Exp. Brain Res. 32, 345–364 (1978)

Experimental Brain Research

Functional Organization of the Corticofugal System from Visual Cortex to Lateral Geniculate Nucleus in the Cat
(With an Appendix on geniculo-cortical mono-synaptic connections)

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Summary. 1. In the cat visual cortex (VC), electrophoretic glutamate application at a depth corresponding to layer VI may have excitatory or inhibitory effects on relay cells of the lateral geniculate nucleus (LGN). Corticofugal excitation was seen, if the receptive field centers (RFCs) of the VC neurons recorded at the application site were within 2.3° of the RFCs of the LGN neurons under test. Inhibitory effects were seen if the RFCs of both cells were further apart up to 3.1°. Glutamate application at more superficial cortical sites had no effect on LGN-neuron activity.

2. Cross-correlation analysis between spontaneous activities of simultaneously recorded VC and LGN neurons revealed excitatory cortico-geniculate connections in 18 pairs with RFCs separated by less than 1.7°. In 15 pairs the peak latency of the excitation was 2–5 msec (3.4 msec in the average), 3 pairs showed long cortico-geniculate latencies (13–18 msec). The existence of a fast and slow cortico-geniculate system is suggested.

3. Inhibitory cortico-geniculate interaction was demonstrated with cross-correlation analysis in 8 pairs of which 4 had RFCs separated by more than 1.7°. The onset latency of the inhibition was 2–7 msec except for 2 pairs with about 20 msec latency.

4. Most of the LGN neurons which were affected by cortical glutamate application or which showed an excitatory or inhibitory connection with a VC neuron were sustained cells, while the majority of VC neurons which were recorded in the effective glutamate application sites or which showed a

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0014–4819/78/0032/0345/$ 4.00

significant interaction with LGN neurons in the cross-correlogram were binocularly driven and complex, with mostly large RFCs (mean diameter 3.5°). They responded briskly to moving small spots as well as to moving slits.

5. It is concluded that the corticofugal excitatory effect is transmitted through monosynaptic links from VC neurons located in layer VI (complex cell) to LGN relay neurons (mostly sustained-cell) and this system is organized in a precise topographical manner.

6. In an *Appendix* neuron pairs which showed a positive correlation in the geniculo-cortical direction were described. The findings may support the view that complex as well as simple cells are driven monosynaptically from geniculo-cortical afferents of the sustained or transient type.

Key words: Visual system – Cortico-thalamic connections – Thalamo-cortical input – Functional organization – Cat

It has been known for a long time, that thalamic projection nuclei receive corticofugal fibers from those cortical areas to which they project (Macchi and Rinvik, 1976; Walker, 1938). The projections from the visual cortex (VC) to the dorsal lateral geniculate nucleus (LGN) of the cat have been repeatedly demonstrated anatomically (for ref. see Macchi and Rinvik, 1976). These projections appear to be topographically organized so that a precise reciprocal connection between LGN and VC can be assumed (Holländer, 1970; Kawamura et al., 1974; Niimi et al., 1971; Updyke, 1975). The cortico-geniculate fibers appear to originate essentially from layer VI pyramidal cells (Gilbert and Kelly, 1975; Lund et al., 1975; Sanides and Donate-Oliver, 1977). Physiological investigations using various methods reported inconsistent results as to the function of the cortico-geniculate pathway. Iwama et al. (1965) and Suzuki and Kato (1965) found that electrical stimulation of VC produced effects within LGN which they interpreted as presynaptic inhibition, while Ajmone-Marsan and his colleagues (Ajmone-Marsan and Morillo, 1961; Widén and Ajmone-Marson, 1960) reported facilitatory effects on one-third of LGN neurons and inhibition of most neurons. Schmielau and Singer (1977) suggest, that such a facilitatory cortico-geniculate effect might be responsible for binocular facilitation of LGN-relay cells.

With electrical stimulation of VC the function of the corticofugal system is difficult to assess because of concomitant antidromic invasion of the recurrent collaterals in the LGN. To avoid such contamination Vastola (1967) used a method of cathodal polarization block of VC activity and described a facilitatory corticofugal effect in most instances. By cooling inactivation of VC, Hull (1968) reported a similar effect in the monkey LGN, whereas in the cat, Kalil and Chase (1970) observed two different effects on LGN neuron activity and suggested two types of corticofugal actions, i.e., a direct excitatory and a disinhibitory (presynaptic inhibition to recurrent collateral inhibition). By the same method, however, Richard et al. (1975) found no significant changes in LGN activity, whereas Schmielau and Singer (1977) mostly observed facilitatory effects.

We have attempted to further clarify the function of the cortico-geniculate pathway by observing changes in LGN activity following the excitation of VC neurons induced by electrophoretic application of glutamate. This method allows a selective activation of neurons and thus avoids antidromic activation of afferent fibers (Curtis and Crawford, 1969; Zieglgänsberger and Fries, 1971). Also, cross-correlation analysis between spontaneous activities of simultaneously recorded VC and LGN neuron pairs was done to disclose a direct interaction between neurons at both sites.

Methods

Preparation

The experiments were done on twenty-four adult cats (weight 2.4–4.1 kg) anesthetized with sodium pentobarbitone (Nembutal) (i.p., 30–40 mg/kg). After the initial surgery, a continuous i.v. infusion with 1 ml (20 mg) Galamine-triethiodide (Flaxedil) in 1.6 ml Ringer solution and 0.4 ml Laevulose solution (Laevosan 40%) per hour was maintained. 20–30 mg Nembutal was added after 6–8 hours. Artificial respiration was adjusted to an end-tidal CO_2 concentration of 3.5–4.0%, the rectal temperature maintained at 37–38° C. The nictitating membrane was retracted with neosynephrine (5%), the pupils were dilated with atropine (1%) instilled into the eyes and refraction was corrected with contact lenses using a Rodenstock refractometer for focussing the cat's eyes on the tangent screen located 1 m in front of the cat. The position of the optic disc was ophthalmoscopically determined (Fernald and Chase, 1971).

Geniculate Recording

Glass micropipettes, filled with 2-M-NaCl-solution, were introduced stereotaxically into the LGN at the level of A 5.5–6.0, L 9.0–10.0 through a chamber closed by agar jelly. Guided by the LGN-map of Sanderson (1971), penetrations were repeated until excitatory receptive fields (RFs) of the encountered LGN unit were located in the central or paracentral visual fields, which project to the dorsal surface of VC, a region conveniently suited for cortical recording. In some experiments the geniculate recording site was marked by iontophoretic ejection of Fast green dye (2–5 μA for about 10 min) (Thomas and Wilson, 1965) and the electrode position was found to be in the LGN.

