Eur Arch Psychiatr Neurol Sci (1986) 236:4–9

European Archives of Psychiatry and Neurological Sciences

The Brain as a Self-organizing System

Wolf Singer

Max-Planck-Institut für Hirnforschung, Deutschordenstrasse 46, D-6000 Frankfurt 71, Federal Republic of Germany

Summary. Clinical evidence and numerous results from animal experimentation indicate that cognitive functions have to be learned. Brain structures subserving these functions require sensory experience for their maturation. Genetic instructions are in principle not sufficient to specify neuronal connections with sufficient precision. Self-organization processes are implemented in addition which allow to optimize genetically determined blue prints of connectivity by making use of functional criteria. Thus, neuronal activity becomes an important shaping factor in the development of the structural and functional architecture of the forebrain. To the extent that this neuronal activity is modulated by sensory signals, environmental factors can influence the development of neuronal networks. Recent experiments indicate that these shaping processes are additionally controlled by modulatory systems. Both, the noradrenergic projection from the locus coeruleus and the cholinergic projection from the basal forebrain facilitate activity-dependent long-term changes of neuronal connections during development. The activity of these modulatory systems in turn depends on central states such as arousal, attention, and perhaps also motivation. It is inferred from this evidence that experience-dependent self-organization should not be considered as a passive imprinting process but rather as an active dialogue between the brain and its environment. The hypothesis is discussed that many developmental disturbances which are commonly attributed to deprivation are in fact due to defaults of the CNS which either lead to the formulation of wrong questions or to the reduction of exploratory drive.

Key words: Brain development – Post-natal experience – Deprivation

Neuronal Activity as a Shaping Factor in Brain Development

The information contained in the organization of organs as complex as the mammalian nervous system exceeds by far the information that can be stored in the genome. The reason is that the neurones in the brain are specified not only with respect to their position within the brain, but also with respect to their inter-connections. Because of the vast number of neurones – in the human brain this number amounts to 10^{12} – the degrees of freedom for combinatory permutations are unimaginably high. With the increasing refinement of neuroanatomical techniques it has become obvious that the connections between neuronal populations are by no means random but highly specific. This is true not only at the macroscopic level of projection patterns between receptor and effector organs and the respective neural centres, but also at the microscopic level of intrinsic circuitry. The amazing complexity and the magnitude of the ensuing specification problem are illustrated by the following numbers: 1 mm^3 of cortical tissue contains approximately 4×10^4 neurones, and each of these neurones receives between 1×10^4 to 4×10^4 synaptic contacts and through local axon collaterals and far-reaching projections interacts with comparable numbers of target neurones. The length of the connections which assure these interactions has been estimated to amount to about 6 km within 1 mm^3 of cortex. This raises the question of how these myriads of cross-connections can be specified in a reproduceable and functionally meaningful way. This question presents itself in a particularly accentuated form in higher mammals and man, where corticalization has led to an enormous increase of neuronal elements and connections, an increase that exceeds by far the disproportionally small increase of the genome.

It follows from these considerations that genetic instructions alone are not capable of specifying with great precision the connections between individual neurones. Nature has overcome this problem by implementing algorithms of self-organization which allow extraction of information for further specifications from epigenetic cues which are available within the micro-environment of the structures that need to be specified. During early phases of brain development this additional information is conveyed mainly by biochemical signals, which are produced by nearby neuronal and glial elements. Later, however, when nerve cells become electrically excitable their activity becomes an increasingly important factor for the self-organization process. Thus, the very neuronal signals which serve information processing in the mature system are used to structure developmental processes. These activity-dependent self-organizing processes are not confined to embryogenesis but extend far into post-natal life whereby the basic strategy appears to be similar at the various stages of embryonic and post-natal development. Specificity of neuronal connections is achieved in two steps. First, connections are formed with rather low precision but with considerable exuberancy. Subsequently, certain connections are selectively stabilized and others are removed and this selection process is guided by neuronal activity. The nervous system becomes spontaneously active in early embryogenesis and this self-generated activity is used to guide selection according to functional criteria.

