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The Cerebral Neocortex

A Theory of Its Operation

JOHN C. ECCLES

1. Introduction

Though the cerebral neocortex has been subdivided into a great many areas on structural and functional grounds, all parts are built of the same neuronal components linked in similar ways. Creutzfeldt (1977) formulated the hypothesis "that the functional structure of all neocortical areas is fundamentally the same and that the *morphologic differences between cortical areas are accidental. Also, the functional differences of the various cortical areas are a function of their different connections with afferent projection systems and with efferent target structures* but do not express differences of their functional structure."

Thus, one is encouraged to search for general principles of design, overlooking the minor differences, which are quantitative, not qualitative. Little more than 5% of the human neocortex is specialized as the primary sensory or motor areas, which deviate considerably from the standard design that is characteristic of the remainder of the neocortex—the so-called association areas. In attempting to gain an understanding of the structure and function of the cortex it is expedient to concentrate on the association cortex. An important generalization is that the pyramidal cells of the neocortex are alone concerned in projections from one area to another (the corticocortical projection) or in subcortical projections.

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2. The Modular Concept of the Neocortex

In order to discover the way in which one area of the association cortex communicated with other areas, Goldman and Nauta (1977) made minute injections of radioactive tracers [^{3}H]leucine or [^{3}H]proline into various areas of the association cortex of monkeys. It is well known that these amino acids are taken up by the neurons and converted into labeled proteins which are then transported along the axons of the neurons to their terminal branches. It is not necessary to go into the details of this reliable technical procedure of radiolabeling for determining the distribution of the pyramidal cell axons of a small cortical area. As recognized by Szentágothai (1978a) the radiolabeling revealed a quite unexpected mode of distribution of the axons that is of the greatest importance.

Figure 1A shows an autoradiograph of columns in the neocortex far removed from the site of the cortical injection in the frontal lobe. There are three well-defined columns with different degrees of radiolabeling and one very faint column to the right. Goldman and Nauta give the dimensions as 200–400 μm across and point out that the labeling extends perpendicularly across all the layers of the cortex, being especially prominent in lamina I. Note the dark spaces between with a grain density hardly above background. It is important to recognize that the labeling is in the association fibers that have come from the injected area to terminate in these labeled columns. In Fig. 1B the sectioning of the cortex was oblique with the consequence that the columns were cut across, there being four nicely separated ovoid labeled areas about 300–500 μm across. In interpreting these results account must be taken of the size of the area injected with the radiotracer, which would include many modules. Thus, the observed projections in Fig. 1 would be from an assemblage of modules. These observed projections are very widely distributed over the ipsilateral cortex, the association connections; and also they are distributed to the contralateral cortex, the commissural connections that are mostly between mirror-image areas, but not entirely so. Such clear modular pictures as those of Fig. 1 are not often seen, because the injections necessarily must cover many modules that result in agglomerations of the labeled modules, often in strips (Goldman-Rakic, 1981).

In Fig. 2A Szentágothai (1978a) gives a diagrammatic representation of the extraordinary finding that the immense sheet of the neocortex is subdivided into a mosaic of quasi-discrete space units. The thesis will be developed that these space units are the modules which form the basic anatomical elements in the functional design of the association neocortex. Twelve closely packed pyramidal cells are shown in one such module or column in the left of Fig. 2A, which has a width of about 300 μm. The axons from these pyramidal cells project

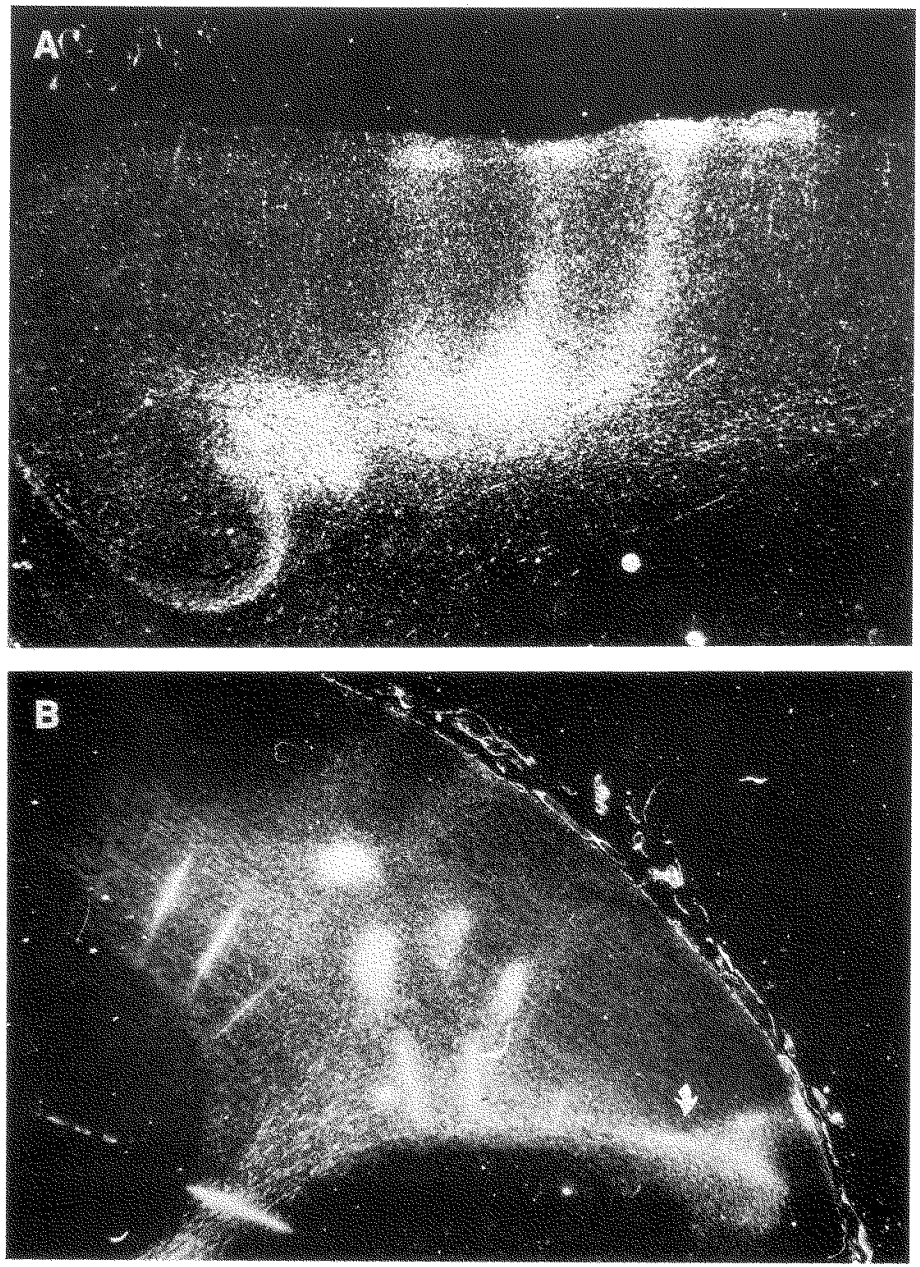

Figure 1. (A) Dark-field autoradiograph illustrating columns in the ipsilateral retrosplenial cortex following a single injection of [^{3}H]leucine and [^{3}H]proline into the dorsal bank cortex of the principal sulcus in a 4-day-old monkey. × 25. (B) Dark-field autoradiograph illustrating columns in the contralateral homotopical cortex from the injection site in the hand and arm area of a 4-day-old monkey. × 10. From Goldman and Nauta (1977).

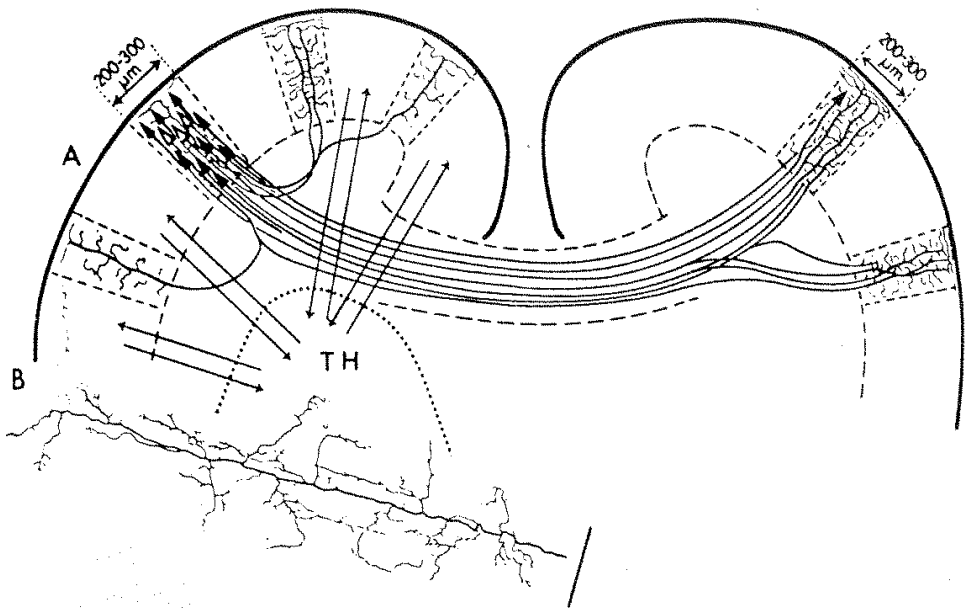

Figure 2. (A) The general principle of corticocortical connectivity is shown diagrammatically in a nonconvoluted brain. The connections are established in highly specific patterns between vertical columns of diameter 200–300 μm in both hemispheres. Ipsilateral connections are derived mainly from cells located in layer III (cells shown at left in *outlines*), while contralateral connections (cells shown in *full black*) derive from all layers II–VI. The diagram does not try to show the convergence from afferents originating from different parts of the cortex to the same columns. TH, thalamus. (B) Golgi-stained branching of a single corticocortical afferent, oriented in relationship to the module with a single afferent in (A), but at several times higher magnification. It illustrates the profuse branching in all laminae. Bar = 100 μm. From Szentágothai (1978a).