Cortical Recordings and Electrophoretic Application of Glutamate

After LGN unitary activities were identified, the exposed VC was stimulated systematically by applying electrical pulses of 0.05–0.1 msec width through a silver ball electrode, and the cortical point was determined from which the LGN neuron could be antidromically invaded with minimum intensity. Around this point double-barrel glasspipettes (theta-type) were inserted into VC through a closed chamber. One channel was filled with 2-M-NaCl-solution for recording, the other with a solution of Fast green dye for histological identification of the recording site. A second theta-pipette for electrophoresis was attached to the recording pipette which protruded 20–30 μm beyond the orifice of the phoresis pipette (Hess and Murata, 1974). Both channels of the phoresis pipette were filled with glutamate solution (L-mono-sodium-glutamate 2M, pH 8.4). For electrophoretic application of glutamate constant currents were drawn from a high-resistance source. When necessary, retaining currents up to 20 nA were used to prevent leakage of glutamate from micropipette tips. Amplification and display techniques for unit activity were conventional.

Visual Stimulation

The response properties of each neuron were explored with moving hand-held black or bright targets. For quantitative analysis, computer guided moving stimuli were projected from the rear onto the screen with a slide projector. Usually, the light stimuli were 1.0–1.5 log units above or below the background illumination, which was kept in the scotopic-mesopic range. Only one eye was stimulated at a time. VC and LGN neurons were classified into simple and complex, and into sustained and transient cells, respectively, according to the published criteria (Cleland et al., 1971; Hubel and Wiesel, 1962; Pettigrew et al., 1968).

Evaluation of Glutamate-Induced Effects

Before glutamate was applied to the VC recording site, an optimal stimulus for the LGN unit was swept back and forth across its RF. Mostly this stimulus consisted of a white or dark bar (width about 0.2–0.5°, length about 1–4°). The speed of movement was usually 4–8°/sec. Peristimulus time histograms (PSTHs) of LGN and VC units were simultaneously calculated with an on-line PDP-12 or PDP-11 system. Usually 10–20 sweeps were averaged with a bin width of 10 or 20 msec. Then, glutamate was ejected to the VC recording site by applying a negative current of 20–100 nA. The current intensity was adjusted so that the cortical unit was clearly excited but not yet suffered from depolarizing inactivation. Sometimes, switching off the positive retaining currents was sufficient. During the glutamate-electrophoresis, PSTHs of the LGN and VC units were repeated with the same stimuli. After stopping glutamate ejection, control PSTHs were made again. Only the neuron pairs from which such a series of at least 3 PSTH-pairs could be recorded were used for analysis of the glutamate effect. In most cases, effects of various intensities of glutamate electrophoresis could be investigated from the same pair.

The background and response activity of LGN neurons were separately determined in the PSTH, and the mean (m) and standard deviation (s) of the PSTHs were calculated for each type of activity. If the activity during glutamate application was beyond $m \pm 2s$, the effect was judged to be attributable to VC excitation.

Cross-Correlation Analysis

Cross-correlograms of LGN and VC neuron spikes were constructed by the PDP-11 with 1 msec binwidth and displayed on a monitor scope during and after their calculation. Usually, activities of both neurons were analysed in the absence of visual stimulation. When the discharge rate of the VC neuron was very low, a small amount of glutamate was ejected in order to sample a sufficient number of spikes during the limited time of recording. Auto-correlograms of both neurons activities provided information on the spike discharge patterns of individual neurons and facilitated interpretation of the cross-correlograms (Moore et al., 1970).

Depth Localization of VC Neurons

In most experiments the cortical recording depth was read from the micromanipulator, by taking the point as 0, when the electrode tip touched the cortical surface. In several experiments the Fast green dye filled in one channel of the theta-pipette was electrophoretically ejected at the end of the penetration. After the experiment, electrode tracks and recording sites were reconstructed and localized with respect to cortical layers. The depth of the recording site as identified by histology corresponded well to that read from the micro-manipulator, if the penetration was at least about 2 mm lateral from the medial longitudinal fissure. Data obtained from more medially located penetrations without histological identification were omitted from depth analysis, because they were not normal to the cortical surface.

Results

The present report is based on 211 pairs of neurons recorded simultaneously from LGN and VC (area 17), 114 of which were studied with glutamate electrophoresis into VC and 133 with cross-correlation analysis. Thirthy-six pairs were studied with both methods.

Effects of Glutamate-Induced Excitation of VC on LGN Unit Activity

All VC neurons showed a clear increase of their spike discharge rates after application of glutamate as long as the tips of the recording and the phoresis electrode were close together (< 50 μm). The phoresis current was adjusted so that the neurons discharged with maximum frequency but avoiding depolarization block.

In thirty-nine of the 114 pairs investigated by glutamate phoresis, the LGN partner showed significant changes in activity during glutamate-induced excitation of the VC partner. The distance between the RFCs of both neurons was one of the important factors which determined the glutamate effect on the LGN neuron activity. An example for this finding is shown in Figure 1. The VC neuron in this example was located in layer VI of area 17, as found out later histologically. It had a fairly large RF ($3.5 \times 3.0°$) near the area centralis, responded preferentially to a fast moving slit (8°/sec) and was driven equally from both eyes. Its response was poor when the slit passed through the periphery of its RF. It could be classified as a complex cell.

Several LGN neurons were tested with the same cortical electrode position. The stimulus was adjusted to be optimal only for the LGN neurons so that responses of the VC neuron were far from maximal in this figure. The RFC of the first LGN-neuron (on-center, contralaterally driven, sustained response) (LGN_1) was separated from that of the VC neuron by about 2.7° and the two RFCs did not overlap (see top of Fig. 1). During glutamate-excitation of the VC neuron we did not find any significant activity changes in the LGN_1 unit.

The next LGN unit (LGN_2, on-center, sustained) had a RF (RF_2) which partly overlapped with that of the VC unit. LGN_2 was driven by the contralateral eye. When glutamate was applied to the cortical recording site, the VC unit showed an increased spontaneous discharge rate, whereas the spontaneous and response activity of LGN_2 were clearly suppressed to about 50% and 60%, respectively (B of the left column). After glutamate ejection the responses and background activity of LGN_2 recovered to the precontrol level (C of the left column).