A classical example for such an activity-dependent acquisition of specificity in neuronal connectivity is the removal of double innervation of limb muscles by motor neurones of the

spinal cord. Initially, the motor units of peripheral muscles have multiple innervation by several motor neurones, in extreme cases this includes even cross-innervations by synergistic and antagonistic motor neurones. Later, these ectopic innervations are removed, and this removal depends on the patterned activation of the motor-neurone pool in the spinal cord. The early movements of embryos can thus be considered as an epiphenomenon of a self-organizing process which serves to increase the specificity of neuronal connections using functional parameters as selection criteria. Meanwhile such activity-dependent shaping of initially exuberant neuronal connections has been observed not only in motor centres but in virtually all structures of the CNS (for review of the extensive literature on these developmental processes see Singer 1986).

Of particular importance in the present context is the fact that these activity-dependent pruning processes extend for several months, in humans perhaps even years into post-natal ontogeny. Neuronal activity, especially in sensory centres, is now modulated by sensory signals from the environment. Hence, during this developmental stage activity-dependent shaping of neuronal connectivity occurs not only as a function of self-generated activation patterns but also as a function of sensory experience. It is this phase of brain development that I shall be dealing with in this brief review.

The Visual System as an Example

Most of the work related to these problems has been performed in the visual system, probably because of the ease with which visual experience can be manipulated. There is ample evidence both from clinical studies and from animal experimentation that "seeing" has to be learned during a critical period of post-natal development. The most dramatic evidence in human pathology comes from cases who suffered from congenital cataract or perinatally acquired corneal opacities and were therefore unable to process signals from spatial contours. With the development of lens and corneal transplants the optical media of these patients could be restored but to the great distress of the eye surgeons these patients were unable to recover visual functions when operated upon as juveniles or adults (for review see Valvo 1971). These patients experienced the newly available visual signals as painful or noisy and were unable to evaluate spatial relations and to recognize patterns. Despite intensive visual training most of the patients failed to acquire these visual functions and many of them, after phases of severe depression, returned to their previous way of living as blinds. Experiments in visually deprived animals have revealed that these functional deficits are not due to retinal factors, but result from abnormal development of visual centres in the brain (for a recent review see Frégnac and Imbert 1984).

Before describing the mechanisms involved in experience-dependent development of cortical functions, I want to address a teleological question to illustrate the problem. Why is the development of cortical centres dependent on the availability of sensory experience with the consequence that transitory disturbances in the uptake of sensory signals, which are quite frequent during early development, lead to severe and irreversible impairments of cognitive functions? One is tempted to speculate that this vulnerability is compensated by the acquisition of functions which cannot be realized by genetic instructions alone but require additional epigenetic information for their development. The following example illustrates and supports this conjecture. Higher mammals and man who have frontally positioned eyes with overlapping visual fields have the ability to match the images encoded by the two eyes and to calculate from the disparities of these two images the distance of objects in space. This ability has two obvious advantages: first, the distance of an object in space can be assessed even if object and observer are stationary and do not produce any motion parallaxes. Second, the separation of figures from ground, a primordial prerequisite for pattern recognition, is greatly facilitated by evaluating spatial cues. To realize the function of stereopsis, however, it is necessary to develop neurones in the visual cortex which possess two receptive fields, one in each eye, which have to be precisely superimposed in visual space. Thus, the 1×10^6 afferents arriving from each eye have to be arranged in a way which assures that only those pairs of afferents converge onto common cortical target cells which originate from precisely corresponding retinal loci. The problem is that there is no way to predict with any great precision which retinal loci will actually correspond in the mature visual system. Retinal correspondence depends on parameters such as the size of the eye balls, the position of the eye balls in the orbit, and the interocular distance. These parameters do depend on a number of epigenetic factors and hence cannot be anticipated by the genome. It follows that genetic instructions alone cannot suffice to determine with the required precision the pattern of interocular connections. An elegant possibility exists, however, to identify fibres as coming from corresponding retinal loci by evaluating functional criteria. Whenever a target is fixated with both eyes, corresponding retinal loci are stimulated by the same points of the target and hence neuronal responses originating from corresponding retinal loci are likely to be more similar than neuronal responses originating from non-corresponding retinal loci. A selection process which is capable of identifying similarities in the activation patterns of fibres arriving from the two eyes and which is furthermore able to selectively consolidate pathways on a common target cell which convey correlated activation patterns would be ideally suited to achieve the required specificity in neuronal connections. Clearly, such a mechanism could only work post-natally when visual signals from the environment are available for the identification of pathways.