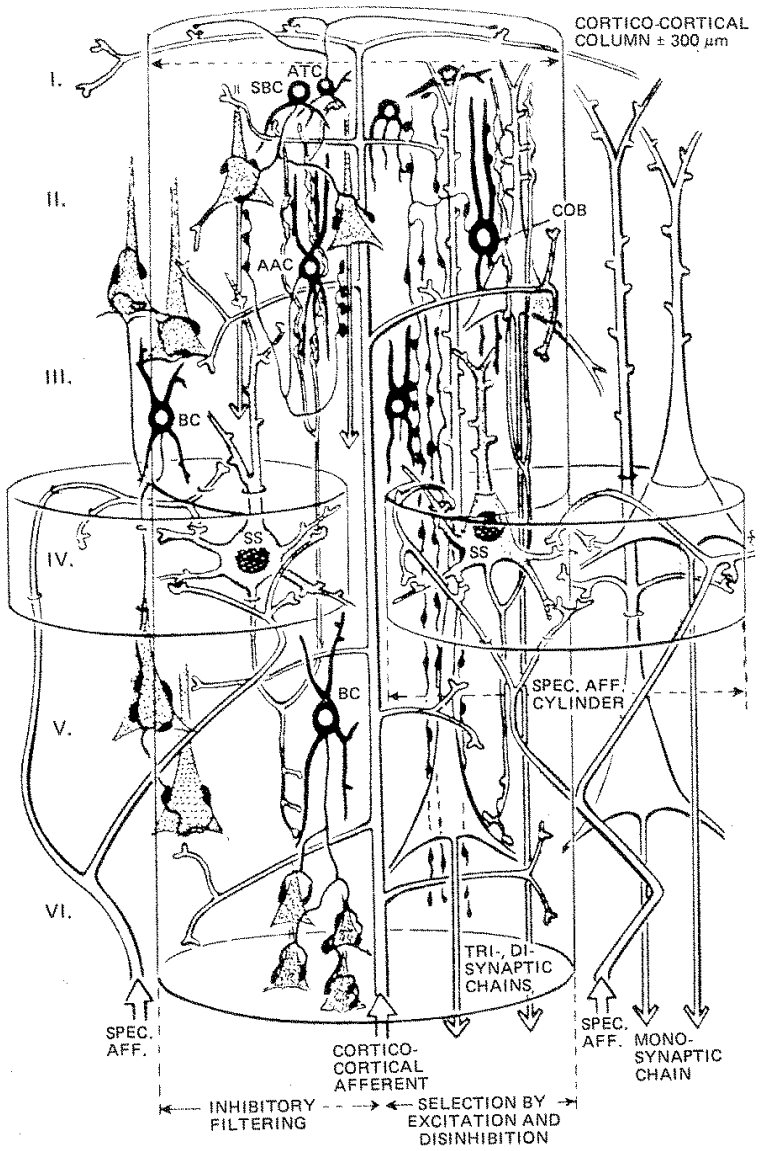

Figure 3. Internal neuron connectivity in a corticocortical column or module, the vertical cylindrical space of about 300 μm in the center. The module is sharing part of its space with two flat discs in lamina IV in which specific afferents (SPEC.AFF.) arborize. The corticocortical afferents (indicated at bottom) terminate all over the corticocortical module, though with different densities of terminals. In lamina I, the tangential spread of the corticocortical fibers extends far beyond the module. The selection of pyramidal cells for output is envisaged in the right half of the diagram over excitatory interneurons (Ss, spiny stellate) or over disinhibitory interneurons, the CDB (cellule à double bouquet of Ramón y Cajal), which are inhibitory interneurons that act specifically upon inhibitory interneurons which are shown in full black. The left side of the diagram explains the action of inhibitory interneurons as some kind of "filter" keeping out of action some of the pyramidal cells (punctate shading). Interneurons that can be defined as inhibitory with a considerable amount of confidence are indicated in full black: the basket cells, BC, in the deeper laminae, the SBC (small basket cells) in lamina II, the axonal tuft cells, ATC, and a very specific axoaxonic cell, AAC, acting upon the initial segments of pyramidal cell axons. Modified from Szentágothai (1979).

to three other modules of that same hemisphere and, after traversing the corpus callosum, to two modules of the other hemisphere. Thus, we have simply displayed the association and the callosal projections of the pyramidal cells of a module.

In Fig. 2A several pyramidal cells of a module project in a *completely overlapping manner* to other modules which are so defined, and which are again about 300 μm across. In Fig. 2A this dimension is already represented by the branches of a single corticocortical fiber for two modules and the overlapping distribution is illustrated for two association fibers and for four and five callosal fibers. Figure 2B shows at higher magnification the actual branching of one corticocortical fiber. The immense input into the cortical modules from the thalamus (TH) is indicated in Fig. 2A by reciprocal arrows. As shown in Fig. 3, this input is probably out of register with the corticocortical modules.

With primary sensory areas the columns are organized with respect to the thalamocortical inputs in the manner pioneered by Mountcastle (1957) and by Hubel and Wiesel (1962). These areas have specific organizational properties (cf. Jones *et al.*, 1975) that are beyond the scope of this review, which concentrates on the association cortex with its columns or modules organized around the corticocortical inputs as illustrated in Fig. 3.

3. The Modular Operation of the Neocortex

Insight into the manner of operation of this neuronal structure is aided by the recognition that Fig. 2A is greatly simplified. In the first place there are about 4000 neurons in a module 300 μm across, almost 2000 of which are pyramidal cells (Fig. 4). On the basis of the fiber count for the corpus callosum, there would be about 80 pyramidal cells projecting from one module to make callosal efferents to the other side, instead of the 6 in Fig. 2A. On an estimate of 15 times as many association fibers than callosal fibers, there would be 1200 pyramidal cells as association projectors instead of the 3 in Fig. 2A. Thus, there would be much more intense convergence of inputs from any one module than is represented, and also probably dispersion to many more modules. Szentágothai (1978a) suggests convergent and divergent numbers as high as 50.

But, even if this massive addition were made to Fig. 2A, the diagram would give the situation of connectivities for only a moment of time. If we assume a strong excitation of the primary module in Fig. 2A with a powerful burst of impulse discharges from the constituent pyramidal cells, there will be within a few milliseconds strong excitatory inputs into many other modules by the association and callosal projections. Some of these secondary modules in turn will be excited sufficiently to discharge to tertiary modules, and these in turn to quaternary. So in a small fraction of a second we have in effect a spreading pattern of excitation that is not random, but strictly specified by the sequential projections from the secondary, tertiary, etc. modules in this particular instance. There are approximately 3 million modules in the human neocortex, so there are immense possibilities for developing spatiotemporal patterns even on the simple assumption that each module operates as a unit in its reception and projection.

4. Inputs into a Module of the Neocortex (Szentágothai, 1983)

If modules are the operational units of the neocortex, it is important to enquire into the inputs to a standard module from adjacent or distant modules and particularly from the thalamic nuclei. Four types of excitatory input can be

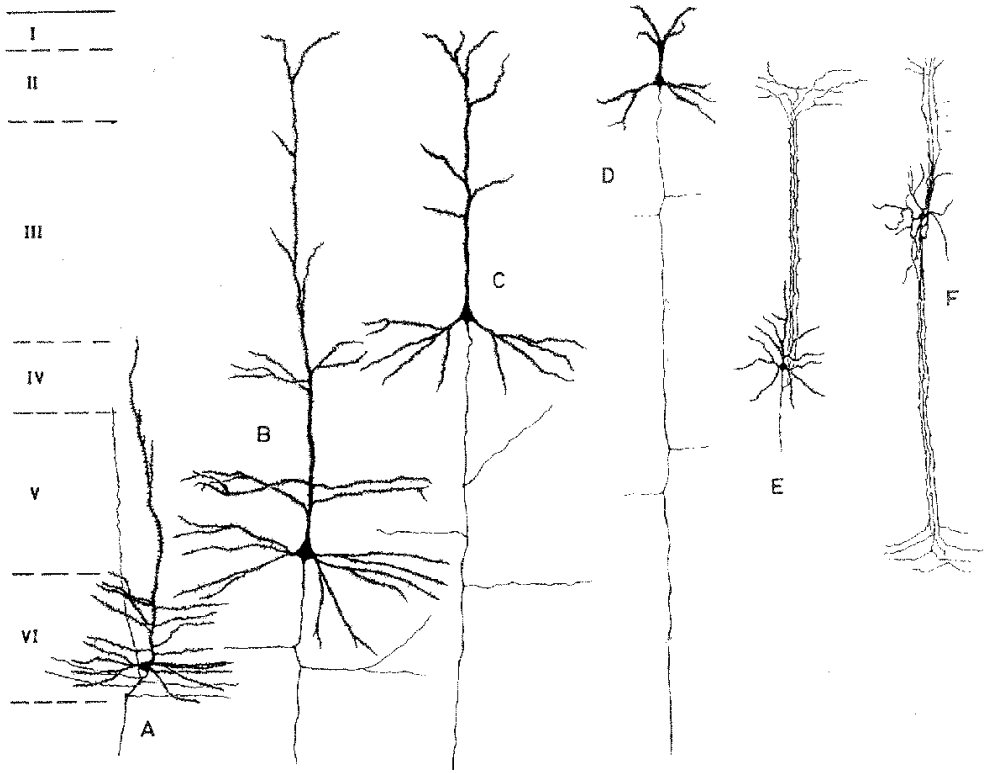

Figure 4. Drawings of typical cells of the cerebral cortex in relation to the lamination shown at the left. A is a cell in lamina VI projecting to the thalamus; B, C, and D are pyramidal cells in laminae V, III, and II, respectively. F is a spiny stellate in lamina IV with the axonal projection to form cartridge synapses on pyramidal apical dendrites. F is a cellule à double bouquet with soma in lamina III and a narrow band of axonal projection from lamina II to V. From Jones (1981).

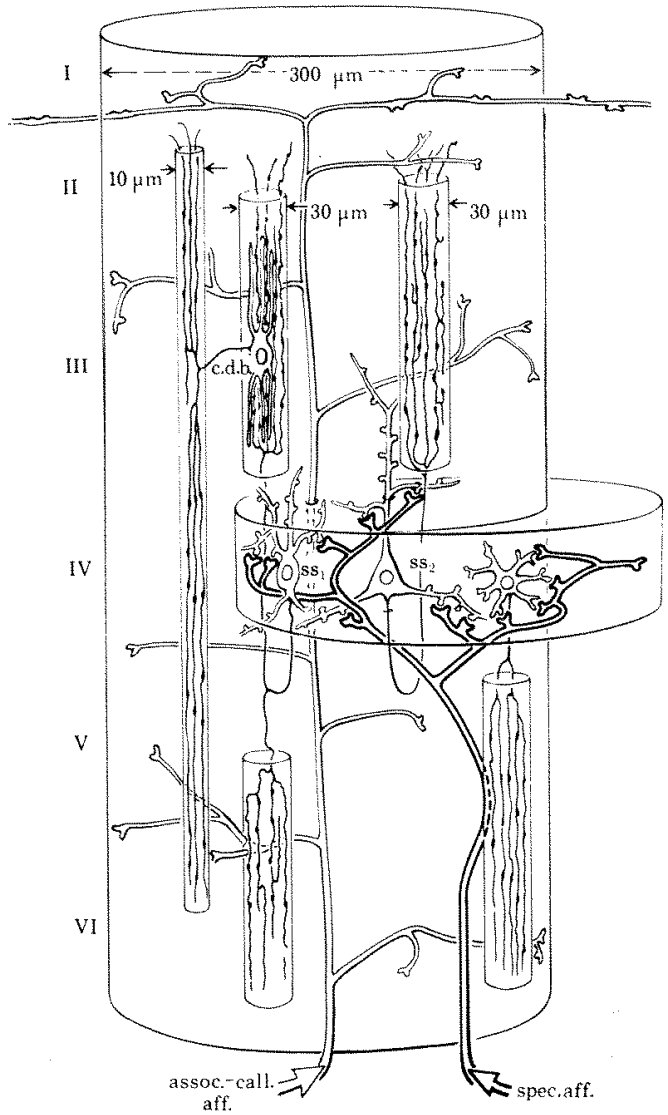

Figure 5. Modular arrangement of excitatory connections and of assumed excitatory interneurons. The large cylinder of 300-μm diameter corresponds to the space of termination of a corticocortical (ipsilateral association or contralateral callosal) afferent. The flat cylinder of the same diameter would correspond to the termination space of a specific (sensory) afferent. Two different types of spiny stellates are shown as monosynaptic target cells of the specific afferents: ss_1 has both an ascending and a descending axonal strand, while ss_2 has only one ascending strand. Neurogliaform cells have more generally descending axon strands of similar diameter (around 30 μm). A typical cellule à double bouquet (c.d.b.) of Ramón y Cajal is shown at the upper left, giving rise to a long vertical axon strand of even smaller diameter. From Szentágothai (1978a).

recognized. There are no primary inhibitory inputs. For a detailed account of the earlier work up to 1965 reference may be made to a review by Eccles (1966).

1. The simplest input is provided by the axon collaterals of pyramidal cells of adjacent modules (Fig. 4), which extend across several modules, as indicated in Fig. 8. By the technique of intracellular recording these collaterals have been shown to evoke a monosynaptic excitation of pyramidal cells and a later inhibition (Phillips, 1959; Stefanis and Jasper, 1964a,b; Armstrong, 1965; Kubota *et al.*, 1965). This corresponds to the belief that axon collaterals of pyramidal cells are excitatory on to both pyramidal cells and inhibitory neurons which produce the disynaptic inhibition of pyramidal cells.

