1

Synaptic Interactions between Cortical Neurons

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1. Introduction

We know a good deal more about the anatomical structure and the topographical organization of the cerebral cortex than about the neural interactions that mediate information processing within cortical networks. For example, cortical columns are commonly assumed to represent a functional module that is replicated in different cortical regions, but the intrinsic synaptic interactions between neurons in such a module are just beginning to be elucidated. How neural activity is processed within cortical columns and how synaptic linkages shape the response properties of cortical cells are being investigated with a variety of correlation techniques. Understanding the synaptic interactions between cortical neurons is an essential prerequisite for explaining the neural operations performed by cortical networks.

A major hypothesis of cortical organization suggests that information is processed by cortical columns and that such modules may have comparable intrinsic structure in different cortical regions. Such a columnar organization is suggested by the anatomical orientation of afferent fibers and cortical cells, and is further supported by the observation that cells within a column often code

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similar response properties. Yet simply documenting the response properties of single neurons does not define the intrinsic interactions between the cells that underlie the extraction of response features. To understand how the intrinsic network connections subserve the computation performed by cortical cells requires information about their synaptic interactions.

1.1. Measures of Synaptic Interactions

The synaptic interactions between neurons can be measured directly by two techniques (Fig. 1): cross-correlation and spike-triggered averaging (STA). If the action potentials of two neurons are recorded simultaneously, a cross-correlation histogram (CCH) will reveal changes in firing probability of one neuron relative to the spikes in the other. The peaks and troughs of the CCH can be interpreted in terms of underlying synaptic connections (Moore *et al.*, 1970; Perkel *et al.*, 1967; Kirkwood, 1979). If one of the neurons is recorded intracellularly, the action potentials of the other can be used to compile STA of the membrane potential, revealing the postsynaptic potentials (PSPs) produced by synaptic linkages. Each technique offers certain advantages. Cross-correlating activity of simultaneously recorded pairs of cells is simpler *in vivo,* particularly in behaving

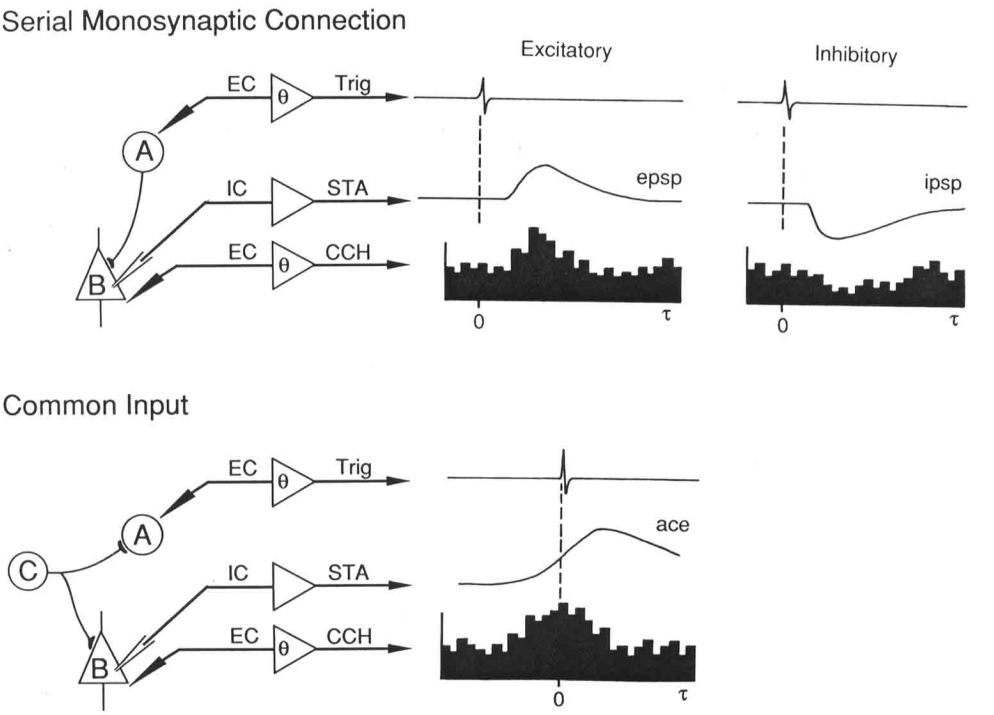

Figure 1. Measurements of synaptic interactions between cortical cells. (Top) A monosynaptic connection between cells A and B can be detected by using extracellular recording (EC) of spikes from A to generate triggers for STAs of intracellular recording (IC) of membrane potential of B. This yields an EPSP or IPSP. Alternatively, extracellular recording of B can be used to calculate a CCH, providing the statistical increase or decrease in firing produced by the connection. A common synaptic input from a third cell, C (Bottom), can be measured in similar ways. The intracellular recording yields the average common excitation potential (ace) and the CCH yields a central peak straddling the origin of the correlogram. τ is time relative to the trigger spike.

animals; this allows one to identify the normal response properties of the correlated cells and to make inferences about the functional consequences of the synaptic interactions in shaping their response properties. The disadvantage of cross-correlation is its limited ability to resolve the statistical effects of weaker connections between the recorded cells. STA of synaptic potentials is considerably more sensitive in detecting synaptic interactions, particularly inhibitory connections, and in defining the latency and time course of the synaptic potentials. But STA requires stable intracellular recording, which can be difficult for *in vivo* preparations and for small target cells. The STA technique has provided good results in cortical slice preparations, in which the layers of the source and target cells can be identified accurately.

Before reviewing the experimental results obtained from cortical cells, it is useful to consider the relation between the PSPs and the cross-correlation features that they produce. If cell A has an excitatory connection to cell B, every spike in cell A would produce a monosynaptic excitatory PSP (EPSP) in cell B after the conduction delay; this can be documented by STA of the intracellular membrane potential (Fig. 1, top). If cell B is active, these EPSPs would enhance its firing probability, producing a peak in the CCH between A and B. The relation between the shape of the EPSP and the CCH peak it produces has been quantified most thoroughly in motoneurons (Fetz and Gustafsson, 1983; Cope *et al.,* 1987). In motoneurons the cross-correlogram peak produced by EPSPs reflects mainly the EPSP derivative. However, synaptic noise that is comparable in size to the EPSP may widen the peak. While the peak becomes wider in the presence of synaptic noise, the correlogram peak area remains relatively preserved. The number of synchronized firings produced in the postsynaptic cell per spike in the presynaptic cell is measured by the correlogram peak area. In motoneurons the number of synchronized spikes per afferent spike increases linearly with EPSP amplitude, with a slope of $1.2 \times 10^{-4}/\mu V$ (Cope *et al.,* 1987). Thus, a single-fiber Ia EPSP of 100 μV produces about 1.2 motoneuron spikes per 100 afferent spikes.

Similar relationships have been found for synaptic potentials in cortical neurons recorded in slices of cat somatosensory cortex (Reyes *et al.,* 1987). Synaptic potentials evoked by white matter stimulation and pulse potentials evoked by intracellular current pulses produced CCH peaks that increased with PSP height, with a similar slope. This relationship can be expected to hold for cells that reset after firing and have a refractory period exceeding the duration of the PSP, such as cortical pyramidal cells and motoneurons. Different relationships appear to apply to cells that may fire repetitively during a single EPSP, such as dorsal column relay cells (Surmeier and Weinberg, 1985), and perhaps cortical interneurons such as stellate cells that generate bursts of activity. For cells that can fire repetitively throughout the EPSP, the correlogram peak may resemble more the EPSP itself, since the firing probability is, to first order, proportional to the EPSP depolarization.

For neurons that fire when the EPSP crosses threshold (typically on its rising edge) and that hyperpolarize after firing, the correlogram peak strongly resembles the EPSP derivative (Knox, 1974; Ashby and Zilm, 1982; Fetz and Gustafsson, 1983). Unlike motoneurons, cortical cells have an additional mechanism to enhance the effectiveness of EPSPs (Fig. 2); in addition to those EPSPs that cross threshold directly, the subthreshold EPSPs may turn on a voltage-dependent inward current that also shortens the interspike interval. As illustrated in

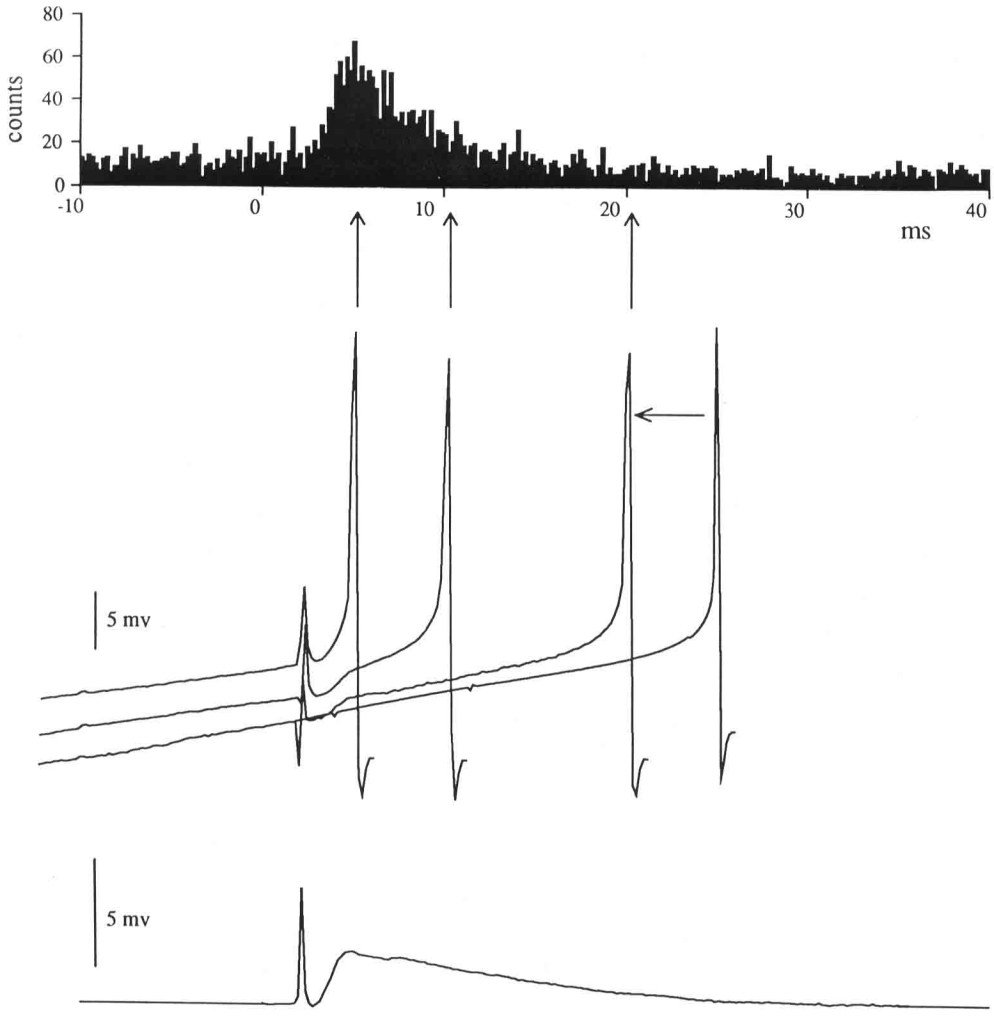

Figure 2. Relation between EPSP and cross-correlogram in a neocortical cell. An EPSP produced by stimulation of white matter in neocortical slice (bottom) produced an increase in firing probability in the CCH (top). Events contributing to counts in the correlogram are illustrated by representative membrane trajectories to threshold with superimposed EPSPs. Counts in correlogram peak are produced by EPSP crossing threshold on its rising edge (exemplified by leftmost trajectory and spike). The rightmost pair of trajectories illustrates a control trajectory and one with an EPSP that shortened the interspike interval (horizontal arrow), not by directly crossing threshold itself, but by turning on a sustained inward current. This contributed to counts past the peak of the correlogram. Reyes and Fetz (unpublished observation).

the rightmost trajectories of Fig. 2, these EPSPs contribute to bins in the CCH after the peak. Although these counts do not appear in the correlogram peak, they clearly contribute to an increase in firing rate by shortening the interspike interval. Thus, EPSPs in cortical cells can have a more potent effect on firing probability than is reflected in the CCH peak.

1.2. Effects of Synaptic Connections

The types of synaptic circuits that generate common correlational interactions are illustrated in Fig. 1 (see Moore *et al.*, 1970; Perkel *et al.*, 1967; Kirk-

wood, 1979). The EPSP produced by an excitatory monosynaptic connection produces a peak in the CCH that is offset from the origin (Fig. 1, top). This peak may be followed by a correlogram trough generated by the advancement of spikes into the peak from the baseline. A serial inhibitory connection produces an IPSP in the STA of intracellularly recorded membrane potential, which generates a trough in the CCH that is also offset from the origin. This trough may be followed by compensatory rebound produced by the delayed spikes.

A third type of connection frequently encountered involves common synaptic input to both of the recorded cells from another neuron (Fig. 1, bottom). An excitatory common source cell (C) would produce nearly synchronous arrival of EPSPs in its targets, generating an average common excitation potential in the STA of the intracellular potential (Kirkwood and Sears, 1978). In the CCH this circuit produces a broad central peak straddling the origin of the correlogram, reflecting the tendency for the common synaptic input to produce synchronous firing (Sears and Stagg, 1976). Such a central peak appears whether the common input is excitatory or inhibitory, although it tends to be broader when the circuit is inhibitory. The effects of synaptic connections from common input cells must be distinguished from the effect of simultaneously arriving input from separate sources. This distinction is particularly important for analysis of sensory cortex cells, which may be coactivated by input evoked by sensory stimuli. As illustrated below, the effect of simultaneous arrival of input from independent pathways can be computed by the shift predictor, derived from shuffled spike trains.

In addition to monosynaptic connections, correlograms and intracellular recordings may also detect effects of polysynaptic linkages. For example, two monosynaptic links in series would produce a disynaptic correlation between the first and third neurons that is the convolution of the successive monosynaptic correlations between the connected pairs (Kirkwood, 1979; Fetz and Cheney, 1980; Fetz, 1988). If both connections are excitatory, the disynaptic EPSP would be broader and more delayed than a monosynaptic EPSP; the corresponding CCH peak would be similarly dispersed. Mediation of such disynaptic effects is of course contingent on the coactivation of all three neurons, and could be gated by the intervening neuron. Although a single disynaptic linkage is considerably weaker than a monosynaptic effect, the net polysynaptic interaction between any two cells is the summed effect over all possible interneurons, and their number may be sufficient to compensate for the weakness of a single disynaptic link.

2. Visual Cortex

2.1. Application of the Cross-Correlation Technique in the Visual System

Interneuronal interaction in the visual system has been studied by recording simultaneously from two or more cells in the same or different brain regions and cross-correlating their activities. The visual system has an advantage over other sensory and motor systems because visual neurons generally demonstrate a well-defined receptive field and response selectivity, which provides helpful cues in the search for correlated neuronal pairs and helps in understanding the functional implication of the demonstrated interaction. The visual system also has precise functional architectures, such as retinotopy, orientation and ocular domi-

nance columns, and laminar structures, which greatly facilitate description and understanding of the neuronal interaction in the visual cortex.

A disadvantage for impulse cross-correlation studies is that visual neurons, particularly those in the visual cortex (area 17), generally demonstrate relatively little spontaneous discharge, making cross-correlation in the resting condition difficult. This problem is solved by activating cells visually by photic stimulation or chemically by electrophoretic application of glutamate, a potent excitant for cortical cells (Kimura *et al.*, 1976; Toyama *et al.*, 1981a; Toyama and Tanaka, 1984). When visual stimulation is employed, the paired cells tend to be activated conjointly by the stimuli. Therefore, the CCH of their impulse discharges includes the pseudointeraction due to coactivation by the visual stimulation as well as the net neural interaction conveyed through the synaptic connections (Perkel *et al.*, 1967). When visual stimulation is applied at fixed intervals, the stimulus-mediated pseudointeraction can be determined by the shift predictor, which is the CCH obtained by cross-correlating the impulse train of one cell with the train of the partner cell, which has been artificially shifted by one stimulus interval. This destroys the time-dependent neural interaction between the paired cells but still preserves the stimulus-mediated coactivation. The neural interaction is then obtained by subtracting the shift predictor from the CCH of activity during visual stimulation (Perkel *et al.*, 1967; Kimura *et al.*, 1976; Toyama and Tanaka, 1984).

Visual stimulation generally activates a group of cells that are responsive to the stimulus; likewise, chemical stimulation activates multiple cells around the recorded cell (within a radius of about 100 μm). Therefore, CCHs may contain the interaction mediated by the common synaptic input shared by the paired cells in addition to the serial synaptic interaction conveyed through direct interneuronal connections (Toyama and Tanaka, 1984; Toyama, 1985). The contaminating effect of the common pathways was significant only in case of visual stimulation (see below).

Chemical activation is free of these problems, but requires a double-barrel microelectrode, one for recording and one for electrophoretic injection of chemical excitants such as glutamate (Toyama and Tanaka, 1984; Toyama, 1985). The stimulation effect of glutamate injection appears to be confined within 100 μm, and the number of activated cells is estimated to be less than a few hundred, many fewer than are activated by visual stimulation. Moreover, these cells are activated less synchronously. The problem with chemical stimulation is desensitization, which impedes prolonged stimulation; continuous stimulation with glutamate lasting for more than a quarter of an hour is difficult.