In the following paragraphs I shall briefly review evidence suggesting that such mechanisms do indeed exist in the mammalian brain. I shall further demonstrate that they are not solely dependent on local interactions but are in addition controlled by more globally organized modulatory systems, the latter being implicated in the control of central states such as arousal, attention and motivation.

The Rules of Activity-dependent Circuit Selection

By the time kittens open their eyes most neurones in the visual cortex respond to stimulation of both eyes and with normal visual experience this condition is maintained (Hubel and Wiesel 1962, 1963). However, when signals from the two eyes are incongruent, either because one eye is occluded (Wiesel and Hubel 1965) or because the images on the two retinae are

not in register – as is the case with strabismus (Hubel and Wiesel 1965), cyclotorsion (Blakemore et al. 1975; Crewther et al. 1980; Yinon 1975), or anisometropia (Blakemore and Van Sluyters 1974; Wolfe and Owens 1979) – cortical cells lose their binocular receptive fields. In the first case they stop responding to the deprived eye; in the other cases they segregate into two approximately equally large groups, one responding exclusively to the ipsilateral and the other exclusively to the contralateral eye. During the critical period of early development these changes are fully reversible indicating that the efficacy of connections does not only decrease but can also increase as a function of retinal stimulation (Blakemore and Van Sluyters 1974; Wiesel and Hubel 1965).

From a series of related experiments (Singer et al. 1977; Rauschecker and Singer 1979, 1981) it was concluded that these modifications of excitatory transmission follow rules which closely resemble those postulated by Hebb (1949), Stent (1973), Changeux and Danchin (1976) and Changeux et al. (1984) for adaptive neuronal connections. The basic assumptions are that changes of synaptic efficacy require activation of the post-synaptic structure and that the direction of the change – increase or decrease of efficacy – depends on the correlation between pre- and post-synaptic activation. The efficacy of excitatory transmission appears to increase when presynaptic afferents and the post-synaptic cell are active in temporal contiguity and to decrease when the post-synaptic target is active while the pre-synaptic terminal is silent. These rules, when applied to circuits where two (or more) afferent pathways converge onto a common post-synaptic target cell, have the effect of selectively stabilizing and hence associating pathways that convey correlated activity. The only requirement is that the conveyed activity patterns are capable of driving the post-synaptic neurone. Likewise, these selection criteria lead to competition between converging pathways if these convey uncorrelated activity. In that case there is always one subset of afferents inactive while the other is driving the post-synaptic cell. Hence, one subset will increase its gain at the expense of the other. Eventually, those afferents which have the highest probability of being active in temporal contiguity with the post-synaptic target cell will win. These rules have so far predicted correctly the results of the numerous studies in which vision has been manipulated in a way that interferes with the correlation between the responses arriving from the two eyes.