2. Another simple input that is often overlooked is by the horizontal fibers of lamina I. Horizontal fibers are formed by the bifurcation of fibers that ascend in a module and then extend for many millimeters in lamina I making excitatory synapses on the apical dendrites of pyramidal cells. This synaptic system is the basis for the hypothesis of memory (Marr, 1970; Eccles, 1978, 1980, 1981), and will be fully discussed in a later section.

3. The thalamocortical inputs are diverse, being specially powerful in the primary sensory areas, but all areas of the neocortex have a thalamic input (Creutzfeldt, 1977; Jones, 1981; Peters, 1981). Thalamic inputs (Fig. 5) tend to concentrate on cells of lamina IV, but also in the deeper part of lamina III. An important feature is the reciprocity of specific connections: corticothalamic matching thalamocortical (Jones *et al.*, 1979; Jones, 1981) as indicated by reciprocal arrows in Fig. 2A.

4. Corticocortical inputs have mostly been studied with commissural fibers. There is usually a brief initial excitation of pyramidal cells and a later inhibition (Amassian, 1954; Latimer and Kennedy, 1961; Asanuma and Okuda, 1962). Labeling reveals that the inputs from a small cortical area are organized in bundles giving the modular arrangements that have been described above (Goldman and Nauta, 1977; Szentágothai, 1978a; Jones, 1981). There is reciprocity of callosal connections.

5. The Neuronal Structure of the Module (Szentágothai, 1983)

Most of the detailed investigation on the neuronal composition and connectivities within a module has been carried out on the modules of the primary sensory and motor areas, but the investigations on the association cortex by Szentágothai and his school in particular reveal a complex organization that is illustrated diagrammatically in Figs. 3 and 5–7. The Golgi technique has been supplemented by electron microscopy and by selective degeneration procedures, but, more importantly, imaginative insight is necessary for the interpretation of the experimental findings so that the various types of neurons, excitatory and inhibitory, are identified with their connectivities, as illustrated in Figs. 3 and 6.

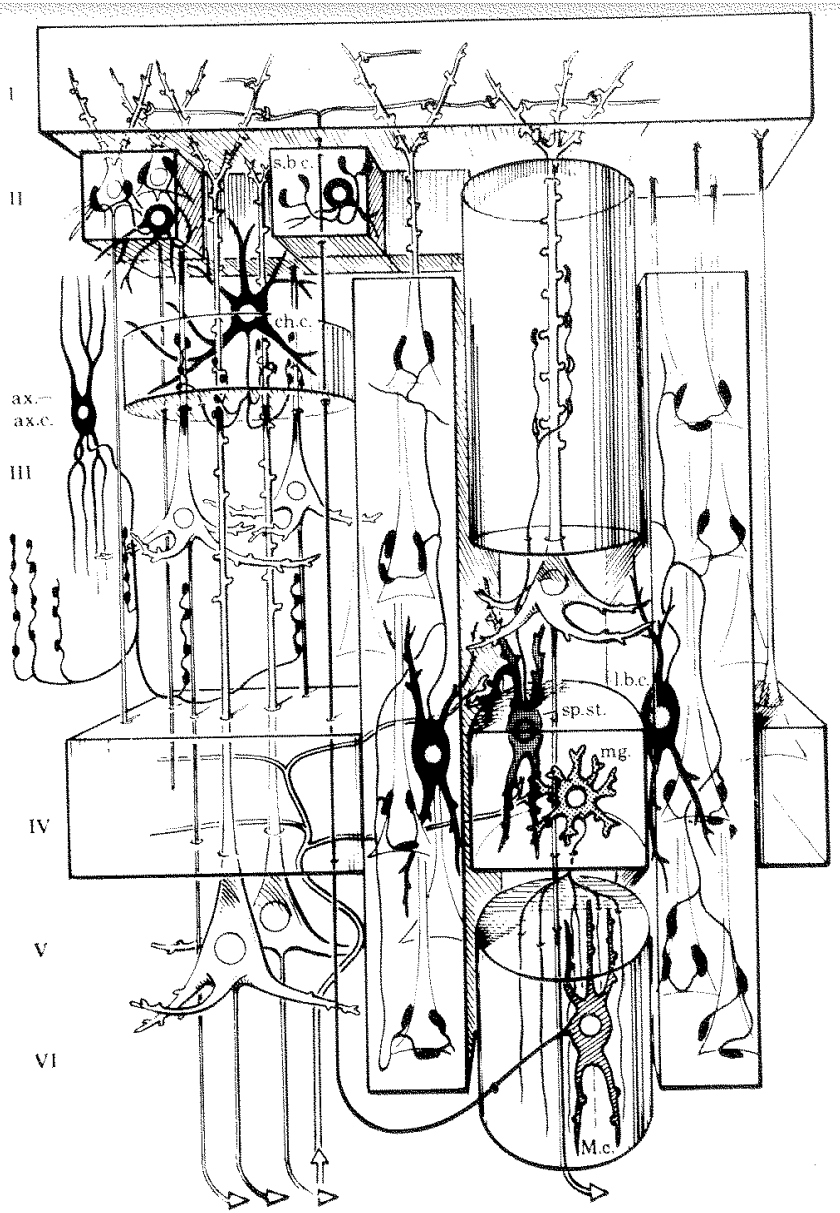

Figure 6. A drawing of the cerebral cortex in a synthetic stereoscopic view with lamina levels shown at the left. It shows some features not represented in Fig. 3: sp.st., a spiny stellate with axon making cartridge synapse; mg., microgliaform cell with axon projecting to Martinotti cell (M.c.) whose axon projects up to lamina I there to bifurcate to form a horizontal fiber; l.b.c., large basket cells making inhibitory synapses on pyramidal cells in lateral slabs; s.b.c., small basket cells with inhibitory synapses. From Szentágothai (1978b).

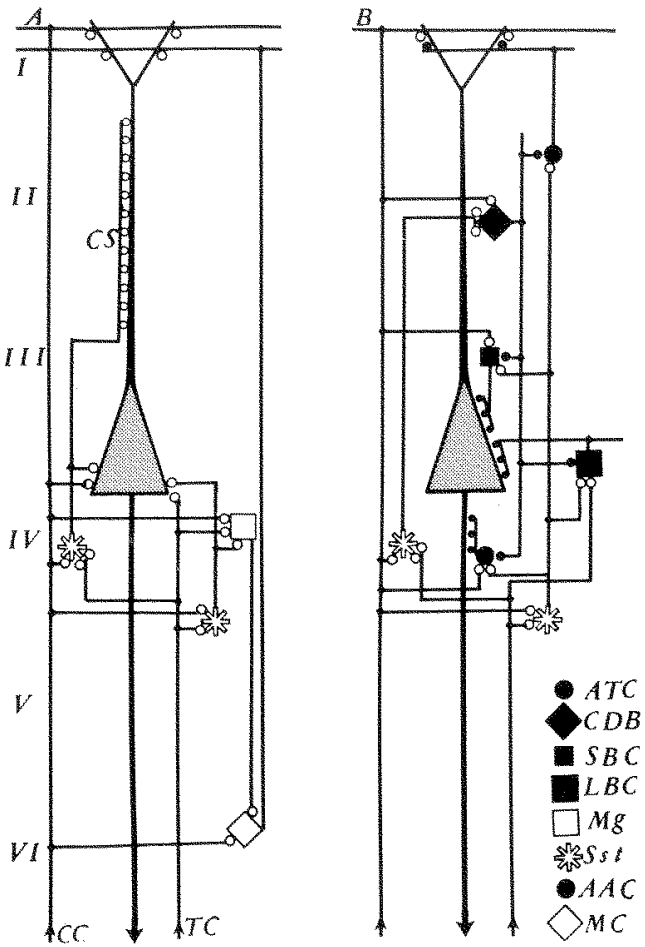

Figure 7. Simplified diagram of modular design in the association neocortex, the laminae being indicated to the left. In (A) are shown the excitatory cells with their excitation by the corticocortical (CC) and thalamocortical (TC) inputs. In (B) are the synaptic connectivities for inhibitory cells. Full description in text. Cell identifications are by symbols except for the pyramidal cell in the center of each diagram. The symbols to the lower right are arranged in the same depth order as the cells in the diagram: ATC, axonal tuft cell; CDB, cellule à double bouquet; SBC, small basket cell; LBC, large basket cell; Mg, neurogliaform cell; Sst, spiny stellate cell; AAC, axoaxonic cell; MC, Martinotti cell. CS indicates cartridge synapse. All excitatory cells and synapses are in outline. All inhibitory cells and synapses are in solid black.

It is to be noted that in Fig. 3 the module is organized around the corticocortical afferents, and that the two thalamocortical inputs (SPEC.AFF.) are shown as ending in discs in lamina IV, that are not in register with the module. The most recent discoveries (Somogyi, 1977, 1978; Somogyi and Cowey, 1980, 1981; Szentágothai, 1981; Hendry and Jones, 1981; Friedman and Jones, 1980; Peters *et al.*, 1982; Peters, 1981; Jones, 1981; Fairén and Valverde, 1980) are incorporated into the account here given, which, however, must be regarded as no more than a provisional story in this most complex and rapidly advancing field.

Figures 3, 5, and 6 have some semblance to the actual neuronal elements with their dendrites and axons, but are too complex for an initial attempt to give an account of the essential modes of operation of a module. Our enquiry is into the possibility that higher order properties may emerge in the functioning of the neural structure of a module. For the purpose of clarifying the problem, the structure of Fig. 3 has to be reduced to the simplest form. In the diagrams of Fig. 7 only one neuron of each species is symbolically represented, and the excitatory and inhibitory operations are shown separately in A and B, respectively. The labeling is the same as in Fig. 3. All synapses are of the conventional chemically transmitting type. Though gap junctions and dendrodendritic synapses have been recognized in the monkey neocortex (Sloper and Powell, 1978a,b), they are of such extreme rarity that they can be neglected in our enquiry concerning the possible higher order functions of the module. Likewise the various monoaminergic inputs into the neocortex are too diffuse in operation for our purpose.

Full descriptions of the constituent neurons are given in Volume 1 of this series, so there will be only summary descriptions except for the all-important pyramidal cells. These cells constitute at least half of the neuronal population and are the most distinctive feature of the neocortex. In Figs. 4B–D the pyramidal cells shown are those with cell bodies in laminae V, III, and II. They have characteristic features: an apical dendrite with branches extending up to terminate in profuse branching in lamina I; basal dendrites arising from the soma; an axon with axon collaterals extending downwards to leave the cortex. Also shown to the left is a cell with soma in lamina VI, but differing from pyramidal cells in that the apical dendrite terminates far below lamina I, so it is doubtful that it is a pyramidal cell (Peters, 1981). These cells have been labeled type 8 of the nonpyramidal cells by Jones (1975). The axons of these cells project to the thalamus, whereas the pyramidal cells of laminae II and III give shorter and longer corticocortical projections, respectively, and those of V project subcortically to the corpus striatum, the red nucleus, the pons, and the spinal cord (Jones and Wise, 1977; Jones, 1981). The dendrites of pyramidal cells are encrusted by spines on which there are excitatory synaptic endings, usually one to a spine. On the soma, the smooth surface of the dendrites, and the initial segment of the axon, there are inhibitory synaptic endings for the pyramidal cells of laminae II and III, but few on axons of the lamina V pyramidal cells.

5.1. Excitatory Synaptic Actions (Szentágothai, 1983)

In Figs. 3 and 5–7 the important monosynaptic excitatory connectivity for the thalamocortical input (TC; SPEC.AFF.) is to spiny stellate cells (sp.st.) in lamina IV, there being minor connections to the neurogliaform (mg.) (Fig. 6) and basal dendrites of the pyramidal cell. Sharply focused disynaptic excitations are made by the focal type of spiny stellate (Fig. 4E; Jones, 1975, type 7; Jones, 1981; Szentágothai, 1975, Fig. 8) to the pyramidal cell by the cartridge synapse (CS) with multiple synapses along the apical dendrites (Figs. 6 and 9; Szentágothai, 1969, 1970, 1975, 1978a). The diffuse type of spiny stellate cell (Szentágothai, 1975, Fig. 9, S3; Jones, 1975, type 7) with widely distributed axon branches is deeper in lamina IV and provides disynaptic excitations to the basal dendrites of pyramidal cells and the neurogliaform cell. The Martinotti cell (M.c.)

