13

Neuronal Representations and Temporal Codes

W. SINGER, A. ARTOLA, A.K. ENGEL, P. KÖNIG, A.K. KREITER
S. LÖWEL, and T.B. SCHILLEN
Max Planck Institute for Brain Research,
6000 Frankfurt am Main 71, F.R. Germany

ABSTRACT

This chapter focuses on the question of how highly evolved brains of mammals develop representations of their environment. Concepts favoring the notion that complex feature constellations are represented by individual, highly specialized neurons are contrasted with theories which postulate that representations consist of large assemblies of spatially distributed, selectively interacting cell groups. It is argued that the first strategy is well adapted for the representation of stimuli that possess a low degree of ambiguity and require rapid behavioral responses, the disadvantages being limited storage capacity, restrictions with respect to the formation of new representations, and low flexibility in the processing of unfamiliar patterns. The second strategy circumvents these restrictions but imposes specific constraints on the dynamical properties of the respective neuronal network. A central issue here is the binding of spatially distributed neurons into functionally coherent assemblies. It is proposed that this binding problem can be solved by a temporal code, neurons participating in a particular assembly being distinguished by the synchrony of their responses. Experimental evidence is reviewed which suggests that cortical networks are, in principle, capable of using such a temporal code to represent feature constellations by dynamically coupled cell assemblies.

TWO COMPETING CONCEPTS

A major challenge of brain research is the identification of mechanisms by which the nervous system creates representations of its environment. Accordingly, a wide spectrum of proposals has been offered at various epochs, and it may indeed turn out that different species have opted for different solutions or that even, in the same brain, different strategies are employed depending on the content that is to be represented. Here we wish to focus on concepts concerning the organization of representations in the mammalian neocortex. One widely accepted proposal is based on the assumption

that not only simple features but also complex constellations of features characterizing natural objects are represented by the responses of individual highly specialized neurons (see, e.g., Barlow 1972). The discovery of hand, face, and action-specific neuronal responses in higher visual areas of the monkey has been taken as support for the view that individual neurons, with highly selective response properties emerge from serial processing of sensory signals in hierarchically arranged cortical areas (Desimone et al. 1984; Gross et al. 1972; Perrett et al. 1987; see Maunsell, chapter 14). However, not all available data support such an interpretation. Cells in areas remote from primary sensory input are often less selective for particular features than those at earlier stages; the response selectivity of neurons activated by complex patterns is not exclusive; apart from face- and hand-specific cells no other object-specific cells have been described so far; and in a particular cortical area, many different cells were found to respond to the same object (see, e.g., Rolls 1990). Moreover, it was realized that parallelism and reciprocity are prevailing principles of cortical connectivity, which makes it difficult to assume that one particular cortical area should serve as the end-stage of a hierarchical process (Felleman and van Essen 1991). If such an area existed, it would have to be a large area because of the enormous demands for storage capacity. This is in conflict with the evidence that at higher levels of processing, the size of individual cortical areas does not increase. Finally, it has been argued that there would probably not be enough cells in the brain if each of the distinguishable feature constellations, i.e. each of the possible views of all distinguishable objects, would have to be represented by a specialized neuron.

To account for these inconsistencies, less extreme versions of this concept have been proposed. They assume that objects or, more specifically, particular views of an object are not represented by individual cells but by sets of cells. Each cell of such sets can then be less selective because the signature for a particular object is contained in the graded responses of a group of cells (see, e.g., Poggio, chapter 7). This coding algorithm requires fewer neurons because different views of a particular object can be represented by interpolation between cells of the set; however, each set of cells can only represent one object. There is still a 1:1 relation between a particular object and the corresponding set of neurons. Thus, if representations of all distinguishable objects would have to be generated in that way, a vast number of neurons would be required, many of which would have to remain uncommitted and unused in order to allow for the generation of representations of new objects. However, because such coding can be achieved with simple feedforward nets, it may be used in the brain to represent stimuli, such as faces that have a particularly high behavioral relevance and/or require particularly fast reactions. It is also conceivable that simpler nervous systems, which have limited abilities to form representations, rely on such a coding algorithm. It appears unlikely, however, that strongly corticalized brains with their virtually unlimited capacity to form representations of nearly any pattern, use only this strategy.

Alternative concepts have therefore been developed. They are all based on the assumption that particular feature constellations are represented by a large number of