It is obvious that this modification algorithm is ideally suited to stabilize selectively those afferents from the two eyes which convey correlated activity and hence originate from corresponding retinal loci. There is, however, an additional and indispensable condition that needs to be fulfilled to render this experience-dependent selection process successful. Reshaping of afferent connections may only occur at instances when the animal is attentively fixating with both eyes and must not take place when the two eyes are moving in an uncoordinated way. In this latter case, retinal signals will be uncorrelated even if they originate from corresponding retinal loci because the images processed by the two eyes are different. If adaptive changes occurred under these conditions, all afferents from the two eyes would compete with each other and the consequence would be complete disruption of binocular connections. Therefore, one is led to postulate that the selection process is not solely dependent on retinal signals, but is in addition gated by non-retinal control systems capable of determining the instances at which retinal activity may be used to induce changes in circuitry. The evidence reviewed in the following paragraphs does indeed suggest the existence of such gating systems.

The Role of Non-retinal Signals in Ocular Dominance Plasticity

The evidence reviewed above suggests that the activation of post-synaptic target cells is a necessary prerequisite for the induction of experience-dependent modifications. However, it has now become clear that the generation of action potentials in the post-synaptic cell is not sufficient to produce a change. Even when contour vision is unrestricted and retinal signals readily elicit responses in the neurones of the visual cortex, vision-dependent modifications of excitatory transmission fail to occur in a variety of rather different conditions. Thus, neurones of the kitten's striate cortex may remain binocular despite monocular deprivation when the open eye is surgically rotated within the orbit (Singer et al. 1982), when large angle squint is induced in both eyes (Singer et al. 1979) or when strabismus is induced by bilateral cyclotorsion (Crewther et al. 1980). In this case contour vision per se is unimpaired but the abnormal eye position and motility lead to massive disturbance of the kittens' visuo-motor co-ordination. Initially the inappropriate retinal signals cause abnormal visuo-motor reactions and during this period are effective in influencing cortical ocular dominance. Subsequently, however, the kittens rely less and less on visual cues and develop a near complete neglect of the visual modality. In this phase, retinal signals no longer modify ocular dominance and they also fail to support the development of orientation-selective receptive fields.

These latter results suggest that retinal signals only influence the development of cortical functions when the animal uses them for the control of behaviour. This view is compatible with two lines of evidence: firstly, independent results from several laboratories indicate that retinal signals do not lead to changes of cortical functions when the kittens are paralyzed and/or anaesthetized while exposed to visual patterns. Even though the light stimuli undoubtedly drive corticals cells they fail to bring about changes of ocular dominance (Freeman and Bonds 1979; Singer 1979; Singer and Rauschecker 1982) or to develop orientation selectivity (Buisseret et al. 1978). Further evidence comes from experiments in which a sensory hemi-neglect was induced in dark-reared kittens by placing unilateral lesions in the intra-laminar nuclear complex of the thalamus (Singer 1982). In addition, in order to instigate changes of ocular dominance, these kittens had one eye sutured closed before they were exposed to light. Later electrophysiological analysis revealed that the neurones in the visual cortex of the normal hemisphere had become monocular as is usual with monocular deprivation. However, neurones in the visual cortex of the hemisphere with the lesion had remained binocular. In addition, the vigour of the neuronal responses and the selectivity of the receptive fields were nearly as low as if this hemisphere had been deprived of vision altogether. Thus, although both hemisphere had received identical signals from the open eye, these signals induced the expected modifications only in the normal hemisphere and remained rather ineffective in the hemisphere which – because of the diencephalic lesion – "attended" less to retinal stimulation. A further consequence of the diencephalic lesion was that it diminished the typical effects of reticular arousal in the lesioned hemisphere.

Another manipulation which prevents retinal signals from inducing cortical modifications is the abolition of proprioceptive signals from the extra-ocular muscles. When this input is disrupted by severing the ophthalmic branch of the IIIrd cranial nerve bilaterally, retinal signals neither stimulate the development of orientation selectivity (Trotter et al. 1981) nor do they induce changes of ocular dominance (Buisseret and Singer 1983). In this case eye movements are virtually normal (Fiorentini and Maffei 1977) and the uptake of visual signals is not hindered at all. Thus, non-retinal signals about eye position and/or motility appear also to be involved in gating vision-dependent modifications. In agreement with this conclusion is the finding that changes in ocularity can be induced in anaesthetized preparations when the eyes are passively moved while the retina is stimulated with contours (Freeman and Bonds 1979).