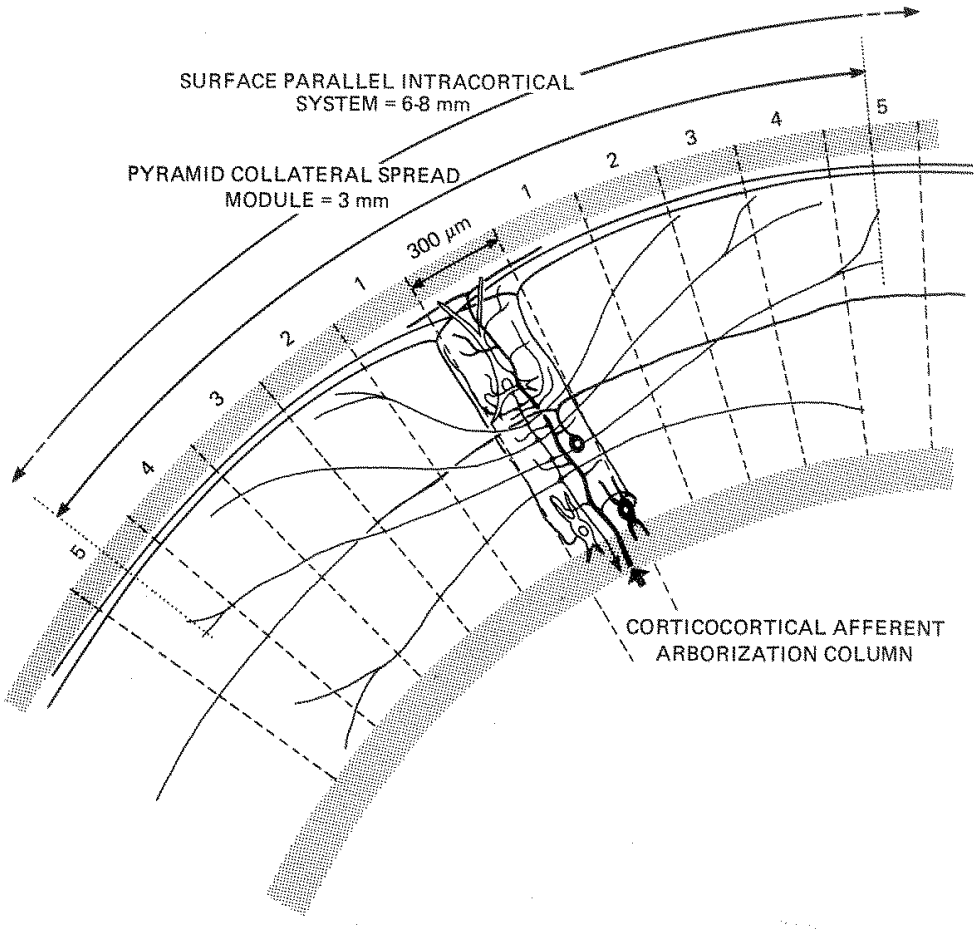

Figure 8. Diagram illustrating long-range intracortical connections. Two Martinotti cells shown in lamina VI with ascending axons bifurcating in lamina I. Pyramidal cell in lamina III has widely distributed axon collaterals. One cell in lamina IV has a bifurcating horizontal axon. Arrow shows corticocortical afferent. From Szentágothai (1978b).

in lamina VI (Figs. 6, 8) is trisynaptically excited via the neurogliaform cell (mg.) and sends its axon to lamina I to bifurcate and run for several millimeters making excitatory synapses with the apical dendrites of pyramidal cells in all modules that it traverses (Fig. 9, MA).

The other input to the module is via the corticocortical fibers (Fig. 3; Szentágothai, 1978a, 1979) that monosynaptically excite Martinotti cells, both types of spiny stellates, neurogliaform cells, and basal dendrites of pyramidal cells (CC, Fig. 7A). They finally bifurcate in lamina I to give the horizontal fibers of 5 mm or more in length that make excitatory synapses with the terminals of the apical dendrites of pyramidal cells in all the modules that they traverse (Figs. 8 and 9) fibers are derived either from the ipsilateral hemisphere (association fibers) or from the contralateral hemisphere (commissural fibers).

The important excitatory connectivities by afferent inputs to excitatory neurons (cf. Fig. 7A) would seem to be: (1) monosynaptic excitation of both types of stellate cells by both the thalamocortical and the corticocortical inputs; (2) disynaptic excitation of pyramidal cells by the cartridge synapses; (3) monosynaptic, disynaptic, and trisynaptic excitation of Martinotti cells, the last, via stellate and neurogliaform cells, probably being the most powerful; (4) horizontal fiber excitation of the apical dendrites of the pyramidal cells either monosynaptically from remote modules via the corticocortical inputs or by Martinotti cells, largely tetrasynaptically (Figs. 7A and 8), but the pyramidal cells of a module will also be excited by Martinotti cells of modules within a few millimeters distance. According to Szentágothai (1978a) there are in lamina I and II 1000–3000 excitatory synapses on the apical dendrite organization of each pyramidal cell.

The axon collaterals of pyramidal cells (Fig. 8) are not shown in Fig. 7A because they seem to provide only a diffuse background excitation (Szentágothai, 1978a,b). Thus, they would not be of importance to our present enquiry into pattern generation. Pyramidal cells in lamina V are not illustrated. Only the pyramidal cells of laminae II and III are effectively concerned in corticocortical connectivities, those of V largely being projection neurons out of the cortex.

5.2. Inhibitory Synaptic Actions (Szentágothai, 1983)

In Fig. 7B the two input lines, the pyramidal cell and both types of stellate cell, are in the same position as in A. Four species of inhibitory cell are indicated in Figs. 3, 6, and 7B, all being in full black.

1. The axonal tuft cells (ATC in Figs. 3 and 7B; type 6?, Jones, 1975). These inhibitory cells are specially related to the spine synapses made by horizontal fibers (Szentágothai, 1975, 1978a). An axonal tuft cell has a profusely branching axon, so it would exert an inhibitory control on many spine synapses, but it would seem that only a fraction of the immense number of spine synapses could be so controlled. On the assumption of a mean number of 2000 spine synapses on a pyramidal cell in lamina I (and II) (Szentágothai, 1978a) and 2000 pyramidal cells in the module, there would be in one module 4 million spine synapses as targets for axonal tuft inhibition. Once wonders what fraction of these synapses on the pyramidal cell dendrites would also be inhibited by electrotonic spread, so the inhibitory action of one synapse could be quite effective for many adjacent excitatory synapses on the branching terminal dendrites.

2. The small and large basket cells (SBC, BC, and LBC, Figs. 3, 6, and 7B; Ramón y Cajal, 1911; Szentágothai, 1975, 1978a; Jones, 1975, type 1; Jones, 1981; Martin *et al.*, 1983). These are probably the most important inhibitory cells because it seems that by convergent action they give a multitude of inhibitory synapses to every pyramidal cell body (Szentágothai, 1975, 1978a). The small basket cells possibly have the potentiality for a spatially selective inhibitory action in laminae II, III, and V. The large basket cells acting lateral to the module [Figs. 3(BC) and 6 (Marin-Padilla, 1969, 1970; Martin *et al.*, 1983)] tend to depress adjacent modules. However, it must be realized that these modules reciprocally are acting back, so there is a continual interaction between the excitatory and inhibitory influences on the pyramidal cells of a module.

3. The axoaxonic cells (AAC, chandelier cells; Figs. 3, 6, and 7B). The synapses of AAC cells on the initial segments of pyramidal cell axons are of special significance (Jones and Powell, 1969b; Jones, 1975, type 4; Somogyi, 1977, 1979; Szentágothai, 1978a, 1979, 1981; Fairén and Valverde, 1980; Sloper and Powell, 1979; Peters *et al.*, 1982; Somogyi *et al.*, 1982). Each of these cells probably is distributed to several hundred pyramidal cell axons and on each axon there is convergence from about five (2–14) cells (Szentágothai, 1978a, 1979; Somogyi, 1979). There is much less convergence in the rat visual cortex (Peters *et al.*, 1982). The precise investigations of Fairén and Valverde (1980) and of Somogyi *et al.* (1982) have shown that AAC inhibition is largely restricted to the pyramidal cells of laminae II and III. Only occasional branches descend to laminae V and VI. It would seem that the population of AACs is sufficient to control the axons of all pyramidal cells of laminae II and III. This control would be different from the basket cell control which would be a graded effect dependent on the relative intensities of the excitatory and inhibitory synaptic action. The axonal inhibition is more likely to be total or not at all. Thus, AACs would have a decisive influence on the output from the module into the corticocortical circuitry, but not on the subcortical projection of the pyramidal cells of lamina V. Probably AACs would be specially activated by the thalamocortical inputs via the spiny stellate cells, but much more investigation is required.

4. The cellule à double bouquet (CDB, Figs. 3, 4F, and 5). There had been confusion between CDB cells and the focal spiny stellate cells (SS in Figs. 3 and 5, sp.st. in Fig. 6, and Sst in Fig. 7) that also had a narrow vertically oriented axonal bundle (Fig. 4E). The distinction is now based on differences in detailed structure and on the location. CDB cells are restricted to laminae II and III (Jones, 1975, type 3; Szentágothai, 1978a; Somogyi and Cowey, 1981), whereas focal spiny stellates are restricted to lamina IV (Jones, 1975, type 7). The CDB cells have been identified as inhibitory by EM observation of the Golgi-stained synapses (Somogyi and Cowey, 1980, 1981) and by the discovery that CDB axons take up a tritiated GABA analog from their endings in laminae V and VI and

transport it up to their cell bodies vertically above in laminae II and III (Somogyi *et al.*, 1981).

The recent discovery (Somogyi and Cowey, 1980, 1981; Szentágothai, 1981) that CDB cells are inhibitory probably to all other inhibitory cells transforms the operational principles of the module. The extremely narrow transverse spread (<50 μm) of the vertically directed axons (Fig. 4F), up and down (cf. CDB, Figs. 3, 5, 7B), achieves new significance in that there will be inhibition of inhibitory cells in this narrow column with the consequent *disinhibitory action* (excitation) on pyramidal cells in what we may call a minicolumn, which may be no more than 100 μm across. Reference to Fig. 3 (Ss to right) suggests that the same focal stellate cell is responsible both for the cartridge synaptic activation of the pyramidal apical dendrite and the excitation of the CDB cell, as is also shown diagrammatically in Figs. 7A and B. Evidently there is here the neuronal design for focal spiny stellate cells to exert an extremely powerful and uninhibited excitation on a minicolumn of pyramidal cells. This remarkable design feature relates to two conjectures. First, it supports the hypothesis that the module is functionally subdivided into many minicolumns, as has been proposed by Szentágothai (1978a) and Mountcastle (1978). Second, the hypothesis that the potentiated cartridge excitation of the pyramidal dendrites causes the hypertrophy of horizontal fiber synapses on the terminal apical dendrites (cf. Fig. 9; Eccles, 1978, 1979, 1980) is now given a new prospect, as will be further mentioned below.