simultaneously active neurons distributed over many cortical areas (Abeles 1991; Braitenberg 1978; Crick 1984; Edelman 1987; Edelman 1989; Edelman and Mountcastle 1978; Grossberg 1980; Hebb 1949; Palm 1982; Palm 1990; von der Malsburg 1985). However, the essential difference between the "single cell" or the "set of cell" concepts and the assembly coding concepts is not primarily the number of cells participating in a representation. The crucial difference is that the latter, not the former, permits individual cells to participate at different times in the representation of different objects. The concept of assembly coding implies that, just as a particular feature can be shared by many different patterns, a particular neuron can be shared by many different representations in that it participates at different times in different "assemblies" of co-active neurons. The code is thus relational; the significance of an individual response depends entirely on the context set by the other members of the assembly. A basic requirement for representing feature constellations or patterns by such assemblies is that the neuronal elements constituting a particular assembly are distinguishable as members of this very assembly. This cannot be done by position codes alone, because what matters is not so much the responses of individual neurons but the relations between these responses. It is assumed therefore that labeling of assemblies is achieved by selective connections between the constituting elements. The idea is that these connections enable cooperative interactions between the respective neurons and, through reverberation, enhance and stabilize the responses of the members of the assembly so that these become distinguishable (see, e.g., Singer 1979). The structure of assemblies is thus determined by the functional architecture of coupling connections between the potential elements of an assembly. It follows from this that these connections must be endowed with adaptive synapses, the efficiency of which can change in a use-dependent way according to some kind of associative learning algorithm. Such adaptivity is required to allow the generation of assemblies representing new objects and patterns. This notion establishes close relations between concepts of assembly coding and associative memory networks (Palm 1990). A related proposal is that the functional units embodying features and constituting the elements of assemblies should be local groups of reciprocally coupled neurons rather than individual cells (Edelman 1987; Edelman 1989; Edelman and Mountcastle 1978). This postulate followed from the concept that analogous to clonal selection in the immune system, representations are created by selection from a vast repertoire of preexisting constellations. Introducing groups which differ from one another by variations of within-group interactions was considered as a possibility to create a sufficiently large and diversified repertoire. In this concept, assemblies would then be constituted by sets of spatially distributed and interconnected groups rather than by distributed individual neurons.

The implication of the concept of assembly coding is that a given set of neurons can be used for the formation of as many different representations as there are possible combinations of active and inactive cells in this set. This economizes on cell numbers but puts high demands on the specificity and diversity of ensemble-forming coupling connections. The following constraints must be met by such networks:

1. There must be selectively tuned reciprocal connections between neurons within the same cortical area and between neurons located in many different areas. Such connections are required for the selection and dynamical stabilization of specific assemblies.
2. These connections must be exceedingly numerous because their number, together with the number of cells, limits the number of possible constellations.
3. The network must exhibit dynamical properties because a particular cell must be able to link at different times with different partners.
4. The linking connections must have adaptive synapses to allow for the formation and stabilization of new representations if a new pattern is seen and learnt.

Implementation of some of these coding principles in artificial neuronal networks permitted us to realize a number of attractive functions resembling, in many respects, those of natural systems. However, there was a serious limitation. As assemblies were distinguished solely by the enhanced responses of their constituents, assemblies representing different objects could not be represented simultaneously in the same matrix because they became confounded. It was impossible to know which of the numerous active and spatially intermingled cells would actually belong to a particular assembly. This superposition problem can be alleviated to some extent by place coding. As long as maps are retinotopically organized, overlap can often be avoided by spatial segregation and at higher levels one can create several matrices (cortical areas) in parallel and again use a spatial code to segregate simultaneously active assemblies from one another. This solution, however, is a compromise. While it reduces ambiguity, it is again expensive in terms of neuron numbers and, most importantly, it sacrifices flexibility. Position coding greatly constrains the degrees of freedom for partner selection: to maintain the position code, interactions between assemblies in different areas are forbidden because they would reintroduce the ambiguity that one wants to overcome.

It has been proposed, therefore, that assemblies should be distinguished by a temporal code rather than by response amplitude (von der Malsburg 1985; von der Malsburg and Schneider 1986). The suggestion was that individual neurons or groups of neurons should engage in rhythmic discharges that occur in synchrony for all members of an assembly. Assemblies that code for different figures in a scene should each engage in their own rhythm and should show no fixed-phase relation between their respective synchronous oscillations. In this way, simultaneously active neurons remain distinguishable as members of a particular assembly because their responses are synchronous with the responses of other cells of the same assembly, but not with cells of other assemblies. In computer simulations this temporal coding principle proved to be very efficient for the solution of problems related to figure-ground segregation (Bienenstock and von der Malsburg 1987; Shimizu and Yamaguchi 1987; von der Malsburg 1988; von der Malsburg

and Schneider 1986). Subsequently, this concept of "binding by synchrony" has been developed further and generalized to intermodal integration (Damasio 1990) and even to integrative processes underlying phenomena such as attention (Crick 1984) and consciousness (Crick and Koch 1990).

Essential properties of cortical organization are compatible with such a concept of assembly coding, where position codes and relational codes are combined to achieve maximal reduction of ambiguity while preserving a high degree of freedom for combinations: the distributed representation of primitive features by specialized neurons, the grouping of neurons with similar response properties in functional columns (Hubel and Wiesel 1963; Mountcastle 1957), the parallel arrangement of a large number of functionally specialized cortical areas, and the incredibly dense network of reciprocal cortico-cortical connections, which in principle should allow for a very large number of combinations of different neurons both within and across cortical areas (for a review, see Felleman and van Essen 1991). However, despite these compatibilities at the level of functional architecture it proved difficult to obtain supportive evidence for the concept of assembly coding from measurements of single-cell activity.

EXPERIMENTAL DIFFICULTIES WITH ASSEMBLIES

Since assemblies are defined by relations between the responses of the constituting elements, one way to identify assemblies is to record simultaneously from spatially distributed neurons in the brain and to search for co-variance of responses (Abeles 1991; Aertsen and Gerstein 1985; Aiple and Krüger 1988). Another possibility is to look for stereotyped temporal response patterns of individual neurons. The idea behind this latter approach is that the specific architecture of the reciprocal connections between the elements of an assembly should lead to specific temporal patterning of the activity circulating within the assembly. This pattern should recur whenever the assembly is organized, and hence its occurrence should show some correlation with stimulation or response conditions (Abeles 1991).

