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Frequency dependent corticofugal excitation of principal cells in the cat's dorsal lateral geniculate nucleus

S. Lindström and A. Wróbel*
Department of Physiology, University of Göteborg, Box 33031, S-440 33 Göteborg, Sweden

Summary. Excitatory postsynaptic potentials (EPSPs) were evoked in principal cells of the cat's dorsal lateral geniculate nucleus by electrical stimulation of cortico-geniculate fibres. The EPSPs had a pronounced frequency sensitivity. They were barely detectable at stimulation frequencies below 3 Hz but increased dramatically in size at higher frequencies. At 30—50 Hz their amplitude typically exceeded that of EPSPs from optic tract fibres. A prominent EPSP potentiation was also obtained with pair pulse stimulation. The findings are discussed in relation to the hypothesis that the cortico-geniculate system serves as a variable gain regulator for the visual input to the cortex.

Key words: Dorsal lateral geniculate nucleus – Principal cells – Cortico-geniculate system – Frequency enhancement – Cat

Introduction

Principal cells in the dorsal lateral geniculate nucleus (dLGN) of the cat are equipped with two disynaptic feed-back pathways, one inhibitory with the interneurones located in the perigeniculate nucleus (Dubin and Cleland 1977; Lindström 1982; Ahlsén and Lindström 1982) and one excitatory with the responsible cells in layer 6 of the primary visual cortex (Gilbert and Kelly 1975; Tsumoto et al. 1978; Ahlsén et al. 1982; Ferster and Lindström 1983). The function of these systems is still unknown although several different ideas can be found in the literature (Singer 1977; Murphy and Sillito 1987). We have recently proposed that the recurrent circuits serve as variable gain regulators for the transmission of visual signals through the dLGN (Ahlsén et al. 1985). In this model the excitatory and inhibitory systems are viewed as positive and negative neuronal amplifiers that increase or decrease the efficiency of the dLGN relay depending on which system is operative. The imposed gain changes may contribute to the neuronal readjustments underlying psychophysical changes in attention (Singer 1977).

Two requirements have to be fulfilled for the recurrent circuits to function as suggested (Ahlsén et al. 1985). They should be controlled by extravisual inhibitory and/or excitatory inputs to the recurrent neurones and, when operative, they should become more efficient the higher the level of activation. As to the first point, an inhibitory projection from the brain stem to perigeniculate neurones has already been identified (Singer 1973; Ahlsén et al. 1984; Ahlsén 1984) and there is indirect evidence for a similar control of layer 6 cells (Singer et al. 1976; Livingstonc and Hubel 1981). Here we demonstrate that synapses of cortico-geniculate neurones have a built-in frequency amplification that fulfils the second requirement for the excitatory circuit. An abstract of the main findings has been published (Lindström and Wróbel 1985).

Present address: Department of Neurophysiology, Nencki Institute of Experimental Biology, Pasteur 3, PL-02-093 Warsaw, Poland
Offprint requests to. S. Lindström (address see above)

Methods

Experiments were performed on pentobarbital anaesthetized cats (Nembutal, Abbott), initial dose *25—35* mg/kg, supplemented as needed to maintain the animal in a state of slow wave sleep. During recordings the animals were paralyzed with gallamine triethiodide (Flaxedil, May & Baker Ltd), *5—7* mg/kg.h and artificially ventilated to an end-expiratory CO_2 of *3.5%*. To reduce movements of the brain a pneumothorax was performed and the animals suspended by a clamp on a midthoracic vertebra. Body temperature was kept at 38^0C and blood pressure maintained above 110 mm Hg by a slow i.v. infusion of ringer-glucose solution.

The visual pathways were stimulated electrically by cathodal constant current pulses (0.2 ms duration) applied to a tungsten electrode in the optic tract or to any in a row of similar electrodes, inserted 2—4 mm into the visual cortex at the border between areas 17 and 18. Evoked potentials and visual responses were used for proper placement of the electrodes. For visual stimulation the pupils were dilated, accommodation paralyzed and the eyes focused by appropriate contact lenses on a tangent screen *1.5* m in front of the animal. Glass micropipettes filled with 3 M potassium or sodium acetate were used for extra- and intracellular recordings from dLGN principal cells, the sodium filled electrodes usually being the best. For intracellular recordings the electrodes had their tips broken back to a diameter of about *0.5* µm, giving a resistance of about *15—30* MÙ. The electrodes were advanced to the dLGN through the overlaying cortex. This resulted in a rather high coupling capacitance which together with the high electrode resistance reduced the frequency response of the recording system to about 1 kHz. Principal cells of the dLGN were identified by their location in laminae A and Al, by their receptive field properties and by antidromic activation from the cortex.