Stimulation experiments support the notion that central core structures which are related to the ascending arousal system have a permissive role in cortical plasticity. By pairing monocular light stimulation with electrical activation of central core structures it proved possible to induce changes of ocular dominance in kittens that were anaesthetized and paralyzed (Singer and Rauschecker 1982). Effective sites for the electrical conditioning stimuli were the mesencephalic reticular formation and that thalamic region whose destruction had prevented cortical modifications in the lesion study. Significant modifications of ocular dominance were observed in the population of cortical cells sampled after 8–12 h of conditioning stimulation (Singer and Rauschecker 1982). More recently it became possible to observe the effects of such conditioning in individual continuously recorded cells. This revealed that measurable changes of ocular dominance and orientation preference can be induced within 30 to 60 min (Geiger and Singer 1986).

The Chemical Nature of Permissive Gating Signals

Kasamatsu and Pettigrew (1979) had shown that neurones of the kitten striate cortex remain binocular despite monocular deprivation when cortical norepinephrine (NE) is depleted by local infusion of the neurotoxin 6-hydroxydopamine (6-OHDA). Since they demonstrated that micro-perfusion of the depleted cortical tissue with NE reinstalls ocular dominance plasticity (Kasamatsu et al. 1979), these authors have proposed that normal NE levels are a necessary prerequisite for ocular dominance plasticity. Subsequently, however, several independent investigations have indicated that ocular dominance changes can be induced despite NE depletion. In these investigations 6-OHDA was either injected prior to monocular deprivation or the noradrenergic input to cortex was blocked by means other than local 6-OHDA application (Adrien et al. 1985; Bear and Daniels 1983; Bear et al. 1983; Daw et al. 1984, 1985). This apparent controversy may now have been resolved by the demonstration that ocular dominance plasticity is influenced both by noradrenergic and cholinergic mechanisms (Bear and Singer 1986). Ocular dominance plasticity is abolished only if both the noradrenergic pathway from the locus coeruleus and the cholinergic projection from the basal forebrain are lesioned. Disruption of either system alone is not sufficient to arrest plasticity. The initial finding that intra-cortical or intra-ventricular application of 6-OHDA blocked ocular dominance plasticity can probably be attributed to an unexpected pharmacological property of 6-OHDA. This drug, in addition to its neurotoxic effect, antagonizes the effects of acetylcholine (Bear and Singer 1986). These results suggest that both neuromodulators, acetylcholine and norepinephrine, have a permissive function in cortical plasticity, either system being capable of substituting the other.

Self-organization and Learning

On a formal level the activity-dependent refinement of projection patterns shares the characteristic features of a learning process. Two sets of variables, in the case of the kitten visual cortex the afferents from the two eyes, become permanently associated with a common effector, the cortical target cell. The criterion for this association is coherency of activation, just as in classical or operant conditioning. For this association to occur it is furthermore required that the activity patterns match some predispositions of the learning organism. In our case the minimal requirement appears to be that the retinal signals conform with the response properties of cortical neurones, i.e. the visual stimuli have to contain spatial contrast gradients. Moreover, as with normal learning, selective associations occur only when the stimulus patterns are processed by an awake and attentive brain. Finally, in our case the associations tend to be very stable once they are established. In this respect similarities exist at least with certain forms of procedural learning and with classical conditioning. The only marked difference between developmental plasticity and adult learning seems to be the existence of a critical period for the expression of the former. In this respect the refinement of binocular correspondence resembles a special form of learning, namely imprinting. Here, too, associations are formed during early ontogeny and these become fixed and irreversible after the end of a critical period (for review see Horn 1981; Immelmann 1984). The adaptive value of such a critical period is obvious in our case. Once binocular correspondence is established this variable must become fixed to serve as a reference frame for higher level processes which compute distance from retinal disparities.