Both experimental strategies have been applied. For closely spaced cells within single functional columns, interactions were rather frequent and cross-correlation analysis proved capable of distinguishing constellations where cells receive either common excitatory or inhibitory input, or where one cell excites or inhibits the other (Abeles and Gerstein 1988; Gochin et al. 1991; Michalski et al. 1983; Toyama et al. 1981). However, for cells located further apart, correlations were difficult to detect and, if present, were interpreted as indicative of common excitatory input (Gochin et al. 1991; Krüger and Aiple 1988; Tso et al. 1986) or of global modulation of excitability (Aiple and Krüger 1988; Krüger and Aiple 1988). Thus, it appeared as if there were no indications of reciprocal cooperative interactions between the analyzed pairs of neurons nor of dynamical changes in the relations between the respective discharge

patterns. The observed relations could be accounted for by assuming bifurcating feedforward connections and lateral inhibition. Likewise, it turned out that recurring temporal patterns in neuronal responses were rare and showed only a loose correlation with particular stimulus or response conditions (Abeles 1991). While not particularly encouraging, these results should, however, not be taken as negative evidence. In most cases, cross-correlation analysis was applied to identify anatomical connections rather than to test the concept of assemblies and, therefore, stimulation and evaluation procedures were inadequate for the latter purpose. Also, some of the difficulties encountered in the search for assemblies should be expected. First, chances are low to record simultaneously from cells actually participating in a particular assembly because their spatial distribution cannot be easily anticipated. Second, it is to be expected that interactions are difficult to detect because they are of short duration and occur at times which cannot be precisely predicted. The theory implies that assemblies are highly dynamic, rapidly changing functional entities. Moreover, because assemblies self-organize through cooperative interactions among their constituting elements, the time of their formation predictably lacks any stereotyped relation with the inducing stimuli.

The recent observation that spatially adjacent neurons in the cat visual cortex have a strong tendency to engage in highly synchronous oscillatory discharges, when presented with their preferred stimulus (Gray and Singer 1987), provided a new motivation to search for temporally structured assemblies: First, this observation indicated that responses of feature-specific neurons can show a distinct temporal patterning, which could in principle be used for the labeling of assemblies by a temporal code. Second, it provided a legitimation for the use of multiunit recordings when searching for correlations between responses of spatially remote groups of neurons. This was crucial in view of the predicted brevity and instability of synchronized response epochs. Using multiunit recordings increases the number of events per time unit and thereby allows the reduction of the duration of the time window required to obtain reliable data from cross-correlation analysis. Third, it was to be expected that response episodes characterized by synchronous discharges in local cell groups should be particularly favorable for the occurrence of response synchronization among remote cell groups. The hypothesis was that the effect of the coupling connections should become detectable more easily if they are active in synchrony. The theory predicts that the effect of any individual neuron on any other individual neuron should be very weak. Hence, the probability of detecting interactions should increase once many cells engage in synchronous discharges because of spatial and temporal summation of the individual weak effects. Thus, focusing cross-correlation analysis on response episodes associated with high local synchrony was expected to increase the probability of observing synchronization over larger distances. Based on these working hypotheses, a series of experiments have recently been performed whose results are fully compatible with the concept that neuronal representations consist of assemblies which are labeled by a temporal code.

EXPERIMENTAL EVIDENCE COMPATIBLE WITH THE CONCEPT OF TEMPORALLY STRUCTURED ASSEMBLIES

The phenomenon of local response synchronization has, in the meantime, been observed in several areas of the visual cortex of anesthetized (Eckhorn et al. 1988; Engel et al. 1991c; Gray and Singer 1989) and awake cats (Raether et al. 1989), and recently awake monkeys (Kreiter and Singer 1991). This supports the proposal (Edelman 1987) that local clusters of neurons with similar response properties behave as a group consisting of tightly coupled elements. It has further been shown, both in the cat and monkey, that response synchronization can occur also between spatially segregated cell groups within the same visual area (Engel et al. 1990; Gray et al. 1989; Kreiter and Singer 1991).

Detailed studies in anesthetized cats have revealed that, in this case, synchronization probability depends on the spatial segregation and feature preference of the respective cell groups as well as on the configuration of the stimuli (Engel et al. 1990; Engel et al. 1991b; Gray et al. 1989). Stimuli that, according to common Gestalt criteria, appear as single figures lead to synchronization among the responding groups, while stimuli appearing as independent figures or as parts of different figures fail to establish synchrony among the groups they excite (Engel et al. 1991a; Gray et al. 1989).

In agreement with a central prediction of the assembly hypothesis is the recent demonstration that two different, spatially overlapping stimuli can be represented by two independently oscillating assemblies of cells, and that individual groups can switch between different assemblies depending on stimulus configuration (Engel et al. 1991b). If groups of cells with overlapping receptive fields but different orientation preferences are activated with a single moving light bar, they synchronize their responses even if some of these groups are suboptimally activated (Engel et al. 1990; Engel et al. 1991b). However, if such a set of groups is stimulated with two independent stimuli that move in different directions, they no longer form one coherently active assembly but split into two independently oscillating assemblies; those groups joining the same assembly that have a preference for the same stimulus. Thus, the two stimuli become represented by two spatially interwoven but temporally segregated assemblies. Groups representing the same stimulus oscillate in phase while no consistent phase relation exists between assemblies representing different stimuli. However, the global aspects of the applied stimulus configurations have no detectable effect on local response parameters, such as amplitude or oscillatory patterning. Thus, it is not possible to tell from the responses of individual groups whether they were activated by coherent or incoherent stimuli. Only the evaluation of the synchronicity of the responses of the groups provides the cue as to whether the groups are activated by one coherent stimulus or by two different, independent stimuli. These results indicate that response synchronization between simultaneously activated groups depends not only on the feature preference of the respective groups but also and to a crucial extent on stimulus configuration. This implies that the coupling between distributed cell groups

is dynamical and changes in a stimulus-dependent way. One methodological caveat following from this is that cross-correlation analysis does not reliably reflect anatomical connectivity (see also Aertsen and Gerstein 1985).

