activity in a cortical network. Due to the high frequency of the oscillatory activity (40–80 Hz) and the resulting short oscillatory period of 12–25 msec, the possible number of discrete cell assemblies oscillating out of phase is rather limited if the activity is induced simultaneously. Assuming a temporal jitter for spiking activity of a few milliseconds, the limited oscillatory period allows for only three–six cell assemblies with separate phases to be active at the same time. The number of possible assemblies, however, increases considerably if one assumes that, due to response latency, their activity onset is stretched over time. Responses to bright objects synchronize earlier than those induced by a darker object and the probability of temporal interference between these two activities is reduced. Thus, also, the latency differences of visual responses might, in several ways, be important for higher level visual processing, which has also been suggested recently by Gawne *et al.* (1996), supported by their experimental findings.

9. THE SIGNIFICANCE OF THE GENICULATE TIME CODE FOR HIGHER LEVEL PROCESSING

Both the overall temporal waveform of the visual responses of LGN relay cells (McClurkin *et al.*, 1991b) and the preponderance of certain spike interval patterns intrinsic to these responses indicates that some kind of temporal encoding is used to transmit information about visual events to cortical areas. This temporal code, however, still is associated with a rate code since mean firing rate scales with stimulus intensity (luminance, contrast, see Troy and Enroth-Cugell, 1993). Yet firing rate also is affected by the size of the stimulus because the simultaneous stimulation of the receptive field center and its antagonistic surround causes a diminished response. The fact that two stimulus parameters, the intensity and the spatial extent, affect the firing rate at the LGN output, causes the following problem: a large and intense stimulus covering the center and the surround of the receptive field could, in principle, elicit about the same mean firing rate than a small, but less intense stimulus, covering only the center. One example is given in Fig. 25. At the single cell level, these two stimuli cannot be distinguished by the mean firing rate alone. However, if the two different stimulus situations induce a different temporal structure based on the observed spike interval patterns, the two stimulus situations can be distinguished. The large and intense stimulus causes a high fundamental firing rate from the center but also an increased inhibition from the surround of the receptive field which prevents the transmission of some spikes. Consequently, the LGN output is a mixture of fundamental and higher-order intervals. The small and less intense stimulus, on the other hand, causes little surround inhibition, but also the stimulation of the center is weaker. The result is a reduced fundamental firing frequency (increased fundamental spike interval length) but with very little higher-order intervals due to the weaker inhibition. Thus, the temporal structure of the output is different, although—in a constant time window—the number of spikes can be identical for the two stimulus situations.

Such a possible encoding of stimuli by a rate code plus a temporal code seems not to be restricted to the visual system. A similar pattern of sensory activity has been found for the multi-modal receptors of the shark ampullae of Lorenzini, which are able to encode the temperature and the electrical field of the surrounding water at the same time (Braun *et al.*, 1994). The temperature is transmitted via the fundamental firing frequency of the sensory fiber and the local electrical field sculptures this activity by generating multiples of the fundamental interval. The mechanisms by which the interval multiples are generated is, however, different. In cat LGN, inhibition causes the interval multiples, in the shark ampullae of Lorenzini the multiples are introduced at the receptor site: the electrical field of the environment acts as electrical noise on the receptor potential, thereby disturbing an ongoing, temperature-sensitive membrane potential oscillation.

One could now argue that the spatial distribution of light contrast could be extracted from the spatially distributed activity in a topographically organized network. Although this is certainly true in a general sense, superimposing a time-structure onto the activity could have some advantages for higher level processings which are not available when using only a rate code. One major problem in image analysis is the perceptual grouping and distinction of different objects. Grouping could be achieved at least in two different ways: (i) by a stepwise spatial integration of converging inputs, leading to growing receptive fields of increasing complexity; or (ii) by a spatio-temporally distributed but synchronous activity in an assembly of neurons or, a combination of both processes. Indications for the first mechanism are given by the face-specific cells found in the inferio-temporal cortex (Desimone *et al.*, 1984) and support the theory of so-called "grandmother cells" (see Marr, 1982; hand-detector cells, Gross *et al.*, 1985), cells specialized for the detection of distinct objects. There exist, however, numerous possible viewing angles for any given object and this immediately leads to a combinatorial explosion as soon as more than one object is considered, Thus, feature detector cells (e.g. grandmother cells) cannot be the ultimate solution to the problem of scene analysis and the theory of feature detector neurons has been supplemented by the theory of assembly coding. This theory states that information is represented by the correlated firing of a distributed cell ensemble. The most reliable way to approach this problem seems to be a combination of both mechanisms,

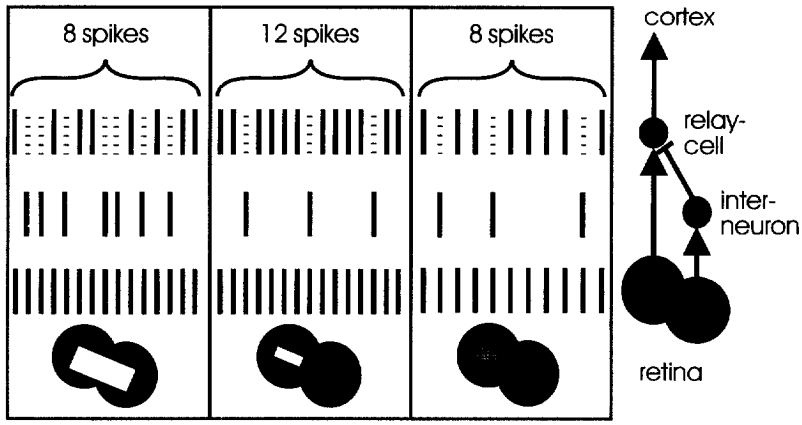

Fig. 25. Schematic diagram showing how conflicting stimulus situations could, in principle, be resolved at the single-cell level in the LGN by taking the interval patterns also into account. The same simple circuitry as in Fig. 13 is assumed (right). The middle panel depicts the response of the regarded relay cell to a small bright stimulus (bottom). In this time window 12 spikes occur, leading to a relatively high mean firing rate. In the left- and right-hand panels, eight spikes occur, and the mean rate computed across this window would be identical. These identical mean rates are due to a large bright stimulus in the left- and to a small dim stimulus in the right-hand panel. In the left-hand panel, the retinal excitation is strong, but so is the surround inhibition, whereas in the right-hand panel, excitation and inhibition are both weak. Thus, these two stimulus conditions (left and right) cannot be distinguished by the mean rate alone. The interval structure in the left and right situation, however, is different. Due to the strong inhibition, we get many second-order (and third-order) intervals for the large bright stimulus, whereas the small dim stimulus mainly leads to a preponderance of fundamental intervals in the response but these intervals are longer that the fundamental intervals elicited with the large bright stimulus.

since spatial convergence is evident by the large receptive fields found in higher visual areas.