Results

Monosynaptic EPSPs were evoked in principal cells by electrical stimulation of cortico-geniculate fibres in the cortex. As described before (Ahlsén et al. 1982) the EPSPs had fairly long latencies (2.7—4.0 ins) and high thresholds (150—300 ~uA), their long latency and high threshold being explained by the fine caliber of the cortico-geniculate axons (Ferster and Lindström 1983; Robson 1983). The cortex stimulation also evoked antidromic spikes and disynaptic recurrent IPSPs in the recorded principal cells. These latter responses typically had lower thresholds from the optimal stimulation electrode and shorter latencies than the EPSPs evoked by cortico-geniculate fibres (Ahlsén et al. 1982). Thus, strong cortex stimulation produced a quite complex response in the principal cells with superimposed postspike afterhyperpolarizations, recurrent IPSPs and cortico-geniculate EPSPs (Fig. lA, cf. also Fig. 1 in Ahlsén et al. 1982).

The different response components could easily be differentiated by careful graded stimulation through the cortex electrode. Since individual principal cells receive convergent excitation from corticogeniculate neurones in a larger cortex area than the termination zone of their own axons (unpublished observations), it was often possible to obtain recordings without antidromic spikes by using another stimulation electrode than the optimal one (Figs. 1G and 2). This technique could not be used to avoid the recurrent inhibition via antidromically activated principal cell axons and perigeniculate neurones since the inhibition had about the same wide convergence as the cortico-geniculate excitation. More than that, stimuli strong enough to activate corticogeniculate axons produced additional IPSP compo

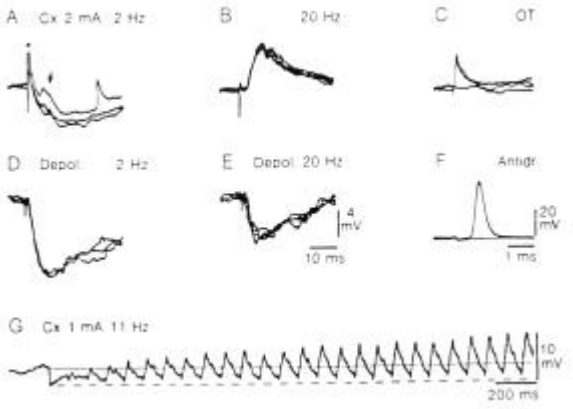

Fig. 1A—G. Increase of cortico geniculate EPSPs by repetitive stimulation. **A,B** Synaptic responses evoked in a principal cell by electrical stimulation of the visual cortex (Cx) at 2 mA. The stimulus repetition rate was 2 Hz for **A** and 20 Hz for **B. C** Monosynaptic EPSP evoked by optic tract (OT) stimulation. **D,E** Same stimuli as in **A,B** but with the cell depolarized by a steady current injection 1 nA) through the ı ecording electrode. **F** Antidromic spike evoked by cortex stimulation at threshold intensity. The spike amplitude is attenuated by an insufficient frequency response of the recording system (see methods). Antidromic spikes were evoked also in **A,B** and **D,E,** but except for the record in A (asterisk), the soma invasion was blocked. Calibration bars in **E** are for **A—E. G** Continuous recording of EPSP enhancement in another cell. Note the recurrent IPSP evoked by the first stimulus and the gradual increases in EPSP amplitude with successive stimuli. Thin line indicates mean resting membrane potential level, dotted line peak voltage for the first recurrent IPSP

nents evoked by corticofugal excitation of inhibitory interneurons in the dLGN circuitry (Dubin and Cleland 1977; Ahlsên and Lindström 1983; Lindström 1983). To minimize effects due to changes in any of these inhibitory mechanisms, the cells were often hyperpolarized to the IPSP reversal level by current injection through the microelectrode (Fig. 2, inserts). The IPSP reversal level was determined at stimulation intensities below threshold for the cortico-geniculate fibres.