The hypothesis of assembly coding implies that assemblies are distributed entities and should extend across different cortical areas. In agreement with this prediction response synchronization has also been found between groups located in different cortical areas. In the cat, interareal synchronization has been observed for field potential responses between areas 17 and 18 (Eckhorn et al. 1988) and for cellular discharges between groups in area 17 and an area specialized for motion processing (Engel et al. 1991c), and even between groups in A 17 of the two hemispheres (Engel et al. 1991a). In all cases, synchronization depended on receptive field constellations and stimulus configurations, similar to the intraareal synchronization. Functionally coherent assemblies can thus be very distributed and comprise cell groups located in different cortical areas.

THE SUBSTRATE FOR RESPONSE SYNCHRONIZATION

It is commonly assumed in cross-correlation studies that synchronization of neuronal responses with zero-phase lag is indicative of common input (Gerstein and Perkel 1972). It has been proposed, therefore, that the observed synchronization phenomena in the visual cortex are due to common oscillatory input from subcortical centers. This notion has received support by the discovery of pacemaker currents in thalamic neurons and corresponding oscillatory activity (Steriade et al. 1988). Moreover, it has been argued that synchronization with zero-phase lag would be difficult to achieve by reciprocal interactions between spatially distributed neurons because of the conduction delays in the coupling connections. However, the concept of assembly coding requires that the binding-together of elements constituting an assembly is achieved through reciprocal connections between the elements of an assembly and not only by common input. It is only with such a scheme of connectivity that the required combinatorial flexibility can be achieved.

Evidence is now available that response synchronization can be achieved by cortico-cortical connections despite considerable conduction delays. It has been demonstrated that response synchronization between cell groups in area 17 of the two hemispheres is mediated by the corpus callosum and hence by a reciprocal cortico-cortical projection that shares many features with the tangential fiber systems interconnecting cell groups within the same visual area (Engel et al. 1991a). In higher mammals signals coming from either side of the fixation point are projected to different hemispheres because of the partial decussation of the optic nerves. Neurons responding to figures extending across the vertical meridian are therefore located in different hemispheres. The responses of these cells have to be bound together in the same way as those of cells located within the same hemisphere. The hypothesis that binding is achieved by response synchronization predicts then that response syn-

chronization between cells in area 17 of different hemispheres follows the same rules as synchronization between cells in area 17 of the same hemisphere. Thus, the demonstration that interhemispheric response synchronization reflects the coherence of stimuli and is mediated by callosal connections has two implications: it emphasizes the putative significance of response synchronization for perceptual grouping and it proves that cortico-cortical connections can synchronize responses with zero phase lag.

Recent simulation studies provide some suggestions on the mechanisms by which synchronization with zero phase-lag can be achieved despite considerable conduction delays in the coupling connections. In the case of the corpus callosum, these delays amount to about 5 to 6 ms. The simulation studies indicate that synchronization can be achieved if coupling delays remain below 1/4 of the oscillation period, which in our case is about 25 ms. Synchronization is facilitated if a fraction of the excitatory coupling connections are made to drive local inhibitory interneurons (König and Schillen 1991; Schillen and König 1991) in the target area and if the reciprocal excitatory connections between pyramidal cells are endowed with nonlinear synapses that increase their gain as a function of the activity of the respective postsynaptic targets (Kirillov et al., in preparation). Both prerequisites appear to be fulfilled in cortical networks: while the large majority of the tangential connections establish reciprocal excitatory links between pyramidal cells, about 10 to 20% of them impinge on inhibitory interneurons in the respective target zone (Kisvárdy et al. 1986; McGuire et al. 1991). Moreover, there is good evidence that the cortico-cortical connections are endowed with synapses which have the required nonlinear transfer function. Most of them possess NMDA receptors (Thompson 1986) and these have precisely the required property: because of the voltage-dependence of the NMDA receptor-gated channel, the efficacy of these synapses increases with postsynaptic depolarization (Ascher et al. 1988; Mayer et al. 1984). Recently, excitatory synaptic potentials have also been identified in visual cortex slices that do not depend on NMDA receptors, but show a very similar voltage dependence (Hirsch and Gilbert 1991).

The models on response synchronization through reciprocal connections with delay have all departed from the notion that the cell groups which become synchronized have a tendency to engage in oscillatory discharge modes of similar frequency. It is conceivable that such local resonant properties facilitate the organization of synchrony over larger distances. One functional role of the observed oscillatory responses could thus be that they provide favorable conditions for synchronization despite conduction delays. The oscillatory nature of the responses may in turn be an emergent property of a self-organizing process. Once responses have become organized and occur in synchrony, i.e., once many distributed cells discharge simultaneously, recurrent inhibition will also increase due to the synchronous input to inhibitory interneurons; this will lead to the characteristic burst-and-pause pattern of discharges that occurs during periods of response synchronization. Oscillatory responses might thus be considered both as a prerequisite and a consequence of response synchronization.