2.2. Geniculocortical Interaction

2.2.1. X- and Y-Geniculate Inputs

Transfer of visual signals to cortical cells was investigated by cross-correlating activities of the retinal or geniculate cells with those of cat visual cortical cells (Lee *et al.*, 1977; Tanaka, 1983). Tanaka (1983) recorded simultaneously from a number of geniculocortical pairs whose response types were identified. The geniculate cells were comprised of the X- and Y-types and the cortical cells included Eon/Eoff (subtype of simple cells with exclusively ON/OFF response

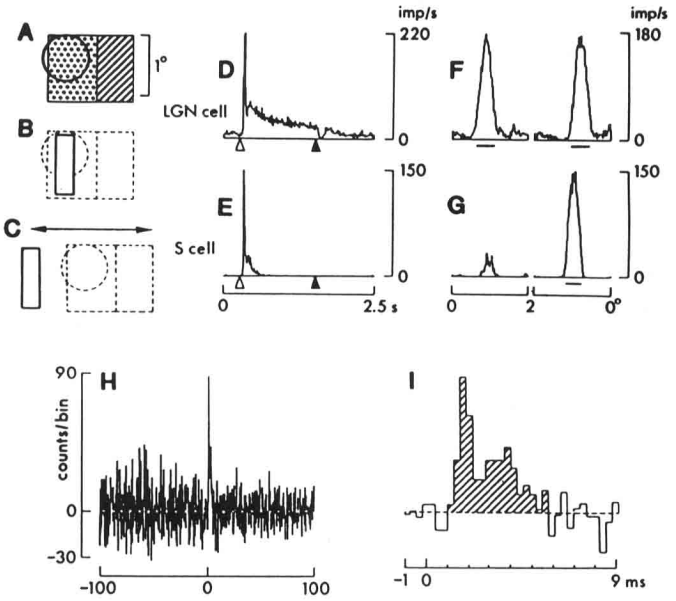

Figure 3. Cross-correlation study of geniculostriate connection. (A) Receptive field of an ON-center X-geniculate cell (circle) and of a simple cell (rectangle; stippling: ON response area; hatching: OFF response area). (B) A stationary light slit presented to the receptive fields of geniculate and simple cells. (C) Moving light slit. (D, E) Responses to stationary stimulus for geniculate and simple cells, respectively. Open and filled triangles represent onset and offset of stationary stimulus, respectively. (F, G) Responses of geniculate and simple cells, respectively, to the moving stimulus. Abscissa represents the space axis converted from time axis based on velocity of the stimulus. (H, I) CCH determined for responses shown in F and G with slow (H) and expanded (I) time axes. The hatched area represents the total number of impulses contained in the excitation of the simple cell by the geniculate cell. The contribution of geniculocortical excitation to the photic response of the striate cell was 0.21. From Toyama and Tanaka (1984).

area), simple cells, and standard and special complex cells (Hubel and Wiesel, 1962; Toyama and Tanaka, 1984; Gilbert, 1977). Cross-correlation of their activities during visual stimulation was studied in relation to the response types.

Figure 3A illustrates receptive field structures of a geniculocortical pair where serial transfer of excitation was demonstrated from the geniculate to the cortical cell. The geniculate cell is the X-type with ON-center field (solid circle in A) and the cortical cell is the simple type with adjoining ON (stippled) and OFF response areas (hatched). The ON-center field of the geniculate cell is completely contained in the ON response area of the simple cell, suggesting that the excitation conveyed from the geniculate cell contributes to the ON response of the simple cell. In agreement with this view, the CCH of their activities, corrected for the shift predictor and representing the net neural interaction, demonstrated a clear positive correlation, which occurred with a short delay (2 msec), rapidly attained a peak (in 1 msec), and lasted for several milliseconds (Fig. 3H and I). The contribution of the serial excitation to the simple cell response was determined as the ratio of the number of impulses contained in the serial excitation (hatched area in Fig. 3I) to that contained in simple cell response to the moving stimulus and was rather small (0.21), indicating that the receptive area of the simple cell was constructed by convergence of excitation from multiple geniculate cells.

Table I. Frequency of Geniculocortical Connections[a]

Geniculate cell	Striate cell			Total
	Eon/Eoff	Simple	Complex	
X	8	18	17	43
Y	1	4	31	36
Total	9	22	48	79

[a]Numbers of observed cases of connections from geniculate X and Y cells to identified visual cortex cells. From Toyama and Tanaka (1984).

Responsiveness to visual stimulation was slightly different for geniculate and cortical cells in two ways. First, response to a stationary light slit (thick solid line in Fig. 3B) lasted longer in the geniculate cell (Fig. 3D) than in the simple cell (Fig. 3E). Second, the geniculate cell responded almost equally to a light slit moving forward and backward (Fig. 3F), while the simple cell responded much more strongly to backward motion than to forward motion (Fig. 3G), suggesting that cortical inhibition is involved in emergence of the cortical cell's differential responsiveness to the direction of motion.

Serial excitation was demonstrated in about one-third (82/243) of the geniculocortical pairs with overlapping receptive areas (Table I). It is remarkable that the geniculate excitation was transferred to all types of cortical cells, but with a strong bias toward certain response types of cortical cells: there were pure Y-geniculate inputs to the special complex cells, mixed X and Y (but predominantly X) inputs to the simple cells, Eon and Eoff, and similar mixed X and Y (but predominantly Y) inputs to the standard complex cells (Table I). These differential X and Y inputs may contribute to the difference in cortical cell responsiveness.

2.2.2. On- and Off-Center Inputs

Another important finding was strict correspondence in the polarity of response areas between the geniculocortical pairs. Exact correspondence such as that between the ON-center field and ON response area of the geniculocortical pairs illustrated in Fig. 3A was found in all of the geniculate versus Eon, Eoff, or simple pairs that exhibited serial excitation. This finding is consistent with the double-line model, assuming that the ON or OFF response areas of the simple, Eon and Eoff cells are constructed by selective convergence of ON- or OFF-center geniculate cells, respectively (Bishop *et al.*, 1971). Since the diameter of the ON- or OFF-center area of the geniculate cells was approximately the same as the width of the ON or OFF response area of the cortical cells, an elongated response area in a cortical cell may be constructed by convergence of excitation from multiple geniculate cells whose receptive areas are lined up along the axial orientation of the receptive area of the cortical cell.

The following evidence supports this view. First, in the simple Eon and Eoff cells, the contribution of the serial excitation was roughly 0.1, which indicates that about 10 geniculate axons converge onto these cells. The contribution was much smaller (about 0.03) in the standard and special complex cells with larger receptive areas, suggesting convergence of more geniculate cells onto these cells.

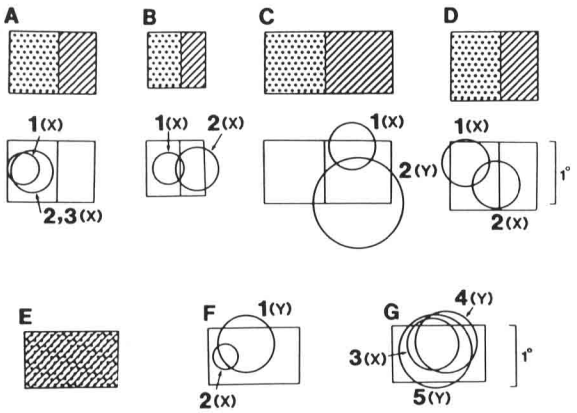

Figure 4. Convergence of geniculate inputs onto single striate cells. (A) Convergence of inputs from three geniculate cells on a simple cell. The simple cell receptive field illustrated at top includes an ON response area (stippling) and an OFF response area (hatching); the center fields of the three geniculate cells (circles, at bottom). (B–D) Similar diagrams representing convergence of geniculate inputs on three other simple cells. (E–G) Convergence of inputs from five geniculate cells (F, G) on single complex cell (E). From Toyama and Tanaka (1984).

Second, convergence of geniculate inputs was demonstrated by cross-correlating multiple geniculate cells with a single cortical cell. Figure 4 illustrates four simple cells that received convergence from two X-geniculate cells (A, B, D) and from one X- and one Y-geniculate cell (C). It also shows a complex cell that received convergence from five (two X- and three Y-) geniculate cells (E–G). Third, in all cases of the simple and complex cells illustrated in Fig. 4, the center fields of the geniculate cells were more or less offset along the receptive area axis of the simple (A–D, horizontal direction) or complex cell (E–G, vertical direction).

An essentially similar observation was made in a cross-correlation study of retinal ganglion cells and simple cortical cells (Lee *et al.*, 1977). Cross-correlating neuronal pairs with overlapping receptive areas during visual stimulation revealed serial excitation in 6 of 29 pairs. The serial excitation closely resembled that reported by Tanaka (1983) in the geniculocortical pairs except for a longer delay (4–5 msec) and longer duration (10 msec), which is attributed to the longer conduction distance and an additional synaptic relay at the geniculate nucleus. Interestingly, the contribution of the serial excitation to the visual responses (determined by Lee *et al.* from their figures) was roughly the same (0.2–0.3) as that reported by Tanaka (1983) for the geniculate–simple pairs; this is consistent with the finding that an almost one-to-one connection is established between the retinal ganglion and the geniculate cells representing the central visual field (Levick *et al.*, 1972). In accordance with Tanaka's results, X-input to the simple cells predominated over Y-input: there was only X-input in three cases, only Y-input in one, and both X- and Y-inputs in one case.

2.3. Corticogeniculate Interaction

Although Tanaka (1983) did not detect cross-correlation evidence of corticogeniculate signal transmission, Tsumoto *et al.* (1978) reported CCHs representing geniculocortical excitation transferred between the cell pairs with over-

lapping receptive areas (18/114), and geniculocortical inhibition between those with slightly offset receptive areas (8/114).

2.4. Intra- and Intercolumnar Interaction in Single and Adjacent Functional Columns of the Visual Cortex

2.4.1. Basic Patterns of Neuronal Interaction

Intra- and intercolumnar neuronal interactions were studied by simultaneous recording of cells in single and adjacent columns with a two-electrode (Toyama *et al.*, 1981a,b; Ts'o *et al.*, 1986; Ts'o and Gilbert, 1988) or multielectrode (Michalski *et al.*, 1983; Kruger and Bach, 1980; Aiple and Kruger, 1988; Kruger and Aiple, 1988) assembly. The results obtained in these studies are in general agreement. Three basic types of neuronal interaction have been demonstrated: common excitation, serial excitation, and serial inhibition (Toyama *et al.*, 1981a).

2.4.1a. Common Excitation. Figure 5A illustrates the common excitation representing the effects of common synaptic inputs to the paired cells, which was the most frequently found correlation during visual stimulation. A sharp

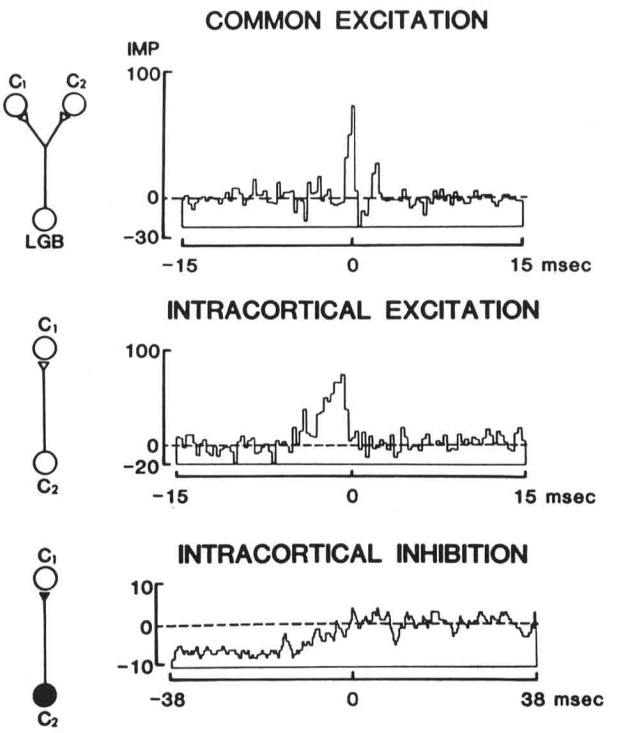

Figure 5. Patterns of intracortical synaptic interactions revealed by CCHs of impulses in two visual cortex cells activated by chemical or photic stimulation. Pseudocorrelation produced by stimulus activation was eliminated by the shift predictor. The peak and trough to the left of the origin indicates serial connection from the reference (C_2) to the trigger cell (C_1). From Toyama and Tanaka (1984).

positivity in the CCH, extending for only 1 msec around zero time, indicates the tendency for the paired cells to be coactivated in precise synchrony. In principle, the neuronal pair may be activated conjointly if it receives a common input, either excitatory or inhibitory, and tends to discharge conjointly (Perkel *et al.*, 1967). However, the precise synchronization of their activities suggests that it is produced by potent excitatory inputs from the lateral geniculate cells. This view is consistent with the fact that the recipient cells of the common excitation are located in the middle layers of the visual cortex where the geniculate axons terminate (see below).

In addition to the sharp common excitation probably due to the shared geniculate inputs, some investigators have reported a broad common excitation extending for several tens of milliseconds around the origin, indicating rather loose synchronization in neuronal activities (Michalski *et al.*, 1983; Aiple and Kruger, 1988; Kruger and Aiple, 1988). The broad common excitation was superposed on the sharp common excitation or appeared in isolation. The source of the broad common input peaks is not clear. However, the common excitation could be mediated by a diffuse intracortical positive feedback system provided with intracolumnar supragranular–layer V, layer V–supragranular, or transcolumnar supragranular–supragranular connections, which may serve to reinforce activities of neuronal groups with like function (see below). Alternatively, it could be transferred by a nonspecific thalamic system that might be involved in control of selective visual attention (Wurtz and Mohler, 1976; Singer, 1979).

2.4.1b. Serial Excitation. Less commonly found is evidence for serial excitation, which is expressed as a positive correlation asymmetric to the origin (Fig. 5B). The correlation peak occurs with a short delay (about 1 msec), attains a maximum in 1 msec, and declines gradually for several milliseconds. A peak to the left of origin indicates serial transfer of excitation from the reference cell (C_2) to the trigger cell (C_1).

2.4.1c. Serial Inhibition. The last type of correlation is serial inhibition (Fig. 5C), which is represented by a negative correlation asymmetric to the origin. The negative correlation occurs with a delay of 1 msec and continues for several tens of milliseconds, indicating serial transfer of inhibition from one cell to the other.

2.4.2. Relation between Interaction Patterns and Response Types

Toyama *et al.* (1981b) studied CCHs of neuronal pairs sampled in layers II–IV during visual and chemical stimulation in relation to the response types. The most frequent type of neuronal interaction observed with visual stimulation was common excitation (95/185 = 51%), which appeared in combinations between all types of visual cortical cells (Eon/Eoff, simple, and complex). Common excitation occurred most frequently and was strongest, as quantified by the contribution to the response, between neuronal pairs of the same response types (Table II).

Similar observations were reported by Michalski *et al.* (1983), who investigated the interaction in neuronal pairs sampled with multichannel tungsten electrodes. Common excitation occurred in about two-thirds (61%) of the 286 neu-

Table II. Rate of Occurrence of Common Excitation[a]

From cell	To cell			
	Eon or Eoff	Simple	Complex	Hypercomplex
Eon or Eoff	0.67 (8/12)	0.38 (6/16)	0.47 (8/17)	0 (0/2)
Simple		0.6 (21/35)	0.72 (26/36)	0 (0/6)
Complex			0.51 (23/45)	0.15(2/13)
Hypercomplex				0.33(1/3)

[a]Figures indicate rate of occurrence of common excitation for each combination of response type. Numerators in parentheses represent the number of neuronal pairs in which common excitation was detectable, and denominators the number of neuronal pairs studied. From Toyama and Tanaka (1984).

ronal pairs, including all combinations of the simple and complex cells. The findings of Toyama *et al.* (1981b) and Michalski *et al.* (1983) are consistent with those of Tanaka (1983) that all of the Eon, Eoff, simple, and complex cells could receive excitation from both X- and Y-geniculate cells.

Toyama *et al.* (1981a,b) found that serial excitation appeared rarely (19/185 = 10%) and was confined to two combinations of response types, from complex to complex cells (14/19) and from complex to hypercomplex cells (5/19). Michalski *et al.* (1983) reported a slightly higher incidence of serial excitation (20%). One reason for the higher proportion may be that Michalski *et al.* identified serial excitation by CCHs obtained during visual stimulation, while Toyama *et al.* (1981a,b) required consistent demonstration of the serial CCH peaks during visual and chemical stimulation. The serial excitation demonstrated during visual stimulation was frequently contaminated by strong common excitation, which made identification difficult. In such cases, the excitation was identified as serial only if it was confirmed by analysis during chemical stimulation. Serial excitation was studied by Michalski *et al.* in relatively few neuronal pairs in relation to the response types, but one case of slight serial excitation, transferred from a simple to a complex cell, was superposed on strong common excitation.

Serial inhibition also occurs in relatively few neuronal pairs. Toyama *et al.* (1981a,b) found serial inhibition in just 23 of 185 pairs (12%) and in only three combinations, between Eon and Eoff (8/23), from Eon/Eoff to simple (3/23), and from simple to complex (12/23). Michalski *et al.* (1983) reported similar serial inhibition, but it was slightly less frequent (7%) and much weaker than that demonstrated by Toyama *et al.* (1981a,b). This difference may be due to differences in experimental methods: Michalski *et al.* used only the CCHs during visual stimulation, which produced serial inhibition superposed on common excitation, while Toyama *et al.* depended more on CCHs obtained during chemical stimulation, which demonstrated serial inhibition in isolation from common excitation.