The spatial integration of inputs generates receptive fields tuned to extract specific features of a stimulus as it has been shown for the detection of the orientation of a contrast border by the elongated receptive fields of the primary visual cortex (Hubel and Wiesel, 1962). The enhanced specificity of the RF is, however, accompanied by an increase in RF size which causes a reduction of the spatial resolution. If sensory information is encoded only by firing rate, the cell has to integrate the incoming activity over a sufficiently long period (the "integrate-and-fire" type neuron) to be able to sum up inputs of both, high and low firing rate, reflecting strong and weak stimuli, respectively. In this way, every input if active at a low or at a high firing frequency contributes to the sum of the postsynaptic response and a cortex cell could be depolarized to spike threshold by a huge number of different combinations of input activities. In other words, several different stimuli might make the cell fire in a similar way and orientation specificity would be weak.

The introduction of a temporal code could improve the performance of orientation detection in a way schematically demonstrated in Fig. 26. The LGN inputs may show a similar temporal pattern of activity when stimulated in the same way, e.g. by a light bar of uniform brightness [Fig. 26(A)]. If the cortex cell performs like a coincidence detector (König *et al.*, 1996) with short postsynaptic time constants, the cell is maximally active only if all LGN inputs exhibit the same activity pattern. In addition, the temporal structure of input activity is maintained in the output and can be used for another similar integration process at the next hierarchical level. Any deviation from the optimal orientation leads to a change in the geniculate input pattern, since some of the LGN receptive fields are either not or only partially stimulated by the bar. If the cortex cell needs a considerable number of simultaneous inputs to generate a spike, then the cell increasingly fails to fire. As a consequence, not only the firing rate but also the temporal structure, of the output varies with changing orientation of the bar [see Fig. 26(B) and (C)]. A bar of reduced brightness will cause a different temporal structure of activity than a brighter bar, but when optimally aligned with the cortical RF it will induce a similar pattern of activity in the contributing LGN inputs and the cortex cell will still be active because of the coincidence of the inputs [Fig. 26(D)]. This way, the specificity of cortical cells can be enhanced and for optimal stimuli the temporal pattern of activity is preserved and can be used for further analysis, e.g. not only for the next hierarchical level but also for gating the flow of afferent activity a level below. In such a feedback loop, an optimally excited cortex cell can gate and improve the temporal correlation of the activity of those LGN cells that supply input to this cell (see also Sillito *et al.*, 1994 and Section 9.2).

9.1. The Contribution of the Geniculate Temporal Structure to Cortical Activity Patterns

In addition to the question about the usefulness of temporally structured activity for sensory processing, one has to ask whether the findings on geniculate activity can be related to findings on temporally structured activity in the visual cortex. The temporal structure of the activity found in the visual cortices

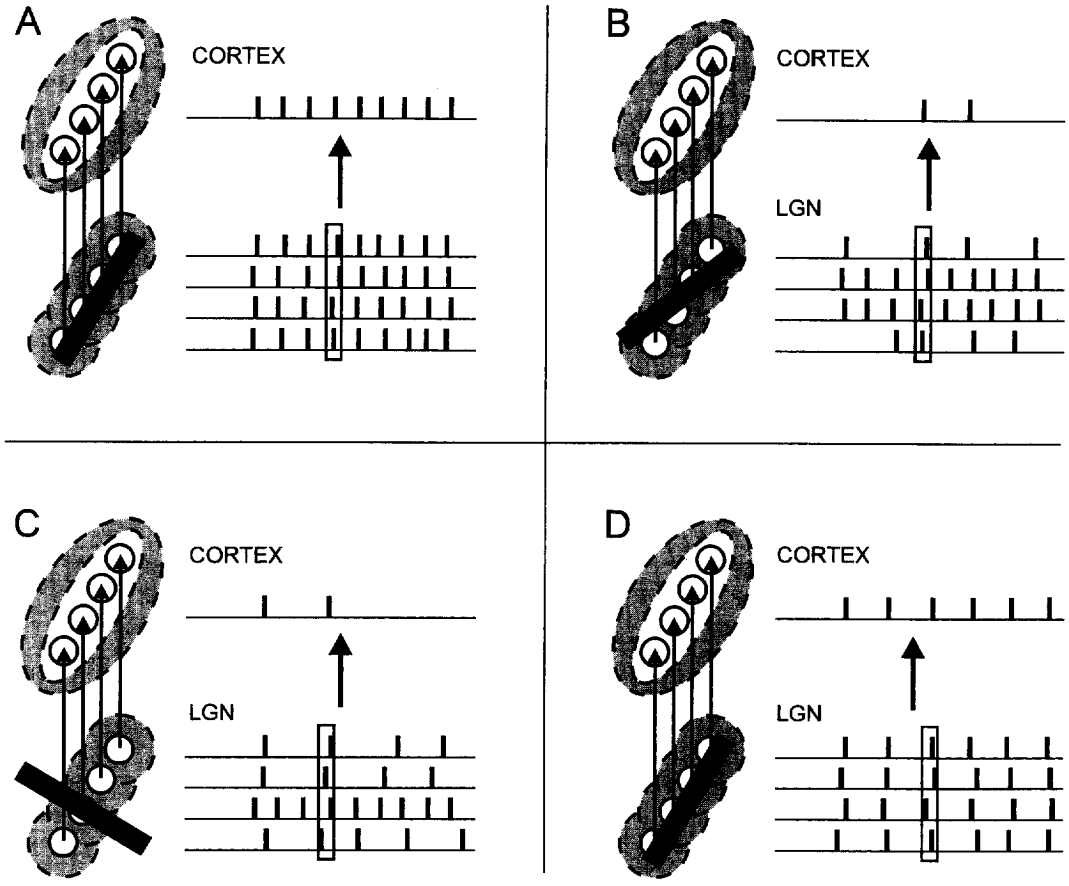

Fig. 26. Schematic illustration of the advantage of temporally structured activity for a process that uses spatial integration to extract specific stimulus features like the orientation of a contrast border. The elongated, orientation-sensitive receptive fields emerge from the orderly convergence of LGN inputs as proposed by Hubel and Wiesel (1962). (A) A light bar of optimal orientation causes a high activity level in all the participating LGN units and leads to a strong cortical response. If the cortex cell has a short time window for the integration of the afferent input (coincidence detector) and if the LGN units show a similar stimulus-dependent temporal distribution of the action potentials, also the cortical output should reflect the temporal structure of the LGN inputs. (B) and (C) A less optimal oriented bar causes a deviating activity pattern in some of the LGN units. If, in this extreme case, all the LGN inputs have to fire within the small time window to elicit an action potential in the cortex cell, then the cortical output is strongly reduced and the time structure of the input is lost. In the case of a long time window for integration, the cortex cell would show a somewhat stronger response, at least in case (B). (D) Also in the case of an optimally aligned but weaker stimulus (lowered contrast), the cortical response again follows the temporal pattern of the LGN input and shows a much better response than to the strong but misaligned stimulus although the mean input activities are similar [compare (B) and (D)]. This mechanism could increase response specificity even without the contribution of lateral inhibitory interactions in the cortex.