In summary it can be stated that the inhibitory system of the module would seem to be extremely potent with four levels of action: the inhibitory synapses of ATCs on pyramidal cell dendrites adjacent to the spine synapses made by horizontal fibers; the basket cell inhibition on all pyramidal cells; inhibitory synapses of AACs on the initial segments of all pyramidal axons in laminae II and III; the synapses of CDB cells on all other inhibitory cells with disinhibition of pyramidal cells. The first three inhibitory effects would depress the pyramidal cells, while the last would excite them. This disinhibition seems to transform our concepts of the operation of the module as we shall see below. Nevertheless it must be concluded that as yet we are only at the beginning of understanding the inhibitory mechanisms of the module. It is a point of concern that there has been no recognition of inhibitory controls of spiny stellate cells, or of neurogliaform and Martinotti cells (cf. Figs. 3, 6).

There has been little physiological investigation to match this neuroanatomy of the inhibitory cells. The only precise studies have been those of Toyama *et al.* (1974, 1977, 1980) on the visual cortex of the cat. Detailed timing of inhibitory synaptic potentials evoked by various inputs showed that some neurons (type 1) were monosynaptically excited by thalamocortical input, and disynaptically inhibited, while others (type 2) were disynaptically excited and trisynaptically inhibited. In Figs. 7A and B pyramidal cells are monosynaptically excited by thalamocortical inputs and are disynaptically inhibited by the LBCs. However, the type 2 cells are not recognizable in the diagram of Fig. 7, because they are not cells with axons projecting out of the cortex. It would appear that there are special neuronal connectivities for the visual cortex as is also suggested by the findings of Bullier and Henry (1979). It is urgently necessary to carry out similar physiological studies on the association cortex. From detailed studies Gilbert and Wiesel (1981) adduced a complex diagram of excitatory and inhibitory connectivities in area 17, but this needs testing by stimulating procedures and precise timing in the manner of Toyama *et al.* (1974, 1977, 1980).

5.3. The Special Design Features of a Cortical Module

As illustrated in Figs. 3, 5, and 7 each module acts as a unit processing the convergent inputs from other modules, the corticocortical fibers, and from the thalamus, the thalamocortical fibers. In turn it projects divergently to many other modules and also reciprocally back to the thalamus (cf. Fig. 2). It thus embodies in a complex way the Sherringtonian principles of convergence and divergence. The output of a module is graded both by the number of pyramidal cells that are excited to fire impulses and by the frequencies of this firing.

It is appropriate now to attempt an integration of the excitatory and inhibitory mechanisms of a cortical module as illustrated in Figs. 3 and 7. The thalamocortical (SPEC.AFF. or TC) and corticocortical (CC) inputs have many excitatory actions (cf. Fig. 7A), some having inhibitory controls (Fig. 7B). So far only two types of neurons are known to receive inhibitory controls: the pyramidal cells by the BC, ATC, and AAC inhibitory cells; these inhibitory cells in turn are inhibited by CDB cells, which thus exert a disinhibitory action on pyramidal cells. As already mentioned a special feature of LBC action is that it sharpens the boundaries of the module by inhibiting the pyramidal cells of adjacent modules (cf. to the left of Fig. 3 and both sides of Fig. 6).

Attention has not yet been given to the significance of the remarkable findings of Fairén and Valverde (1980), Sloper and Powell (1979), and Somogyi *et al.* (1982), that the powerful axoaxonic synaptic mechanism is largely restricted to the pyramidal cells of laminae II and III, which are the cells that give corticocortical projections (cf. Fig. 2). Thus, the AAC inhibition would serve selectively to diminish the corticocortical generation of patterns. This effect of AACs may be of importance in averting or limiting the development of epileptic seizures. It could also be that the AAC inhibition would serve to restrict selectively the output from a module and hence to fractionate that module, as proposed in the minimodule hypothesis. By contrast the projection out of the cortex by lamina V pyramidal cells is largely free of AAC control (Sloper and Powell, 1979; Fairén and Valverde, 1980). Some of these lamina V pyramidal cells project via the corpus callosum (cf. Fig. 2). It is of particular importance that the specific corticothalamic projection is mediated by large fibers (cf. Ramón y Cajal, 1911, Fig. 260) that mostly arise from lamina VI "pyramidal cells" (Peters, 1981; Jones, 1981).

6. Pattern Generation in the Neocortex

The concept of the patterned performance of modules is of fundamental significance. This pattern is played out in space and time. A module can participate in an unlimited number of spatiotemporal patterns. Its ongoing per-

formance is dependent on the input pattern in which it is for the moment embedded, as has been illustrated in a simple diagram (Eccles, 1980, Fig. 2-9).

Though the neural machinery of a module has an intricate pattern of design with interacting excitatory and inhibitory neurons, it does not seem to have the propensity for the internal generation of complex spatiotemporal patterns that could be the neural counterpart of memories and of conscious experiences. For example there seems to be no internal system of communication that could give reverberatory loop operation *within* a module. The axon collaterals of the pyramidal cells seem to be randomly distributed so as to exert a mild excitatory action on pyramidal cells of that module and adjacent modules with no discernible specificity of connections (Szentágothai, 1978a, 1979). By contrast the modules seem to be specially designed for participation in patterns in which they are the units. Three distinct pattern-generating features can be distinguished.

First, there are the patterns created by the module-to-module interaction by virtue of the corticocortical fibers. It is conjectured that each module projects to as many as 50 other modules and receives from a like number (Szentágothai, 1978a; Eccles, 1980). Each unit of the projection occurs by a number of output lines (pyramidal cell axons) that form a bundle distributed in overlapping manner to another module and so on (Fig. 2A). Thus, the projection from one module occurs in a spotty manner to some selected groups of modules on the same side, and on the crossed side mostly to a mirror focus that may in part project back to the initiating module. There could be opportunities for reentrant loop operation, as indicated for the same side (Eccles, 1979, Fig. 10-9), and for the contralateral side (Fig. 2).

Second, there is the possibility of reentrant loops between the thalamus and the cortex. It is now well established that thalamocortical connectivities are reciprocal (cf. Fig. 2A) and generally are precisely localized (Ramón y Cajal, 1911; Scheibel and Scheibel, 1966; Tömböl, 1966; Jones and Powell, 1968, 1969a; Pearson *et al.*, 1978; Graybiel and Berson, 1982). Projections to the thalamus occur almost entirely via "pyramidal cells" of lamina VI (Jones, 1981; Peters, 1981) that have little or no AAC inhibition (Fairén and Valverde, 1980; Somogyi *et al.*, 1982). Thus, they are particularly fitted for the continual reverberatory circuit operation of thalamocortical inputs (cf. Fig. 2A), and so could provide repetitive activation of the cartridge synapses on the pyramidal cells that have been conjectured to be concerned in the laying down of "memory traces" (Eccles, 1978, 1979, 1981).

Third, there is the unique system of communication by the horizontal fibers in lamina I and the adjacent superficial part of lamina II. In the hypothesis developed recently for cognitive memory (Eccles, 1978, 1979, 1981) the horizontal fiber system participated uniquely in the formation of "memory traces" and in the retrieval of memories.

7. The Function of Horizontal Fibers (Jones and Powell, 1970a)

As illustrated in Fig. 4 all pyramidal cells of laminae II, III, and V send their apical dendrites up to lamina I, there to branch profusely. Each receives in lamina I excitation by 1000–3000 horizontal fiber synapses on its spines, which is about 20% of its total input. With the so-called "pyramidal cells" of lamina VI the apical dendrites stop short in lamina IV or III (Fig. 4A) and so fail to receive horizontal fiber synapses. It is surprising that this unique and powerful synaptic input into all pyramidal cells of laminae II, III, and V has received so little attention. There are two reasons for this neglect. Any one horizontal fiber makes relatively few crossing-over synapses on the apical dendrites of one pyramidal cell (Fig. 9; Szentágothai, 1978a), but convergence of many horizontal fiber inputs compensates for this. The synapses are remote from the presumed site of impulse generation at the axonal origin. However, it has been shown that with motoneurons synapses remote on the dendrites are unexpectedly potent (Iansek and Redman, 1973; Jack *et al.*, 1981), and it is known that remote synapses tend to be larger (Jones and Powell, 1970b).

8. Patterns in Cognitive Memory

We must distinguish between two distinct origins of the horizontal fibers, both arising from the bifurcation of axons that ascend in the module to lamina I and the superficial part of lamina II.

First, there are the corticocortical fibers around which each module is built (cf. Figs. 3 and 5). Their origin is in the pyramidal cells of laminae II and III of other modules that may be closely adjacent or far removed, even to the other hemisphere (cf. Fig. 2A). It can be estimated that as many as 1200 corticocortical fibers enter one module, but some modules may contribute as many as 100 fibers to this input, the total number of modules contributing being perhaps no more than 50 (Szentágothai, 1978a).

Second, there are the axons of Martinotti cells in lamina VI (Figs. 6, 7A, and 8). In contrast to the first group, these cells are in the module of origin of the horizontal fibers, and they are predominantly activated by the thalamocortical input via the neurogliaform cells. According to Peters and Regidor (1981) Martinotti cells are numerous only in the embryo, but this is in area 17 and Szentágothai's (1965a,b) undercutting observations indicate that Martinotti cells are the principal origin of horizontal fibers.

In the conjunction hypothesis of cognitive memory (Marr, 1970; Eccles, 1978, 1979, 1980, 1981) it is proposed that there is selective potentiation of the synapses made by horizontal fibers on pyramidal cell dendrites when impulses in these fibers are in approximate temporal conjunction with the activation of the apical dendrites of this same cell by the cartridge synapses (cf. Fig. 9). In that way there is potentiation of only a selected group of the synapses made by horizontal fibers entering from a module.

It has to be appreciated that the pyramidal cells of a module have background activity and that, though the activation of their synapses in lamina I (and II) may not be powerful because of its remoteness from the pyramidal cell body, it can very effectively increase the firing rate of these cells, and hence the output from their module. However, as indicated in Figs. 9 and 11, the synapses on only a selection of pyramidal cells would be potentiated for some particular horizontal fiber activation. Hence, in the memory and retrieval process there is a selection from the pyramidal cells of a module.

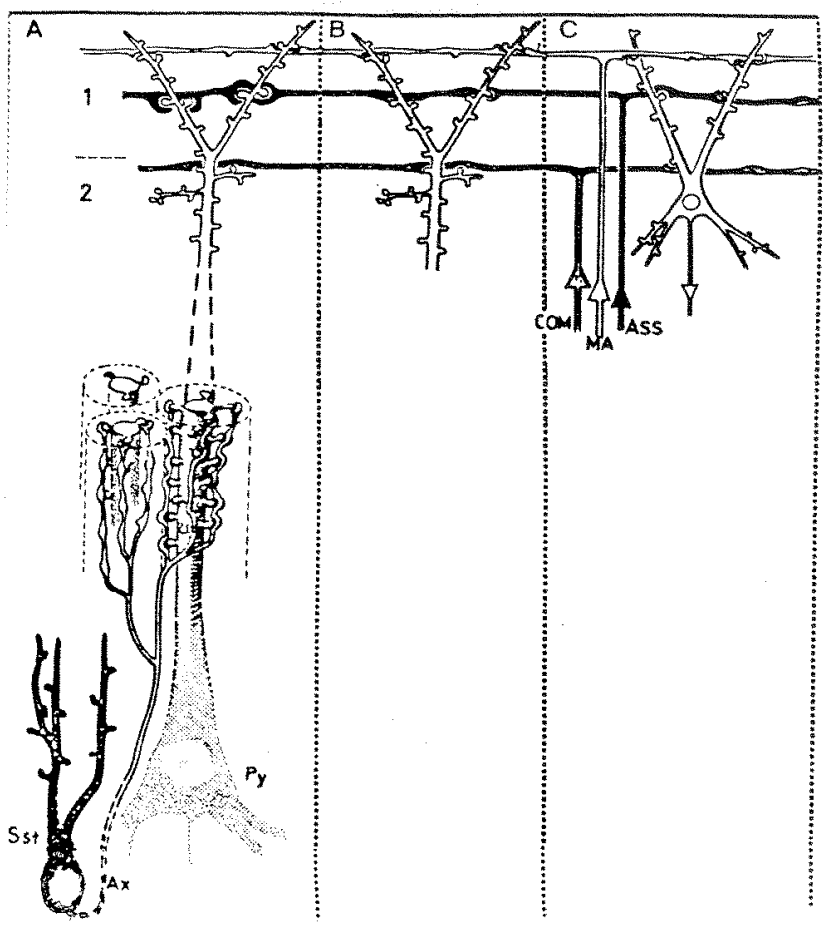

Figure 9. Simplified diagram of connectivities in the neocortex that is constructed in order to show pathways and synapses in the proposed theory of cerebral learning (cf. Eccles, 1978, 1981). The diagram shows three modules, A, B, C. In laminae I and II there are horizontal fibers arising as bifurcating axons of commissural (COM) and association (ASS) fibers and also of Martinotti axons (MA) from module C. The horizontal fibers make synapses with the apical dendrites of the stellate pyramidal cell in module C and of pyramidal cells in modules A and B. Deeper there is shown a spiny stellate cell (Sst) with axon (Ax) making cartridge synapses with the shafts of apical dendrites of pyramidal cells (Py). Due to conjunction hypertrophy the association fiber from module C has enlarged synapses on the apical dendrites of the pyramidal cell in module A. Modified from Szentágothai (1970).