2.4.3. Range of Neuronal Interaction

The recipient area of these neuronal interactions was studied by cross-correlating activities in many cells (circles in Fig. 6A) sampled with a microelectrode advanced perpendicularly to the cortical surface with activity of a single reference cell (double circle) sampled with an obliquely advanced microelectrode (Toyama *et al.*, 1981b). The recipient area of the common excitation

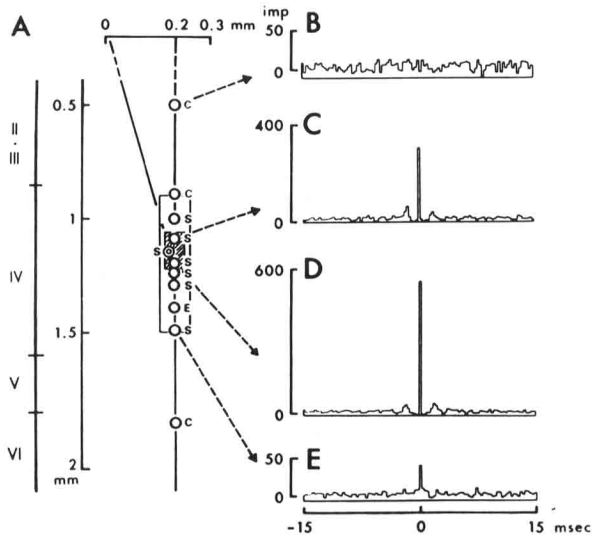

Figure 6. Depth profile of distribution of common excitation in visual cortex. (A) Diagram of location of cells recorded along vertical and oblique electrode tracks. Circles are test cells sampled by vertical electrode. Double circle indicates reference cell recorded by oblique electrode. Letters represent response types of cells (S, simple cell; C, complex cell; E, Eon cell). Hatched rectangle indicates area within which test cells exhibited strongest common excitation with reference cell; open rectangle represents area of weak common excitation. (B–E) CCH obtained from representative cell pairs. From Toyama *et al.* (1981b).

existed in the middle layers of the visual cortex. When cross-correlated with a simple reference cell in layer IV (double circle in Fig. 6A), common excitation was demonstrated in all of the eight partner cells, including one Eon, six simple, and one complex cell (single circles) located in a region roughly within a few hundred micrometers above or below the reference simple cell. Common excitation was extremely strong in simple cells close to the reference simple cell (Fig. 6B) and decreased as a function of the distance between the partner and reference cells (Fig. 6C–E; see also Figs. 7B–D and 8B–E). No common excitation was demonstrable for two complex cells several hundred micrometers distant from the reference cell (Fig. 6B). The recipient area of common excitation extended rather broadly from layer III to layer V (open rectangle in Fig. 6A), and there was a small area where partner cells exhibited extremely strong common excitation (hatched rectangle).

Common excitation is shared even between neuronal pairs with different orientations (by as much as 40°) and with opposite directional preference, but never between pairs with different ocular dominance. Therefore, the recipient area of the common excitation extends perpendicularly across several hundred micrometers in the middle layers of the visual cortex, and tangentially across many orientation columns, but is limited to a single ocular dominance column. In agreement with this view, Michalski *et al.* (1983) also reported common excitation shared between cells separated by a horizontal distance of 1 mm and probably located in different functional columns. The findings in the two laboratories indicate that single geniculate axons activate cortical cells of diverse response types contained in many orientation columns of a single ocular dominance column.

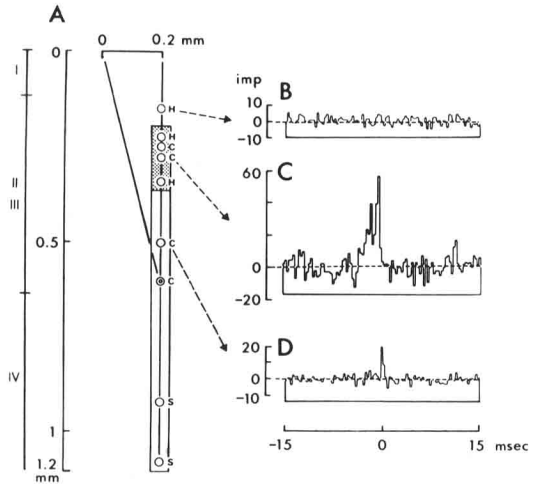

Figure 7. Depth profile for intracortical excitation. (A) Diagram similar to Fig. 6. H represents hypercomplex cell. Stippled rectangle represents area within which test cells received intracortical excitation from the reference cell. (B–D) CCHs for three representative cells. From Toyama *et al.* (1981b).

In contrast to common excitation with its broad spatial distribution, serial excitation had a rather localized distribution. The source cells were often located in the border area between layers III and IV (double circle in Fig. 7A), and the recipient area was located in layers II–III a few hundred micrometers superficial to the source cell (stippled rectangle). Serial excitation was demonstrable in all cells in the recipient area (two complex and two hypercomplex cells in the case illustrated in Fig. 7). Serial excitation was restricted to neuronal pairs with similar orientation preference (difference $< 15°$) and the same directional and ocular preferences. Therefore, the recipient area of the serial excitation would probably be limited tangentially to a single orientation and ocular dominance column, and perpendicularly to a distance of about 200 μm. Michalski *et al.* (1983) also reported that serial excitation was limited to neuronal pairs in the same functional column.

Likewise, serial inhibition was limited to a small cortical space. The source cells of the serial inhibition were usually located in or near layer IV (solid circle in Fig. 8A), and recipient cells appeared in a cluster in a region of layers III–V extending across a perpendicular distance of a few hundred micrometers (Fig. 8A). The recipient cells regularly demonstrated the same ocular preference as the source cell, but could have the same or different (as much as 20–30°) orientation preference and the same or opposite directional preference. Therefore, the recipient area of the serial inhibition was also confined to a single ocular dominance column but extended across several orientation columns and across a perpendicular distance of a few hundred micrometers.

2.4.4. Contribution of Neuronal Interaction

Toyama *et al.* (1981a,b) reported that the contribution of common excitation varied greatly (0.1–0.7) according to the response types. In general, it was larger between cells with the same response types than between those with different response types. In cell pairs with the same response types, common excitation was largest for Eon/Eoff cells, modest for simple cells, and smallest for complex cells (Table II). They found contributions of a similar order of magnitude for serial excitation (0.1–0.3) and inhibition (0.1–0.2). Michalski *et al.* (1983) re-

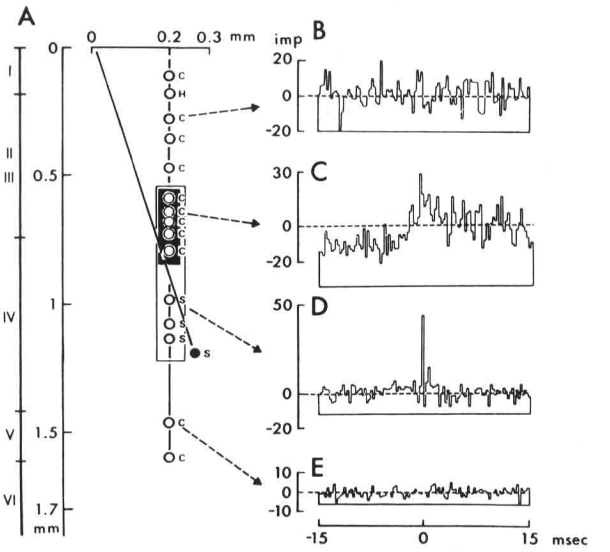

Figure 8. Depth profile for intracortical inhibition. (A) Diagram similar to Fig. 6. Solid circle is reference cell. Solid rectangle, zone of intracortical inhibition. Open rectangle, zone of common excitation. (B–E) CCHs for representative cells. From Toyama *et al.* (1981b).

ported the same range of contribution values (0.1–0.3) for common and serial excitation.

2.5. Transcolumnar Interaction between Distant Columns

To investigate spatially periodic interactions, Ts'o *et al.* (1986) sampled numerous supragranular cells (dots in Fig. 9A) with one microelectrode advanced perpendicularly to columnar structures over a distance of several millimeters, while holding a single reference cell (asterisk) in the supragranular layer with another electrode. They demonstrated positive correlation of neuronal activities in distant columns. The strength of the correlation was reduced with the distances between the neuronal pairs, but not as a monotonic function of distance. The positive correlations waxed and waned over successive sites, with a tendency for cells with positive correlation to appear in clusters. For most of the neuronal pairs, the positive correlation straddled the origin of the CCHs, but many peaks were asymmetric to the origin, suggesting that the CCH may represent a mixture of common and serial excitation.

The strength of the positive correlations depended on the ocular dominance and orientation preferences of the neuronal pairs. Strong correlations were predominant in neurons whose orientation preference differed by less than 30°, and were absent in cells whose orientation preferences differed by more than 60°. Likewise, correlations were stronger in neurons with the same ocular preference than in cells with opposite preferences. No such dependency was found for directional preference of stimulus movement.

Comparable results were obtained in monkey striate cortex (Ts'o and Gilbert, 1988), where color coding was also examined (Table III). Cells with similar orientation preference (within 30°) showed a higher incidence of cor-

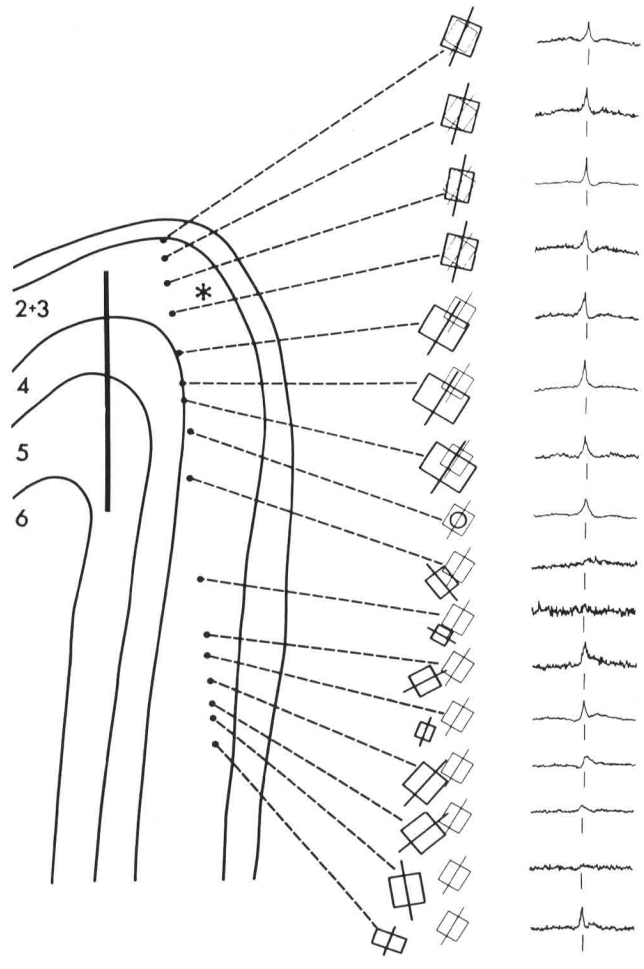

Figure 9. Correlations between cells in medial bank of cat visual cortex. Traces at right are corrected CCHs between reference cell (*) and cells recorded in a tangential track at sites indicated by dots. Receptive field of reference cell was 1° × 1°, with orientation preference of 60°, as shown by light lines; receptive fields of test cells are shown by dark lines. Correlogram peaks indicate strongest correlation between cells of similar orientation. From Ts'o *et al.* (1986).

relogram peaks (77%) than cells with different orientation preference (3%). Cells with similar ocular dominance (differing in group ranking of 2 or less) showed a higher incidence of correlogram peaks (66% for interblob cells and 58% for blob cells) than cells with different ocular dominance (5 and 0%, respectively). In addition, these authors found a higher incidence of synaptic interactions between blob cells with similar types of receptive field and color opponency (76%) than between cells that differed in these properties (10%). There was no synaptic interaction between blob and interblob cells.

Studying correlations between pairs of infragranular cells in monkey striate cortex, Kruger and Aiple (1988) distinguished between narrow and broad correlogram peaks. The narrow peaks were only a few milliseconds wide; in layer VI cells they extended over about 220 μm and depended on ocularity. In layer V cells the range of the narrow peaks was greater and their dependence on ocularity was weaker. The broad correlogram peaks were 30 to 100 msec wide

Table III. Relation between Receptive Field Properties and Correlation Peaks[a]

Cells	Peaked (%)	Not peaked (%)	Sample size	Significance
Interblob cells				
Orientation				
Similar	77	23	82	$p<<0.005$
Different	3	97	36	
Ocular dominance				
Similar	66	34	97	$p<<0.005$
Different	5	95	21	
Blob cells				
Ocular dominance				
Similar	58	41	51	$p<<0.005$
Different	0	100	48	
RF type and color opponency				
Similar	76	24	36	$p<<0.005$
Different	10	90	63	
Interblob cells versus blob cells				
	0	100	32	

[a]Pairs of cells were recorded in primate visual cortex and cross-correlated. Correlograms were designated as "peaked" or "nonpeaked" according to the strength of interaction. Orientations of pairs of interblob cells were considered similar if they differed by 30° or less. The ocular dominance of cells was considered similar if their group ranking differed by 2 or less [with groups ranging from 1 (100% contralateral) to 7 (100% ipsilateral)]. The receptive field types of pairs of blob cells were classed as "same" if the chromatic and spatial classifications (Types I, II, mod II, III, IV) were identical and the color opponencies and signs (ON versus OFF spatial organization) were identical. Significance level was computed with a chi-squared contingency test. From Ts'o and Gilbert (1988).

and extended over distances larger than 1 mm; broad peaks were strongly dependent on ocularity and on receptive field separation.

Although the positive correlation represented by the narrow common excitation peaks may be at least partly mediated through the geniculate axons which extend horizontally over a few millimeters (Humphrey *et al.*, 1985), the serial excitation is entirely ascribed to the transfer of cortical excitation by axon collaterals of supragranular cells. Therefore, excitatory signals may be transferred between distant columns with the same ocular dominance and with the same or similar orientation preference. Interestingly, a similar dependence (on ocular dominance and orientation preference and interneuronal distance) was found for the common excitation mediated by the geniculate axons (see above).

It would be interesting to know the relative strength of the trans- and intracolumnar interactions. Direct quantitative comparisons are difficult because Ts'o *et al.* (1986) used a different measure than contribution to express the strength of the transcolumnar interaction. However, the transcolumnar interaction appears to be at least one order of magnitude smaller than the intracolumnar interaction, as judged from the number of impulses used to determine the interactions. Roughly five times as many impulses were used to demonstrate the transcolumnar interaction as for the intracolumnar interaction [about 15,000 in Ts'o *et al.* (1986) versus 3000 in Toyama *et al.* (1981a,b)], and the strength of the

cross-correlation increased as a function of the product of the numbers of impulses in neuronal pairs used for the analysis.

Multiunit recordings with multiple implanted electrodes have revealed oscillatory interaction between distant orientation columns in cat's striate cortex (Eckhorn *et al.*, 1989; Gray *et al.*, 1989; Engel *et al.*, 1990). Such oscillations are demonstrable by binocular stimulation, and are much weaker with monocular stimulation. Figure 10 shows oscillatory multiunit activity (MUA) recorded simultaneously at five recording sites (1–5) separated by 400 μm; receptive fields at these sites overlapped, but orientation selectivity differed (Fig. 10A). Responses were evoked by binocular stimulation with a light bar moved at three different orientations (Fig. 10 B1, C1, and D1). Autocorrelograms demonstrated a strong oscillatory tendency in the visual responses at some recording sites (e.g.,

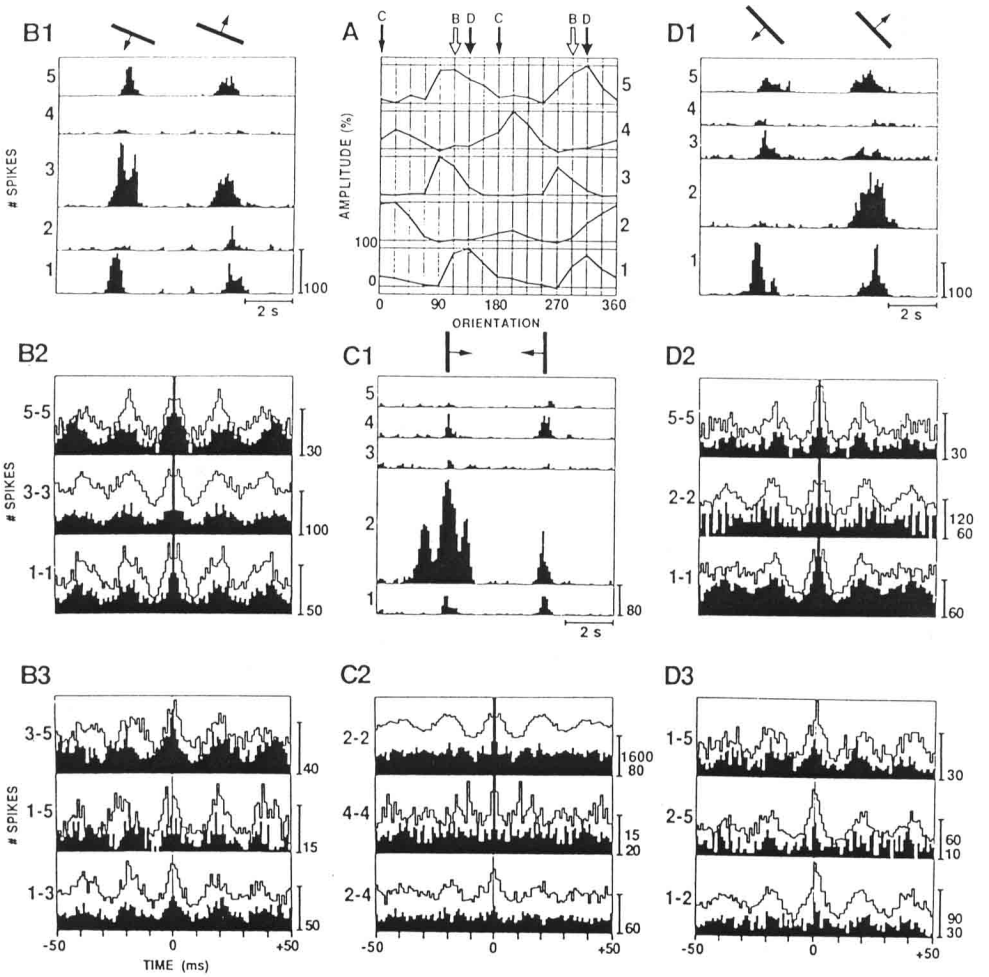

Figure 10. Interactions between oscillatory multiunit activity (MUA) at separate cortical sites. (A) Normalized orientation tuning curves of MUA at five cortical sites (1–5) separated by 400 μm. Arrows indicate the orientation of stimuli evoking responses in B (112°), C (0°), and D (135°). (B1, C1, D1) Stimulus histograms of responses to moving light bars; MUA had overlapping receptive fields. Remaining sections show autocorrelograms at each site, indicated by 1-1, 2-2, etc. and cross-correlograms between sites, indicated by 1-3, 3-5, etc. Open and solid histograms indicate correlograms for forward and backward directions of movement. From Engel *et al.* (1990).