The RF of LGN_3 was essentially overlapping with one corner of the RF of the VC unit, the centers of both cells being separated by about 1.8°. LGN_3 was also contralaterally driven, on-center and sustained. During glutamate application to the cortical site responses to the moving slit were not significantly changed but the background activity was increased to about 230% of the control (middle of the center column).

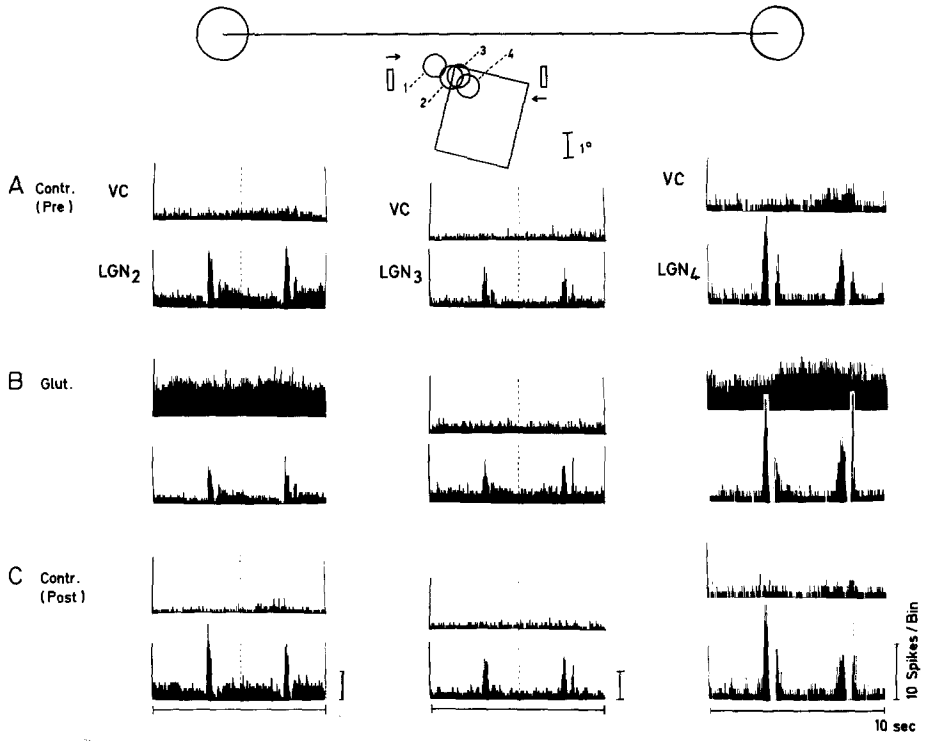

Fig. 1. Effects of intracortical glutamate application on 4 LGN-neurons successively recorded and a simultaneously recorded VC-neuron. Top: arrangement of RFs and stimulus. The numbers 1 to 4 indicate the RF of the neurons LGN_1 to LGN_4, the large RF is that of the VC-neuron. Stimulus speed was about 2°/sec. The slit position was adjusted to the excitatory receptive field of the LGN-neuron tested. Each column shows a series of PSTHs from the same neuron pair. The LGN-neuron is indicated for each column. **A**: control PSTH-pairs made before glutamate application. **B**: PSTH-pairs obtained during glutamate application. **C**: control PSTH-pairs made after stopping glutamate application. Ten sweeps for each PSTH, bin width 10 msec

The effect of cortical glutamate application on LGN-activity was, to some extent, dependent on the magnitude of the electrophoresis current. At 20 nA, no significant activity changes were observed in the VC or the LGN_3 neuron. At 50 nA, the discharge rate of the VC unit increased to about 200% of the control and that of LGN_3 to 230%. The responses of LGN_3 to the moving slit did not show significant changes. At 80 nA the discharge rate of the VC unit was doubled again, while the background activity of LGN_3 was even slightly less marked than at 50 nA. This tendency that too much current (usually more than 80 nA) made the effects less clear or absent was observed quite frequently.

The RFC of LGN_4 in Figure 1 was still closer to that of the VC unit (1.1°) (see top of Fig. 1). RF properties were the same as the previous LGN units. During glutamate-induced excitation of the VC unit, responses of LGN_4 to forward and backward movements of the slit increased to about 120% and

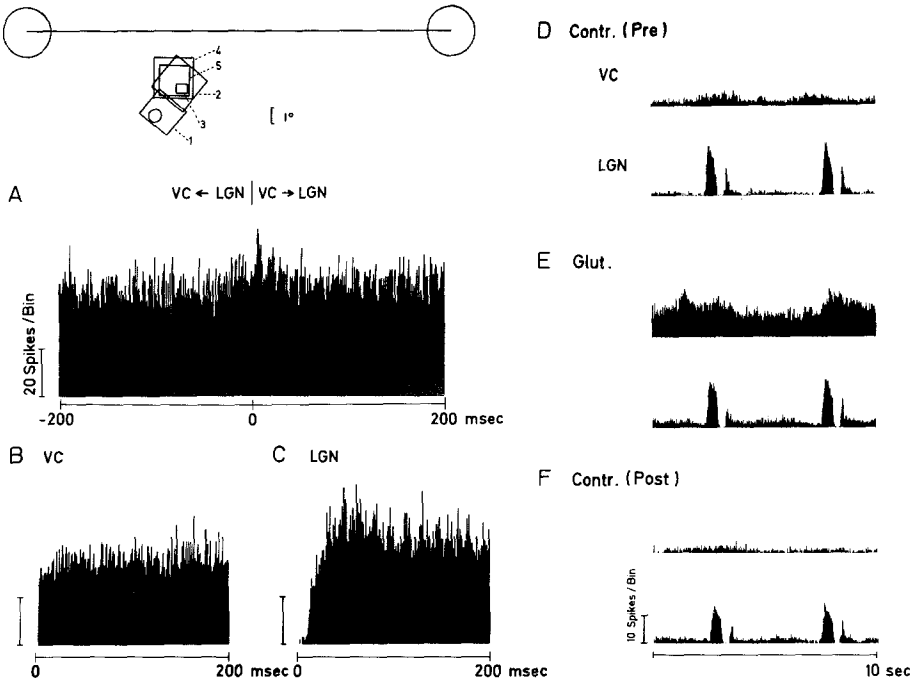

Fig. 2. Excitatory corticofugal interaction between a VC and an LGN neuron. Top left: RF-arrangement, relative to blind spots, of one LGN- (circle) and 5 successively recorded VC-neurons. Numbers 1 to 5 indicate the RF of VC_1 to VC_5. **A**: cross-correlogram between spontaneous activity of the VC_1 and LGN neuron (4005 VC_1 and 4263 LGN neuron spikes). Bin width 1 msec. The activity of VC_1 was slightly increased by glutamate application. **B** and **C**: auto-correlograms of VC_1 and the LGN neuron activity during the same period as A. D–F: PSTH-pairs of VC_1 and the LGN neuron to a horizontally moving slit which was optimal only for the latter. **D**: control PSTHs before glutamate application. **E**: PSTHs during glutamate application with 60 nA current, **F**: PSTHs after stopping glutamate application. Bin width of PSTHs, 10 msec, 10 sweeps. Total numbers of LGN-neuron discharges in D 2172, E 3343, F 2232

150%, in the two directions, respectively, and the spontaneous discharge rate increased likewise to about 130% of the control.