of cat and monkey is often characterized by an oscillatory pattern. Furthermore, two or more cells stimulated by the same stimulus or two stimuli sharing features like the border of orientation and the direction and the velocity of motion, show a synchronous firing within the sub-millisecond range (Eckhorn *et al.*, 1992, 1993a,b; Engel *et al.*, 1992; Gray *et al.*, 1989). Synchronization of activity was found for cells within the same area and for cells of different areas of the same or opposite hemisphere (see Section 5). It has been suggested that oscillatory activity is generated by the cortex itself and that cells responding to the same object quickly synchronize their firing via horizontal connections. The spatio-temporal dynamics of such a network have been studied with the aid of computer simulations which demonstrate that a network of reciprocally connected cells can quickly synchronize at the basis of oscillatory activity within the gamma range (see Chawanya *et al.*, 1993; Gerstner *et al.*, 1993; van Hemmen *et al.*, 1992; Hopfield and Herz, 1995; von der Malsburg and Schneider, 1986; Niebur *et al.*, 1993; Niebur and Koch, 1994; Nischwitz and Glünder, 1995; Opara and Wörgötter, 1996; Schillen and König, 1994; Sompolinsky *et al.*, 1990). The potential for oscillatory activity might be intrinsic to the majority of cortical cells and its expression might be controlled by afferent or modulatory

inputs. The oscillatory activity, however, might also be initiated by a few "pacemaker" cells which could influence larger cell populations. Indeed, Gray and McCormick (1996) found some cortex cells that produce oscillatory activity around 40–50 Hz when stimulated (chattering cells). Although oscillations around 40–50 Hz are the most frequently described phenomenon, oscillatory activity in the visual cortex of cats and monkey can span the full range of gamma (30–80 Hz) and beta (15–30 Hz) frequencies of the EEG. Thus, single cortical oscillators either operate at different frequencies or the control of oscillation is a network feature. The factors, however, that control the establishment and frequency of an oscillation are poorly understood. In some cases, a stimulus-dependent variation of the oscillatory frequency was found (Bauer *et al.*, 1995; Eckhorn *et al.*, 1993b) and brainstem arousal centers seem to control the strength of the oscillatory activity (Munk *et al.*, 1996). Owing to these and other findings, it is also reasonable to suggest that the oscillatory pattern of activity is under the control of, or is even introduced by, afferent activity.

With intracellular recordings of postsynaptic responses of cells in cat visual cortex, Bringuier *et al.* (1992) could demonstrate that the sub-threshold afferent inputs already display some kind of oscillatory pattern. In this study, the presence of oscillations was tested against some of the most prominent properties of cortical processing, but the authors did not observe any correspondence; i.e. the oscillatory activity was not stronger for the optimal orientations and the preferred directions of moving stimuli compared to non-optimal conditions. Hence, they concluded that these oscillations evolve from subcortical responses to visual stimuli and not from intra-cortical processes. An oscillatory pattern of activity in the gamma range also was described for cat lateral geniculate activity (Doty and Kimura, 1963; Funke and Wörgötter, 1995; Ghose and Freeman, 1992; Neuenschwander and Singer, 1996; Podvigin *et al.*, 1992). Most of these authors found the rhythmic geniculate activity to be associated with visual stimulation. Ghose and Freeman (1992) stated that oscillatory activity is most prominent during spontaneous activity and rarely found during visual stimulation. However, these authors have used moving light bars for stimulation which seem to be less efficient to induce oscillatory activity in the LGN than stationary, contrast-modulated stimuli or rather slowly moving objects. Indeed, cortical oscillations have been reported to occur predominantly with stimuli moving slowly across the receptive field (usually less than 10 deg/sec, Brosch *et al.*, 1995; Eckhorn *et al.*, 1993b; Kreiter and Singer, 1996 or of "appropriate or preferred velocity" see Engel *et al.*, 1990, 1991b; Gray *et al.*, 1989). Ongoing cortical oscillations are indeed inhibited when transient responses are elicited by fast accelerations of the moving texture (Kruse and Eckhorn, 1996). These results indicate that tonic activity induced by stationary or slowly changing stimuli might be important for the development of stretches of temporally structured (oscillatory) activity in LGN and cortex. Flashed stimuli have also been reported to induce oscillatory activity in cortical mass potential (EEG) recordings (see Basar, 1980). It is, however, also conceivable that moving objects elicit oscillations different from those induced by stationary stimuli. Furthermore, it has been argued that oscillations in one frequency range can be a harmonics of an oscillation in another range (Jürgens *et al.*, 1995).

Using high contrast stimuli, multi-modal spike interval distributions of LGN activity were found to show peaks at on average 8, 16 and 24 msec, corresponding to a firing rate of 125, 63 and 42 Hz, respectively (Funke and Wörgötter, 1995). Cortical oscillations were primarily found between 30 and 90 Hz, a range consistent with the frequencies of the dominating geniculate interval modes. Oscillation frequencies above 90 Hz, often found in the LGN for a dominating fundamental interval mode around 7 msec, might be lost in the cortical network or they are less detectable because they are more strongly affected by temporal jitter. In addition, it has to be considered that larger objects, like a bar, also stimulate the inhibitory surround of peripheral receptive fields and thereby accentuate the higher-order interval modes in geniculate activity often strongly reducing the number of the short fundamental spike intervals.