B2 and D2), but not at others (C2). Cross-correlograms between oscillatory units demonstrated that their oscillations tended to be synchronized, usually without any phase difference (e.g., B3). At other sites in this study, where the receptive fields were nonoverlapping, the oscillatory interaction was demonstrable between units with similar orientation preference. Cells with overlapping receptive fields also showed synchronization if their orientation preferences were different. In the latter group, synchronized oscillations occurred even in cases in which the stimulus was optimal for only one of the sites.

These findings suggest the existence of excitatory interaction which extends to many adjacent columns of different orientations; the oscillatory nature of the activity suggests that this interaction involves a positive feedback loop through which the visual responses in the neighboring functional columns can somehow reinforce each other.

2.6. Synaptic Interaction Demonstrated by STA

Cross-correlation analyses of impulse discharges in neuronal pairs have provided much important information about synaptic interactions between identified visual cortical cells. However, the application of impulse cross-correlation has been restricted to the basic circuitry of the visual cortex, which probably consists of focal and dense axonal projections. Many neural connectivities suggested by morphological studies (Gilbert, 1983) continue to elude detection by impulse cross-correlation. These pathways probably involve diffuse and weak axonal projections, whose effects are difficult to demonstrate by impulse cross-correlation. Study of single-fiber-evoked EPSPs in spinal motoneurons indicates that EPSPs below 80 μV produce no significant cross-correlation peaks (Cope *et al.*, 1987). A slowly rising EPSP would produce a broad, shallow correlogram peak that may not reach statistical significance, particularly if synaptic noise is high (Fetz and Gustafsson, 1983). Although the effect of a single axonal projection may be small, the convergence of many axons could have a significant net effect on the response selectivity of the cortical cells and information processing in the visual cortex. Another potential problem is the relatively low sensitivity of CCH to detect inhibition, as suggested by a simulation study of interneuronal interaction (Aertsen and Gerstein, 1985). However, this conclusion should be reconsidered in light of the strong shunting action of cortical inhibition demonstrated by STA (see below).

Komatsu *et al.* (1988) compiled STAs of unitary synaptic potentials in slice preparations of cat visual cortex (Fig. 11). Using glutamate stimulation to evoke spikes (upper traces), they recorded a target cell intracellularly in the supragranular layer with one microelectrode (upper trace in Fig. 11A) while obtaining extracellular recordings from a cell in the juxtagranular region with another electrode, using glutamate stimulation to evoke spikes (lower traces). Inhibitory PSPs (IPSPs) were revealed by superposing or averaging the intracellular trace of the target cell, triggered by the largest impulses in the extracellular trace (Fig. 11B,C). Thus, the trigger cell is the source cell producing the unitary IPSPs (Fig. 11A). The delay of the IPSPs was roughly 0.6 msec (Table IV), which is as short as that reported for synaptic transmission in central neurons. This short delay may be due to small distances (150 μm) between the target and source cells (Table IV). Although the IPSPs were relatively large (2 mV in

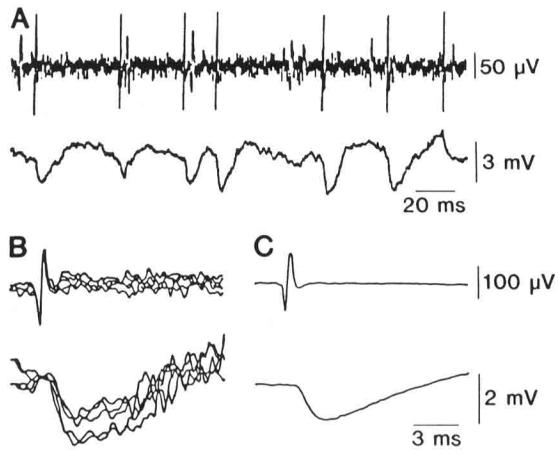

Figure 11. Simultaneous recording of a pair of cells with serial inhibitory connection in visual cortex slice. (A) Extracellular recording of action potentials evoked by glutamate (upper trace) recorded simultaneously with membrane potential recorded intracellularly in neighboring cell (lower trace). (B) Superimposed traces of IPSP. (C) STA of IPSP triggered from 481 impulses. From Komatsu *et al.* (1988).

amplitude) in the trace of Fig. 11A–C, they were enhanced by slight (10 mV) depolarization of the membrane potential, and were much smaller (100 μV) in the resting condition (Table IV; see also Fig. 11B). The strong enhancing effect of the membrane polarization despite the relatively small potential effect indicates that the IPSPs are probably produced at the soma or proximal dendrites, which is consistent with the rapid time course of the IPSPs (Table IV). These IPSPs would thus have a large shunting conductance—probably an order of magnitude greater than that of the unitary EPSPs of the juxtagranular–supragranular pathway (see below), as estimated by the effect of membrane depolarization. This inhibition probably corresponds to the serial inhibition demonstrated by the impulse cross-correlation transferred from layer IV to neighboring cortical cells (Fig. 7).

Likewise, STA demonstrated unitary EPSPs transmitted from juxtagranular cells to supragranular cells (Fig. 12C), which probably corresponds to the serial

Table IV. Neuronal Connections and Unitary PSPs Demonstrated by STA[a]

	Number	Intercellular distance (μm)	Delay (msec)	Amplitude (μV)	Rise time (msec)	Half width (msec)
IPSP						
JG-SG	7/89	150 ± 60	0.6 ± 0.1	90 ± 50	1.6 ± 0.8	7.5 ± 2.7
EPSP						
JG-SG	7/89	230 ± 70	0.7 ± 0.3	140 ± 90	1.7 ± 0.6	6.3 ± 1.8
SG-V	3/27	720 ± 130	2.8 ± 1.4	210 ± 70	1.7 ± 0.1	5.0 ± 0.9
V-SG	4/23	660 ± 80	2.2 ± 0.3	60 ± 30	2.8 ± 0.9	12.8 ± 5.0

[a]The numerators in column "Number" represent number of neuronal pairs with synaptic connections and the denominators represent total number of neuronal pairs examined. JG-SG, SG-V, and V-SG represent juxtagranular–supragranular, supragranular–layer V, and layer V–supragranular connections, respectively. Parameters of unitary PSPs were measured under membrane potentials between −50 and −70 mV without current injection. From Komatsu *et al.* (1988).

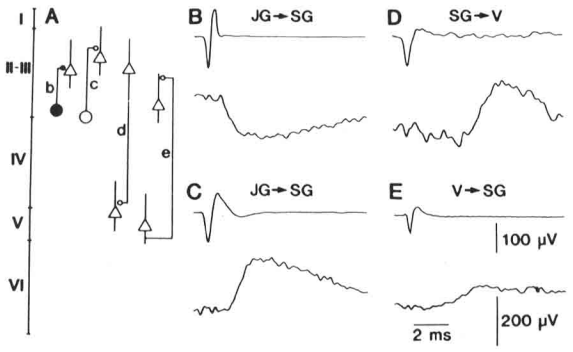

Figure 12. Unitary PSPs demonstrated by STA in cortical slice. (A) Schematic diagram representing laminar location of source and target cells. (B–E) Representative PSPs for the serial connections illustrated in A. See also Table IV. From Komatsu *et al.* (1988).

excitation shown by impulse cross-correlation (Fig. 6). The amplitude and time course of the unitary EPSPs (Table IV) were similar to those of EPSPs in the soma of spinal motoneurons (Cope *et al.*, 1987). The juxtagranular–supragranular EPSPs had a longer delay (0.7 msec) than the juxtagranular–supragranular IPSPs, probably owing to larger distances (230 μm) between the source and target cells (Table IV).

In addition to the synaptic interactions already identified by the impulse cross-correlation technique, STA demonstrated two new types of excitatory interaction between supragranular and layer V cells, in both directions. The supragranular–layer V EPSPs resembled the juxtagranular–supragranular EPSPs (compare C with D in Fig. 12), except for a longer latency (2.8 msec), which is probably ascribable to the longer distances (700 μm) between supragranular and layer V cells (Table IV). In contrast, the layer V–supragranular EPSPs were smaller in amplitude and slower in time course (compare E with D in Fig. 12; see Table IV), suggesting that the EPSPs are produced at remote dendrites of the supragranular cells.

In the established pathways, STA revealed that a cluster of target cells commonly received excitation or inhibition from a single source cell; similarly, neighboring source cells affected common targets, suggesting the existence of dense convergence and divergence in the previously found pathways for synaptic interaction. In contrast, neither the source cell nor the target cell was ever shared between neuronal pairs in the newly found pathways. These results are consistent with the view that the old pathways probably establish focal and dense connections, while the new pathways are comprised of diffuse and weak connections.

Thus, the STA technique was able to elucidate the neural interaction that remained undetected by the impulse cross-correlation technique and is therefore superior in detecting weak and diffuse neuronal interaction.

2.7. Functional Conclusions

The impulse cross-correlation and STA studies have provided a number of important findings concerning structure–function relations in the visual cortex.

Studies of geniculocortical interaction revealed that visual inputs are conveyed through parallel geniculate channels (Xon/Xoff and Yon/Yoff) to a variety of cortical cells, namely: (1) mixed X- and Y-inputs (but predominantly X-inputs) to the simple cells and their subtypes (Eon/Eoff), (2) pure Y-inputs to the special complex cells, and (3) mixed X- and Y-inputs (but predominantly Y-inputs) to the standard complex cells. The differential, although not completely specific, X- and Y-geniculate inputs to various types of cortical cells should contribute significantly to the response types of cortical cells. In support of the double-line hypothesis (Bishop *et al.*, 1971), evidence shows that ON and OFF response areas of the cortical cells are constructed by convergence from the ON- and OFF-center geniculate cells, respectively. The receptive area of the cortical cells is constructed by convergence of several to a few tens of geniculate axons, as estimated by contribution analysis of the serial excitation of cortical cells by geniculate cells.

Cross-correlation analysis also demonstrated the corticogeniculate interaction, which may serve as positive feedback of excitatory signals to the geniculate cells with an overlapped receptive area, and negative feedback of inhibitory signals to those cells with a nonoverlapping receptive area. Since cortical layer VI cells are mostly binocular, the positive feedback may enhance visual signals with binocular disparities within the fusion range, while the negative feedback may depress those beyond the fusion range (Schmielav and Singer, 1977). The negative feedback may also contribute to the end-stop properties of the lateral geniculate cells.

Studies of intracolumnar interaction in the visual cortex have also provided evidence for the parallel model of information processing (Stone and Dreher, 1973; Toyama *et al.*, 1977a,b; Toyama, 1985). Single geniculate axons extend across many orientation columns and over the entire extent of a single ocular dominance column, and they affect cortical cells of diverse response types with the same or opposite directional preference. Therefore, the geniculate inputs are specific to neither the orientation nor the direction selectivity. In contrast, intracortical excitation and inhibition is restricted to a rather small cortical region, probably confined to one or several orientation columns, and is specific to both the response types and orientation preference.

Conclusions about connectivity derived from these studies are summarized schematically in Fig. 13. Selective excitatory inputs from ON- or OFF-center X-geniculate cells yield ON and OFF response areas of Eon, Eoff, and the simple cells (see Fig. 4B), while mixed inputs from ON- and OFF-center Y-geniculate cells construct ON–OFF response areas of the complex cells (see Fig. 4F,G). These geniculate inputs may provide the basis for the response selectivity of cortical cells, such as ocular dominance and orientation and directional selectivity, and the selectivity is refined by cortical inhibition.

Reciprocal inhibition between Eon and Eoff may yield direction selectivity. Inhibition of the simple cell by Eon and Eoff probably mediates antagonistic interaction between ON and OFF response areas of the simple cell, which in turn generates orientation and direction selectivity in the simple cell. Likewise, orientation and direction selectivity in the complex cell may also be produced by inhibition exerted by the simple cells with the same orientation selectivity but with the opposite direction selectivity, as well as by those with different orientation and direction selectivities. Therefore, the primary selectivity is established in the simple cells and their subtypes by intracolumnar inhibition. The higher-

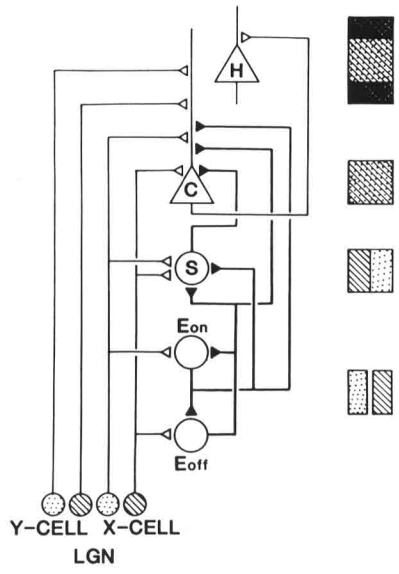

Figure 13. Model of synaptic connections in striate cortex based on cross-correlation experiments. Inhibitory synapses are filled in black. Geniculate inputs from X and Y cells are shown to affect four different classes of striate cell: S, simple cell; C, complex cell; H, hypercomplex cell. Shading indicates ON (stippled area) and OFF (hatched area) regions of receptive fields. From Toyama and Tanaka (1984).

order selectivity is constructed in the complex cells by intercolumnar inhibition extending across several orientation columns in the manner of lateral inhibition; it is further transferred to other complex and hypercomplex cells in the same orientation column by cortical excitation (Fig. 13).

Another remarkable finding is that long-range interaction was exerted between supragranular cells in functional columns representing similar orientation and ocular preference, but separated by a tangential distance of a few millimeters (corresponding to the retinotopic distance of several degrees). This finding indicates the existence of a transcolumnar pathway which conveys excitation between distant functional columns representing similar visual information. The strength of the transcolumnar interaction was estimated as at least one order of magnitude weaker than the intracolumnar interaction, and may serve as a diffuse excitatory system reinforcing activities in a neuronal group of like function, whose existence is suggested by numerous psychophysical and neurophysiological studies (Julesz, 1971, 1984; Hammond, 1984; Livingstone and Hubel, 1988; Gray *et al.*, 1989).

3. Auditory Cortex

As in the visual cortex, synaptic interactions between pairs of cells in the auditory cortex can be tested by cross-correlating spontaneous and stimulus-evoked activity. Cross-correlations between stimulus-driven pairs of cells include the effect of stimulus coordination, which can be subtracted by the shift predictor. Dickson and Gerstein (1974) analyzed interactions between pairs of neurons in the auditory cortex of paralyzed and locally anesthetized cats. They presented a variety of auditory stimuli, including tone and noise bursts. Most neurons in their sample responded to at least one of the auditory stimuli. Central peaks indicated common synaptic input in about 50% of their 168 neuron pairs. The most likely source of this common input was thought to be thalamic medial

geniculate cells. Serial synaptic interactions were relatively rare, appearing in fewer than 5% of the neuron pairs; in some cases, these serial effects were associated with common input. The probability of finding synaptic interactions was a strong function of spatial separation; correlogram features were observed in 93% of neuron pairs recorded with a single microelectrode but only 35% of the pairs recorded with separate microelectrodes.

The authors found evidence that neural coordination was modulated by auditory stimuli in 10% of the neuron pairs. Figure 14 illustrates such a pair of auditory cortex cells, whose CCH of spontaneous activity exhibited a central peak (Fig. 14E). Both units responded to noise-burst stimulation (Fig. 14C,D). The CCH compiled during auditory stimulation (Fig. 14F) showed a large peak. The shift predictor, i.e., the CCH for the spike trains shifted by one stimulus interval (Fig. 14G), had a shallow peak, indicating that the stimulus made a small contribution. Nevertheless, the difference histogram (Fig. 14H) had a larger peak than the CCH of spontaneous activity (Fig. 14E), indicating that the stimulus enhanced the neural interaction. However, 90% of Dickson and Gerstein's correlated pairs had similar CCH peaks for spontaneous and evoked activity, suggesting that synaptic interactions were usually independent of stimulus.