The frequency sensitivity of the cortico-geniculate EPSPs were studied in 48 principal cells with stable recordings. The sample included both X and Y type cells and the findings were similar for both cell types. The EPSPs were barely detectable at stimulation rates below 2—3 Hz even if maximal stimulation intensity (2 mA) was used. The response in Fig. lA is quite typical for an unpolarized cell. Here the EPSP is revealed only by the small irregularities on the early phase of the recurrent IPSP. A quite sizeable EPSP developed in the same cell, however, when the stimulation rate was increased above 5—10 Hz. The record in B shows the steadystate EPSP at 20 Hz, smaller EPSPs were obtained at

10 and 5 Hz. A similar dramatic change in EPSP amplitude with repetitive stimulation was found in all tested cells. The EPSPs increased 4—8 fold and in most cases they became much larger than the maximal EPSPs from retinal ganglion cells (cf. Fig. lB and C).

The transition from a response dominated by the recurrent IPSP (Fig. 1A) to an EPSP dominated response (Fig. 1 B) occurred quite rapidly as illustrated for another cell in Fig. 1G. The first stimulus evoked a large recurrent IPSP but an EPSP was obvious already with the second stimulus. The EPSP grew successively with each stimulus up to a plateau level after about 25 stimuli. The dramatic frequency enhancement of the EPSP was not due to changes in IPSP or EPSP driving forces or to IPSP depression. In the illustrated case, each successive EPSP started from a slightly hyperpolarized level (2 mV), the hyperpolarization apparently caused by a lasting effect from the hidden recurrent IPSPs evoked by each stimulus (cf. first three stimuli). Such a small hyperpolarization would have a negligible effect on the driving force for the EPSP. A change in driving force would neither explain that the peak of the enhanced EPSP by far exceeds the resting membrane potential level (thin line). Since the EPSP starting point is on the positive side of the initial peak IPSP level (dotted line), the depolarization is not due to a reversed recurrent IPSP.

To estimate the high frequency effect on the complex recurrent IPSPs (see above), the cells were much depolarized to enhance the amplitude of the IPSPs at the expense of the EPSPs. The records in Fig. 1D and E were obtained in this way, using the same stimulation parameters as in A and B. In this situation the IPSP was at most halved when the frequency increased from 2 to 20 Hz. We believe that the IPSP depression was smaller and that most of the difference between D and E was due to an increased EPSP current. Recurrent IPSPs, evoked at sub-threshold intensities for the EPSP, were only marginally affected by a similar frequency increase and EPSP enhancement was still seen when cells were polarized beyond the reversal level of the IPSP. If the enhancement effect was due mainly to IPSP depression, the depolarization would in the latter case be smaller at 20 than at 2 Hz. The opposite was always found. We conclude that IPSP changes can only account for a fraction of the observed increase in EPSP amplitudes. This would be true even if the recurrent inhibitory synapses were on proximal dendrites and had a shunting effect on distal corticogeniculate synapses.

Two further observations support the notion that the EPSP potentiation is due to an increased excitatory action of cortico-geniculate fibres. The potentiation process was associated with an increased cell conductance as revealed by tests with small current pulses superimposed on the synaptic responses. We also observed a pronounced frequency enhancement of extracellular field potentials, evoked in the dLGN by cortico-geniculate fibres. This effect was particularly striking after blockade of geniculate inhibitory mechanisms by local injections of picrotoxin. In this situation the change in the field potential can only be explained by an increased excitatory synaptic action. Note that the net effect of repetitive stimulation of corticofugal fibres was always excitation, even with the inhibitory mechanisms intact. In extracellular recordings the principal cells started to fire bursts of spikes corresponding to the enhanced field potential. Thus, the EPSP enhancement outweighted any inhibition generated by corticofugal inputs to geniculate interneurones.

The enhanced EPSP could be finely graded in amplitude by changing the stimulation intensity. Thus, the response was a compound EPSP formed by the convergent action of many cortico-geniculate fibres. The slow rise time and long duration of the response, compared to optic tract EPSPs, is to be expected from the large dispersion in conduction times of cortico-geniculate fibres (ranging from 2.5 to more than 40 ins; Ferster and Lindström 1983, cf. also Tsumoto and Suda 1980) and from their synaptic termination on distal dendrites (Robson 1983). The overall time course of the compound EPSP remained about the same at different frequencies. Therefore, there is no reason to invoke recruitment of unknown polysynaptic pathways to account for the frequency effect. More likely, the entire EPSP enhancement is due to an increased efficiency of the inonosynaptic synapses onto principal cells. When evoked from two stimulation electrodes in the cortex, separated by 2 mm, the EPSP component evoked from one electrode was unaffected by frequency enhancement of the EPSP from the other. Such independence might suggest a presynaptic mechanism for the enhancement. A postsynaptic component involving N-methyl-D-aspartate (NMDA) receptors (Koch 1987) seems to be less important. A pronounced frequency enhancement of EPSP field potentials was obtained also after j.v. injections of the non-competitive NMDA antagonist Ketamine (5—10 mg/kg), although the EPSP amplitude was somewhat reduced (by 10—20%).