The Nature-Nurture Dichotomy

Although we are still at the very beginning of understanding the interactions of genetic and epigenetic factors in brain development some preliminary conclusions can be drawn. Available evidence suggests that nature has implemented very elaborate algorithms of self-organization to economize and complement genetic instructions. The genome specifies the general layout of the system and the rules of the self-organization process. The latter in turn serves to subsequently optimize the relations between the components of the system and between the system and its particular environment.

Based on these new insights the classical nature-nurture question can be re-addressed and some preliminary answers can be formulated. In the visual system, and probably in other sensory systems, too, the genome determines the development of feature detectors whose specific response properties emerge independently of experience. This specification process defines the criteria according to which the brain classifies sensory signals from the outer world. The blue print according to

which feature detectors and processing areas in the brain are inter-connected is predetermined. The resulting connectivity pattern in turn determines the set of possible relations that can be established between the various feature domains and different sensory modalities. Furthermore, the genome specifies the rules according to which these predetermined connections can be changed as a function of their activity. We have seen that these modification rules can mediate associative functions, associations of connections occurring whenever there is contingency of activity in time and space. This then is the fundamental principle according to which the self-organizing system establishes relations between its building blocks and between the central representation of sensory activation patterns. These are also the rules according to which relations between the phenomena in the outer world are evaluated and internalized through structural modifications of connectivity. It can be assumed that these premisses are well adapted and reflect the knowledge which the genome has accumulated during phylogeny about the physical reality within which the developing organism evolves.

Experience-dependent self-organization, thus, has little in common with passive imprinting of a tabula rasa but rather appears as an interactive process which is subject to numerous genetically determined constraints. It became clear that sensory activation patterns have to match prespecified response properties of the already existing and highly active nerve nets in order to promote long-term modifications. Moreover, the adaptive processes appear to have a threshold which is different from the activation threshold that needs to be trespassed to relay sensory signals. To induce a long-term modification it was not only necessary to appropriately excite the respective neuronal pathways, but modulatory systems had to be activated in addition. These modulatory systems influence the functional state of virtually all cortical and subcortical areas through widely distributed efferent connections and receive their input from numerous centres of the brain. Thus, large neuronal arrays are involved in the decision process which determines from moment to moment whether a particular activation pattern should lead to long-lasting modifications of circuitry. The modulatory systems identified so far as having a permissive function in neuronal plasticity, the noradrenergic and the cholinergic projections, seem to be involved in the central control of the arousal level, in the maintenance of attention and their activity probably also reflects fluctuations in motivation.

I suggest therefore that the developing brain ought to be considered as a highly active and primarily self-containing system which, when born, already possesses substantial knowledge about the structure of the world to which it is going to adapt istself. As deduced above this knowledge is stored in the brain's architecture and in the rules allowing for activity-dependent modification of this architecture. Thus, when the brain is born and confronted with a dramatic expansion of accessible environment, it poses a number of precise questions to this environment with the purpose of optimizing and adapting its internal structure to reality. In a number of neuronal systems these questions are raised only during a brief and critical period. If answers are not available the prospective functions do not develop and these deficits are in most cases irreversible. There is thus an early and very active dialogue between the developing brain and its environment, whereby it soon becomes impossible to distinguish between cause and consequence of certain developmental bifurcations. The brain and its environment appear as components of a closed, highly interactive system.