The results of these experiments suggest that the effect of cortical glutamate application on the LGN activity may change from suppression to facilitation, when both RFs of the recording pair approach each other. Also, the background activity of LGN neurons appeared to be more sensitive to the glutamate-excitation of VC than responses to a moving slit. These findings will be further elaborated later.

Excitatory Linkage from VC Neuron to LGN Neuron

Cross-correlation analysis between spike trains of VC and LGN neurons showed that the facilitatory effect of VC on LGN activity may be transmitted through direct corticofugal links. An example of this is shown in Figure 2. This LGN unit

had a concentric on-center RF (X-type) and was driven by the contralateral eye. It was held sufficiently long to perform cross-correlation and glutamate application analyses successfully with 5 different VC neurons encountered in one penetration. The cross-correlogram between spontaneous discharges of VC_1 and the LGN neuron showed a clearly distinguishable although not very prominent peak in the corticofugal direction (Fig. 2A). The latency of this peak was about 4 msec and its width about 10 msec. Since the auto-correlograms (Fig. 2B and C) of both neurons showed no strong periodicity which could be reflected in the cross-correlogram, this peak can be interpreted as excitation of the LGN neuron by the VC neuron. The very short latency and the shape and time course of the peak, similar to those of EPSPs (McIlwain and Creutzfeldt, 1967) suggest a monosynaptic connection. Yet, the excitatory cortico-fugal effect must be considered rather weak. This was also the case in other pairs with positive cortico-geniculate correlation.

Glutamate application to the VC recording site induced an activation of the LGN neuron (Fig. 2D–F). The background activity of the LGN neuron increased to about 220% of the control, and the responses to the moving slit increased to about 120%. The cortical unit was located deep in the cortex, probably near the grey/white border. This was confirmed by histological identification of the recording site. During withdrawal of the electrode we recorded 4 more VC neurons (VC_2–VC_5) successively. Their RFs are shown in the inset of Figure 2. None of these VC units showed a positive cross-correlation with the activity of the LGN unit. When glutamate was applied to the recording site of VC_4, which was recorded at a depth of about 1400 μm, no significant changes were observed in the spontaneous and the response activity of the LGN unit. After having pulled the recording electrode out of the cortex antidromic action potentials could be elicited in the LGN neuron by electrical stimulation applied to the same cortical spot through a silver ball electrode. This allows to identify this neuron as a relay neuron.

Inhibitory Effects of VC

Figure 3 shows an example of an inhibitory effect of a VC neuron on an LGN neuron. The RF arrangement of the neuron pair is shown on top. The LGN unit (on-center and X-type) was driven by the ipsilateral eye. The VC unit had complex properties but a relatively small RF; it responded preferentially to fast moving stimuli (8–16°/sec) and inhibitory side bands were not clearly distinguishable. The cross-correlogram between the spontaneous discharges of both neurons showed a deep trough in the direction of VC to LGN, with an onset latency of 4 msec, a peak latency of 11 msec and a duration of 35 msec, which suggests an inhibition of the LGN by the VC-neuron. Its shape and time course resemble those of IPSPs and the suppression of activity is significantly deeper than the superficial troughs due to the clustered activity of the VC-neuron as it is demonstrated in the auto-correlogram of its activity (Fig. 3B). Glutamate application to the VC recording site caused only a slight activation of the VC neuron which correlates to the only small inhibitory effect

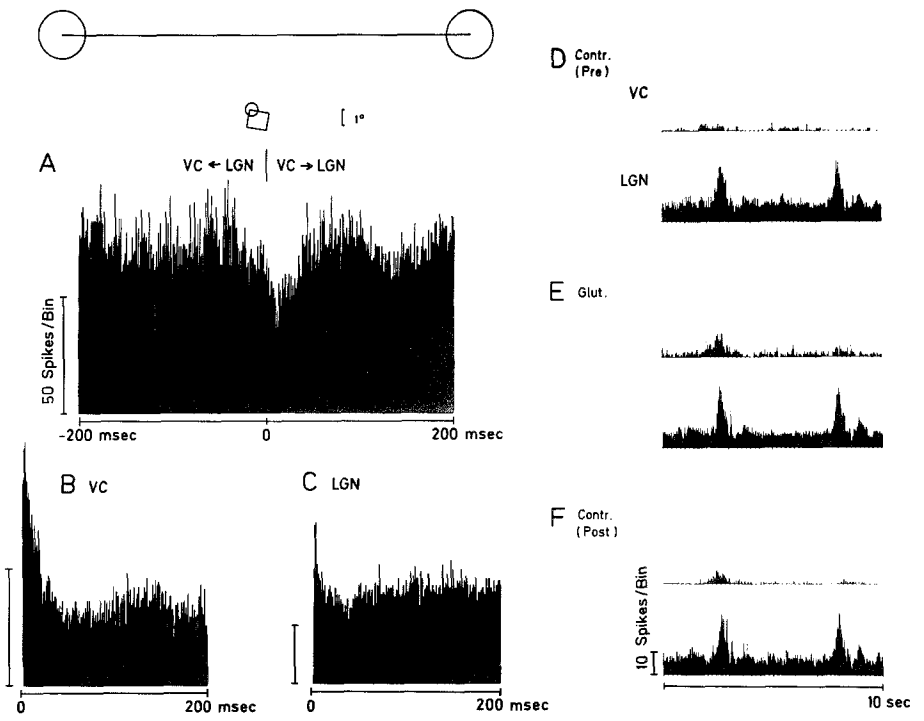

Fig. 3. Inhibitory corticofugal interaction between a VC and a LGN neuron. Top left: arrangement of their RFs (with the position of the blind spots). **A**: cross-correlogram between the spontaneous activities (3089 spikes of VC- and 8192 of LGN-neuron). The activity of the VC-neuron was slightly elevated by glutamate application. **B** and **C**, auto-correlograms of the VC and LGN neuron activity during the same period as A. **D–F**: PSTH-pairs of the neurons to a moving slit. Speed of the movement is about 2°/sec. Bin width 10 msec, 10 sweeps. **D**: control PSTHs before glutamate application. **E**: PSTHs during glutamate application. **F**: control PSTHs after stopping the application. Total discharges of the LGN-neuron in D 6998, E 5523, F 6389

on the background activity of the LGN unit to about 80% of the control; responses to the moving slit were not significantly altered (Fig. 3D–F).