The plot in Fig. 2A show in more detail the relative amplitude of cortico-geniculate EPSPs at different frequencies. The measurements were obtained from a different principal cell then the

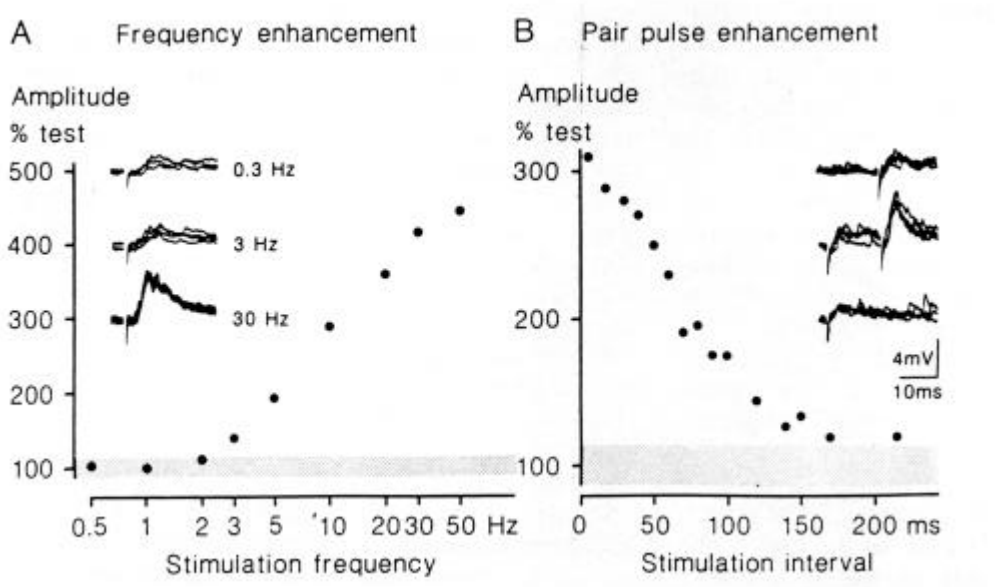

Fig. 2A,B. Frequency enhancement and pair pulse enhancement of cortico-geniculate EPSPs in another principal cell. The EPSPs were evoked by cortex stimulation at 2 mA and the recorded cell hyperpolarized to the reversal level for the recurrent IPSP. The plot in **A** shows the amplitude of maximally enhanced EPSPs at different frequencies in per cent of the mean amplitude at 0.2—1 Hz. In **B** the amplitude of the second EPSP in a pair is plotted in per cent of the unconditioned test response against the stimulus pulse interval. Each point in the diagrams is the mean of at least 20 traces and the hatched fields represent the mean test levels SEM. Calibration bars in **B** refer to all inserted records

recordings in Fig. 1 and the reference low frequency potentials were obtained with the cell hyperpolarized to the IPSP reversal level (insert). With repetitive stimulation there was a monotonic, almost linear increase in EPSP amplitude with frequencies above 2 Hz; the EPSP at 50 Hz attaining an amplitude about *4.5* times the reference level. These transient EPSPs were superimposed on a parallel, steady depolarizing shift of the membrane, away from the IPSP reversal level, at higher frequencies (up to 12 mV at 50 Hz; not illustrated). Due to the change in driving force this depolarization should allow also a sizeable recurrent inhibitory current at the peak of the enhanced EPSP. Accordingly, the plot in Fig. 2A presumably underestimates the EPSP enhancement.

The EPSP enhancement in the same cell following a single preceding stimulation of the cortico-geniculate fibres is shown in Fig. 2B. At short intervals there was a three-fold increase in amplitude of the conditioned EPSP. The pair pulse enhancement decreased at longer intervals along an approximately exponential curve with a time constant of about 100 ins. The frequency enhancement in Fig. 2A is in reasonable agreement with this decay time course. For instance, there was still a small but significant pair pulse enhancement at 215 ins, the longest interval tested. This would correspond to a critical frequency' for EPSP enhancement somewhat below *5* Hz, which is not too far from the observed 3 Hz. Compared to the steady state frequency effect, the optimal pair pulse enhancement was also quite substantial. With a linear summation process an even larger frequency enhancement than in Fig. 2A would be obtained. The discrepancy could easily be explained by the steady depolarization induced by repetitive stimulation (see above).