The second aspect of cortical time structure is the synchronization of activity. Coherent activity has been assumed to play an important role in the process of feature binding. A single object induces synchronous activity in a group of cells (cell assembly), several simultaneously presented objects then lead to the formation of a corresponding number of cell assemblies that show synchronous activity for those members that represent one object but uncorrelated activity for members of assemblies representing different objects. One cell can also participate in the group discharges of more than one assembly. The formation of such coherently active cell assemblies can, in principle, be attained in two ways. It could be either controlled by the characteristics of the afferent input or by the activity of a higher-order instance involved in object recognition. The separation of rather "simple" objects, like lines or surfaces of uniform brightness, could be achieved by borders of contrast, color or aspects of motion. It is reasonable to suggest that this could be directly derive from the pattern of afferent input. More complex objects, like the famous dalmation dog in front of a patched background (shown in Eckhorn, 1994), cannot be simply segregated using the pattern of afferent input. In this case, additional information presumably delivered by an area concerned with recognition and memory for objects is needed.

Synchronization of activity controlled by the afferent input pattern can be achieved in different ways. For cortex cells with overlapping or adjacent RFs it can be assumed that, due to the huge di- and convergence of thalamic axons, both cells share a number of common geniculate inputs. Stimulation of both RFs with one object will then cause a fraction of synchronous activity due to the common input from the LGN. A coincidence process presumed for cortical cells (König *et al.*, 1996) would even pronounce this effect. Synchronization of activity over longer distances could be achieved by lat-

eral intra-cortical connections but also through afferent inputs of similar temporal structure and sufficient degree of synchronism. In a recent study, Neuenschwander and Singer (1996) could demonstrate that retinal ganglion cells and LGN relay cells driven from the same eye show synchronous oscillatory activity when stimulated with large uniform objects or moving gratings. Correlated activity was found for receptive fields spaced more than 10° apart, but is most pronounced for ganglion cells with overlapping receptive field centers (Meister *et al.*, 1995). Mastronarde (1989) has shown that neighboring retinal ganglion cells tend to fire synchronously in the sub-msec range, especially in the case of cell pairs of the same type (Y–Y, X–X, On–On, Off–Off). In addition to these indications for a peripheral origin of synchronous activity, evidence has been found for a contribution of the corticofugal feedback in the enhancement of temporal correlation in the LGN. Sillito *et al.* (1994) have shown that the activity of a pair of cat LGN relay cells is partly synchronous when the RFs of both cells are stimulated with a moving bar or grating, thus a stimulus type suitable to elicit spatially coherent activity in the cortical network but possibly also in the afferent input (Neuenschwander and Singer, 1996). However, correlation of geniculate activity was strongly reduced after complete removal of the visual cortex, favoring a cortical origin of synchronization in this study (Sillito *et al.*, 1994). Using reversible inactivation of visual cortical areas 17 and 18 either by cooling the cortex or by applying GABA to layer VI, the site of origin of cortico-geniculate projections, Funke *et al.* (1996) could demonstrate that the cortico-geniculate feedback controls the temporal accuracy of retino-geniculate transmission. During cortex inactivation, the temporal jitter of spike intervals in the LGN increased, leading to a broadening of peaks in the multi-modal interval distributions. A computer simulation of this process furthermore predicted a loss of correlation between the activity of individual cells as has been found experimentally by Sillito *et al.* (1994).

The temporal structure of sensory activity could be even relevant for some psychophysically observed processes like the "filling-in" of visual structures in a region of scotoma. Filling-in not only works for isoluminant or isospectral surfaces but also for patterns. One physiological example is the blind spot in each eye resulting from the exit of the optic nerve. Even with monocular view the blind spot is not perceptible because it is filled by the pattern of the surrounding areas. It is rather unlikely that a filling-in with a pattern is realized by lateral inputs using only a rate code. A temporal code, however, could carry information about the spatial distribution of the contrast surrounding the lesion and could thereby induce the illusion of a pattern inside the region of scotoma.

9.2. The Importance of the Cortico-geniculate Feedback for the Maintenance and the Modulation of the Temporal Structure

A fundamental prerequisite for the analysis of temporally structured activity by a cortical coincidence detector is a sufficient temporal correlation of the incoming signals. If the spike trains generated by retinal ganglion cells carry sensory information encoded in the temporal pattern of the spike sequences, this pattern has to be preserved to prevent loss of information. However, due to synaptic noise and different delays involved in postsynaptic integration, the jitter of spike intervals should increase along the ascending pathway, leading to a blurring of the temporal order of the spikes. Unexpectedly, in most cases of simultaneous recordings of retinal and geniculate activity (LGN spike and S-potentials, see Kaplan and Shapley, 1984), we found that the geniculate spike interval distribution was somewhat sharper than that of the S-potential (see Fig. 27). Since it is very unlikely that this effect results from the process of retino-geniculate transmission itself, we proposed a contribution of one type of the numerous extraretinal inputs to LGN relay cells. The cortico-geniculate feedback appeared to be the most suitable candidate for this process. Geniculo-cortical, intra-cortical and cortico-geniculate projections show a high degree of di- and convergence (Freund *et al.*, 1985; Gilbert and Wiesel, 1979; Humphrey *et al.*, 1985; Murphy and Sillito, 1996; Robson, 1993), which could serve to correct the timing of geniculate spikes via spatial averaging procedures. Recently, it has been shown that the temporal correlation (synchrony) between cat LGN cells was weakened when the primary visual cortex has been removed (see also Sillito *et al.*, 1994).

Due to re-setting effects by a new stimulus situation it can be expected that the temporal correlation is strongest for the activity directly following stimulus onset. During long-lasting tonic activity the correlation may then progressively deteriorate. This has been shown by Mainen and Sejnowski (1995)

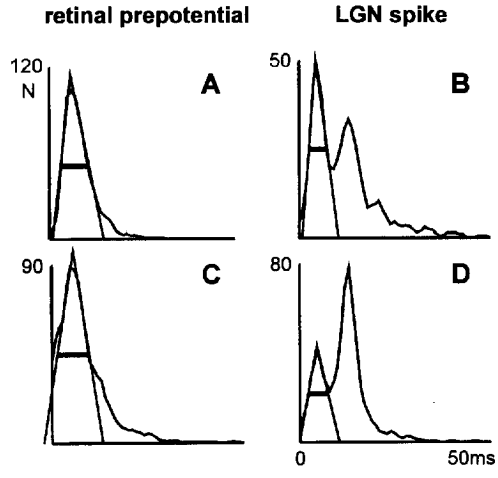

Fig. 27. The ISIHs of two pairs of simultaneously recorded retinal prepotentials and the corresponding spikes elicited in the LGN target cells (both recordings from X-On cells). The activity of the LGN cells is lower than that of the corresponding prepotentials and higher order peaks are observed only for the LGN. Triangles fitted to the peaks and horizontal bars plotted at half height of the peak demonstrate that the ISIH peaks of the retinal prepotentials are wider than those of their target cells.