SELECTIVITY OF SYNCHRONIZING CONNECTIONS

The theory of assembly coding implies that the structure of assemblies is determined by the functional architecture of the coupling connections. Therefore, these have to be selective; their functional architecture should reflect the criteria according to which particular features are grouped together rather than others. Psychophysical evidence and the electrophysiological data on synchronization probability both suggest that continuity, vicinity, colinearity, and coherent motion of contours serve as such grouping criteria. This predicts that within area 17 nearby cell groups should be coupled more tightly than distant groups and that cell groups preferring related features should be coupled preferentially. Anatomical data on the architecture of cortico-cortical connections are compatible with this postulate. In the visual cortex, cells separated by less than 1 mm are interconnected by a dense network of radial axon collaterals (Fisken et al. 1975). Beyond this range, connections link selectively cell groups that show a regular spacing with a periodicity of about 1 mm (Rockland and Lund 1982). Analysis of response properties of interconnected groups suggests that these prefer similar features (Gilbert and Wiesel 1989; Tso et al. 1986) (but see (Matsubara et al. 1985). Similar principles should also apply for the binding connections between different areas. Yet as grouping criteria in higher processing areas are likely to be less constrained by retinotopic relations and need to be adapted to evaluate complex constellations in feature space, the architecture of these reciprocal inter-areal connections can be expected to be very complicated.

Experience-Dependent Development of Synchronizing Connections

While the basic organization of cortico-cortical connections is with all likelihood determined genetically, additional shaping by an experience-dependent process is an attractive possibility for two reasons. First, the topographical arrangement of cell groups preferring particular features is not solely determined by genetic instructions but is, in addition, influenced by experience (Singer et al. 1981). Therefore, it would seem that the architecture of the coupling connections cannot be fully predetermined by genetic instructions either. Second, it would be advantageous if the grouping criteria could be adapted to frequently occurring feature constellations in natural scenes and, in particular, to those constellations which are behaviorally relevant.

Evidence compatible with such a use-dependent selection of synchronizing cortico-cortical connections is now available. In the cat, development of cortico-cortical connections extends far into postnatal life (Callaway and Katz 1990; Innocenti 1981; Luhmann et al. 1986; Price and Blakemore 1985a), and data from cat visual cortex suggest that the connections attain their final specificity through an experience-dependent selection process (Callaway and Katz 1991; Innocenti and Frost 1979; Luhmann et al. 1990; Price and Blakemore 1985b). Moreover, as summarized below,

recent data from strabismic cats indicate that this experience-dependent selection is based on some kind of correlation analysis.

Evidence for Use-Dependent Selection of Synchronizing Connections

Raising kittens with artificially induced strabismus leads to changes in the connections between the two eyes and cortical neurons so that individual cortical neurons become connected to only one eye (Hubel and Wiesel 1965). Thus, the population of cortical neurons splits into two subpopulations of about equal size, each responding rather selectively to stimulation of one eye only.

Most strabismic animals develop normal monocular vision, particularly if they are exotropic and alternate. It must be assumed, therefore, that the interactions required for feature-binding are unimpaired between cortical cells connected to the same eye. This is not the case for signals conveyed by different eyes. Psychophysical evidence indicates that strabismic subjects suppress signals coming from one eye in order to avoid double images; they actually become unable to bind signals conveyed by different eyes, even if these signals are made contiguous by optical compensation of the squint angle (von Noorden 1990). This implies that in strabismics, binding mechanisms should be abnormal or missing between cells driven from different eyes. If one accepts that response synchronization is equivalent to binding and that the architecture of cortico-cortical connections determines the probability of response synchronization, two predictions follow for strabismic animals: First, response synchronization should be normal between cell groups connected to the same eye but should be very rare, if present at all, between cell groups connected to different eyes. Second, tangential cortico-cortical connections should extend preferentially between territories served by the same eye.

Both predictions were found to be fulfilled (König et al. 1990; Löwel and Singer 1992) and this has several important implications. First, it corroborates the notion that tangential intracortical connections are the substrate for response synchronization. Second, it is strong support for the hypothesis that the architecture of tangential connections is shaped by experience. Third, it suggests that this selection occurs according to a correlation rule. The latter conclusion is based on the plausible assumption that in strabismics, once cortical cells have become monocular, responses of cells connected to the same eye will, on the average, show a much higher degree of correlation than responses of cells connected to different eyes. The close correlation between the loss of the ability to bind signals conveyed by the two eyes, the loss of response synchronization between cells driven by the two eyes, and the loss of connections between the cortical territories of the two eyes is thus in very good agreement with the hypothesis that the architecture of cortico-cortical connections, by determining the probability of response synchronization, determines the criteria for feature binding. Since this architecture is shaped by experience it follows that at least

some of the binding and segmentation criteria are acquired by experience or in other terms, are learned during early life.