Discussion

The frequency enhancement of cortico-geniculate EPSPs resembles similar processes at other synaptic sites like the neuro-muscular junction (Magleby 1973) or the perforant path-dentate granule cell synapse in hippocampus (Lomo 1971; McNaughton 1980). For the neuro-muscular junction it has been demonstrated with quantal analysis that the frequency enhancement is due to a presynaptic process (Del Castillo and Katz *1954)*. A comparable analysis is not feasible with the present in vivo system but it seems likely that a similar process is at work. The kinetics of the enhancement is comparable and there is independence between different sets of cortico-geniculate fibres. An enhancement involving postsynaptic NMDA receptors. as hypothesized by Koch (1987). seems less likely in view of the resistance of the effect to NMDA blockade with Ketamine. The main difference with

other systems is quantitative. To our knowledge, no other mammalian synapse has a frequency enhancement as pronounced as the cortico-geniculate synapse. where a 4—8 fold increase is a common finding. A doubling would be a good effect in other systems. The dramatic effect here might be related to an unusually low probability of transmitter release at low stimulation rates. Other observations seem to indicate that the degree of frequency enhancement is inversely related to the "resting" probability of transmitter release (McNaughton 1980).

The extreme behaviour of the cortico-geniculate synapse on principal cells should be considered in relation to the connectivity and possible function of the system. The layer 6 cortico-geniculate cells form one limb in an excitatory recurrent pathway to principal cells from which they in turn receive monosynaptic excitation (Ahlsén et al. 1982; Ferster and Lindström 1983). They also send excitatory collaterals to excitatory simple cells in layer 4, the main cortical targets of dLGN principal cells (Ferster and Lindström 1985a,b), and this synapse too has a pronounced frequency sensitivity. Thus, the layer 6 cells will influence the visual input to the cortex by a combined positive feed-back-feed-forward action onto the excitatory input neurones of the cortex. To maintain stability in such a system it is probably necessary to keep the resting gain low. Otherwise occasional spikes in layer 6 cells might generate an input signal to the cortex that could be interpreted as a real visual event. During visual activation, on the other hand, the gain should be increased in order to influence the input to the cortex significantly. This is exactly what happens with the found frequency enhancement.

We have earlier proposed that the layer 6 cortico-geniculate system might serve as a positive neuronal amplifier and, together with its perigeniculate recurrent inhibitory counterpart, be used in attention control (Ahlsén et al. 1985). The described property of the cortico-geniculate synapses fits nicely into this model. Their frequency enhancement would, by necessity, increase the gain of the input-output relation of the dLGN (cf. Fig. 5B in Ahlsén et al. 1985). It is obvious that such a gain change should occur without a reduction in spatial resolution of the visual signal. This would require a proportional gain change for both centre and surround mechanisms of the principal cell receptive field. The balancing effect might be obtained via the corticofugal projection to both principal cells and intrageniculate interneurones (Dubin and Cleland 1977, Lindström 1983). Earlier observations indicate that the corticofugal system is indeed organized as required with opposite effects on the centre and antagonistic surround (Schmielau and Singer 1977; Tsumoto et al. 1978). In view of this arrangement it is somewhat surprising that Murphy and Sillito (1987) in a recent study observed a reduced surround effect (manifested as a change in length tuning) but no effect on the centre response of principal cells following cortical ablation.

The advantage with the gain control hypothesis is that it can be applied easily to other sensory thalamic nuclei. In an independent theoretical study Crick (1984) also proposed an excitatory feed-back as the neuronal substrate for attention control. He located the responsible neurones to the reticular nucleus. This was an unfortunate choice since these structures contain the recurrent inhibitory interneurones of the thalamic nuclei rather than excitatory cells. This mistake apart, he proposed that the attention control system should contain a mechanism for transient strengthening of the synaptic effects, especially at high firing frequencies. The correspondence between this aspect of his hypothesis and the properties of the cortico-geniculate system is indeed remarkable.