9. A Neuronal Model of Memory Built on the Role of Calcium in Long-Term Potentiation

Recently (Eccles, 1983) it has been possible to develop a most promising model of memory that is based on several remarkable series of experiments on the hippocampus, particularly on the granule cells. The first report was by Bliss and Lømo (1973). When the synapses made by perforating pathway fibers on the dendrites of the granule cells are activated by a brief repetitive stimulation at 20 to 400 Hz, no more than a few hundred stimuli, there follows an extraordinarily prolonged potentiation of those activated synapses. For example the response to a later testing single stimulation of the same synapses may be doubled in size over the period of several weeks (McNaughton, 1983). Evidently this long-term potentiation (LTP), as it is called, is a promising candidate for incorporation in a neuronal model of memory (Eccles, 1983).

There is now much evidence to support the hypothesis that LTP supervenes when there is a substantial increase in the concentration of calcium intracellularly in the granule cells (Eccles, 1983). This explains why for an effective LTP there must be strong stimuli in brief high-frequency bursts. There has to be a rather large postsynaptic depolarization to open the Ca^{2+} gates of postsynaptic membranes, so that Ca^{2+} ions pass inwards down the large electrochemical gradient of about -200 mV. There is much evidence that the intracellular Ca^{2+} combines selectively with a small protein, calmodulin, four Ca^{2+} to one molecule of calmodulin (Cheung, 1982). This Ca^{2+}–calmodulin complex is a powerful second messenger system, phosphorylating proteins, increasing protein synthesis, and accelerating the transport of proteins and other macromolecules by microtubules up the dendrites and so into the spines. As a consequence there is swelling of the activated spines (Fifková and van Harreveld, 1977) and an increased uptake of the postsynaptic membrane for glutamate (Lynch *et al.*, 1983), which is the transmitter (Storm-Mathisen, 1977). It is postulated that there is a reorganization of the protein structure of the postsynaptic densities with their composition of actin, tubulin, calmodulin, and PSD 51 (Matus, 1981; Matus *et al.*, 1982). This leads to an increase in the receptor sites for glutamate (Lynch *et al.*, 1983). Such postsynaptic changes could account for the prolonged potentiation of LTP and hence could be the molecular basis of memory. It is suggested (Eccles, 1983) that the presynaptic changes in LTP (Bliss and Dolphin, 1982) could be secondary to the postsynaptic.

The Marr (1970) conjunction hypothesis of cerebral memory has been developed (Eccles, 1978, 1979, 1980, 1981) in relation to the advances in understanding of the neocortex as described above, but there have always remained two unanswered questions: How do the horizontal fiber synapses "know" of the cartridge activation? Can a precise time relationship be given in place of the vague "approximate temporal conjunction"?

In the calcium hypothesis a sufficient activation of the cartridge synapse would result in a depolarization of the whole pyramidal cell including the terminal dendritic branches in lamina I to a level that widely opens the Ca^{2+} gates. Simultaneous activation of the CDB with disinhibition of the pyramidal cells in the narrow minicolumn (Figs. 3, 5, 7B) would augment this depolarization. Thus, the conjunctive interaction of the Marr hypothesis is simply attributable to the

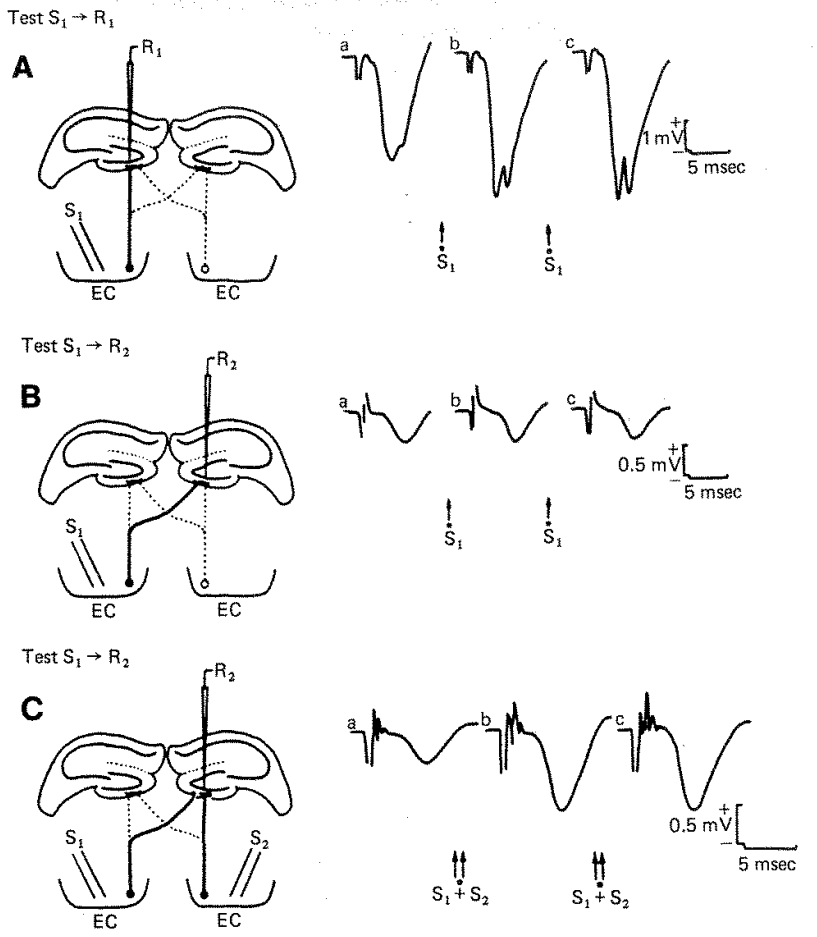

Figure 10. Effect of entorhinal conditioning stimulation S_1 or S_2 on testing responses evoked by a testing entorhinal cortex (EC) stimulation, S_1. Extracellular recording from dentate granule cells gives population excitatory postsynaptic potentials (EPSPs). In (A), S_1 stimulation of EC excites the perforating path to the ipsilateral granule cells for both testing and conditioning stimulation. The conditioning was by eight trains of 8–10 pulses at 400 Hz delivered every 10 sec. In (a) is shown the population EPSP recorded by microelectrode R_1 before conditioning and (b) at about 2 min after the conditioning tetanus. A second conditioning tetanus was applied at 16 min after the first and (c) gives the population EPSP about 2 min later, revealing a slight further increase in LTP. In (B) there were the same EC stimulation procedures by S_1, but the recording by R_2 was for the population EPSP of the contralateral side. Note absence of LTP in (b) and (c). In (C) there was recording by microelectrode R_2 as in (B), but there was now conditioning by a conjoint stimulation of both entorhinal cortices, S_1 and S_2, as indicated. As a consequence there was (b, c) a large LTP of the testing contralateral response S_1 in great contrast to the absence of LTP in (B). From Levy and Steward (1979).

electrotonic spread of the dendrite depolarization with Ca^{2+} influx over the whole surface membrane of the pyramidal cell. However, there is still a question. Since weak synaptic activation, as may be assumed for the horizontal fiber synapses, does not itself cause an LTP, can these synapses participate in the LTP evoked by the cartridge activation? There is the general concept of synaptic cooperativity in LTP production (McNaughton, 1983), but of particular relevance are the experiments of Levy and Steward (1979) as illustrated in Fig. 10. The ipsilateral entorhinal cortex projects strongly to the dendrites of the granule cells, and a conditioning tetanus evokes an LTP (A). By contrast with the contralateral entorhinal cortex stimulation there is a weak excitation and after a conditioning tetanus there is no LTP (B). It can be assumed that the synaptic depolarization was inadequate for opening Ca^{2+} gates. However, if the conditioning tetanus is applied to both contralateral and ipsilateral entorhinal cortices, then the contralateral input shares in the LTP (C). On the calcium hypothesis the contralateral synapses can take advantage of the increased intracellular Ca^{2+} produced by the strong ipsilateral excitation. However, this can only occur if these contralateral synapses are excited in "approximate temporal conjunction." Levy and Steward (1983) have now determined the requisite time relationship. The LTP occurs only if the weak contralateral stimulus burst occurred at a time *before* the ipsilateral of not more than 20 msec, simultaneity also being effective, but not the reverse sequence.

10. Generation of Module Patterns in Relation to Memory and Retrieval

Figure 9 illustrates symbolically the selective synaptic potentiation that occurs when there is conjunction of the cartridge activation of the pyramidal cell in module A with the horizontal fiber arising from association fiber bifurcation in module C. We have to ask: How far can that selection have a meaningful influence on the pattern generation? This question is particularly relevant to pattern generation by virtue of the module-to-module transmission by the corticocortical fibers. In Fig. 11 the modules are shown in plan as seen from the surface, each being enclosed by a circle of 300-μm diameter. In this pattern two modules with corticocortical inputs are shown about 600 μm apart with outward radiating horizontal fibers, and around both are modules with a gradually diminishing horizontal fiber activation, as indicated by the progressive decrease in the density of horizontal fiber distribution. Potentiation of the horizontal fiber synapses to several modules, as illustrated in Fig. 9, is shown in Fig. 11 by the convention of a thickening of some lines as they traverse these modules. It can be seen that around the two excited modules there will be a constellation of modules with an augmented input to pyramidal cells from horizontal fiber synapses, and that consequently in the memory process these pyramidal cells could be excited to initiate via a modular discharge the development of spatiotemporal pattern that could form the neural basis of the remembered experience. The augmented discharge of these pyramidal cells will have opened up new lines of modular communication that were hitherto ineffective. We might term the situation il-

lustrated in Fig. 11 as "modular jumping." It could provide a very simplified model of the changes in modular patterns that are responsible for the storage and retrieval of the cognitive memory.