SYNAPTIC PLASTICITY OF COUPLING CONNECTIONS IN THE ADULT

In vitro studies on slices of the visual cortex of adult rats have revealed that excitatory connections to cells in supragranular layers are still susceptible to use-dependent, long-term modifications of their coupling strength (Artola and Singer 1987). The gain of a given set of connections can both increase and decrease in a reversible way, the control parameter being postsynaptic depolarization (Artola et al. 1990). Thus, the modifications occur according to an associative algorithm; however, the correlation rule is more complicated than that initially proposed by Hebb. It resembles, in some respects, the biphasic modification rule that has been proposed by Bienenstock, Cooper, and Munroe (Bienenstock et al. 1982) regarding the self-organization of thalamo-cortical connections; it differs in that it also allows for weakening of inactive presynaptic afferents. Simulation studies indicate that such a biphasic modification rule is very effective when applied in associative memory networks (Hancock et al. 1991). Available evidence indicates that intra-cortical connections are endowed with such adaptive synapses, yet there is still no direct proof that the connections in question actually participate also in response synchronization. If they did—and at present there is no evidence against this possibility—it would imply that binding and segmentation criteria can still be acquired, or at least modified, in the adult. Recent psychophysical evidence suggests the same conclusion (Karni and Sagi 1991). As such modifications would be addressed as learning, we might actually be looking at the substrate of learning new associations when we look at use-dependent synaptic modifications of cortico-cortical connections. The only difference with respect to the developmental changes in the functional architecture of cortico-cortical connections would be the extent and the reversibility of modifications. The developmental modifications lead to actual modifications of the wiring scheme and are irreversible once growth of these pathways has come to an end, while the changes which persist in the adult consist only of modifications of synaptic gain and are most likely reversible.

CONCLUDING REMARKS

In conclusion, it appears that many of the predictions derived from the theory of temporal assembly coding are supported by experimental evidence. As far as the visual system is concerned, the data on response synchronization appear, without exception, compatible with the hypothesis that neuronal representations of visual objects consist of assemblies of cells that are distinguished by the synchrony of their temporally structured responses. The data are also compatible with the hypothesis that feature-

specific response synchronization can serve to group features according to Gestalt criteria and hence can be used as a mechanism for figure/ground segregation and scene segmentation. However, proving that natural systems actually function the way the theory of temporal assembly coding assumes will require controlled manipulation of assemblies and relating these modifications to specific changes in behavioral functions. The experiments in strabismic animals can be considered a first step in this direction.

REFERENCES

Abeles, M. 1991. Corticonics. Cambridge: Cambridge Univ. Press.

Abeles, M., and G.L. Gerstein. 1988. Detecting spatiotemporal firing patterns among simultaneously recorded single neurons. *J. Neurophysiol.* **60**:909–924.

Aertsen, A.M.H.J., and G.L. Gerstein. 1985. Evaluation of neuronal connectivity: Sensitivity of cross-correlation. *Brain Res.* **340**:341–354.

Aiple, F., and J. Krüger. 1988. Neuronal synchrony in monkey striate cortex: Interocular signal flow and dependency on spike rates. *Exp. Brain Res.* **72**:141–149.

Artola, A., S. Bröcher, and W. Singer. 1990. Different voltage-dependent thresholds for inducing long-term depression and long-term potentiation in slices of rat visual cortex. *Nature* **347**:69–72.

Artola, A., and W. Singer. 1987. Long-term potentiation and NMDA receptors in rat visual cortex. *Nature* **330**:649–652.

Ascher, P., P. Bregestovski, and L. Nowak. 1988. N-methyl-D-aspartate-activated channels of mouse central neurons in magnesium-free solutions. *J. Physiol.* **399**:207–226.

Barlow, H.B. 1972. Single units and cognition: A neuron doctrine for perceptual psychology. *Perception* **1**:371–394.

Bienenstock, E., L.N. Cooper, and P. Munro. 1982. Theory for the development of neuron selectivity: Orientation specificy and binocular interaction in visual cortex. *J. Neurosci.* **2**:32–48.

Bienenstock, E., and C. von der Malsburg. 1987. A neural network for invariant pattern recognition. *Europhys. Lett.* **4**:121–126.

Braitenberg, V. 1978. Cell assemblies in the cerebral cortex. In: Lecture Notes in Biomathematics 21, Theoretical Approaches in Complex Systems, ed. R. Heim and G. Palm, pp. 171–188. Berlin: Springer.

Callaway, E.M., and L.C. Katz, 1990. Emergence and refinement of clustered horizontal connections in cat striate cortex. *J. Neurosci.* **10**:1134–1153.

Callaway, E.M., and L.C. Katz. 1991. Effects of binocular deprivation on the development of clustered horizontal connections in cat striate cortex. *Proc. Natl. Acad. Sci.* **88**:745–749.

Crick, F. 1984. Function of the thalamic reticular complex: The searchlight hypothesis. *Proc. Natl. Acad. Sci.* **81**:4586–4590.

Crick, F., and C. Koch. 1990. Towards a neurobiological theory of consciousness. *Sem. Neurosci.* **2**:263–275.

Damasio, A.R. 1990. Synchronous activation in multiple cortical regions: A mechanism for recall. *Sem. Neurosci.* **2**:287–296.

Desimone, R., T.D. Albright, C.G. Gross, and C. Bruce, 1984. Stimulus-selective properties of inferior temporal neurons in the macaque. *J. Neurosci.* **4**:2051–2062.

Eckhorn, R., R. Bauer, W. Jordan, M. Brosch, W. Kruse, M. Munk, and H.J. Reitboeck. 1988. Coherent oscillations: A mechanism for feature linking in the visual cortex? *Biol. Cybern.* **60**:121–130.