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References

Ahlsén G (1984) Brain stem neurones with differential projection to functional subregions of the dorsal lateral geniculate complex in the cat. Neuroscience 12: 817-838

Ahlsén G, Lindström S (1982) Excitation of perigeniculate neurones via axon collaterals of principal cells. Brain Res 236: 447-481

Ahlsén G, Lindström S (1983) Corticofugai projection to pen-geniculate neurones in the cat. Acta Physiol Scand 118: 181-184

Ahlsén G, Grant K. Lindström S (1982) Monosynaptic excitation of principal cells in the lateral geniculate nucleus by corticofugal fibres. Brain Res 234: 454-458

Ahlsén G, Lindström 5, Lo F-S (1984) Inhibition from the brain stem of inhibitory interneurones of the cat's dorsal lateral geniculate nucleus. J Physiol (Lond) 347: 593-609.

Ahlsén G, Lindström 5, Lo F-S (1985) Interaction between inhibitory pathways to principal cells in the lateral geniculate nucleus of the cat. Exp Brain Res 58: 134-143

Crick F (1984) Function of the thalamic reticular complex: the searchlight hypothesis. Proc Natl Acad Sci USA 81: 4586-4590

Del Castillo J, Katz B (1954) Statistical factors involved in neuromuscular facilitation and depression. J Physiol (Lond) 124: 574-585

Dubin MW, Cleland BG (1977) Organization of visual inputs to interneurons of lateral geniculate nucleus of the cat. J Neurophysiol 40: 410-427

Ferster D, Lindström 5 (1983) An intracellular analysis of geniculo-cortical connectivity in area 17 of the cat. J Physiol (Lond) 342: 181-215

Ferster D, Lindström 5(1*985a)* Augmenting responses evoked in area 17 of the cat by intracortical axon collaterals of corticogeniculate cells. I Physiol (Lond) 367: 217-232

Ferster D, Lindström S (1985b) Synaptic excitation of neurones in area 17 of the cat by intracortical axon collaterals of cortico-geniculate cells. J Physiol (Lond) 367: 233-252

Gilbert CD, Kelly JP (1975) The projection of cells in different layers of the cat's visual cortex. J Comp Neurol 163: 81-106

Koch C (1987) The action of the corticofugal pathway on sensory thalamic nuclei: a hypothesis. Neurosci 23: 399-406

Lindström S (1982) Synaptic organization of inhibitory pathways to principal cells in the lateral geniculate nucleus of the cat. Brain Res 234: *447-453*

Lindström S (1983) Interneurones in the lateral geniculate nucleus with monosynaptic excitation from retinal ganglion cells. Acta Physiol Scan~l 119: 101-103

Lindström 5, Wróbel A (1985) Frequency enhancement of corticofugal excitation in the lateral geniculate nucleus of the cat. Neurosci Lett [Suppl] 22: S311

Livingstone MS, Hubel DH (1981) Effects of sleep and arousal on the processing of visual information in the cat. Nature 291: 554-561

LqSmo 1 (1971) Potentiation of monosynaptic EPSPs in the perforant path-dentate granule cell synapse. Exp Brain Res 12: 46-63

Magleby KL (1973) The effect of tetanic and post-tetanic.potentiation on facilitation of transmitter release at the frog neuromuscular junction. J Physiol (Lond) 234: 353-371

McNaughton BL (1980) Evidence for two physiologically distinct perforant pathways to the fascia dentata. Brain Res 199: 1-19

Murphy PC, Sillito AM (1987) Corticofugal feedback influences the generation of length tuning in the visual pathway. Nature 329: 727-729

Robson JA (1983) The morphology of corticofugal axons to the dorsal lateral geniculate nucleus in the cat. I Comp Neurol 216: 89-103

Schmielau F, Singer W (1977) The role of visual cortex for binocular interactions in the cat lateral geniculate nucleus. Brain Res 120: 354-361

Singer W (1973) The effect of mesencephalic reticular stimulation on intracellular potentials of cat lateral geniculate neurones. Brain Res 61: *35-54*

Singer W (1977) Control of thalamic transmission by corticofugal and ascending reticular pathways in the visual system. Physiol Rev *57:* 386-420

Singer W, Tretter F, Cynader M (1976) The effect of reticular stimulation on spontaneous and evoked activity in the visual cortex. Brain Res 102: 71-90

Tsumoto T, Suda K (1980) Three groups of cortico-geniculate neurons and their distribution in binocular and monocular segments of cat striate cortex. I Comp Neurol 193: 223-236

Tsumoto T, Creutzfeldt OD, Legendy CR (1978) Functional organization of the corticofugal system from visual cortex to lateral geniculate nucleus in the cat (with an appendix on geniculo-cortical monosynaptic connections). Exp Brain Res 32: 345-364

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