Some Properties of the Whole Sample

The topograpic relationships between cortical and geniculate recording points, for which effective interaction could be demonstrated, can be estimated from the relative visual field positions of the interacting sites in Figure 4. The distances between the geometrical centers of the RFs of the LGN units tested and the VC neurons recorded at the glutamate application site (A) or tested for cross-correlation (B) are shown on the abscissa, and the number of pairs on the ordinate.

An excitatory corticofugal effect by glutamate (black) can only be elicited from recording sites in which the RFC of a VC neuron is separated by less than 2.3° from that of the affected LGN cell, while inhibitory cortical sites (hatched)

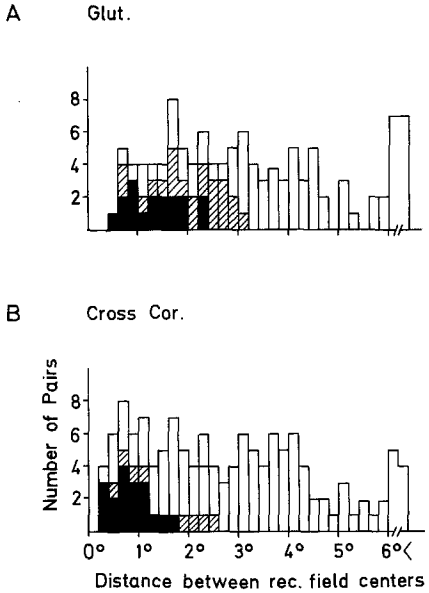

Fig. 4. Dependency of the glutamate-effect (**A**) and of the corticofugal correlations (**B**) on distance between RF-centers of simultaneously recorded VC- and LGN-neuron. **A**: The experiments, in which glutamate was applied at a site where a VC neuron could be recorded simultaneously, are sampled. On the abscissa, the distance between the RF-centers of the LGN and VC neuron are recorded. On the ordinates, numbers of pairs in which cortical glutamate application had an excitatory (filled columns), an inhibitory (hatched columns) and no effects (empty columns) on activity of the LGN-neuron. **B**: Number and RF-center separation of VC-LGN neuron pairs, in which the cross-correlogram showed a corticofugal excitatory (filled columns), an inhibitory (hatched) or no correlation (empty)

tend to contain neurons with RFCs further away. The same trend is seen when the RFs of neuron pairs with direct interactions in the cross-correlogram are evaluated (B). The 18 neuron pairs with excitatory interactions have nearly concentric RFs, most of them separated by less than 1.2°. In these pairs, the onset latency of the excitation was ±3.4 msec in the average, except that 3 pairs had a latency of 13–18 msec. The duration of the excitation was about 13 msec on average. Inhibitory interactions are seen in 8 pairs of which 4 had RFCs separated more than 1.8°. In those pairs the onset latency of the inhibition was 4.0 msec in the average except for 2 pairs with about 20 msec latency. The duration of the inhibition was about 40–50 msec.

The corticofugal glutamate effects were, in some neurons, slightly asymmetric in the sense that they were more prominent on the geniculate response to stimulus movement in one or the other direction. These effects were, however, not systematically related to the preferred direction of the cortical neuron recorded at the application site.

Functional Properties of Neurons

The majority of LGN-cells which were influenced by cortical glutamate application showed sustained responses to flashing light spots. Less than 10% had purely phasic responses. In our total sample, nearly 35% of the LGN-cells were purely phasic responders. There was no significant difference between on- and off-center, nor between ipsi- or contralaterally driven cells in the sample of LGN-cells influenced from the cortex.

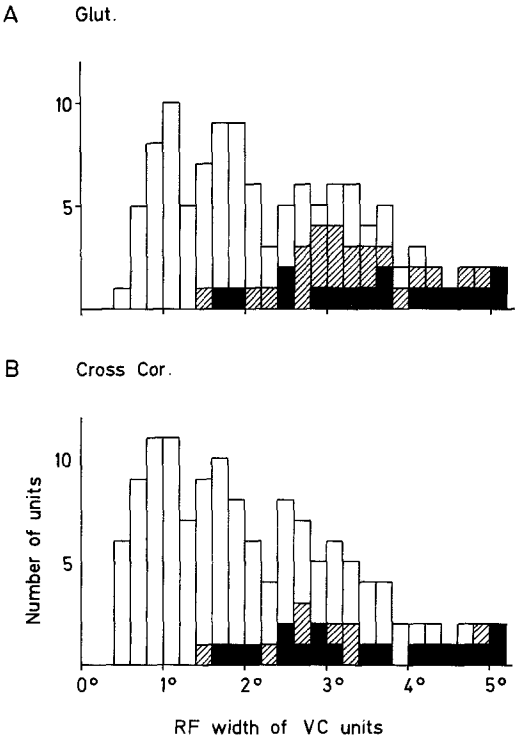

Fig. 5. RF width (abscissa) of VC neurons which were recorded at the glutamate application sites (**A**), or which were examined in the cross-correlation analysis with the LGN partner neuron (**B**). RF width was taken along the axis of the optimal direction. **A**: Filled columns: VC neurons recorded at the site where glutamate application had an excitatory effect on the LGN partner. Hatched columns: VC neurons at the site where glutamate had an inhibitory effect. Empty columns: no effect. **B**: Filled columns: VC neurons which had an excitatory corticofugal interaction with the LGN partner in the cross-correlogram. Hatched columns: VC neurons with an inhibitory interaction. Empty columns: no significant interaction

The majority of cortical cells recorded in the effective glutamate application spots were complex cells, while only few may be classified as simple (proportion 8.3 : 1). All cortical cells with excitatory or inhibitory interaction with LGN-cells in the cross-correlogram had complex properties. In contrast, the complex : simple proportion in our whole cortical sample was 2.4 : 1.