In a similar preparation (i.e., unanesthetized, paralyzed cats), Frostig *et al.* (1983) examined correlations between local neural groups recorded with a single microelectrode. They also found relatively little evidence for serial interactions between neurons; the predominant effect was a common synaptic input, presumably from sources outside the group. In contrast to Dickson and Gerstein (1974), Frostig *et al.* found a larger proportion of cases in which stimulation modified the correlation between neurons and suggested that this may be related to stimulus coding.

Comparable proportions of synaptic interactions have also been observed in other parts of the auditory system. Recording 950 pairs of cells in the medial geniculate nucleus of cats anesthetized with nitrous oxide, Heierli *et al.* (1987) found that 40% of the pairs showed independent firing during spontaneous activity. But CCH features suggesting simple synaptic connections were found in 38% of the pairs. These features suggested a common synaptic input (20%) or serial excitatory (15%) or inhibitory (3%) synaptic linkages. More complex histogram features characterized the remaining 22% of the sample. Heierli *et al.* found some statistical relations between the types of synaptic interactions and other descriptive features of neuronal behavior, such as bursting pattern of spontaneous firing and sensitivity to acoustic stimuli.

The existence of correlations among three auditory cortex neurons, as opposed to two, has been explored by Abeles (1982, 1983), who used techniques such as the snowflake display of Perkel *et al.* (1975). These snowflake histograms suggest the existence of correlations among triplets of neurons that may occur spontaneously or that may be evoked by acoustic stimuli representing some unique pattern of activation by the acoustic stimulus.

Creutzfeldt *et al.* (1980) have documented synaptic interactions between medial geniculate and primary auditory cortex neurons. Cross-correlating the spontaneous activity of 69 simultaneously recorded pairs, they found correlogram peaks in nine pairs that had identical characteristic frequencies and similar spectral sensitivity. When tested with a sweep of frequency from zero to 12 kHz, the response peaks at the characteristic frequencies were sharper and narrower in the cortical neurons than in thalamic neurons. The correlogram

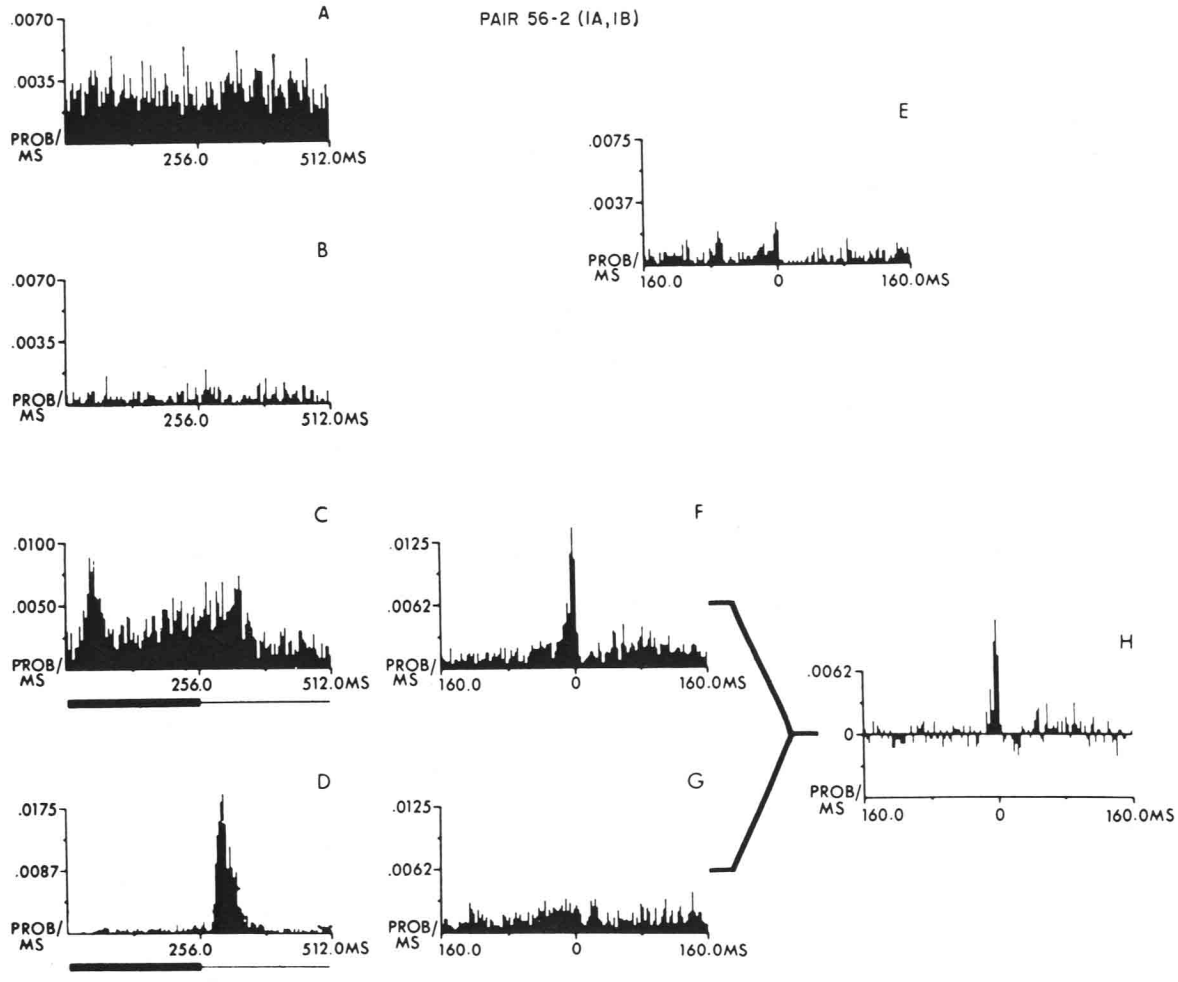

Figure 14. Cross-correlation analysis of pair of cells in auditory cortex showing stimulus dependence of correlation. (A, B) Spontaneous discharge of cells A and B. (C, D) Poststimulus time histogram of responses to noise-burst stimulation for duration indicated by dark bar. (E) Cross-correlogram of spontaneous activity of cells. (F) Cross-correlogram of cells during auditory stimulation. (G) Cross-correlogram between spike trains after relative shift of spikes by stimulus interval (i.e., shift predictor). (H) Difference between F and G, indicating neural correlations. From Dickson and Gerstein (1974).

peaks began about 2–5 msec after discharge of the geniculate neuron and were relatively broad, lasting 7–18 msec. The responses of cortical neurons to pure tones were more transient than those of corresponding medial geniculate neurons and extended over a narrower frequency range, suggesting the presence of cortical inhibition. These authors also analyzed and compared the responses of cortical and thalamic neurons to various natural stimuli such as vocal calls of the same species (guinea pigs). The thalamic cells represented more components of a call than cortical cells, even if the two were synaptically connected.

4. Somatosensory Cortex

4.1. Cross-Correlation Studies

Correlation studies of synaptic interactions between neurons in somatosensory cortex are relatively few. Metherate and Dykes (1985) cross-correlated extracellular spikes from pairs of neurons with overlapping receptive fields in cat somatosensory cortex. Cells were activated by glutamate injection as well as by stimulation of their receptive fields. The major finding was the existence of cross-correlation peaks between all pairs of cells that were both within the rapidly adapting (RA) region ($n = 6$) or both within the slowly adapting (SA) region ($n = 8$). The correlogram peaks straddled the origin but showed offsets consistent with both common synaptic input and serial connections between cells. These peaks included the effects of stimulus coordination, since the shift predictor was not subtracted. In contrast to the pairs within each region, none of the five pairs consisting of one SA and one RA neuron showed any evidence of cross-correlation peaks.

The presence of inhibitory neurons in the pericruciate cortex of the cat was documented in the cross-correlation study of Renaud and Kelly (1974). Pairs of neighboring pyramidal tract (PT) and nonpyramidal tract (NPT) neurons were recorded extracellularly. As illustrated for the pair in Fig. 15A, localized iontophoretic injection of glutamate activated NPT neurons and simultaneously inhibited PT neurons. Evidence that the NPT inhibited PT neurons was provided by troughs in the cross-correlograms between these cells (Fig. 15D,E) and by their reciprocal responses to electrical stimulation of afferent pathways and transcortical pathways. The putative inhibitory neurons were found in the neighborhood of the inhibited PT neurons, in both superficial and deeper cortical layers. These relationships were demonstrated in pre- as well as postcruciate cortex.

4.2. STA Studies

Unitary EPSPs evoked in layer III PT neurons by source neurons in layers III and IV have been documented in slices of rat cingulate and sensorimotor cortex (Thomson, 1988; Thomson *et al.*, 1988). These unitary EPSPs ranged in amplitude from 0.079 to 2.3 mV, with a mean of 0.41 mV (all values were measured around −70 mV polarization). EPSP amplitudes were not a function of input resistance. Figure 16 plots the amplitudes of the unitary EPSPs against

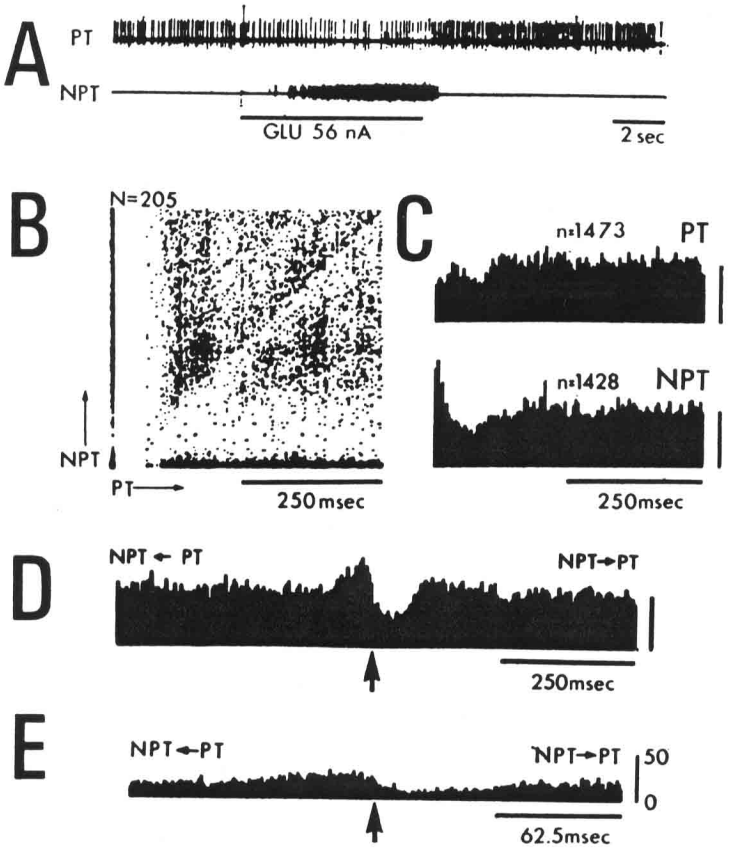

Figure 15. Interaction between inhibitory NPT and PT neurons in cat somatosensory cortex. (A) Injection of glutamate evokes activity in NPT neuron and suppression in PT neuron. (B) Cross-interval histogram in response to PT stimulation shows antidromic PT neuron response followed by suppression and a burst of activity in the NPT neuron. Diagonal features indicate that the PT neuron tended to be suppressed following NPT spikes. (C) Autocorrelograms of PT and NPT neurons. (D, E) Cross-correlogram between NPT and PT neurons at two time scales. From Renaud and Kelly (1974).

their normalized rise times and half widths. For most cells, depolarization increased the amplitude and prolonged the decay of the unitary EPSP, as illustrated for the two EPSPs produced by the same source cell and recorded at different polarization levels (Fig. 16, inset). This increase in EPSP size was associated with a corresponding increase in the amplitude of voltage responses to small injected current pulses, suggesting the activation of a voltage-dependent inward current (c.f. Fig. 2, which illustrates this phenomenon in a rhythmically firing cell and its consequences for increasing the firing rate). The latencies of the unitary EPSPs averaged about 2.1 msec, indicating that the intracortical axons had very slow conduction velocities (approximately 0.1 m/sec; see Table IV).

Intracellular studies in somatosensory cortex slices have also characterized the intrinsic firing properties of cells in specific layers (McCormick *et al.*, 1985; Chagnac-Amitai and Conners, 1989; Spain *et al.*, 1990) and led to hypotheses about their synaptic interactions (Chagnac-Amitai and Conners, 1989). As previously found in guinea pig neocortical slices (McCormick *et al.*, 1985), cells in rat

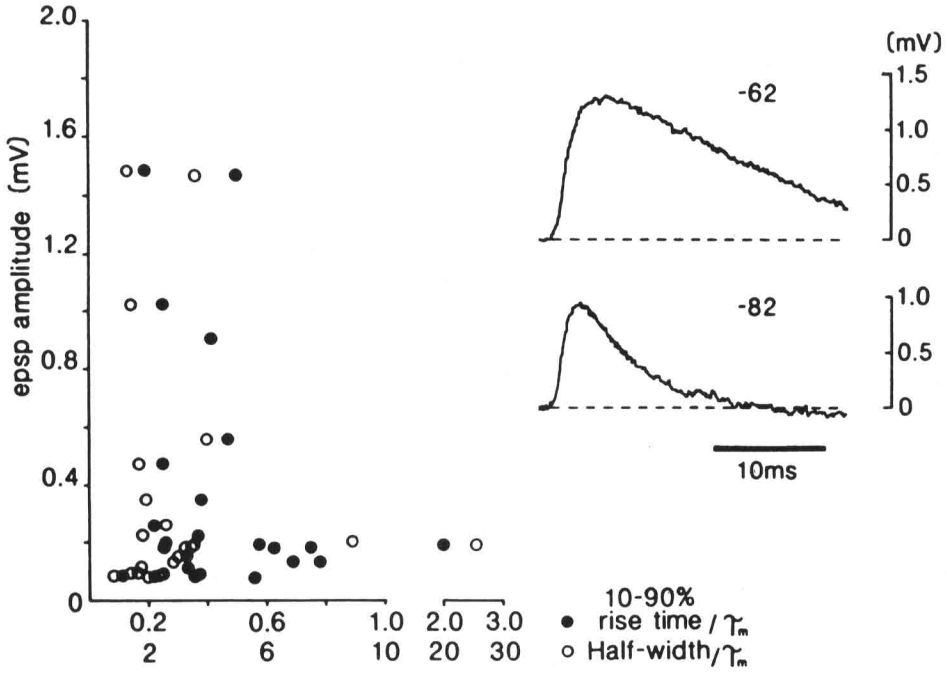

Figure 16. Unitary EPSPs recorded in rat cortical slices. Inset shows unitary EPSP from same source with membrane depolarization of −62 and −82 mV showing change in shape. Scatter plot shows amplitude of 25 EPSPs recorded at −70 mV (± 4 mV) plotted against normalized 10–90% rise time (solid circle) and half-width (open circle). Times are normalized by the membrane time constant. From Thomson *et al.* (1988).

neocortex could be classified into three groups: (1) regular spiking (RS) cells are found in cortical layers II–VI and are presumably excitatory pyramidal or spiny stellate cells; (2) intrinsically bursting (IB) cells, which respond with a burst discharge to a current step, are found in cortical layers IV and V, and are also presumed to be excitatory pyramidal or spiny stellate cells; (3) fast spiking (FS) cells are found in all layers and are presumed inhibitory (GABA) aspiny or sparsely spiny nonpyramidal neurons. Synaptic interactions between these groups could explain the tendency to synchronous discharge under conditions of reduced inhibitory control, as described by Chagnac-Amitai and Conners (1989). In this model, IB cells form strong interconnections with each other, and also excite both FS and RS cells. The FS cells in turn inhibit RS cells. When inhibition is reduced, the IB cells can initiate widespread synchronous activity in neocortex, as found in sleep or epilepsy.

5. Motor Cortex

5.1. Cross-Correlation Studies

The analysis of synaptic interactions between cells in the motor cortex provides opportunities that differ from those in primary sensory cortical areas. The activity of motor cortex cells typically has been recorded in awake, un-

anesthetized animals while they performed trained movements. Under these conditions, the interactions revealed by cross-correlograms would represent the synaptic interactions during normal motor function, uncompromised by anesthetics. Moreover, since the cells' activation during movements is typically modulated over several hundred milliseconds, the correlogram features are less likely to be confounded by stimulus synchronization. Synaptic interactions can be documented for motor cortex cells characterized by their responses to natural stimulation as well as their relation to active movement, their cortical location, and, in some cases, their output projections.

A number of studies have investigated synaptic interactions between motor cortical neurons by cross-correlating spike trains recorded simultaneously (Allum *et al.*, 1982; Cheney and Fetz, 1985; Fetz and Cheney, 1978; Kwan *et al.*, 1987; Murphy *et al.*, 1985a,b; Renaud and Kelly, 1974; Smith, 1989; Smith and Fetz, 1989). Recording pairs of neurons in the hand region of the motor cortex of monkeys trained to squeeze a force transducer between thumb and index finger, Allum *et al.* (1982) found that half of the 14 cross-correlated pairs showed correlogram peaks around the origin. Neuronal pairs were recorded on the same microelectrode and their action potentials were separated by waveform template analysis. The seven pairs with correlogram peaks covaried similarly with the task. In addition, Allum *et al.* found four pairs with troughs in the correlogram peak and three pairs that showed no correlation feature.