Edelman, G.M. 1987. Neural Darwinism: The Theory of Neuronal Group Selection. New York: Basic Books, Inc.

Edelman, G.M. 1989. The Remembered Present. New York: Basic Books, Inc.

Edelman, G.M., and V.B. Mountcastle. 1978. The Mindful Brain. Cambridge, MA: MIT Press.

Engel, A.K., P. König, C.M. Gray, and W. Singer. 1990. Stimulus-dependent neuronal oscillations in cat visual cortex: Inter-columnar interaction as determined by cross-correlation analysis. *Eur. J. Neurosci.* **2**:588–606.

Engel, A.K., P. König, A.K. Kreiter, and W. Singer. 1991a. Interhemispheric synchronization of oscillatory neuronal responses in cat visual cortex. *Science* **252**:1177–1179.

Engel, A.K., P. König, and W. Singer. 1991b. Direct physiological evidence for scene segmentation by temporal coding. *Proc. Natl. Acad. Sci.* **88**:9136–9140.

Engel, A.K., A.K. Kreiter, P. König, and W. Singer. 1991c. Synchronization of oscillatory neuronal responses between striate and extrastriate visual cortical areas of the cat. *Proc. Natl. Acad. Sci.* **88**:6048–6052.

Felleman D.J., and D.C. van Essen . 1991. Distributed hierarchical processing in the primate cerebral cortex. *Cerebral Cortex* **1**:1–47.

Fisken, R.A., L.J. Garey, and T.P.S. Powell. 1975. The intrinsic, association and commissural connections of area 17 of the visual cortex. *Phil. Trans. Roy. Soc. Lond. B* **272**:487–536.

Gerstein, G.L., and D.H. Perkel. 1972. Mutual temporal relationship among neuronal spike trains. Statistical techniques for display and analysis. *Biophys. J.* **12**:453–473.

Gilbert, C.D., and T.N. Wiesel. 1989. Columnar specificity of intrinsic horizontal and corticocortical connections in cat visual cortex. *J. Neurosci.* **9**:2432–2442.

Gochin, P.M., E.K. Miller, C.G. Gross, and G.L. Gerstein. 1991. Functional interactions among neurons in inferior temporal cortex of the awake macaque. *Exp. Brain Res.* **84**:505–516.

Gray, C.M., P. König, A.K. Engel, and W. Singer. 1989. Oscillatory responses in cat visual cortex exhibit inter-columnar synchronization which reflects global stimulus properties. *Nature* **338**:334–337.

Gray, C.M., and W. Singer. 1987. Stimulus-specific neuronal oscillations in the cat visual cortex: A cortical functional unit. *Soc. Neurosci. Abstr.* **13**:404.3.

Gray, C.M., and W. Singer. 1989. Stimulus-specific neuronal oscillations in orientation columns of cat visual cortex. *Proc. Natl. Acad. Sci.* **86**:1698–1702.

Gross, C.G., C.E. Rocha-Miranda, and D.B. Bender. 1972. Visual properties of neurons in inferotemporal cortex of the macaque. *J. Neurophysiol.* **35**:96–111.

Grossberg, S. 1980. How does a brain build a cognitive code? *Psychol. Rev.* **87**:1–51.

Hancock, P.J.B., L.S. Smith, and W.A. Phillips. 1991. A biologically supported error correcting learning rule. *Neural Comput.* **3**, in press.

Hebb, D.O. 1949. The Organization of Behavior. New York: Wiley.

Hirsch, J.A., and C.D. Gilbert. 1991. Synaptic physiology of horizontal connections in the cat's visual cortex. *J. Neurosci.* **11**:1800–1809.

Hubel, D.H., and T.N. Wiesel. 1963. Shape and arrangement of columns in cat's striate cortex. *J. Physiol.* **165**:559–568.

Hubel, D.H., and T.N. Wiesel. 1965. Binocular interaction in striate cortex of kittens reared with artificial squint. *J. Neurophysiol.* **28**:1041–1059.

Innocenti, G.M. 1981. Growth and reshaping of axons in the establishment of visual callosal connections. *Science* **212**:824–827.

Innocenti, G.M., and D.O. Frost. 1979. Effects of visual experience on the maturation of the efferent system to the corpus callosum. *Nature* **280**:231–234.

Karni, A., and D. Sagi. 1991. Where practice makes perfect in texture discriminations: Evidence for primary visual cortex plasticity. *Proc. Natl. Acad. Sci.* **88**:4966–4970.

Kirillov, A.B., G.N. Borisyuk, R.M. Borisyuk, and W. Singer. 1992. Modeling synchronized assemblies of cortical oscillators using multilayered neural networks, in preparation.

Kisvárday, Z.F., K.A.C. Martin, T.F. Freund, Z. Maglóczky, D. Whitteridge, and P. Somogyi. 1986. Synaptic targets of HRP-filled layer III pyramidal cells in the cat striate cortex. *Exp. Brain Res.* **64**:541–552.

König, P., A.K. Engel, S. Löwel, and W. Singer. 1990. Squint affects occurrence and synchronization of oscillatory responses in cat visual cortex. *Soc. Neurosci. Abstr.* **16**:523.2.

König, P., and T.B. Schillen. 1991. Stimulus-dependent assembly formation of oscillatory responses: I. Synchronization. *Neural Comp.* **3**:155–166.

Kreiter, A.K., and W. Singer. 1992. Oscillatory neuronal responses in the visual cortex of the awake macaque monkey. *Env. J. Neurosci.* **4**:369–375.