Clinical Perspectives

To conclude I want to emphasize one aspect of this self-organizing process which may have an unexpected clinical relevance. In the literature on developmental disorders much attention has been attributed to the deleterious effects of deprivation. The normal brain, however, seems to know rather well which questions need to be asked and the normal environment is usually rich enough to sooner or later provide the appropriate answer if the questioner is sufficiently insistant. Thus, while deprivation and false answers from the environment are certainly a potential risk for the developmental process they are probably rather rare causes of misdirected development. Another, and perhaps much more important cause of developmental errors is suggested by the particularities of the self-organization process. The possibility must be considered that the brain does not formulate the right questions or does not ask with sufficient insistency to obtain answers. Thus, any malfunction of the highly complicated modulatory systems that are involved in the gating of drives, motivation and attention and any disturbance in the genetic a priori "knowledge" about the nature of the world can be expected to entrain severe developmental disorders. As has to be inferred from the experimental results reviewed above these disturbances are likely to be indistinguishable from those induced by deprivation. It is thus conceivable that developmental disorders which cannot be attributed to deprivation or to distinct lesions in sensory or motor systems but nevertheless lead to disturbances of cognitive functions similar to those expected from deprivation are in fact due to malfunctions of the modulatory systems and to disturbances in the brain's architecture, the former interfering with the drive to ask questions, the latter leading to inappropriate questions. It may be worthwhile to re-investigate in this context the aetiology of syndromes such as e.g. autism which are commonly attributed to developmental errors and to search more intensively for causes within the brain rather than within the environment.

References

Adrien J, Blanc G, Buisseret P, Frégnac Y, Gary-Bobo E, Imbert M, Tassin JP, Trotter Y (1985) Noradrenaline and functional plasticity in kitten visual cortex: a re-examination. J Physiol 367:73–98

Bear MF, Daniels ID (1983) The plastic response to monocular deprivation persists in kitten visual cortex after chronic depletion of norepinephrine. J Neurosci 3:407–416

Bear MF, Singer W (1986) Acetylcholine, noradrenaline and the extrathalamic modulation of visual cortical plasticity. Nature 320: 172–176

Bear MF, Paradiso MA, Schwartz M, Nelson SB, Carnes KM, Daniels JD (1983) Two methods of catecholamine depletion in kitten visual cortex yield different effects on plasticity. Nature 302:245–247

Blakemore C, Van Sluyters RC (1974) Experimental analysis of amblyopia and strabismus. Br J Ophthamol 58:176–182

Blakemore C, Van Sluyters RC, Peck CK, Hein A (1975) Developmen of cat visual cortex following rotation of one eye. Nature 257: 584–586

Buisseret P, Singer W (1983) Proprioceptive signals from extraocular muscles gate experience-dependent modifications of receptive fields in the kitten visual cortex. Exp Brain Res 51:443–450

Buisseret P, Gary-Bobo E, Imbert M (1978) Ocular motility and recovery of orientational properties of visual cortical neurones in dark-reared kittens. Nature 272:816–817

Changeaux JP, Danchin A (1976) Selective stabilization of developing synapse as a mechanism for the specification of neuronal networks. Nature 264:705–712

Changeaux JP, Heidmann T, Patter P (1984) Learning by selection. In: Marler P, Terrace HS (eds) The biology of learning. Dahlem Conferences. Springer, Berlin Heidelberg New York, pp 115–133

Crewther SG, Crewther DP, Peck CK, Pettrigrew JD (1980) Visual cortical effects of rearing cats with monocular or binocular cyclotorsion. J Neurophysiol 44:97–118

Daw NW, Robertson TW, Rader RK, Videen TO, Cosica CJ (1984) Substantial reduction of noradrenaline by lesions of adrenergic pathways does not prevent effects of monocular deprivation. J Neurosci 4:1354–1360

Daw NW, Videen TO, Parkinson D, Rader RK (1985) DSP-4 depletes noradrenaline in kitten visual cortex without altering the effects of monocular deprivation. J Neurosci 5:1925–1933

Fiorentini A, Maffei L (1977) Instability of the eye in the dark and the proprioception. Nature 269:330–331

Freeman RD, Bonds AG (1979) Cortical plasticity in monocularly deprived immobilized kittens depends on eye movement. Science 206:1093–1095

Frégnac Y, Imbert M (1984) Development of neuronal selectivity in primary visual cortex of cat. Physiol Rev 64:325–434

Geiger H, Singer W (1986) A possible role of Ca++-currents in developmental plasticity. Exp Brain Res [Suppl] (in press)