Recording activity of neighboring motor cortex neurons in monkeys performing a reaching task, Murphy *et al.* (1985a) found evidence for shared synaptic input in the form of central correlogram peaks in 24% of 237 pairs. As illustrated in Fig. 17, they used the shift predictor to eliminate the broad response-related component of the correlogram. They also found delayed peaks, interpreted as evidence of serial synaptic connections. The percentage of correlated pairs was highest for pairs recorded on the same electrode (39%) and decreased monotonically with distance for pairs recorded on separate microelectrodes (Murphy *et al.*, 1985b). The strength of correlation, as measured by the percent change in the peak or trough, also decreased somewhat with electrode separation (Kwan *et al.*, 1987). Murphy *et al.* (1985b) characterized the functional zones of the recorded cells by intracortical microstimulation; surprisingly, they found no statistical difference in the frequency of correlations between neurons located in zones affected by the same joint, or by adjacent or noncontiguous joints.

Recording the activity of neighboring motor cortex cells in monkeys performing alternating wrist responses, Smith (1989) found that 84 of 215 pairs showed significant cross-correlogram features. Ninety percent of these correlograms had features spanning the origin, consistent with common synaptic input; 5% had lagged peaks and 5% had lagged troughs, suggesting serial excitation and inhibition, respectively. These neurons also were identified with respect to projection in the PT and, in some cases, their postspike effects on target muscles in STAs of EMG. Figure 18 illustrates the relation between a PT neuron and an NPT neuron recorded just superficially to the PT neuron. The two cells were related reciprocally to the alternating flexion–extension task, as shown by the response histograms. The similarity in the histograms was assessed by the correlation coefficient of their corresponding bin values, which in this case had a negative value of -0.6. The CCH between the two cells (Fig. 18, top) reveals a lagged trough, suggestive of serial inhibition from the NPT to the PT neuron;

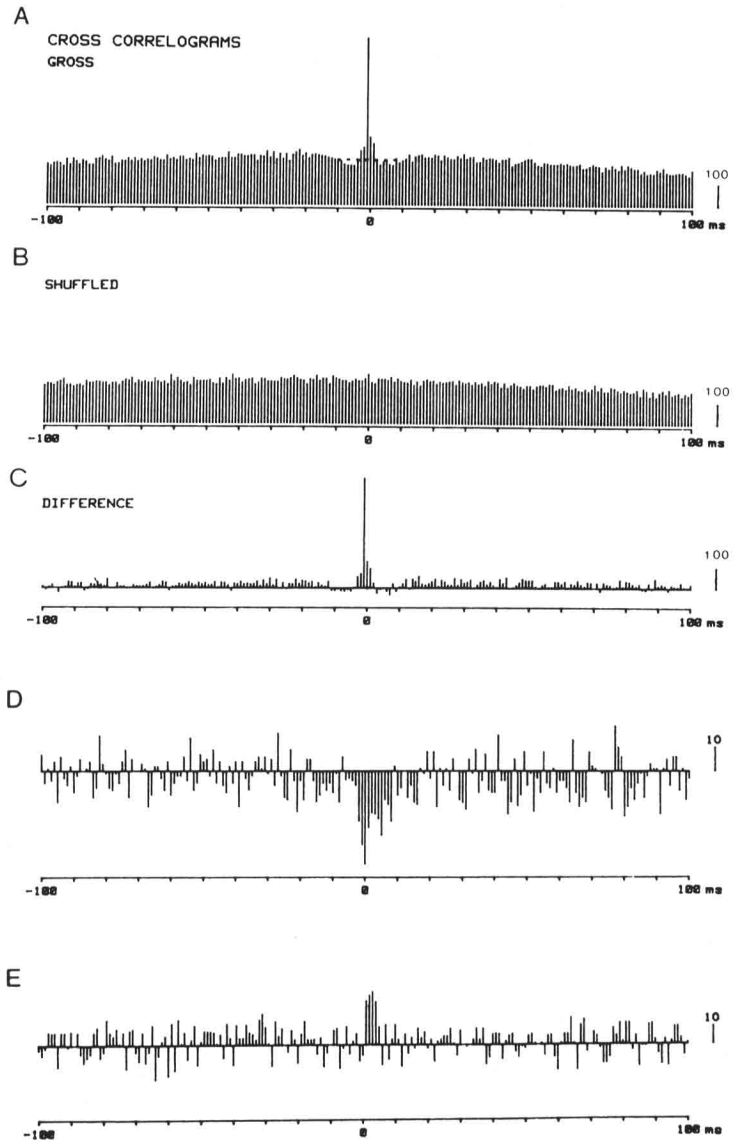

Figure 17. Cross-correlograms of primate motor cortex cells during active movement. (A–C) Two elbow extension cells recorded from same electrode. (A) Raw correlogram. (B) Correlogram of shuffled spikes (shift predictor). (C) Difference between A and B, showing central peak. (D) Difference correlogram of two shoulder rotation cells from same electrode. (E) Difference correlograms of elbow flexion cell and wrist supination cell recorded with independent electrodes. From Murphy *et al.* (1985a).

the CCH also has a shallow central peak suggesting some common excitatory input. These relationships are summarized in the lower left diagram by the simplest synaptic connections mediating such correlogram features. This pair shows an inhibitory linkage similar to those found by Renaud and Kelly (1974) in cross-correlations of spontaneous activity of cat motor cortex cells (see Fig. 15). In the behaving monkey (Fig. 18), the cells exhibited reciprocal discharge patterns during movements that were functionally consistent with the inhibitory linkage.

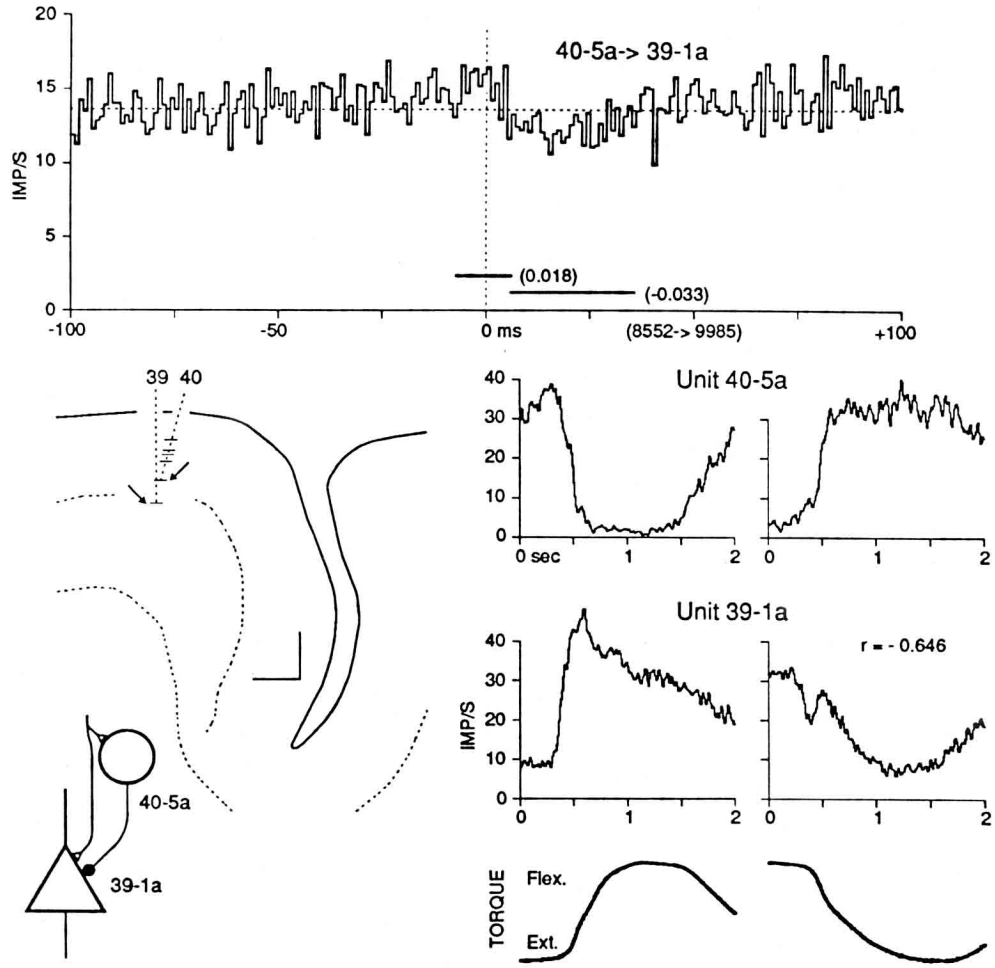

Figure 18. Relation between primate motor cortex cells recorded on independent electrodes during wrist movement. Top shows cross-correlation histogram between cells, indicating lagged trough. Response averages of NPT neuron (unit 40-5a), and a PT neuron (unit 39-1a), shown at right, with the isometric torque trajectory. Reciprocal firing patterns had a correlation coefficient of −0.6. Inset shows relative position of cells in precentral cortex and diagram indicates the synaptic connectivity suggested by CCH. From Smith (1989).

To determine whether the response patterns of motor cortex cells show a consistent relation to the strength and polarity of their correlational linkage, Smith (1989) quantified the response similarity of correlated pairs by the correlation coefficient of their averaged firing rates during the wrist movement. Figure 19 plots the area of the correlogram feature against the cells' response similarity; the regression line shows a positive slope, although the points exhibit considerable scatter. This result indicates that cells with positive synaptic connections tend to show positively correlated discharge patterns, although many exceptions can be found. Some paradoxical relationships include pairs of cells that discharge reciprocally, even though they share common excitatory synaptic drive (points in upper left quadrant).

Of particular functional interest are the synaptic connections of corticomotoneuronal (CM) cells, which produce postspike facilitation (PSF) in their target muscles (Fetz and Cheney, 1980). These output cells have demonstrable correlational links to motoneurons, so their synaptic inputs and interactions are

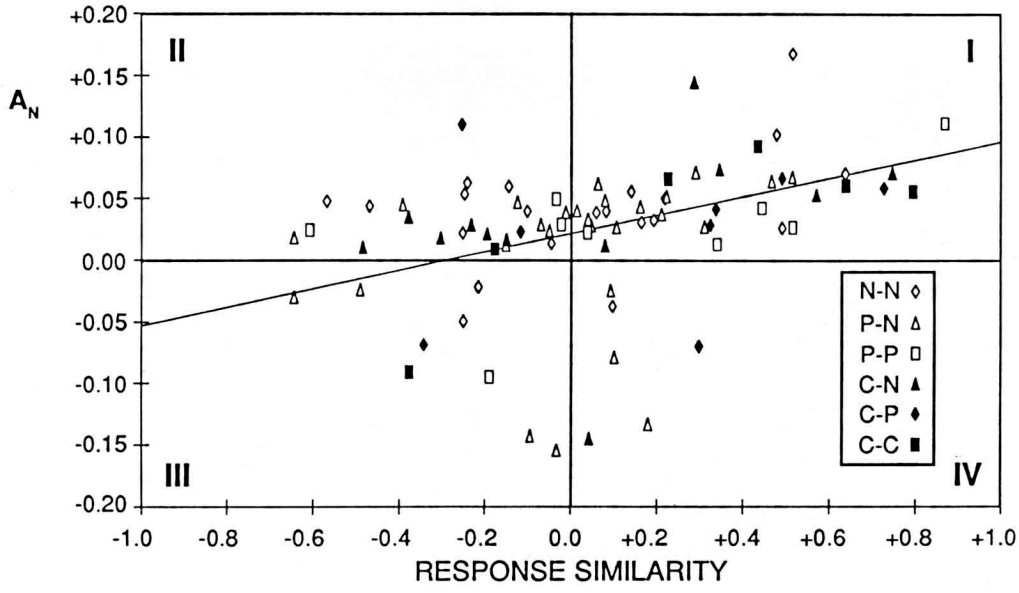

Figure 19. Relation between area of correlogram feature and response similarity for pairs of precentral cells recorded in monkey performing wrist movement. Magnitude of correlogram feature is expressed as A_N; the feature area count was normalized to the algebraic mean of target and reference cell spikes. Positive A_N represent correlogram peaks and negative A_N, correlogram troughs. Response similarity is the correlation coefficient between response averages. From Smith (1989).

of significance in understanding intracortical mechanisms controlling muscle activity. CM cells typically facilitate a group of synergistic target muscles, and some have reciprocal inhibitory effects on antagonists of their target muscles (Fetz and Cheney, 1980; Cheney *et al.*, 1985). Single-pulse microstimuli applied at sites of CM cells produce a pattern of PSF that resembles the profile of PSF of the CM cell, but the facilitation is much larger, suggesting that such stimuli activate many CM cells with similar muscle fields (Cheney and Fetz, 1985). CM cells with common target muscles are often clustered together in cortex, as shown by sequential and simultaneous recording of neighboring CM cells (Cheney and Fetz, 1985; Smith, 1989).

To examine synaptic interactions involving CM cells, Smith (1989) investigated 74 pairs of simultaneously recorded cells which included at least one CM cell. One issue resolved by these pairs is the degree to which synchronization between precentral cells may produce spurious PSF mediated not by the trigger cell but by CM cells synchronized with the trigger cell. In 20 cases, CM cells were significantly synchronized with simultaneously recorded non-CM cells which did not yield PSF themselves, indicating that synchrony is insufficient to mediate PSF. Similar results were reported by Lemon *et al.* (1985) for six correlated pairs which included one CM cell.

In this study, 11 pairs of CM cells were recorded simultaneously; in 5 pairs the cells had overlapping muscle fields and exhibited synchronous discharge. The potential contribution of this synchrony to PSF was analyzed by two techniques: (1) selective STAs that eliminated the above-chance synchrony yielded PSF almost identical to that obtained in unedited STAs, but revealed that synchrony had made a small contribution to early onset of the unedited PSF; (2) convolving the pair's cross-correlogram peak with the PSF of each cell revealed that the effects that would be expected to be mediated by synchronous events

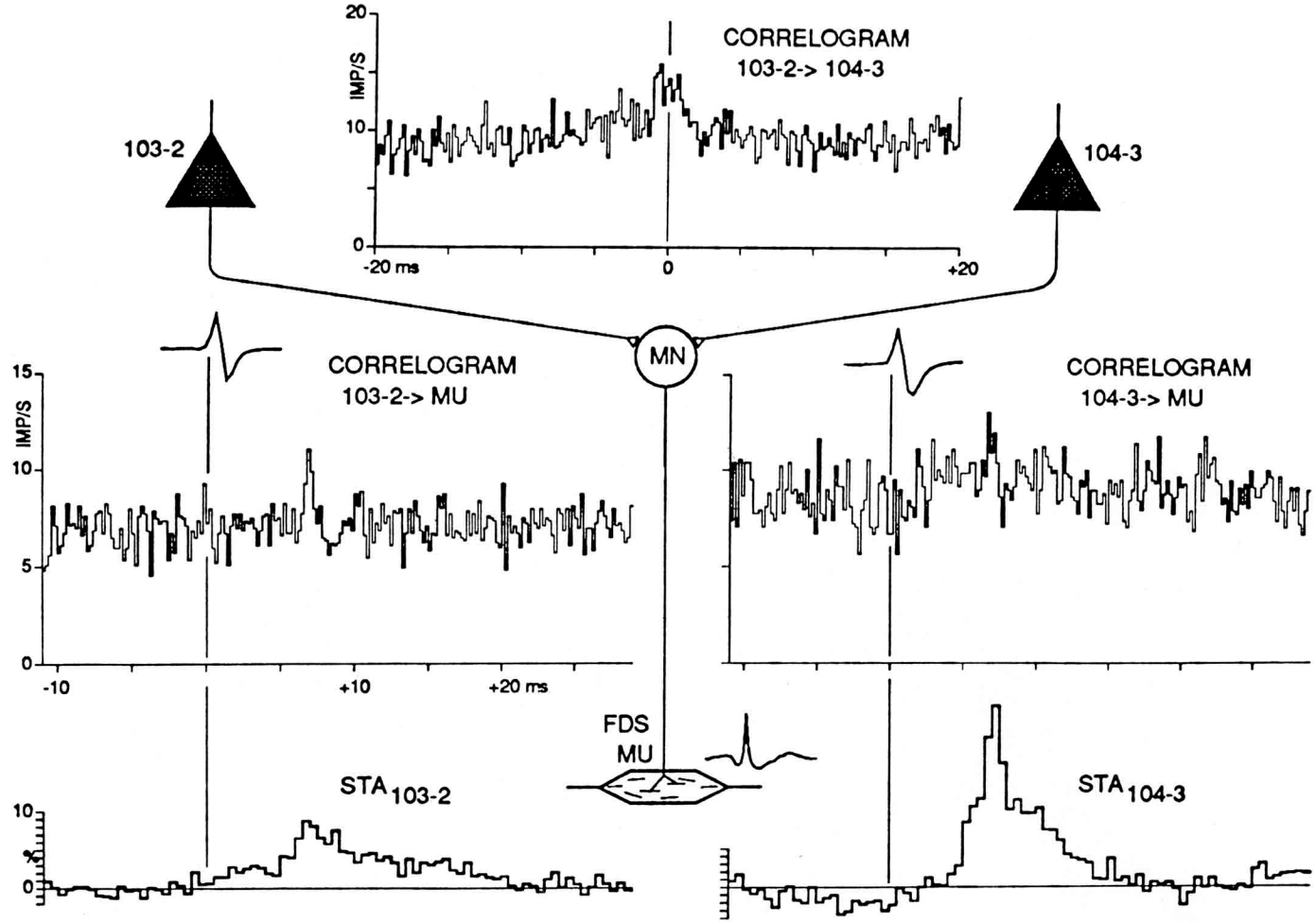

Figure 20. Correlations between two CM cells and a common target motor unit. Both CM cells produced PSF in the FDS muscle (bottom) and both facilitated a single motor unit within the muscle, shown by the left and right correlograms. The CCH between cells (top) shows a common input peak. Independent analysis indicates that this synchrony between the CM cells was insufficient to mediate postspike effects in motor units. From Smith and Fetz (1989).

were small and dispersed (Smith and Fetz, 1989). Both methods indicate that the PSF is composed predominantly of effects mediated by the output of the triggering cell, but may also include a broad, shallow component mediated by synchrony with other CM cells.