Krüger, J., and F. Aiple. 1988. Multimicroelectrode investigation of monkey striate cortex: Spike train correlations in the infragranular layers. *J. Neurophysiol.* **60**:798–828.

Löwel, S., and W. Singer. 1992. Selection of intrinsic horizontal connections in the visual cortex by correlated neuronal activity. *Science* **255**:209–212.

Luhmann, H.J., L. Martinez Millán, and W. Singer. 1986. Development of horizontal intrinsic connections in cat striate cortex. *Exp. Brain Res.* **63**:443–448.

Luhmann, H.J., W. Singer, and L. Martinez-Millan. 1990. Horizontal interactions in cat striate cortex: I. Anatomical substrate and postnatal development. *Eur. J. Neurosci.* **2**:344–357.

Matsubara, J., M. Cynader, N.V. Swindale, and M.P. Stryker. 1985. Intrinsic projections within visual cortex: Evidence for orientation-specific local connections. *Proc. Natl. Acad. Sci.* **82**:935–939.

Mayer, M.L., G.L. Westbrook, and P.B. Guthrie. 1984. Voltage-dependent block by Mg^{2+} of NMDA responses in spinal cord neurons. *Nature* **309**:261–263.

McGuire, B.A., C.D. Gilbert, and P.K. Rivlin. 1991. Targets of horizontal connections in Macaque primary visual cortex. *J. Comp. Neurol.* **305**:370–392.

Michalski, A., G.L. Gerstein, J. Czarkowska, and R. Tarnecki. 1983. Interactions between cat striate cortex neurons. *Exp. Brain Res.* **51**:97–107.

Mountcastle, V.B. 1957. Modality and topographic properties of single neurons of cats somatic sensory cortex. *J. Neurophysiol.* **20**:408–434.

Palm, G. 1982. Neural Assemblies. Heidelberg: Springer.

Palm, G. 1990. Cell assemblies as a guideline for brain research. *Concepts Neurosci.* **1**:133–147.

Perrett, D.I., A.J. Mistlin, and A.J. Chitty. 1987. Visual neurons responsive to faces. *TINS* **10**:358–364.

Price, D.J., and C. Blakemore. 1985a. The postnatal development of the association projection from visual cortical area 17 to area 18 in the cat. *J. Neurosci.* **5**:2443–2452.

Price, D.J., and C. Blakemore. 1985b. Regressive events in the postnatal development of association projections in the visual cortex. *Nature* **316**:721–724.

Raether, A., C.M. Gray, and W. Singer. 1989. Intercolumnar interactions of oscillatory neuronal responses in the visual cortex of alert cats. *Eur. J. Neuroscience ENA Abstr.* **12**:72.5.

Rockland, K.S., and J.S. Lund. 1982. Widespread periodic intrinsic connections in the tree shrew visual cortex. *Science* **215**:1532–1534.

Rolls, E.T. 1990. The representation of information in the temporal lobe visual cortical areas of macaques. In: Advanced Neural Computers, ed. R. Eckmiller, pp. 69–78. Amsterdam: North Holland.

Schillen, T.B., and P. König. 1991. Stimulus-dependent assembly formation of oscillatory responses: II. Desynchronization. *Neural Comp.* **3**:167–178.

Shimizu, H., and Y. Yamaguchi. 1987. Synergetic computer and Holonics: Information dynamics of a semantic computer. *Physica Scripta* **36**:970–985.

Singer, W. 1979. Central-core control of visual cortex functions. In: The Neurosciences, Fourth Study Program, ed. F.O. Schmitt and F.G.Worden, pp. 1093–1109. Cambridge, MA: MIT Press.

Singer, W., B. Freeman, and J. Rauschecker. 1981. Restriction of visual experience to a single orientation affects the organization of orientation columns in cat visual cortex: A study with deoxyglucose. *Exp. Brain Res.* **41**:199–215.

Steriade, M., R. Curro Dossi, D. Paré, and G. Oakson. 1988. Fast oscillations (20–40 Hz) in thalamocortical systems and their potentiation by mesopontine cholinergic nuclei in the cat. *Proc. Natl. Acad. Sci.* **88**:4396–4400.

Thompson, A.M. 1986. A magnesium-sensitive post-synaptic potential in rat cerebral cortex resembles neuronal responses to N-Methyl-D-aspartate. *J. Physiol.* **370**:531–549.

Toyama, K., M. Kimura, and K. Tanaka. 1981. Organization of cat visual cortex as investigated by cross-correlation technique. *J. Neurophysiol.* **46**:202–214.

Tso, D.Y., C.D. Gilbert, and T.N. Wiesel. 1986. Relationship between horizontal interactions and functional architecture in cat striate cortex as revealed by cross-correlation analysis. *J. Neurosci.* **6**:1160–1170.

von der Malsburg, C. 1985. Nervous structures with dynamical links. *Ber. Bunsenges. Phys. Chem.* **89**:703–710.

von der Malsburg, C. 1988. Pattern recognition by labeled graph matching. *Neural Networks* **1**:141–148.

von der Malsburg, C., and W. Schneider. 1986. A neural cocktail-party processor. *Biol. Cybern.* **54**:29–40.

von Noorden, G.K. 1990. Binocular Vision and Ocular Motility, Theory and Management of Strabismus. St. Louis: C.V. Mosby C.