It is to be noted that the horizontal fiber system in lamina I (and II) is purely excitatory. Even the corticocortical input probably does not have a strong inhibitory influence on a module. These input fibers do not appear strongly to excite inhibitory cells either directly or via spiny stellate cells (cf. Figs. 6 and 7B). On the contrary with the thalamocortical input the inhibitory cells appear to be strongly excited via spiny stellate cells and strongly inhibited by CDB cells (Figs. 3 and 7B; Szentágothai, 1975, 1978a, 1981). For this reason reverberatory circuits

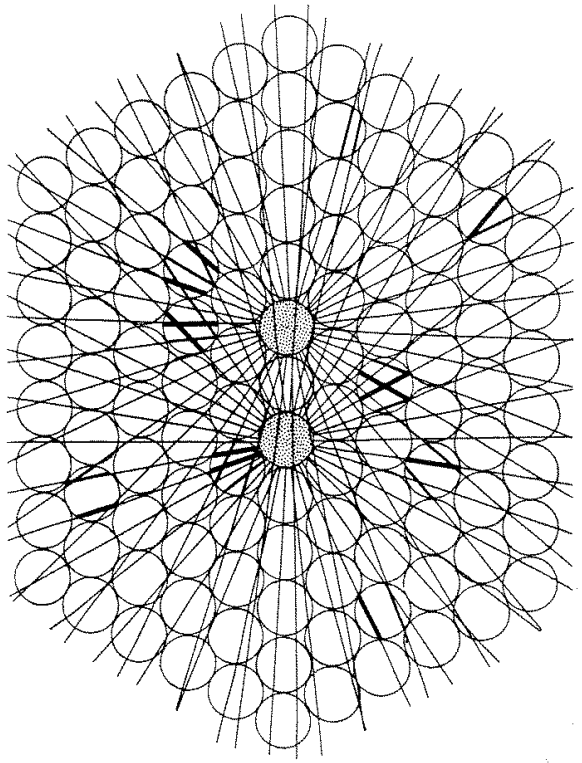

Figure 11. Diagram of a large assemblage of modules as seen in plan, each outlined by a circle. From two modules there are seen 38 radiating horizontal fibers that would travel far beyond this illustrated zone. Each is of course bifurcated in laminae I and II (cf. Fig. 9), so the number of radiating fibers is twice the numbers of fibers of origin—association, callosal, and Martinotti (cf. Figs. 8, 9). In several modules there has been hypertrophy of the synapses made by the traversing horizontal fibers as shown in Fig. 9 and this is shown by thickening of the lines. Further description in text. According to Maurer and Fleischhauer (1979) the horizontal fibers are not isotropically radiating as in Fig. 11, but have a strongly preferred orientation in the rabbit neocortex. Such an arrangement can easily be assimilated into the principles of operation depicted in Figs. 11 and 12.

via the thalamus, as could occur through the reciprocal thalamocortical connectivities (Scheibel and Scheibel, 1966; Jones and Powell, 1968, 1969a; Pearson *et al.*, 1978; Graybiel and Berson, 1981), have to be considered as playing an important role in neocortical activity. A continued thalamic input is made probable by the freedom of "pyramidal cells" in lamina VI from inhibition by AAC cells. This continued activity would be of particular significance in enhancing the excitation of cartridge synapses that are postulated to be the effective agents in producing the large depolarization required for the Ca^{2+} influx. Hence, the thalamocortical input plays a key role in the conjunction hypothesis of synaptic potentiation (Eccles, 1978, 1979, 1980, 1981). The thalamocortical input is also of great significance because it provides an input from the limbic system (Graybiel and Berson, 1981) that would give emotional overtones to memory and also provide motivation (Kornhuber, 1973; Eccles, 1980).

11. A Simple Model of Cognitive Memory

As a consequence of the synaptic potentiation, the horizontal fibers would be able selectively to activate the pyramidal cells involved in the conjunction potentiation (cf. Figs. 9 and 11) and this could occur in the absence of the initiating thalamocortical input to the focal Sst's (cf. Fig. 13B). The laying down and retrieval of a memory will now be considered in more detail in relation to Figs. 12 and 13.

In Figs. 12 and 13 an attempt is made to diagram the conjectured development of modular patterns during a cognitive memory, and the associated mental events. In the lowest row of Fig. 12 there are five modules (A–E) that are serially connected by association fibers in the conventional corticocortical manner (Fig. 2). For diagrammatic simplicity only two pyramidal cells are shown for each module, a 1000-fold reduction. Further association fiber projections shown by a downward arrow from each module would contribute to the spatiotemporal patterns developed in response to thalamo cortical and corticocortical inputs into modules A and B. Each connecting arrow for modules A to E would represent a bundle of up to 100 association fibers. The ongoing activation is indicated by the punctate shading of modules. Modules F and G and those sequential therefrom are inactive in the absence of inputs into F and G.

Figure 13A depicts the modular connectivities at the time of *conjunction* of the TC inputs to modules F and G with the TC inputs into modules A and B. These latter inputs excite the horizontal fiber (H) projections to modules F and G. When there is conjunction between on the one hand the cartridge activation of pyramidal cells by the TC inputs into modules F and G and on the other hand the horizontal fiber activation from module B, there is conjectured to be an enduring hypertrophy of the horizontal fiber synapses (Fig. 9) and this is shown by the convention of thickening in Fig. 13B (cf. Fig. 11). As a consequence of this hypertrophy, even in the absence of TC inputs to modules F and G, the pyramidal cells of modules F and G would be excited to discharge by horizontal fiber activation from module B (cf. Fig. 9) as illustrated in Fig. 13B, which is in contrast with Fig. 12. There has been module jumping from module B to mod-

ules F and G with the consequent initiation of ongoing spatiotemporal activation of the upper two rows of modules, as indicated by the weaker punctate shading. Thus, the patterned development inside the box (outlined by broken lines) is a weak replica of that initiated in A by the normal TC input into F and G modules, but it now occurs in the absence of this input. This pattern is conjectured to be the neural correlate of the cognitive memory and the associated conscious experience. Thus, Fig. 13B illustrates the retrieval of the memory laid down in the conjunction process of Fig. 13A. It also illustrates that memory retrieval is best secured by some related sensory input (the TC inputs to A and B) or by a deliberate mental effort to conjure up related signals, as when trying to remember a name.

As an aside, I find the simplest exemplar of a cognitive memory is provided by the learning of a name for a perceptual experience, for example of the picture of some person. After repeated display of the picture plus name, the subject has to remember the name when presented by the unnamed picture. This would be the situation in Fig. 13B where the "picture" inputs into modules A and B activate by modular jumping the ongoing modular pattern from F and G that

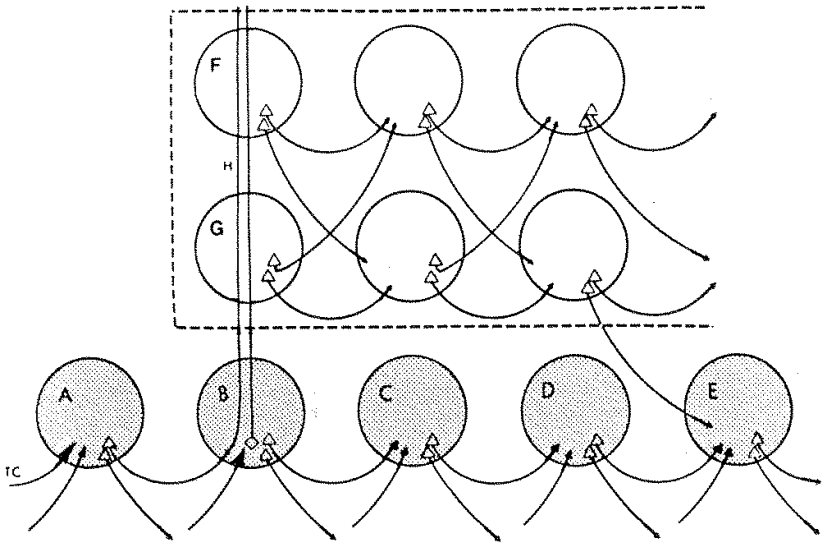

Figure 12. Diagram of modular arrangement looked at from above with the modules separated so as to allow drawing of the corticocortical fibers. Modules A to E represent a basically connected sequence of modules (cf. Fig. 2A). Only two pyramidal cells are shown for each module and input and output lines in part connect to modules out of the diagram. In A and B thalamocortical (TC) input lines are indicated by large arrowheads. Pyramidal cells project by corticocortical fibers to other modules (small arrowheads) that are activated, as indicated, by the punctate shading. From module B there are projecting upwards two horizontal fibers (H) as in Fig. 9, one being the continuation of a corticocortical fiber, the other the projection of a Martinotti cell (diamond) (cf. Fig. 8). In the absence of inputs to modules F and G, the H fiber input is ineffective, as is shown by the empty modules, F and G and onwards.

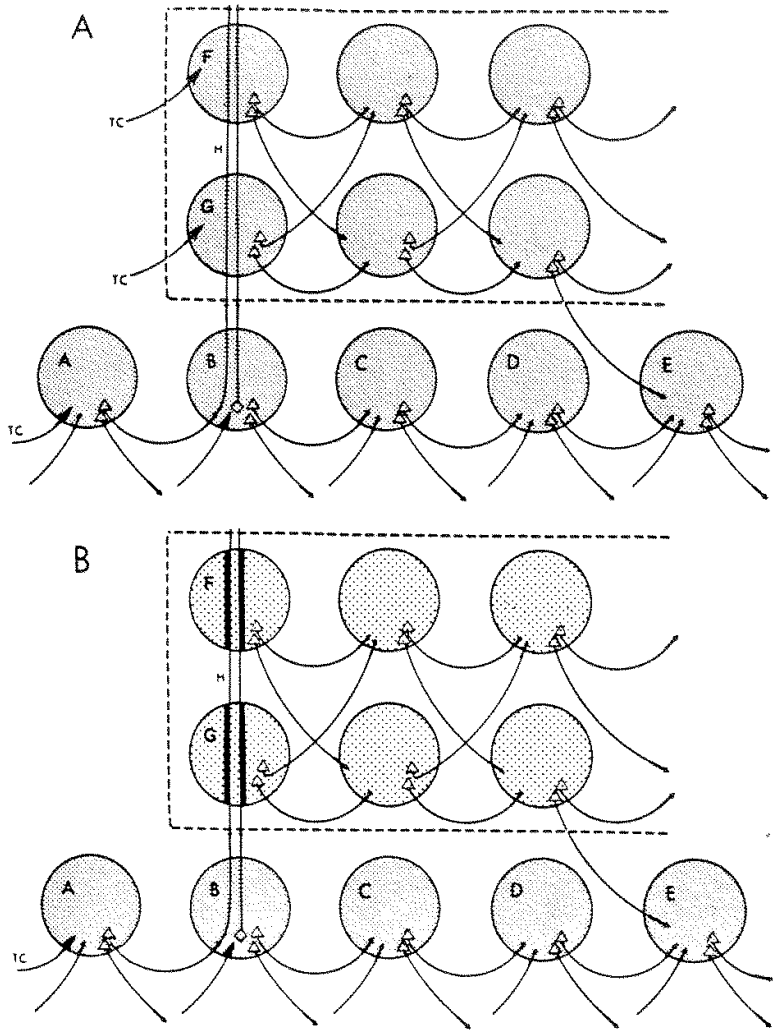

Figure 13. As in Figure 12, but in A there are thalamocortical inputs (large arrowheads) into modules F and G at the same time as the inputs into modules A and B with the activation of the H inputs to modules F and G. The spread of activation from modules F and G to the next modules in sequence is indicated by the punctate shading. The conjunction between the horizontal fiber input to modules F and G and the TC input into these modules is postulated to result in an enduring hypertrophy of the horizontal fiber synapses on the apical dendrites of some pyramidal cells (cf. Fig. 9), which is shown in Fig. 13B by thickening of the H fibers as in Fig. 11. As a consequence, even when there are no TC inputs into modules F and G, there will be discharge of impulses from their pyramidal cells in response to the inputs into modules A and B, as is indicated by the punctate shading. Thus, by the connecting pattern of corticocortical fibers there can be activation of the modular pattern enclosed by the broken line, which otherwise (cf. Fig. 12) would not have been activated in the absence of the TC inputs into F and G.

gives the memory of the name. This is a standard memory test that can be applied years later, if there has been sufficient training.

It must be recognized that in Figs. 12 and 13 there has been a tremendous diagrammatic simplification. There should be an amplification of at least 1000-fold in the pyramidal cell population and in their axons, the corticocortical fibers. Moreover, instead of the two output lines from each module there should be connectivities to up to 50 other modules. It would seem that with this transformation into many parallel modular connectivities the diagram could represent both the distributed system of Mountcastle (1978), with modular elements in echeloned parallel and serial arrangement, and the modular operation of superstructures suggested by Szentágothai (1978b, 1979) and by Sperry (1980) in his nested hierarchies.