Synaptic interaction between two CM cells facilitating the same target muscle is illustrated in Fig. 20 (Smith and Fetz, 1989). Both CM cells facilitated flexor digitorum sublimis (FDS), as shown by the two PSFs at the bottom of the figure. In this case, a single motor unit within the FDS muscle was also recorded, and each of the CM cells was cross-correlated with the motor unit. The postspike effects of the CM cells on the motor units are shown by the brief correlogram peaks. The synchrony between the two CM cells is indicated by the central CCH peak (top). Clearly this peak is too broad to mediate the post-spike effect of either cell on its target motor unit. Nevertheless, the common input specifically to those CM cells with common target muscles (Smith, 1989) and the serial excitation between such cells (Cheney and Fetz, 1985) indicates the existence of selective synaptic interactions reinforcing their activity.

The correlograms between CM cells with common target muscles show that

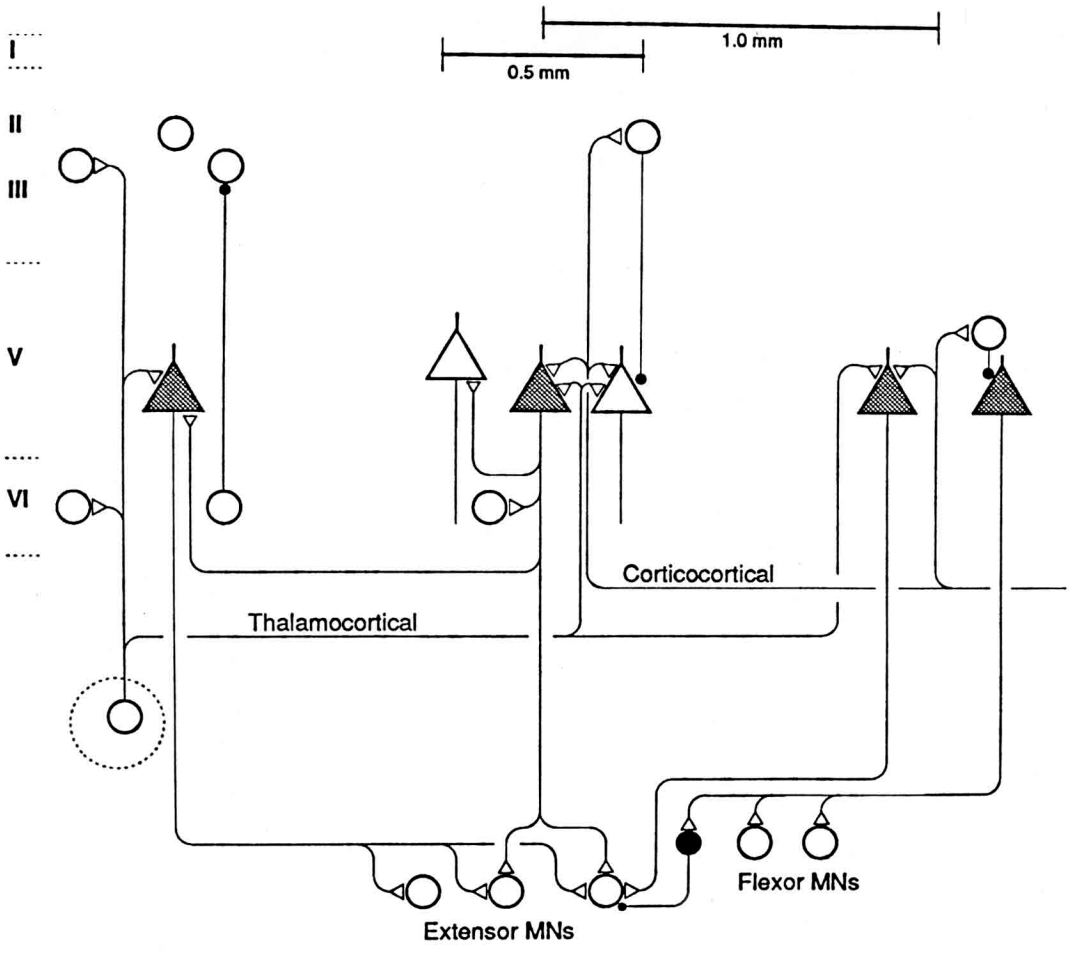

Figure 21. Summary diagram of synaptic connections between motor cortex cells revealed by cross-correlation features. Cells are characterized by location in cortical laminae and by projection: NPT neuron (circle), PT neuron (open triangle), and CM cell (filled triangle). Inhibitory linkages shown with solid synapse and excitatory with open synapse. From Smith (1989).

they tend to receive common synaptic input and/or to be interconnected. In contrast, the pairs of CM cells which facilitated different target muscles showed no evidence of any synaptic interaction, even when the muscles were synergists. One pair facilitated antagonist muscles and had an inhibitory correlational linkage. Thus, surprisingly, the intracortical circuitry appears to provide separate synaptic inputs to CM cells controlling different forelimb muscles, even when they are synergistically coactivated.

The types of correlational linkages observed by Smith (1989) in the motor cortex are summarized schematically in Fig. 21 by the simplest connections that could mediate the observed correlations. For example, CM cells in layer V facilitating common target muscles received common synaptic input from sources which are suggested here to be corticocortical or thalamocortical. Similarly, cross-correlation peaks revealed common synaptic input to cells in layers II–III, V, and VI. Serial inhibitory connections were found from NPT neurons in layers VI to II–III as well as from layers II–III to V. In this study, as in others (Murphy *et al.*, 1985b), the proportion of correlated pairs dropped off significantly with cell separations beyond about 500 μm.

5.2. STA Studies

Synaptic interactions between neighboring PT cells in the cat motor cortex were studied with STA by Kang *et al.* (1988). Recurrent unitary EPSPs from neighboring PT neurons were documented by STAs and by stimulus-triggered averages. The amplitudes of these unitary EPSPs averaged 111 μV (range: 30–390 μV). The rise times of EPSPs in fast PT cells tended to be shorter for axon collaterals of other fast PT cells (1.3 ± 0.4 msec; $n = 10$) than for collaterals of slow PT cells (2.4 ± 0.5 msec; $n = 20$). Assuming that the rise time reflects the electrotonic distance of the synaptic site, this would suggest that small PT neurons terminate more distally than fast PT neurons on their target PT cells.

The intracortical connectivity between motor cortex cells in the cat was investigated with intracortical microstimulation (ICMS) by Asanuma and Rosen (1973). Minimal ICMS of 4 μA applied in superficial layers II, III, and IV produced monosynaptic PSPs only in adjacent neurons within 0.5 mm of the stimulation site. Polysynaptic effects were evoked at distances of up to 1 mm from the stimulation site in horizontal and vertical directions, with inhibitory effects spreading more widely than excitatory effects. ICMS of 4 μA in the deeper layers (V and VI) produced both mono- and polysynaptic PSPs in cells within these layers and in superficial layers; these effects were mixed, but predominantly inhibitory. STAs revealed unitary PSPs in 6 of 19 pairs, and only when triggered from cells at sites where ICMS evoked monosynaptic effects. The synaptic input arising from spatially distant cortical regions has also been elucidated by microstimulation (e.g., Ghosh and Porter, 1988; Zarzecki, 1986).

STA of synaptic potentials is more sensitive than cross-correlating extracellular spike trains for detecting synaptic connections, and is feasible *in vivo* in the large neurons of the motor cortex (Matsumura and Kubota, 1983; Matsumura *et al.*, 1989; Zarzecki *et al.*, 1989). Using an extracellular electrode to record trigger spikes and an intracellular pipette to record synaptic potentials, Matsumura and Kubota (1983) compiled STAs of membrane potentials of neighboring cortical neurons in monkeys. Extracellular spikes were either

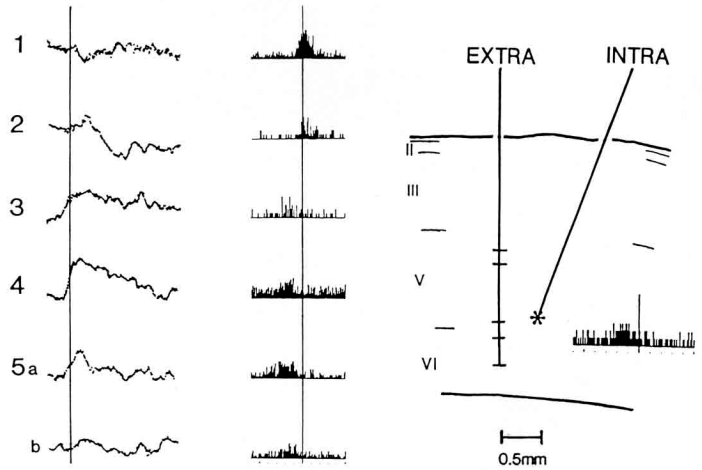

Figure 22. Synaptic interactions between motor cortex cells in awake monkey revealed by STA. Diagram indicates location of neurons recorded extracellularly in vertical track near intracellularly recorded cell (*). Records at left are STAs of membrane potential for each trigger cell. Histograms illustrate firing patterns of cells during hand movement associated with lever release (at center line). Matsumura, Sawaguchi, and Kubota (unpublished observations).

evoked by injection of glutamate in lightly anesthetized monkeys or recorded during task performance in behaving monkeys (Matsumura, Sawaguchi, and Kubota, unpublished observations). These investigators found evidence of excitatory and inhibitory synaptic potentials from single source cells to multiple, neighboring target neurons within a column. Conversely, they also demonstrated convergence of synaptic input from neighboring neurons onto a given target cell. Common excitatory synaptic drive occurred much more frequently in awake, behaving monkeys than in anesthetized animals, in which STAs more often yielded pure postsynaptic potentials. Figure 22 illustrates synaptic potentials averaged from intracellular recordings of a deep layer V cell (located at the asterisk) in STAs compiled from six neurons recorded successively in an adjacent vertical track. STAs indicate the presence of postsynaptic inhibition from the more superficial layer V cells and a common excitatory input with neighboring layer VI cells. These cells were also recorded while the monkey performed a wrist movement; the time histograms of unit activity show their discharge relative to the release of a bar (vertical line). Comparison of STAs with response histograms indicates that common excitatory input appeared in the pairs that fired similarly during movement, whereas serial inhibition was observed from cells that fired after the target cell (1 and 2). These difficult experiments illustrate the elegance of combining information on synaptic connections obtained from STA with behavioral determination of the response patterns of the correlated cells.

6. Association Cortex

Relatively few investigators have studied synaptic interactions between neurons in association areas. Noda and Adey (1970) cross-correlated pairs of cells in the middle suprasylvian gyrus of cats. They were particularly interested in docu-

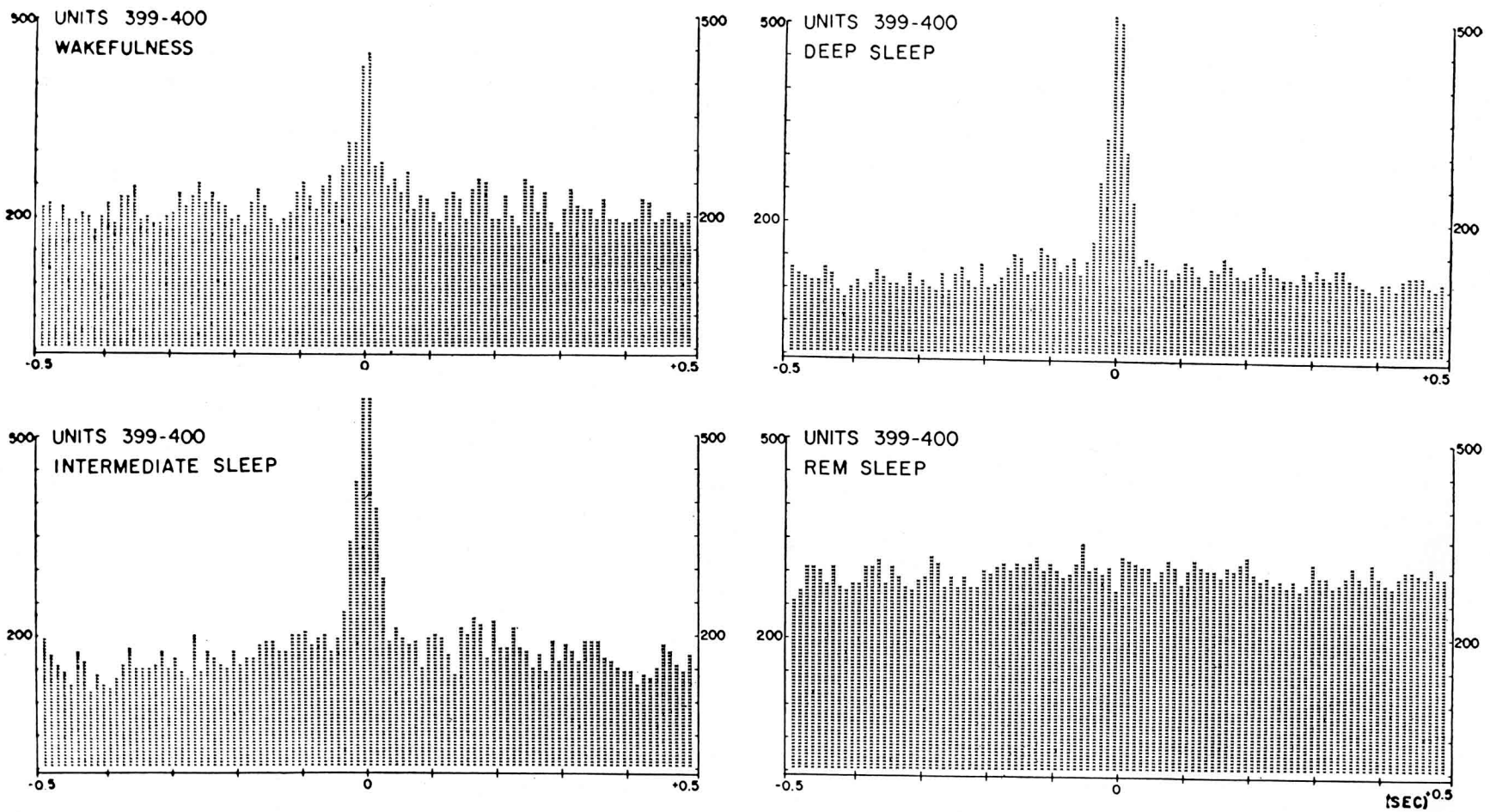

Figure 23. Cross-correlograms between same pair of association cortex cells during different behavioral states. Ordinate indicates number of spikes in each bin. Changes in correlogram peak indicate higher correlations during sleep than during wakefulness or REM sleep. From Noda and Adey (1970).

menting the changes in correlations with behavioral states. Their results are probably characteristic of other cortical areas as well. Figure 23 illustrates CCHs between the same pair of cells compiled during wakefulness, deep sleep, intermediate sleep, and REM sleep; these results are typical of the larger population of cell pairs. The highest level of synchrony occurred during deep sleep, when cells tended to burst simultaneously on a relatively low background level of activity; during deep sleep the magnitude of the central correlogram peaks averaged 2.7 times higher than baseline. The next highest synchrony was found in intermediate sleep (mean peak/baseline ratio = 2.2). During wakefulness the correlogram peaks tended to be smaller (1.6 times baseline) and to be associated with higher levels of activity. Along the same continuum, REM sleep showed the least amount of synchronous activity and the highest baseline rates (mean peak/baseline ratio = 1.1); the desynchronizing of cells during REM sleep was, in fact, more similar to arousal than to other states of sleep. Synchronous activity between neighboring cells is characteristic of not only sleep, but also levels of deep anesthesia (Holmes and Houchin, 1966). While the correlogram peaks observed during sleep are indicative of a tendency toward synchronous bursting, much of this may be due to synchronous arrival of input from independent sources, as opposed to common input from the same synaptic source. The shift predictor should be subtracted from the correlograms to determine the relative amount of input from common sources.

7. Hippocampus

7.1. Cross-Correlation Studies

The correlation between activity of neighboring hippocampal neurons was studied by Noda *et al.* (1969) as a function of sleep and wakefulness. Results were quite similar to those reported for cells in association cortex (see above and Fig. 23). During deep sleep with cortical high-voltage slow-wave activity, the burst patterns of neuronal pairs were highly correlated. When the behavioral state shifted from sleep to wakefulness, the discharge became less correlated. In behavioral arousal or in REM sleep, which are characterized by hippocampal theta activity, firing in neuronal pairs showed minimal correlation.