The RF-width of VC neurons which were recorded at an effective glutamate application site or which showed direct interaction with an LGN-neuron in the cross-correlation were between 1.6 and 5.2° (mean 3.5°) (Fig. 5). These RF-diameters are at the large end of the distribution of cortical RF's in our sample. Most cortical cells with cortico-fugal geniculate effects also responded briskly to relatively fast moving stimuli although their responses were poor to the stimuli crossing the border of RF as seen in Figures 1 and 3. Most of them were equally driven from both eyes and had a broad tuning for orientation of the slit and for direction of the spot movement. On- and off-responses to stationary spots of the same size were very poor or absent.

Cortical Depth Localization of the Neurons Related to the Corticofugal Effects

In most of the experiments using glutamate, excitatory or inhibitory effects of LGN neuron activity were observed only when the cortical electrode was near

the end of a penetration, i.e., in the deepest layers of the cortex. Except for 4 cases the effective cortical sites were located between 2000 and 2500 μm depth, which approximately corresponds to layer VI of the cortex. This was confirmed by histological identification of the VC recording site in several experiments. No significant differences were found between the depth of VC sites from where excitatory and inhibitory effect could be elicited. Also, fifteen of the 17 neurons, which showed an excitatory or inhibitory corticofugal interaction with the partner LGN neurons in the cross-correlograms were found at a depth of 2000–2500 μm, corresponding to layer VI of the cortex.

Discussion

Anatomical Properties of the Cortico-Geniculate System

The findings reported here demonstrate a rather precise topographical corticofugal excitatory connection from VC to LGN. In fact, excitatory corticofugal connections between a cortical and a geniculate cell were seen in the cross-correlogram only if the centers of their RFs were within 1.7° of each other. Assuming a magnification factor of about 0.5 mm. degree^{-} in the central/paracentral cortical projection field, in which our cortical recordings were done, this would indicate a preciseness within the millimeter range. Topographically, it may be still better if the scatter of the cortical retino-topic map and thus the unreliability of the visual field projection for an exact anatomical point location in the cortex were taken into account (Albus, 1975; Creutzfeldt et al., 1974). The physiological findings presented here extend to the microscopic dimension, the basically retino-topical organization of the corticofugal system to the LGN, repeatedly demonstrated with anatomical methods (see Introduction).

The depth distribution of corticofugal neurons and of effective glutamate spots deep in the cortex is also in good agreement with the anatomical localization of cortico-geniculate neurons essentially in layer VI (Gilbert and Kelly, 1975; Robson and Hall, 1975; Sanides and Donate-Oliver, 1977). Since the apical dendrites of these deeply located pyramidal cells reach through the whole cortex up to layers I/II, one might have expected a cortico-geniculate effect also from glutamate injections at more superficial cortical sites. That this was seen only exceptionally may be due to the small dendritic density of layer VI neurons in superficial parts of the cortex or may even indicate a lesser glutamate sensitivity of the apical dendrites.

Neurophysiological Properties of the Excitatory Corticofugal Pathways

The latency of corticofugal excitation as demonstrated by the cross-correlograms between single VC-LGN neuron pairs (2–5 msec, mean 3.4 msec) is relatively long but may still be compatible with a direct link between the respective neurons. For geniculate electrical stimulation, the response latency of

VC cells has a range of 1.0–7.0 msec (Singer et al., 1975; Toyama et al., 1974), and the few antidromic responses recorded in cortical cells after LGN-stimulation yielded latencies of 1.4 ±0.56 (Toyama et al., 1974) and 1.2 ± 0.4 msec (Singer et al., 1975). But considering that these were shortest values measured at the beginning of the intracellularly recorded action potentials, while ours were peak values of discharge probabilities, and taking into account a possibly long synaptic delay in the geniculate cells because of the distal dendritic location of the corticofugal synapses (Guillery, 1967, 1969; Jones and Powell, 1969), a considerable difference between the antidromically determined conduction time of the corticofugal fibres and the actual corticofugal transmission time may be expected. Anatomically, corticofugal fibres are thinner than the afferent radiation fibres as was remarked by Ramón y Cajal, and there are no anatomical findings available which might indicate a further excitatory synaptic relay from cortex to geniculate. The latency values of corticofugal excitation found in our experiments (2–5 msec) therefore support the view that the cortico-geniculate path is, on the average, slower than the afferent path.

In fact, *some corticofugal fibres may have an extremely slow conduction velocity,* as an exceptionally long latency (13–18 msec) of corticofugal excitatory interaction was observed in the cross-correlograms of 3 pairs in the present experiments. This has been confirmed in recent experiments, in which we had placed electrical stimulation electrodes in the LGN. Some VC units, in these experiments, had an extremely long antidromic latency (15–28 msec), although their orthodromic latency was within the normal range of monosynaptic conduction time (2–3 msec). They could be driven by visual stimuli (weak, complex type responses), but some were not activated directly by the afferent radiation volley nor by light stimuli. Another feature of these cells was the almost complete absence of spontaneous activity.

These findings suggest the existence of a fast and slow cortico-geniculate projection system. The conduction velocities of the fast and slow fibres may be estimated to be 5–20 m/sec and 0.7–1.7 m/sec, respectively. Such very slow conduction velocities of corticofugal fibres were first described by Orem and Schlag (1971) from the frontal cortex to the internal medullary lamina of the cat thalamus and later by Singer et al. (1975) from VC to the thalamus. Although the final destination of the antidromically identified corticofugal fibers is not absolutely sure in the experiments using electrical stimulation, the present results on the excitatory connections in the cross-correlogram led us to the conclusion that the slow as well as the fast corticofugal fibres project to LGN.

As to the type of LGN neurons which could be excited by local cortical glutamate application or which were in direct excitatory contact with single VC neurons, we assume that they were relay neurons because of their well defined center-surround organisation. In some cases, we were able to support this by antidromic excitation after electrical VC stimulation. Using double recordings from retinal and geniculate cells with excitatory connections, Dubin and Cleland (1977) found LGN cells which were only orthodromically driven from the VC, while relay cells showed no signs of orthodromic excitation after electrical VC stimulation. It could be that the antidromically evoked action

potentials and recurrent inhibition in the LGN cancelled the weak orthodromic corticofugal effects in their experiments, if the orthodromic potential were conducted slower than the antidromic volleys as suggested above.