12. Self-Consciousness and Memory

It has been argued (Popper and Eccles, 1977) that without memory we would not experience self-consciousness, and that all experiencing is tinged with remembering. On the basis of the generalization that cognitive memory and self-consciousness are intimately related phenomena, *the conjectured modular patterns subserving memory on the conjunction hypothesis should also be the modular patterns correlated with self-consciousness in all of its manifestations.*

As shown in the information flow diagram of Fig. 14, mental events in World 2 and neural events in World 1 are independent entities that interact across the interface in the manner indicated by the reciprocal arrows which signify transmission of information, not energy. The neural correlates of the conscious experiences are in the neocortex—the liaison brain, with its modular columns.

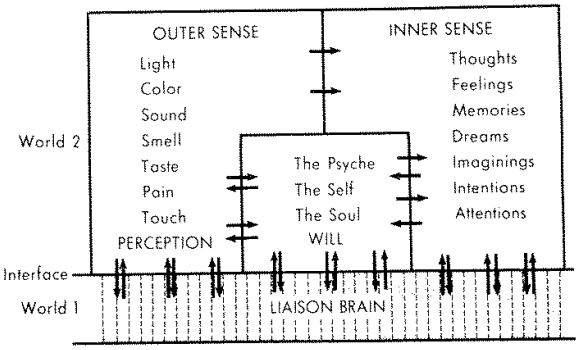

Figure 14. Information flow diagram for brain–mind interaction. The three components of World 2—outer sense, inner sense, and the psyche, soul, or self—are diagrammed with their communications shown by arrows. Also shown are the lines of reciprocal communication across the interface between World 1 and World 2, that is from the liaison brain to and from these World 2 components. The liaison brain has the columnar arrangement indicated by the vertical broken lines. It must be imagined that the area of the liaison brain is enormous, with open modules numbering over a million, not just the two score here depicted. Full description in text.

Since each cognitive experience is embedded in memories that are being retrieved, the modules in the boxed area of Fig. 13B would contain the neural correlate of the conscious experience. This experience is for giving as well as receiving. It is here that we have the most subtle and sensitive dynamic operations of the neocortex. The voluntary retrieval of a simple memory, for example of a name or a number, involves the initiation of a cerebral action that is designed to deliver the required information from the data banks, for example the boxed area of Fig. 13B. That information is then evaluated for correctness by what can be called a recognition memory in the mind, that appears under Inner Sense in Fig. 14. It may be judged erroneous—perhaps a slight error in a name or in a number sequence. This leads to a renewed attempt at retrieval, which may again be judged faulty—and so on until the retrieval is judged to be correct, or until the attempt is abandoned. It is therefore conjectured that there are two distinct kinds of memory: (1) brain storage memory held in the data banks of the brain, especially in the cerebral cortex as in Fig. 13B, and (2) recognition memory tht is applied by the self-conscious mind in its scrutiny of the retrievals from the brain storage memories.

In a voluntary memory retrieval the input to modules A and B in Fig. 13B must somehow be influenced by the mind so that it activates the modular operations in the punctate shaded modules F and G and onwards that are the neural correlate of the memory. As suggested above, this influence is exerted initially by the potentiated synapses of the horizontal fibers from module B, so that they become more effective in exciting some of the modules they traverse. In this way modular jumping is initiated with the consequent development of the unique patterns of modular activity that are conjectured to be the neural substrate of the memory. The retrieved memory is momentarily encoded in the spatiotemporal patterns of the boxed area. According to dualist-interactionism all interactions between neural and mental events are reciprocal (cf. Fig. 14). Hence, it can be conjectured that the neural events in the whole modular ensemble are in reciprocal relationship to the mental events of the experienced memory. At this simplest level, name or number retrieval, conscious experiences can be identified with conscious memory. However, at all levels of self-conscious experiences it would seem that there is a matching level of memories.

Though the potentiated horizontal fiber synapses may be the first target of the mental influences in retrieval, it is postulated (cf. the reciprocal arrows across the interface of Fig. 14) that the whole of the spatiotemporal pattern stemming from that origin is also recognized and controlled by the mental influences in attention, in interpretation, and in the quest for meaning. It can be further proposed that at any one instant not all modules in the cerebral cortex have this transcendent property of being "open" to mental influences (World 2) and thus being the World 1 components of the interface of Fig. 14. For example they would have to be at the appropriate level of activity. Figure 15 gives a diagrammatic illustration of the conjectured relationship of open and closed modules as viewed by looking down at the surface of the cortex. A convenient diagrammatic liberty is to show the columns as separate discs, and not in the close contiguity

that is the actual relationship (Szentágothai, 1978a). Furthermore, it has to be recognized that the normal intensely dynamic situation is frozen in time. The convention is that open modules are shown as open circles, closed as solid, and that there are also partly open modules. It can be conjectured that the self-conscious mind probes into this modular array, being able to receive from and give to only those modules that have some degree of openness. Figure 15 has been designed to show several zones of excited modules interspersed in large dark areas. Also there are smaller patches of excitation. Figure 15 represents just a fragment of a coded representation in a moment of time. The complexity of the real situation can be appreciated when it is recognized that the modular assemblage of the neocortex would be represented by increasing the area of Fig. 15 almost 5000 times. When in memory retrieval by modular jumping there is activation of the boxed area of Fig. 13B, for example, there will be a change in the modular pattern of Fig. 15 that in its developing dynamic patterns is the neural counterpart of the remembered experience.

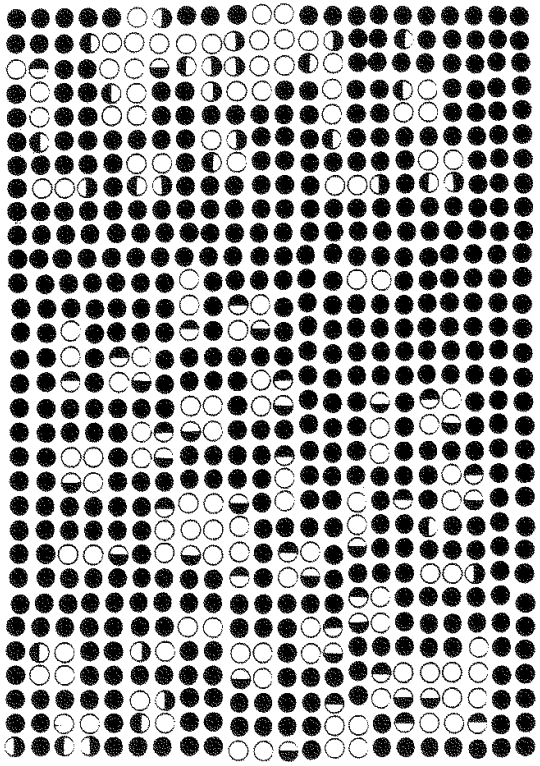

Figure 15. Diagrammatic plan of cortical modules as seen from the surface (cf. Fig. 12). As described in the text, the modules are shown as circles of three kinds, open, closed (solid black), and half open. Further description in text.

It is important to realize that the separateness of the two modular systems of Figs. 12 and 13 is related to some specific TC input. With another input there would be a complete rearrangement. The modules A to F could be triggered by an appropriate horizontal fiber system, and so be the neural correlates of some other memory. Any one module could participate in the spatiotemporal patterns for an indefinitely large number of memories with their embedded conscious experiences.

It is difficult to understand how the self-conscious mind can relate to such an enormous complexity of spatiotemporal modular patterns as in Fig. 15. This difficulty is mitigated by three considerations. First, we must realize that our self-conscious mind has been learning to accomplish such tasks from our infancy onwards, a process that is colloquially called "learning to use one's brain." Second, by the process of attention the self-conscious mind selects from the total ensemble of modular patterns those features that are in accord with its present interests. Third, the self-conscious mind is engaged in extracting "meaning" from all that it reads out. This is well illustrated by our experiences with ambiguous figures, for example a drawing that can be seen holistically either as a staircase or as an overhanging cornice, but never with some compromise solution.

13. Special Design Features of the Neocortex

1. As illustrated in Fig. 4 the apical dendrites of all pyramidal cells of laminae II, III, and V extend up to lamina I (cf. Sholl, 1956, Fig. 12), where their branches are covered with the spine synapses made by the horizontal fibers (Figs. 3, 6, and 9). Thus, according to the hypothesis here formulated they have the propensity for participating in the selective synaptic potentiation of the memory process.

2. The axons of the large neurons of lamina VI also project out of the cortex as the corticothalamic fibers (Peters, 1981; Jones, 1981), but the apical dendrites extend only up to laminae IV and III (Fig. 4A) and so miss the horizontal fiber connectivities of lamina I. However, there have long been recognized the horizontal fiber projections in laminae III and IV as the external and internal striae of Baillarger, which extend over most of the neocortex (Lorente de Nó, 1938). The external stria is prominent as the stria of Gennari in area 17. Focal lesions of the cortex reveal that degenerating fibers extend for several millimeters, particularly in laminae III and V (Creutzfeldt *et al.*, 1977; Fisken *et al.*, 1973, 1975), and mostly make excitatory synaptic connections with dendritic spines. As shown in Fig. 8 a horizontal fiber arises from a neuron in lamina IV.

It is suggested that the apical dendrites of lamina VI "pyramidal cells" may not project up to lamina I because they are "satisfied" by their synaptic connections from the horizontal fibers in deeper laminae. These neurons are concerned in the generation of thalamocortical reverberatory circuits, as indicated by the reciprocal arrows in Fig. 2A. The thalamocortical projection would be to stellate cells of lamina IV that participate in the horizontal fiber activation of the apical dendrites of lamina VI cells. These corticothalamic projecting cells thus can

participate in reverberatory circuits which would be most importantly concerned in giving a sufficiently long synaptic activation of the apical dendrites of pyramidal cells (cf. Fig. 9) for the influx of Ca^{2+} and the consequent generation of the prolonged potentiation of the horizontal fiber synapses of lamina I.

3. As already stated the pyramidal cells of laminae II and III have a strong inhibitory control by axoaxonic synapses (Figs. 3, 6, and 7), which may be of importance in blocking the buildup and spread of cortical excitation that occurs for example in epileptic seizures. This control of pyramidal cells in lamina V and of "pyramidal cells" in lamina VI is much weaker or even nonexistent. Three main output lines of the neocortex are recognized: (1) the corticocortical, association, and commissural, of pyramidal cells in laminae II and III; (2) the pyramidal projection from lamina V cells to lower levels; and (3) the "pyramidal cell" projection of lamina VI to the thalamus. Categories 1 and 2 share in the horizontal fiber synapses of lamina I with the propensity for the prolonged synaptic potentiation of the learning process. Category 1 is remarkable for the strong inhibitory control of its axons.

4. The CDB inhibitory action on neurons that inhibit pyramidal cells (Somogyi and Cowey, 1980, 1981) with its narrow vertical column of action (Fig. 4F) becomes meaningful in respect to the narrow vertical column of cartridge activation of pyramidal cells (Figs. 4E and 9; Szentágothai, 1975, 1978a, 1981). The collusion of these two effects would result in a strong membrane depolarization of a minicolumn of pyramidal cells with an enhancement of the Ca^{2+} input into their dendrites and of the consequent long-term potentiation of those horizontal fiber synapses activated at about the same time.

These four exemplars of meaningful features of the structural design of the neocortex provide encouragement for further ventures in the field. The much simpler structural design of the cerebellum allowed experimental investigations which revealed its principal features. With the cerebral neocortex the structural design is much more complicated. However, there is progress. It must be recognized that the theoretical treatment of this chapter is derived from present knowledge. It is presented not with any claim of being the ultimate story, but merely as a stage on the way in our attempt to understand the most complicated and important structure that exists.

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