Hebb DO (1949) The organization of behaviour. Wiley, New York

Horn G (1981) Neural mechanisms of learning: An analysis of imprinting in the domestic chick. Proc R Soc London Ser 8 213:101–137

Hubel DH, Wiesel TN (1962) Receptive fields, binocular interaction and functional architecture in the cat's visual cortex. J Physiol (Lond) 160:106–154

Hubel DH, Wiesel TN (1963) Receptive fields of cells in striate cortex of very young, visually inexperienced kittens. J Neurophysiol 26:994–1002

Hubel DH, Wiesel TN (1965) Binocular interaction in striate cortex of kittens reared with artificial squint. J Neurophysiol 28:1041–1059

Immelmann K (1984) The natural history of bird learning. In: Marler P, Terrace HS (eds) The biology of learning. Dahlem Conferences. Springer, Berlin Heidelberg New York, pp 271–288

Kasamatsu T, Pettigrew JD (1979) Preservation of binocularity after monocular deprivation in the striate cortex of kittens treated with 6-hydroxydopamine. J Comp Neurol 185:139–162

Kasamatsu T, Pettigrew JD, Ary ML (1979) Restoration of visual cortical plasticity by local microperfusion of norepinephrine. J Comp Neurol 185:163–182

Rauschecker JP, Singer W (1979) Changes in the circuitry of the kitten's visual cortex are gated by postsynaptic activity. Nature 280:58–60

Rauschecker JP, Singer W (1981) The effects of early visual experience on the cat's visual cortex and their possible explanation by Hebb synapses. J Physiol (Lond) 310:215–239

Singer W (1979) Central core control of visual cortex functions. In: Schmitt FO, Worden FG (eds) The neurosciences fourth study program. Cambridge, MA, MIT Press, pp 1093–1109

Singer W (1982) Central core control of developmental plasticity in the kitten visual cortex: I. Diencephalic lesions. Exp Brain Res 47:209–222

Singer W (1986) Activity dependent self-organization of synaptic connections as a substrate of learning. In: Changeux IP, Konishi M (eds) Neural and molecular mechanisms of learning. Dahlem Conferences. Springer, Berlin Heidelberg New York Tokyo (in press)

Singer W, Rauschecker J (1982) Central core control of developmental plasticity in the kitten visual cortex: II. Electrical activation of mesencephalic and diencephalic projections. Exp Brain Res 47:223–233

Singer W, Rauschecker J, Werth R (1977) The effect of monocular exposure to temporal contrasts on ocular dominance in kittens. Brain Res 134:568–572

Singer W, von Grünau M, Rauschecker J (1979) Requirements for the disruption of binocularity in the visual cortex of strabismic kittens. Brain Res 171:536–540

Singer W, Tretter F, Yinon U (1982) Central gating of developmental plasticity in kitten visual cortex. J Physiol 324:221–237

Stent GS (1973) A physiological mechanism for Hebb's postulate of learning. Proc Natl Acad Sci 70:997–1001

Trotter Y, Gary-Bobo E, Buisseret P (1981) Recovery of orientation selectivity in kitten primary visual cortex is slowed down by bilateral section of ophthalmic trigeminal nerves. Dev Brain Res 1:450–454

Valvo A (1971) Sight restoration after long-term blindness: The problems and behavior patterns of visual rehabilitation. In: Clarck LL, Jastrzemska ZZ (eds) The American foundation for the blind. Consulting Psychologists Press Inc. Palo Alto, California New York

Wiesel TN, Hubel DH (1965) Extent of recovery from the effects of visual deprivation in kittens. J Neurophysiol 28:1060–1072

Wolfe JM, Owens DA (1979) Evidence for separable binocular processes differentially affected by artificially induced anisometropia. Am J Optom and Physiol Optics 56:279–284

Yinon U (1975) Eye rotation in developing kittens: The effect on ocular dominance and receptive field organization of cortical neurons. Exp Brain Res 24:215–218

Received December 12, 1985