The predominance of cells with sustained responses (presumably X-cells), receiving corticofugal effects is interesting in the light, that X-cells were also predominantly affected by stimulation of the reticular formation (Fukuda and Stone, 1976; Singer and Bedworth, 1974), and the frontal eye field (Tsumoto and Suzuki, 1976). But as we do not yet understand, satisfactorily, the functional significance of the X-/Y-distinction in the cortex, a further interpretation of these differences would be premature.

Corticofugal Inhibitory Effects

The inhibitory effects of cortical glutamate application and of single cortical neuron activity could be due to intracortical as well as to intrageniculate inhibition. In the cortex, it has been demonstrated that glutamate applied at distances above 100–200 μm from a neuron inhibits its spontaneous and response activity (Hess et al., 1975), and recurrent intracortical inhibition is a well-established mechanism. In the LGN, mutual inhibition between relay neurons through recurrent collaterals is also clearly demonstrated and extends over a larger area (Burke and Sefton, 1966; Singer and Creutzfeldt, 1970). It is thus possible that the cortico-geniculate inhibitory effects are due to the functional organisation of inhibition within the cortex and the LGN.

Functional Characteristics of the Corticofugal Neurons

Recently Gilbert (1977) reported that neurons in layer VI were binocularly driven, and preferred fast moving stimuli and had large elongated RFs. Our observations are in agreement with this except that excitatory RFs of the cortico-geniculate neurons presented here were mostly square. This discrepancy may be accounted for by the fact, also noted by Gilbert (1977), that stimulation of the periphery of RFs of such neurons were not effective for eliciting clear responses particularly if a small slit was used; the lateral borders of RFs of the neurons are vague so that their shape might appear to be different depending on techniques used to plot excitatory RFs.

The properties of our cortico-geniculate neurons are to some degree similar to those of neurons projecting from layer V to the superior colliculus (Palmer and Rosenquist, 1974). This might suggest that we recorded from layer V neurons and stimulated in layer VI. But the arrangement of electrodes was opposite: the recording electrode was always protruding and contained Fast green dye for histological identification of electrode position. Neurons in layer V and VI are said to be distinguishable by their spatial summation properties, whereas else they have rather similar properties (Palmer and Rosenquist, 1974; Gilbert, 1977). Since we did not systematically determine spatial summation, we cannot comment on this.

Functional Implications

The actual functional significance of the corticofugal retino-topically organized excitatory connections with the afferent relay nucleus is not known and it is not easy to suggest a reasonable hypothesis based on our experiments. In fact, the cortico-fugal effect must be considered as being very weak in terms of excitation and inhibition of geniculate neurons. Therefore, also the effect of cortical cooling inactivation on geniculate activity may be so small that it may escape experimental demonstration, at least in anaesthetized animals (Richard et al., 1975, see Introduction). The fact that there appears to be a center-surround organisation also of the cortico-fugal system may further explain the evasiveness of the effects of global cortical inactivation. Our findings may suggest that local afferent excitation of a cortical spot would lead to an enhancement of the afferent activity within and decrease activity in the relay nucleus around that spot, thus providing a positive feedback loop with lateral inhibition for focal amplification of afferent and thus cortical activity. Schmielau and Singer (1977) suggest, in a recent report, that the cortico-geniculate pathway may also be responsible for binocular facilitation of LGN-cells. This would be in agreement with our observation that all cortico-geniculate cells were binocular. But as they could also be driven monocularly, this cannot be their only function. A proper model within which the corticofugal mechanisms described in this paper play an integral part is not yet available. The function of the extremely slowly conducting corticofugal fibres described here in the visual system, is even more obscure yet. On the other hand, since the reciprocal thalamo-cortical connections seem to be a general feature for all thalamo-neocortical systems (Macchi and Rinvik, 1976) *the precise topographical organization and the excitatory nature of the corticofugal pathways demonstrated here for the visual system might be generalized for the whole neocortex.*

Appendix

While analyzing the tape-recorded data of VC-LGN neuron pairs for cross-correlation, we found 9 pairs which showed a sharp peak following the LGN-action potentials, indicating a simultaneous recording from a cortical and an LGN cell afferent to it. It appears worthwhile to communicate these observations, albeit scanty, as it is rather by chance that one can collect such data. One example is shown in Figure 6. The PSTHs of the cortical cell (VC in A) showed a narrow response peak with the moving slit indicating a small excitatory center (about 1° wide) as is typical for simple cells. The response peak of the on-center LGN-cell had the same width but was much higher. The responses on the VC- and LGN-cells coincide during the forward and backward movement of the stimulus. The cross-correlogram (C), calculated from the spontaneous activity of the LGN- and VC-cell shows a peak from –1 to –12 msec. The VC cell was slightly activated by a low dosis of electrophoretically applied glutamate in order to lower its threshold for afferent impulses. The original recording of Figure 6B, in which the oscilloscope beam was triggered by the LGN action potentials, shows a minimum latency of the triggered cortical