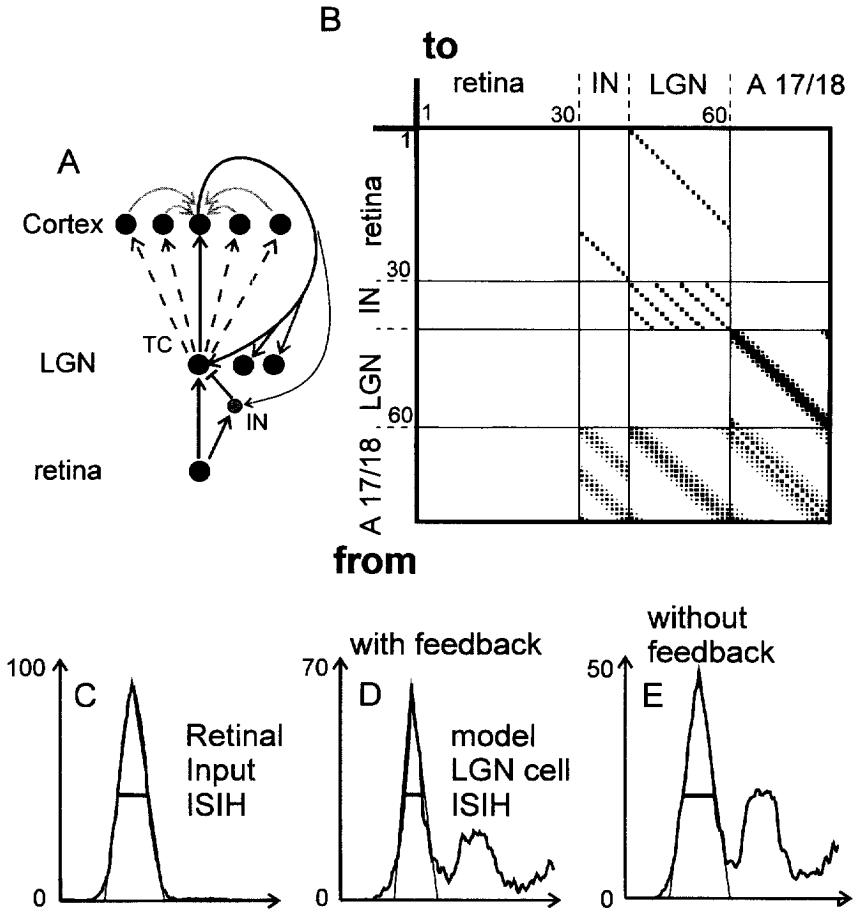

Fig. 28. Part (A) of this figure shows the schematic set-up of the retino-thalamo-cortical pathway in the computer model: a retinal ganglion cell projects to a single LGN relay neuron, that also receives inhibitory input from an LGN interneuron. The primary thalamo-cortical loop is indicated by the solid black arrows. The dashed arrows show additional projections of the same relay neuron, and the shaded cortical arrows represent intra-cortical feedback. The loop is closed by a cortico-thalamic back-projection to the topographically aligned LGN relay neuron (thick black arrow), its neighbors (shaded arrow) and to the inhibitory interneuron, as well (thin black arrow). The spatial structure of the connections is depicted in the connection matrix shown (B) for a total of 80 cells in the retino-thalamo-cortical pathway: Each row and each column contains 80 entries, representing the connection from cell x (row x) to cell y (column y). The strength of a connection is encoded by a black square at location (x,y), whose size corresponds to the strength of the projection from cell x to cell y. In this set-up, there are 30 retinal (ganglion) cells, of which the first 20 project to LGN relay neurons and the last 10 to inhibitory interneurons. The next 10 neurons are inhibitory interneurons, projecting pairwise on the LGN relay cells. Following are 20 LGN relay neurons, that project to also 20 cortical cells according to the indicated gaussian-shaped spatial weighting functions. The 20 cortical cells project onto other cortex cells and back to the thalamus. (C)–(D) Show the reduction of the temporal dispersion of LGN spiking obtained from the computer model similar to that seen in the ISIHs of real LGN cells (e.g. see Fig. 29). (C) The ISIH of the retinal input. (D) The corresponding ISIH of the target LGN cell in the presence of inhibition leading to a partial elimination of spikes and the generation of higher order interval peaks. The corticofugal feedback is active in (D). (E) The ISIH of an LGN cell in the absence of corticofugal feedback. We observe the expected reduction of fundamental intervals, and hence the size of the primary peak in the LGN [(D) and (E)]. The shape of the fundamental peak remains almost unaltered between the retinal input (C) and the LGN response in the presence of inhibition but without feedback (E). During active feedback, the peak becomes much sharper [(D); compare triangles and horizontal bars].

using long-lasting depolarizing voltage steps repeated several times while intracellularly recording from neocortical cells in a slice preparation. According to this observation, one can expect that two neighboring cells simultaneously excited by the same stimulus will show a progressively declining strength of correlation in the spiking activity. Lateral interactions within the cortex and the cortico-geniculate feedback projection could perform an integration of activity in a way that finally improves the correlation of activity also for long-lasting trains of action potentials. Since processes involving large neuronal networks are difficult or even impossible to measure by conventional electro-

physiology, we designed a detailed computer model to simulate the activity in a reciprocally connected geniculo-cortical network (see Fig. 28). A total number of 80 neurons was sufficient for this approach because the main intention was to analyze the effect of the network activity only considering the temporal aspect of activity. It was not necessary to implement spatially organized receptive fields selective for stimulus orientation. Nevertheless, also receptive fields employed with distinct spatial characteristics can perform the same operation (see Fig. 26).

According to the electrophysiological findings, the retinal input to LGN relay cells and interneurons was simulated by a uni-modal spike interval distribution based on a fundamental firing frequency and with the spike intervals jittered by 25% of the mean spike interval length. Feed-forward inhibition by LGN interneurons produced a multi-modal spike interval distribution in LGN relay cells very similar to those found for cat geniculate activity (Funke and Wörgötter, 1995). With intra-cortical interactions and an active cortico-geniculate feedback, the geniculate interval peaks were indeed somewhat sharper (on average 25%) than those of their retinal afferents [Fig. 28(C)–(E)]. The peaks significantly broadened when the feedback was switched off. A second aspect of cortico-geniculate feedback is the gating of retino-geniculate transmission. Without the facilitatory cortical feedback, a substantial number of retinal spikes will not be transmitted to the cortex, due to the action of the intra-geniculate inhibition. This leads to a dominance of the second-order intervals (second peak). The excitatory input from the cortex is able to override partially the inhibitory potentials, thereby pushing additional retinal EPSPs above spike threshold. The result is a reduced number of second-order intervals and an increased number of fundamental intervals. During active corticofugal feedback, the number of fundamental intervals usually exceeded the number of higher-order intervals and the mean rate of transmission was higher in total.