7.2. STA Studies

Numerous investigators have studied the synaptic connections between hippocampal neurons by STA in slice preparations. Recording pairs of neurons separated by less than 200 μm in the stratum pyramidale of the CA3 region of the guinea pig hippocampus, Miles and Wong documented unitary IPSPs (1984) and unitary EPSPs (1986). With amplitudes averaging 1.4 mV, unitary EPSPs were substantially larger in hippocampal CA3 neurons than in neocortical neurons (see Komatsu *et al.*, 1988; Thomson *et al.*, 1988) or in spinal motoneurons (Cope *et al.*, 1987). Miles and Wong found considerable fluctuation in the latency and amplitude of the unitary EPSPs produced by a given connection (Fig. 24). The rise times, averaging 8 msec, are considerably longer than those found in

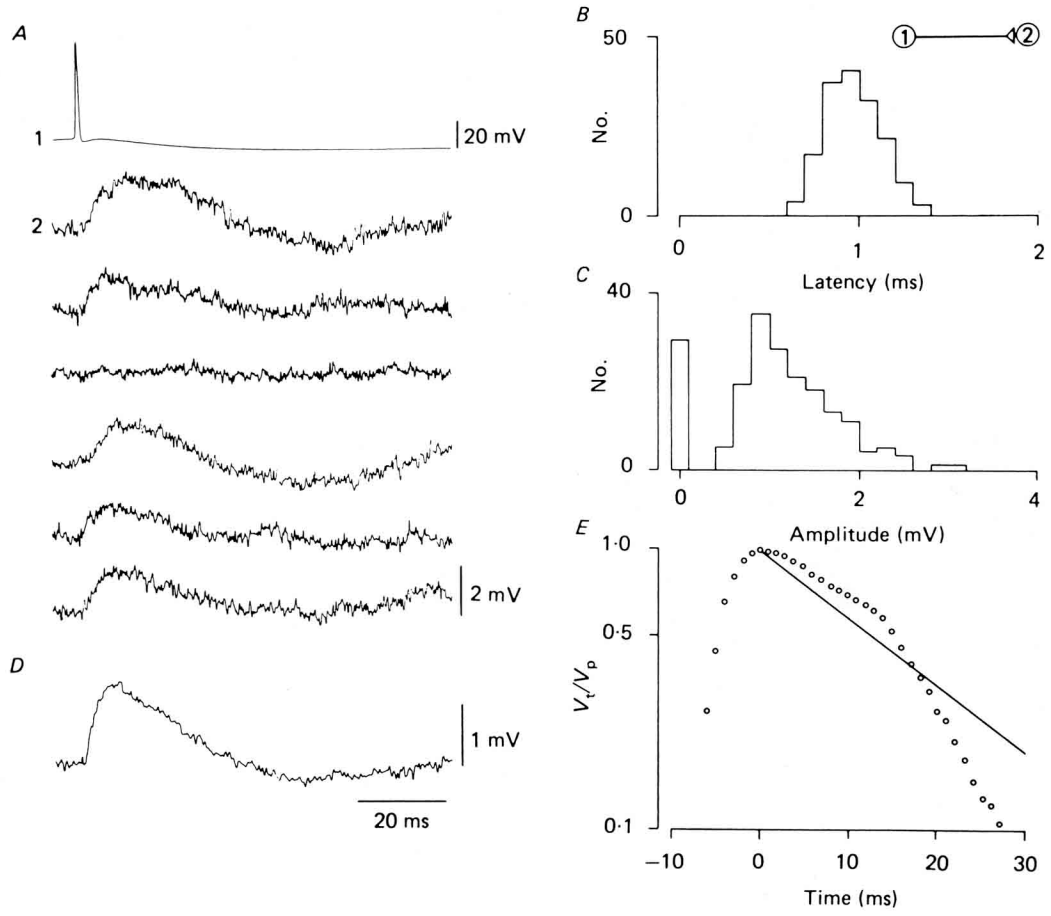

Figure 24. Unitary EPSPs recorded in CA3 region of hippocampus. (A) Successive examples of single EPSPs from same source cell. (B) Histogram of EPSP onset latency. (C) Distribution of peak EPSP amplitudes recorded at potentials of −66 to −70 mV. (D) STA of 20 EPSPs. (E) Semilog plot of averaged EPSP. From Miles and Wong (1986).

neocortical and spinal neurons. These huge unitary EPSPs explain the increased synaptic efficacy of transmission through polysynaptic relays in the CA3 region of hippocampus compared with neocortical circuits (see Miles and Wong, 1984). The size of unitary EPSPs has been shown to increase with frequency and external Ca^{2+} concentration (Sawada *et al.*, 1989). Similarly, unitary IPSPs in hippocampus (Miles and Wong, 1984) were also larger than those found in other regions of the nervous system (see Komatsu *et al.*, 1988; Jankowska and Roberts, 1972). The mean IPSP amplitudes were 2.2 mV and time-to-peak was 3 to 5 msec. Particular unitary IPSPs, again, showed considerable variation in amplitude and latency (Fig. 25).

Evidence for reciprocal circuits in CA1 has been obtained by simultaneous intracellular recordings in the slice (Knowles and Schwartzkroin, 1981; Lacaille *et al.*, 1987; Lacaille and Schwartzkroin, 1988). Combining electrophysiological and staining techniques, Lacaille *et al.* (1987) documented local circuit interactions between interneurons in the oriens/alveus (o/a) layer and pyramidal cells in guinea pig hippocampus. Figure 26 illustrates a reciprocal circuit between an o/a interneuron and a CA1 pyramidal cell. A burst of activity in the interneuron was required to summate the small IPSPs recorded in the pyramidal neuron. Spikes

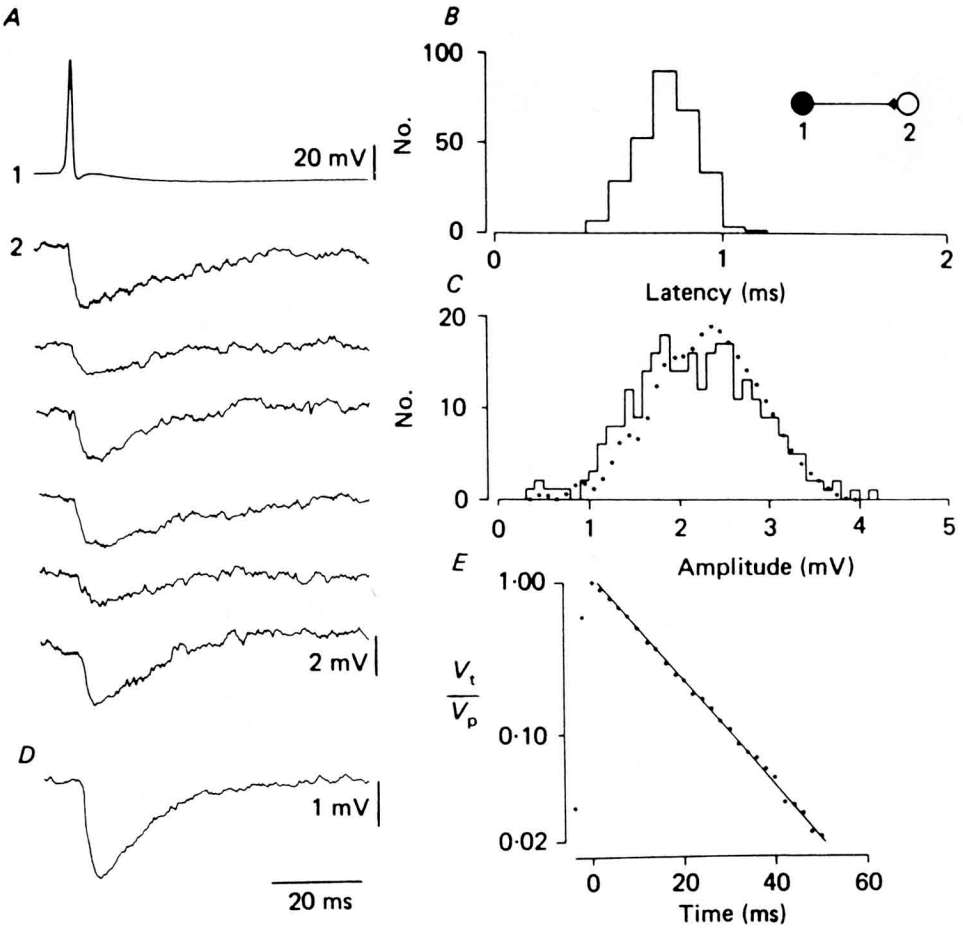

Figure 25. Unitary IPSPs recorded in CA3 region of hippocampus. Same convention as in Fig. 23. From Miles and Wong (1984).

evoked in the pyramidal cell produced recurrent EPSPs in the same interneuron, confirming a mutually reciprocal circuit in the same pair of cells.

Sayer *et al.* (1989, 1990) analyzed single-fiber EPSPs in CA1 pyramidal cells evoked from CA3 cells. The mean amplitude of 71 unitary EPSPs was 131 μV (range 30 to 665 μV). The rise times and half-widths averaged 3.9 and 19.5 msec. Using deconvolution analysis, Sayer *et al.* analyzed the fluctuation of these unitary EPSPs in terms of intermittent failure in synaptic transmission of more fundamental quantal units. Mechanisms of long-term potentiation (LTP) in this preparation were analyzed by Friedlander *et al.* (1990), who compared the effect of LTP on compound EPSPs elicited by stimulation of a group of CA3 neurons with the effect of LTP on unitary EPSPs elicited by stimulation of a single CA3 neuron in the same CA1 neurons. The tetanization protocol induced LTP in most of the compound EPSPs (seven of nine cases), but it produced LTP in only one of the nine unitary EPSPs for the same neurons. This effect suggests a threshold mechanism for controlling the expression of LTP.

A method of analyzing electrophysiologically the organization of local synaptic circuits in hippocampus was demonstrated by Christian and Dudek (1988a,b). Recording membrane potentials intracellularly, they evoked PSP activity from surrounding foci by microapplication of glutamate to specific neigh-

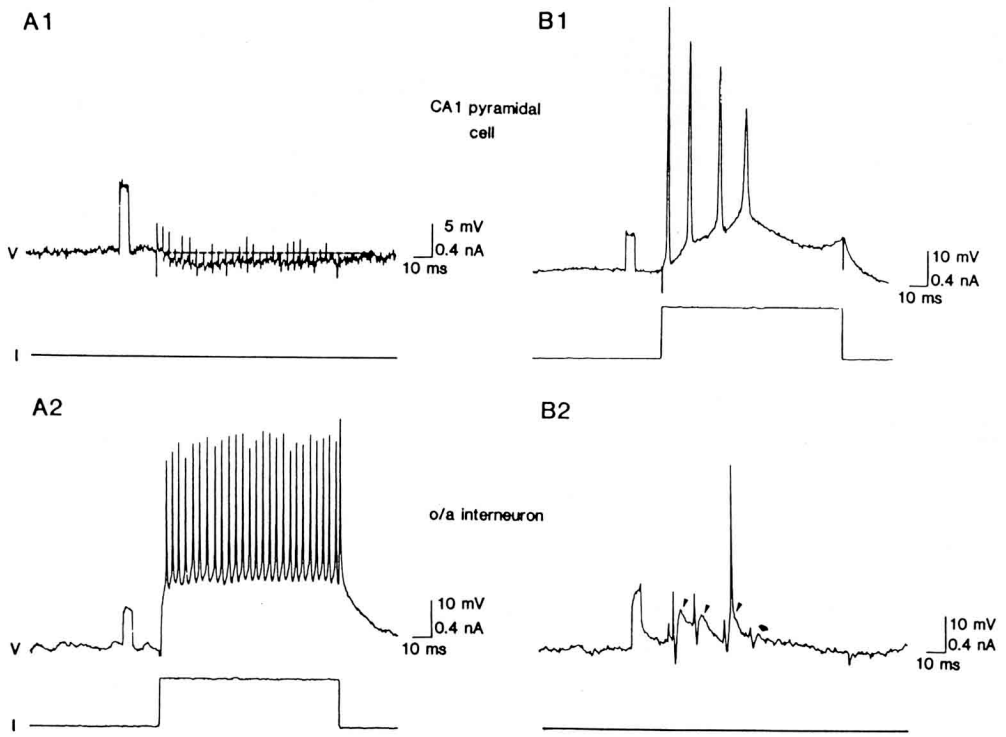

Figure 26. A reciprocal connection between CA1 PT neuron (top) and o/a interneuron (bottom) recorded simultaneously with intracellular electrodes. Left shows IPSPs in PT cell produced by burst of spikes in interneuron. Right shows EPSPs in interneuron evoked by spikes in PT cell. From Lacaille *et al.* (1987).

boring sites. The relative frequency of EPSPs and IPSPs evoked from an application site was indicative of the density of synaptic convergence from cells at that site. This technique, in combination with specific lesions and blocking compounds, provides a useful method for analyzing the organization of cortical microcircuitry.

8. Summary and Conclusions

8.1. Common Features of Synaptic Interactions

Taken together, the studies reviewed here represent significant strides in the analysis of synaptic interactions between cortical neurons. They have documented the magnitude of the interactions between cells in terms of unitary PSPs and cross-correlations, and have elucidated connections between particular layers within a column. The most detailed information is available for visual cortex, but some common features can already be discerned in the interactions observed in different cortical fields. In most studies, the probability of finding synaptic interactions between neurons decreases as a function of their cortical separation, with the highest probability occurring within the dimensions of a column (Toyama *et al.*, 1981a,b; Murphy *et al.*, 1985b; Smith, 1989).

Evidence on interlaminar connections remains too scanty to resolve the

intrinsic columnar organization. In all cortical regions, cells in different layers receive common synaptic input. To date, the serial inhibitory connections documented in visual cortex tend to be from deep to superficial layers (Figs. 8 and 12), while the reverse is true for those documented in motor cortex (Figs. 15, 18, and 22); whether this is due to sampling variance remains to be seen. Clearly, much more extensive analysis will be required before the detailed features of local interactions within a column are understood, no less whether these intrinsic interactions are similar in different cortical regions.

In addition, a broader range of intercolumnar synaptic interactions has also been documented in visual cortex (Ts'o *et al.,* 1986; Kruger and Aiple, 1988; Eckhorn *et al.,* 1988; Gray *et al.,* 1989; Engel *et al.,* 1990). These appear to interconnect cells with similar orientation preference. The ability of cortical circuits to sustain rhythmic oscillations that are synchronized in different columns suggests a possible mechanism for associating stimulus features (Gray *et al.,* 1989; Eckhorn *et al.,* 1989; Engel *et al.,* 1990).

Comparing thalamic with cortical cells, many investigators have found much greater response selectivity in the cortical neurons, even when the cells had correlational links (Creutzfeldt *et al.,* 1980; Tanaka, 1983). This sensory specificity in cortex is probably mediated by potent inhibitory interactions between cortical neurons. The importance of intracortical inhibition is further confirmed by the dramatic effects of bicuculline on response properties of cortical cells (Sillito, 1977, 1979). In view of their significant effect, the candidate inhibitory cells have been relatively elusive in cross-correlation studies. This may be related to the lower probability of isolating small neurons with local dendritic fields, as well as the difficulty in detecting inhibitory linkages in CCHs (Aertsen and Gerstein, 1985).

Cross-correlating the spike trains of neighboring neurons *in vivo* reveals that the most ubiquitous feature is the common synaptic input, producing correlogram peaks straddling the origin. These common input peaks greatly outnumber the lagged peaks or troughs representing serial connections, and may indeed conceal such features. Serial connections can be revealed more clearly by activating cells in the anesthetized animal, using glutamate to generate trigger spikes.

The intracellular recordings of unitary synaptic potentials are ideally done in *in vitro* preparations. The recording stability of the slice provides opportunities to document detailed mechanisms of synaptic interactions, as well as controlled study of transmitter release and ionic channel properties that would be difficult in the *in vivo* preparation. However, these advantages are gained by sacrificing information about the relation of the cells to the whole organism, such as their normal response characteristics. Even the local circuitry may be affected; the probability of recording from a connected pair of cells in the slice is typically quite low, perhaps because some of the more circuitous connections between neurons may be cut.

The dependence of correlogram features on behavioral state is clear from several studies showing that levels of arousal can affect cell interactions in similar ways across different cortical regions. Thus, in the awake or REM sleep state, the neighboring neurons fire less synchronously than in sleep, which is characterized by synchronized bursting between neighboring cells in hippocampal cortex (Noda *et al.,* 1969) as well as association areas (Noda and Adey, 1970).

8.2. Future Directions

Reviewing the studies to date suggests many opportunities for future investigations of synaptic interactions. There is a clear need for more systematic detail about specific interactions between identified cells, characterized with respect to their cortical location and projections, as well as their normal response properties (White, 1989). In correlation studies, the magnitudes of these interactions should be quantified in terms of the contribution of one cell to the other, to provide a more quantitative picture of how synaptic interactions extract response features. The function of these interactions can also be probed with pharmacological techniques (Bolz *et al.,* 1989; Sillito, 1977, 1979). Second, there is ample opportunity to investigate changes in synaptic interactions with behavioral states and to document the time-varying changes in interactions during ongoing sensory or motor behavior (Aertsen *et al.,* 1989; Murphy *et al.,* 1985b; Gerstein *et al.,* 1985a; Gerstein and Michalski, 1980; Smith and Fetz, 1986).

Although we have dealt primarily with interactions between pairs of neurons, techniques for recording larger populations of cells simultaneously (Eckhorn *et al.,* 1988; Gerstein *et al.,* 1985a,b; Kruger, 1983; Kruger and Aiple, 1988) present the challenge of dealing with group interactions and the representation of information in larger ensembles of neurons. Analytical techniques have been developed to help identify significant relationships between cells in large populations (Abeles, 1982; Gerstein *et al.,* 1978, 1985a,b). Finally, new techniques of neural modeling provide opportunities to synthesize anatomical and physiological data into simulations of synaptic interactions in larger networks (e.g., Traub *et al.,* 1989; Eckhorn *et al.,* 1989). Neural network models based on the strength of connections between cells and incorporating the types of response patterns observed experimentally can elucidate the neural interactions underlying cortical information processing.

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