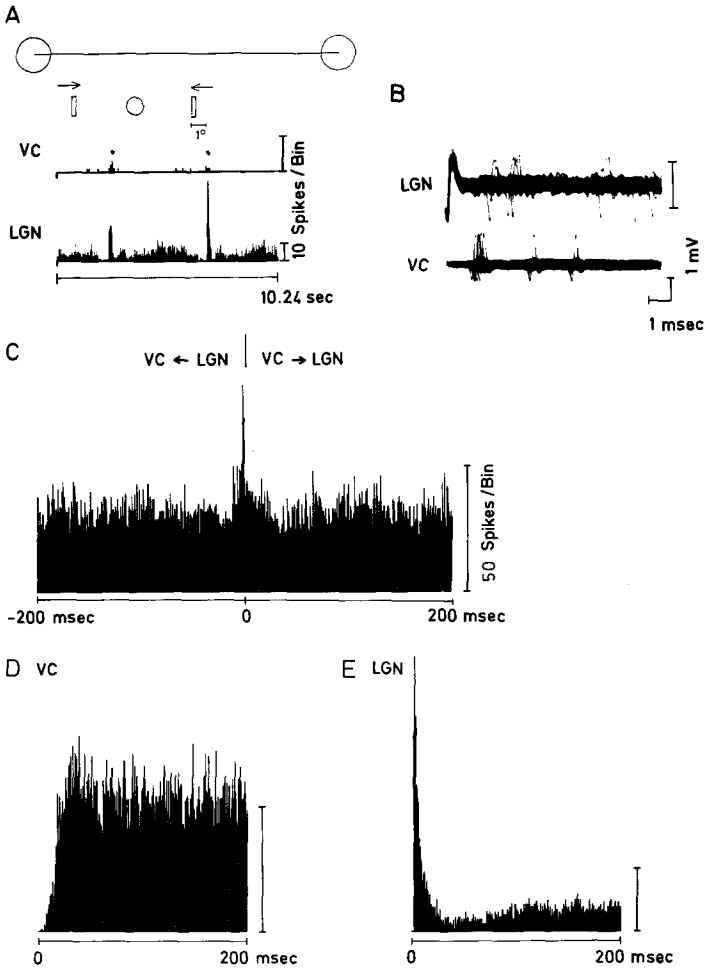

Fig. 6. Excitatory geniculo-cortical interaction between a simple VC and a LGN neuron. **A**: Arrangement of the RF of the LGN-neuron and responses (PSTH) of the two neurons to a light slit moving as indicated. Speed of movement about 4°/sec, 10 sweeps, bin width 20 msec. The weak response of the cortical neuron (stimulation in non-optimal orientation) is marked by a dot. **B**: Superimposition of 20 sweeps triggered by spikes of the LGN neuron. Spikes of the VC neuron followed those of the LGN neuron with a latency of about 1.2 msec. **C**: Cross-correlogram between the spontaneous activities of the recorded pair, based on 3181 discharges of the VC and 2889 of the LGN neuron. VC neuron was slightly activated by switching off the retaining current of the glutamate-electrophoresis channel. **D** and **E**: Auto-correlograms of the VC and LGN neuron activity during the same period as C

action potentials of 1.2 msec. The auto-correlograms of the cortical and the geniculate cell demonstrate a tendency of the latter to discharge in burst (D and E). The peak in this geniculate auto-correlogram is at 4 msec. The high values in the cross-correlogram between –4 and –12 msec may be, in part, due to such bursty afferent volleys which may reach threshold occasionally.

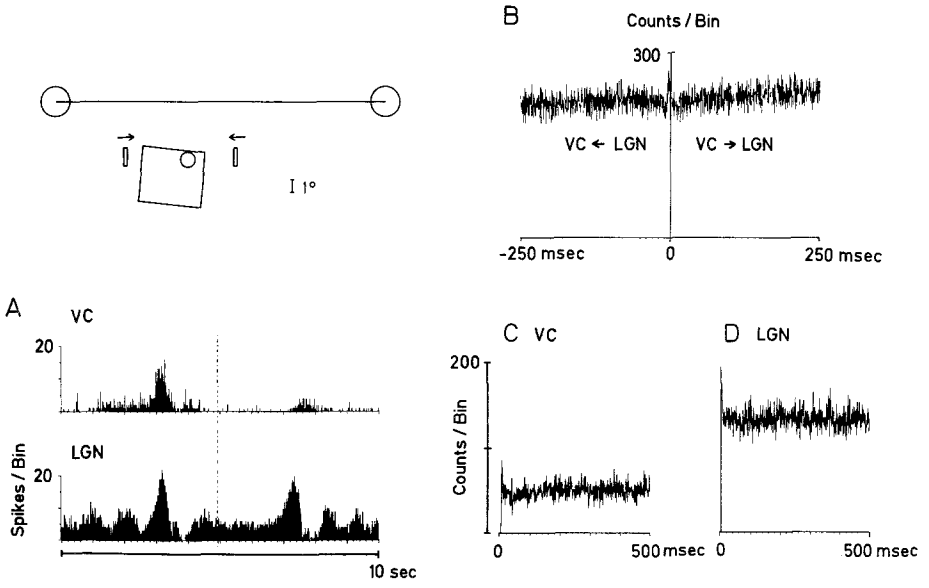

Fig. 7. Excitatory geniculo-cortical interaction between a complex VC and an LGN neuron. In the top left an arrangement of their RFs and of a stimulus is shown. Speed of the slit movement was about 2°/sec. **A**: Responses of the two neurons to a moving slit (20 sweeps, bin width 10 msec). **B**: Cross-correlogram between the spontaneous activities of the recorded pair (3029 discharges of the VC and 6900 of the LGN neuron). A sharp peak is seen at –2 msec indicating an excitatory drive from the LGN to the VC neuron. **C** and **D**: Auto-correlograms of the VC and LGN neuron activity during the same period as B

A precise assessment of the success rate of geniculo-cortical afferent discharges in eliciting a cortical action potential is not possible, since the cortical neuron was excited also directly by glutamate. But in any case, the short latency indicates a direct, monosynaptic excitation of this cortical cell, and the complete coincidence of the responses during light stimulation would be compatible with a specific and exclusive visual excitation of this cortical cell through this afferent fibre (for further discussion of this see Lee et al., 1977).

Since most of the cells which were recorded for a sufficient length of time in this study were cells in the deeper cortical layers, the cortical partners of the other 8 cell pairs with geniculo-cortical connections were complex cells. An example of such a pair is shown in Figure 7. The response of the cortical cell to a moving bar is stretched over a wider area than that of the LGN-cell, and the cortical neuron discharges even during an inhibitory pause of the LGN-neuron (see backward movement of the stimulus, right side of PSTH in A). The geniculo-cortical latency of the sharp peak in the cross-correlogram was about 2 msec (B), which is compatible with a monosynaptic excitation from the geniculate cell. This suggests that the cortical cell must get additional visual afferent input, possibly with a less powerful drive as can be judged from the PSTH.

Of the 8 complex cells, in which a geniculo-cortical excitation could be demonstrated in the cross-correlograms, the geniculate partner happened to be a phasically responding, presumably Y-cell in 3 pairs and the peak latencies in this group were between 1.2 and 2.0 msec, while in the other 5 pairs the geniculate cells showed sustained responses to stationary stimuli and the peak latencies were 3.0–6.0 msec, suggesting X-cells. In all cases, the RFs of the two partner cells were completely or partially overlapping. These findings support the view that complex cells as defined here may be driven monosynaptically from geniculo-cortical afferents of the X- or Y-type, but due to the experimental design we were not able to determine completely the degree of afferent excitatory convergence on these complex cells in the deeper cortical layers.

Acknowledgements. We wish to thank Mr. I. Hammond and D. Michael for improving the computer programme of cross-correlation analysis, and Mrs. R. Rauschenbach and J. Tolksdorf for preparing the figures. C. R. Legéndy was supported by the Alexander von Humboldt Stiftung.

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Accepted January 16, 1978