To test whether the corticofugal pathway is really involved in the improvement of the temporal transmission accuracy, we reversibly inactivated the primary visual cortex (area 17/18) of anesthetized cats while recording the visual responses of LGN relay cells. Figure 29 demonstrates the effect of removing the cortico-geniculate feedback for the spike interval distribution of three LGN relay cells before (left) and during (right) inactivation of the visual cortex either by GABA application or by cooling. A comparison of the left and right histograms shows the two main effects of cortical blockade: the relative number of the higher-order intervals increases relative to the shorter intervals and the individual peaks are getting broader. In 24 of 44 cases, the peaks widened at half-height on average by 1.44 ± 0.79 msec (24%), in 17 cases the effect of cortical blockade was insignificant (less than 7.5% change) and only in three cases, the peaks became sharper (on average by 29.3%). In 31 cases, the spike interval distribution shifted to peaks of higher order. Thus, the experimental findings quite sufficiently support the predictions made by the computer model.

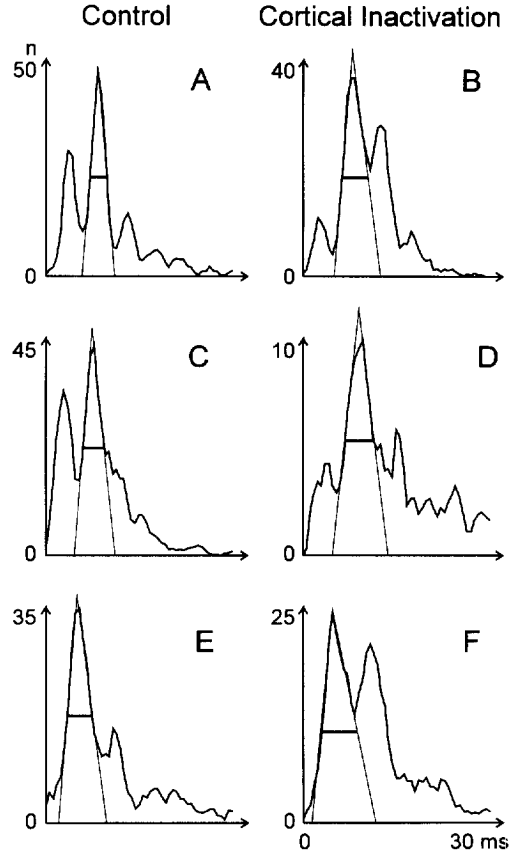

Fig. 29. Three ISIH pairs from LGN cells before and during cortical inactivation obtained from cross-sections through the corresponding intervalograms at 950 msec, (all recordings from X-On cells). During cortical inactivation, higher-order peaks dominate and the peaks get wider than before (compare triangles and horizontal bars).

An active corticofugal input to LGN cells also enhanced the correlated firing in populations of LGN cells. Figure 30 shows a result of the model. Cross-correlograms obtained from the activity of two neighboring LGN relay cells clearly demonstrate a higher degree of synchronous spike discharges with the corticofugal input being active. Experimental support for the model results is given by the study of Sillito *et al.* (1994): correlated firing of cat LGN relay cells during simultaneous stimulation of their receptive fields with the single bars of a moving grating was considerably reduced when the visual cortical areas 17, 18 and 19 had been removed.

So far, we have demonstrated that a system consisting of convergent and reciprocal connections is able to prevent the deterioration of temporally organized spike patterns by noise or other uncorrelated inputs. In the electrophysiological experiments, it is impossible to measure the mechanisms which actually perform the temporal correction of spike timing directly. In this case, the model is a reliable supplement. Figure 31 shows membrane potential traces of a model LGN relay cell for individual inputs and their interactions (for details see legend of the

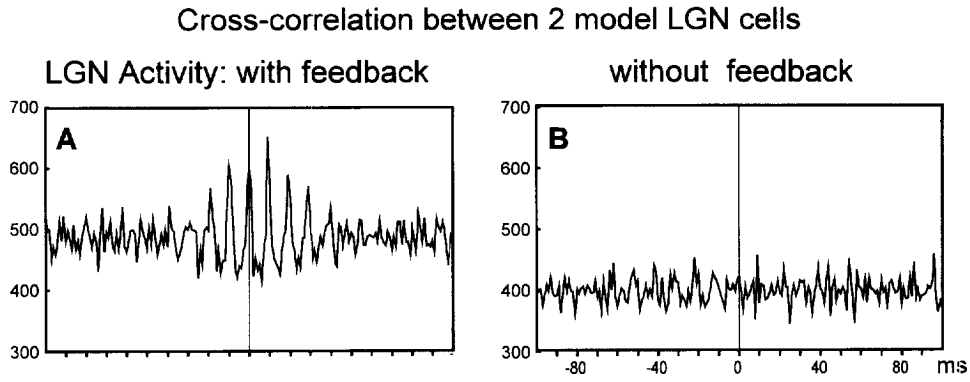

Fig. 30. This figure demonstrates that during active corticofugal feedback two neighboring LGN cells in the model will synchronize their activity. The oscillation frequency thereby reflects the fundamental interval length.

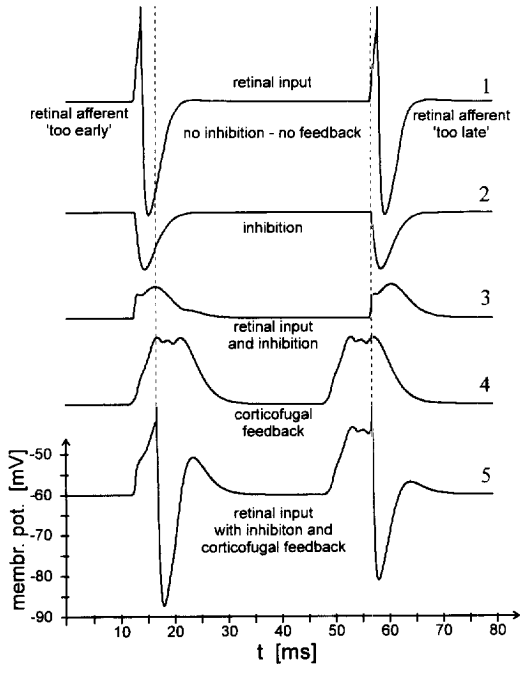

Fig. 31. Presumed intracellular mechanism for the reduction of the temporal dispersion of LGN spike trains as seen in the computer simulations. The top trace (1) shows the action potentials in a model LGN cell generated by a retinal input that is slightly ahead (left-hand side) or slightly delayed (right-hand side) with respect to the inputs to neighboring LGN cells. In the case where the generation of the action potential is masked by inhibition (trace 2)—presumably from thalamic interneurons—the combined input would remain subthreshold (trace 3). However, the corticofugal feedback (trace 4), representing a temporally averaged bulk signal, further modulates the membrane potential of the LGN cell and leads to a temporal shift of the misplaced action potentials (trace 5) towards the timing represented by the bulk signal (dotted line). In addition, most *totally* misplaced inputs (not shown) will not, in the presence of inhibition, be raised above threshold by the (temporally mismatching) corticofugal feedback. Thus, in these cases, spike generation is prevented, thereby further reducing the temporal dispersion of the LGN spike train.

figure). When the retinal EPSP is affected by inhibitory inputs or other fluctuations of the membrane potential it can either remain subthreshold or it reaches the spike threshold at different points during the rising phase. The result is an increased jitter in the timing of LGN spikes compared to the retinal input. The cortical input to LGN relay cells can improve the spike timing in two different ways: (i) the depolarization caused by the excitatory cortical input brings the cell membrane closer to spike threshold when the retinal input arrives and the EPSPs crosses the spike threshold more often during the steep part of its rising phase; and (ii) the di- and convergence pattern of the cortico-geniculate projection and the periodicity of the cortical input induced by the preferred spike intervals leads to a periodic gating of retino-geniculate transmission in adjacent cells, thereby enhancing the amount of correlated activity. Less correlated retinal inputs are blanked out during the periods between corticofugal facilitation.

A tonic depolarization (mechanism 1) can sharpen the interval peaks to some extent but cannot enhance the correlation in the activity of neighboring LGN cells. In the case of periodic corticofugal activity (mechanism 2), the convergence of corticofugal inputs onto an LGN relay cell results in a composite EPSP as long as the inputs are sufficiently synchronous. Some degree of correlation in geniculate and cortical activity is already given by the stimulus onset and the presence of the preferred spike intervals for a constant input by the stimulus. However, due to some fundamental jitter between the different inputs, the summed corticofugal EPSP is not sharp but results in a flat and broad subthreshold depolarization. Nevertheless, this broad potential is suitable to correct the timing of the LGN spike induced by the retinal input towards the mean spike interval length represented in the corticofugal population input.

The findings described above highlight one of several possible functions of the cortico-geniculate feedback. Modulation of the temporal structure of visual responses either at the level of spike patterns (Funke *et al.*, 1996; Sillito *et al.*, 1994) or at the

level of the overall waveform of the response (McClurkin *et al.*, 1994) is one aspect of corticofugal control, gating of retino-geniculate transmission for the binocular integration (Schmielau and Singer, 1977) and the adjustment of the spatial properties of LGN receptive fields (Cudeiro and Sillito, 1996) are additional aspects. The latter processes may be either independent of the temporal modulation of geniculate activity, or they may also use a mechanism based on the temporal structure of activity. In a theoretical study Köhn and Wörgötter (1996) could demonstrate that the cortico-geniculate feedback loop can also be used to shorten the latency of responses to novel stimuli (a sudden change in contrast inside the RF).

10. TRANSDUCTION OF A RATE CODE TO A TEMPORALLY STRUCTURED CODE IN THE LGN?

What could be the particular role of the LGN regarding temporal encoding? One can speculate that the LGN is a connecting link between the rate code produced by the peripheral sensors and the temporal codes involved in central area processing strategies. The geniculate time structure seems to originate in the retina: in a contrast-dependent way, retinal ganglion cells generate spike sequences of a rather constant firing frequency which more or less quickly slows down as a consequence of adaptational processes. Lateral couplings between individual ganglion cells via the horizontal retinal network favor the synchronization between neighboring ganglion cells (Mastronarde, 1989; Meister *et al.*, 1995). Large stimuli of uniform contrast have been shown to promote the occurrence of synchronous oscillatory activity in retina and LGN (Ariel *et al.*, 1983; Laufer and Verzeano, 1967; Neuenschwander and Singer, 1996) and also in the cortex (Bauer *et al.*, 1995). This way, the retina seems to initiate a temporally structured spiking activity, but the code is rather simple: a discrete firing frequency (oscillatory frequency) represents stimulus contrast while several objects of uniform brightness cause a temporal coupling of the activity. The temporal structure of geniculate activity is more complicated since it is composed of more than one firing frequency leading to a multi-modal spike interval distribution. The dominating spike intervals are multiples of a fundamental interval (fundamental firing frequency) that is already present in the retinal input (Funke and Wörgötter, 1995). Therefore, this visually elicited pattern of geniculate activity is not a reflection of a rhythm intrinsic to the LGN relay cells. The basic temporal pattern of the retinal input is still preserved in geniculate activity but the temporal structure of the spike trains is enriched by the generation of a considerable number of spike intervals of multiple length. The relative number of multiple intervals depends on the strength of the inhibitory inputs. This is controlled by the stimulus itself or by modulatory inputs like those from cortex or brainstem. According to our findings, the LGN modulates the retinal input pattern in three different ways: (i) via a stimulus-specific spatial distribution of the interactions between local inhibitory inputs and retinal inputs; (ii) via a state-dependent global variation of the tonic intra-geniculate inhibition; and (iii) via a cortically controlled gating of retino-geniculate transmission associated with the improvement of the temporal correlation of spikes. The first mechanism is used to encode stimulus features. For example, because of the action of the surround inhibition areas within an object of uniform brightness produce a higher number of multiple intervals than the borders of the object. This way, contrast borders can not only be detected by a changing mean firing rate, but also by a changing temporal composition of the activity across the contrast border. Modulations of the tonic intra-geniculate inhibition —either globally by the activity of the arousal centers of the brainstem or focally by the corticofugal feedback (mechanism 2)—change the overall relation of multiple to fundamental intervals and might work as a gating mechanism. The excitatory cortico-geniculate feedback may not only serve to gate the transmission of retinal signals like a searchlight, it also seems to maintain or even increase the accuracy of the spike interval pattern by reducing the temporal jitter that would otherwise increase with each synaptic transmission (mechanism 3).

In addition, LGN neurons exhibit a stimulus-dependent response dynamic, which is reflected in the temporal change of the mean firing rate (McClurkin *et al.*, 1991b; Wörgötter and Funke, 1995). This dynamic seems to be based on the stimulus-locked occurrence of distinct stretches of spike patterns not visible in the retinal spike trains (Wörgötter and Funke, 1995). Therefore, it can be assumed that also the overall temporal waveform of the light response is generated at the level of the LGN. Inhibitory interactions established by local interneurons as short-range circuits and by PGN neurons in a long-range lateral fashion seem to be ideal mechanisms to shape the visual response. Even the cortico-geniculate feedback could shape the gross temporal waveform of geniculate responses via a temporally varying gating process. Some indications for such a process are given by the study of McClurkin *et al.* (1994), where the authors show that the richness of temporal structure and the possible amount of information carried by geniculate visual responses is reduced when the activity in the visual cortex is blocked.

The importance of the rate code generated at the peripheral site of the system seems to be increasingly diminished as soon as "higher cortical areas" along a sensorimotor pathway are approached. Neurons of the primary visual areas still respond more vigorously to optimal than to suboptimal stimuli but in some cases, different stimulus situations may induce only marginal changes in the mean firing rate but a clearly different temporal correlation between units responding to the common stimulus (Engel *et al.*, 1992; Freiwald *et al.*, 1995; Kreiter and Singer, 1996). Information processing in the frontal cortex might even work without significant changes in mean firing rate. By simultaneously recording single unit activity at multiple sites in the frontal cortex, Abeles and coworkers described distinct spatio-temporal activity patterns which occur repetitively with

high precision. They introduced the synonym "synfire-chain" (Abeles, 1991; Abeles *et al.*, 1993, 1994) to describe such a pattern of activity. The idea is that a single volley of activity (at least one action potential) that occurs synchronously in a set of spatially distributed neurons reflects one step of information processing. This could represent a distinct internal state of the system and could trigger a behavioral response.

The often found oscillatory nature of peripheral and cortical activity could also be interpreted as a pacemaker that controls serial steps of information processing in the brain. Based on psychophysical studies, Pöppel (1994) argued that the brain uses a 30 msec rhythm during the performance of cognitive and motor tasks. Any decision made by the brain seems to be dependent on a neuronal process that is characterized by sequential information processing quanta of approximately 30 msec. Reaction times and the preferred latencies of saccadic eye movements show a multi-modal distribution with 30 msec inter-modal distances. Visual thresholds oscillate at about 30 msec and serial scanning of similar objects in a visual scene (without eye movements) takes about 30 msec for each object. Two colors or parts of a word each presented for 6 msec within less than 30 msec are merged to one object but are seen as two independent objects when separated by more than 30 msec (for review, see Pöppel, 1994).

Before we close this section on the significance of temporally structured activity in the LGN, we would like to give a short comment on a review on sensory coding by Field (1994). He argued that sensory systems perform some kind of data compression by reducing the redundancy in the sensory signal either by "compact coding" or by "sparse coding". Although our data do not fit completely to this scheme, the introduction of a temporal code might be one way to finally end up with a sparse code (see also Palm, 1991 on "sparse" storage and the capacity of networks). The temporal waveform of the sensory response itself can be taken as some kind of compact code, since it includes more information than a code simply based on the mean firing rate (see also McClurkin *et al.*, 1991b). This view is also supported by Meister (1996) and Meister *et al.* (1995) for the concerted firing of retinal ganglion cells. In his opinion the retinal output is not a simple collection of independent lines, each transmitting information only about local brightness. In a multiplexed fashion the ganglion cell output also incorporates information about the spatial distribution of light pre-processed by horizontal interactions in spiking amakrine cells. For example, the synchronous firing of two neighboring ganglion cells signals that a stimulus is not within one or the other receptive field but in between the two or covering both at the same time.

No remarkable reduction in the redundancy of sensory information by spatio-temporally correlated activity seems to take place in the retina and the LGN; however, the integration of these activity patterns by a cortex cell that acts like a coincidence detector (see also König *et al.*, 1996) would lead ultimately to a reduced number of active elements, since the cell fires only if the input pattern fulfills the criteria for temporal correlation (synchrony). During the course of this review, the reader may have realized that the sensory coding of physical parameters by the brain displays multiple facets. Some of these are rather simple, i.e. the encoding of stimulus intensity by a rate code; others are more sophisticated, for example the variable formation of stimulus-specific cell assemblies firing in concert. Some aspects, like the presence of oscillatory patterns, are long-known features of sensory activity, recently revived in the course of establishing new concepts of information processing for the brain.

The generation and the processing of temporally structured activity may be an important and efficient neuronal mechanism to analyze sensory information and to solve specific problems like the binding and segregation of objects in a complex visual scene. On the other hand, oscillatory and correlated activities may be features that emerge as an epiphenomenon of the processes associated with the basic electrical properties of single neurons or neuronal networks. Nevertheless, the exact timing of activity seems to play an important role in sensory processing because mechanisms like the depth perception and the perception of apparent motion critically depend on the timing of stimuli and responses. For example, a potent illusion of three-dimensional depth is induced if motion of a pendulum in a frontal plane is viewed with a neutral filter in front of one eye (Pulfrich stereo-phenomenon, Lit, 1949). In another example, a vernier offset for apparently moving bars can be induced if the upper part of the bar is displayed shortly before the lower (Burr, 1979). The acuity for the detection of this illusionary offset is almost as good as that for detecting real offsets. The intrinsic differences in the (axonal) transmission delays (e.g. at different retinal eccentricities) can reach values of more than 10 msec. None the less, this vernier offset effect can be induced with stimulus presentation intervals of only 2 msec. Therefore, the system needs to find a way of how to compensate for the intrinsic temporal inaccuracies. If a system is able to handle these problems, it is also conceivable that is uses the exact timing of spikes for fast and efficient processing. Due to the influence of noise, all these mechanisms are probably rather unreliable at the single cell level, but the parallel analysis of several channels can overcome this problem. Thus, the analysis of the temporal structure in the activity of complete cell assemblies seems to be an important analysis mechanism in the brain on which sensorial information processing relies to a large degree even at early stages like in the dorsal lateral geniculate nucleus.

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