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Theoretical article

THE STRATEGIES OF BRAIN PLASTICITY RESEARCH

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Abstract. In the investigation of brain plasticity two stages can be usually distinguished. In the "training stage" some plastic changes are produced, while other, developing under normal conditions, may be reduced. In the "testing stage" those effects are analysed. Four methods are used in the training stage: developing conditioned reflex, sensory deprivation, "abnormal" sensory stimulation, and causing a local damage to the animal's brain. Accordingly four research strategies are distinguished in the brain plasticity research. The features of these strategies, their effectiveness, and possible further development are discussed.

Brain plasticity, similarly to many other biological terms of a general character, is variously defined by various scientists. In this paper we accept a definition which seems in accord with the opinions of most scholars. It defines brain plasticity as the brain's capability to undergo lasting changes in result of sensory stimuli and to undergo similar changes as a consequence of damage. Such changes are called "plastic", though the term does not seem fortunate from a linguistic viewpoint. Correspondingly, we shall use the term "plastic processes" with reference to processes leading to plastic changes. Anatomical, electrophysiological and biochemical results obtained in recent years (some of them will be discussed here) suggest that the essence of plastic changes lies in the reorganization of synaptic connections of the brain's neurons. Plasticity is therefore to be opposed to the brain neurons' faculty of synaptic organization occurring only in result of a genetic programme action.

To avoid terminological misunderstandings, one has to consider the relation of "plasticity" to "learning ability" (remembering, memorizing ability), which is responsible for plastic changes called memory traces. Although both terms cover partly the same ground, two essential differences should be noted between them. First, "learning ability" has a narrower meaning and corresponds to the form of plasticity to be found only in the awake animal, when among others its drive system is active. However, plasticity does not comprise the "short-term memory" faculty, which has presumably different mechanism. Second, learning ability is a more descriptive notion and omits the neuronal mechanism.

To understand the strategy of brain plasticity research one should realise that it generally has two distinct stages. In the first "training stage", definite plastic changes are produced. In the second "testing stage", the location and nature of the produced plastic changes is studied along with related changes in the animal's behavior. Yet it should be borne in mind that the factor producing plastic changes, applied in the training stage, can be still active in the testing stage. Besides, when we intend to study plastic changes in the course of their appearance, i.e., the dynamics and mechanism of plastic processes, we can begin directly with the testing stage.

To bring about plastic changes, four methods are used:

I. Developing conditioned reflexes,
II. Sensory deprivation,
III. "Abnormal" sensory stimulation,
IV. Causing a local damage to the brain.

We shall now concentrate on some properties of these methods and on some differences between them.

First it should be noted that as a consequence of a given method not only plastic changes are produced but also may appear the lack of plastic changes which would be formed under normal conditions. The second effect plays a great role with the use of methods II to IV. For instance, in a visually deprived animal the plasticity of its visual system cannot be used (thus some plastic changes do not appear) while compensation processes based on undeprived analyzers are under way (thus some unusual plastic changes appear). Therefore, when methods II to IV are applied, the picture of changes in the animal's behavior is the result of summation of those two opposite effects.

Methods I, III and IV are destined mainly for the study of associative plasticity, whereas method II is used for the study of perceptive as well as associative plasticity. For instance, neither perceptive connections within the visual system, nor associative connections directed from the visual to other brain systems and *vice versa,* are being formed in the animal reared under visual deprivation.

Methods II to IV are most effective in the early life when brain plasticity is highest, whereas age factor may even play opposite role in method I, as it is hard to develop conditioned reflexes in a very young animal devoid of motor skill and needing a constant contact with its mother. However, with the use of methods II to IV the animal is at the same time loosing and gaining, as in the early age the massive loss of certain plastic processes is counteracted by smoothly running compensation processes. On the summation of these two opposite processes depends for example whether a behavioral deficit following a definite lesion is greater or smaller in the young animal than in one operated upon at an adult age.

In methods I to III the factor controlling the plastic changes formation acts during a definite time (when either conditioned reflex is being developed, or the animal is undergoing deprivation, or abnormal stimulation is being applied). It frequently coincides with the "training" stage of research, though, as already mentioned, it can still be active in the "testing" stage. On the other hand, in method IV this factor is permanently active (brain damage is usually irreversible).

During testing stage we investigate the already existing plastic changes using various methods, in particular electrophysiological, anatomical and biochemical. We also apply two of the methods used in training stage — the conditioned reflex method and the lesion method. But the part they now play is different: they serve not to form plastic changes, but to study them. With the conditioned reflex method we evaluate behavioral deficits produced in training stage and with the lesion method we localize the plastic changes.

There is no doubt that a decisive factor in the strategy of brain plasticity research is the method of "producing" plastic changes. Accordingly, we distinguish four research strategies and give them names corresponding to these methods. And so, the strategy where plastic changes are obtained through developing conditioned reflexes is named "conditioned reflex strategy", the one where they are controlled by sensory deprivation is called "deprivational strategy", and so on.

Strategy I: conditioned reflex strategy

It appeared at the beginning of this century as a strategy of the study of learning. Its invention was an independent achievement of Russian physiologists (I. P. Pavlov and his school) and of American behaviorists (E. Thorndike and others). Conceptual differences between these two groups of scholars, initially big, have gradually diminished. Besides, the behaviorists have on the whole accepted Pavlov's terminology.

In simplification, the conditioned reflex procedure runs as follows: the animal is isolated from the influence of accidental stimuli by being placed in a Pavlovian chamber, a Skinner box etc.; in such circumstances, conditioned and unconditioned stimuli are presented in a determined time sequence; presentation of unconditioned stimulus may be subject to the animal's performance of a definite movement. The effect of this procedure is the development of conditioned reflex or of a more or less elaborate complex of conditioned reflexes (e.g., conditioned differentiation).

Let us note some properties of the conditioned reflex strategy:

1. It has a limited range and serves to study only such associations as are addressed to the systems controlling the effectors (11, p. 265 and 353). It should be noted that, especially in man, a considerable part of learning processes does not have the character of a conditioned reflex.

2. The experimenter has a full behavioral control over the conditioning process. A successive presentation of a conditioned stimulus improves the produced reflex, i.e., the desired plastic change, and at the same time the magnitude of conditioned reaction speaks of the actual intensity of the change. In other words, in respect of behavior the investigations immediately enter testing stage.

3. This strategy is highly selective. A strictly defined conditioned stimulus generally evokes a strictly defined response.

4. The strategy is very effective. On the whole, the conditioned reflex develops quickly, sometimes after a single presentation of a given combination of stimuli (the so-called "one trial learning").

During nearly a hundred years' use of this strategy two important groups of behavioral results have been obtained. First, some laws governing the formation, extinction, differentiation etc. of conditioned reflexes have been described. Second, results have been achieved which located the conditioned reflex arches, i.e., places of origin of conditioned associations. This information is obtained by removing a definite part of the brain before or after the formation of conditioned reflex, by stimulating electrically a definite part of the brain, or eventually by registering electric activity of definite parts of the brain while the conditioned reflex is present.

On the other hand, the efforts to identify neurons engaged in a definite conditioned reflex have not proved effective (see 23, p. 459–606).

It has been found, upon recording electrical activity from single neurons, that in many neurons it undergoes changes during the occurrence of the conditioned reflex. But specific neurons are lost in a jungle of neurons unspecifically engaged. The conditioned reflex is generally a complex process in which an arousal reaction occurs, muscles controlling body posture are activated etc.

The efforts to get direct information concerning a synaptic base of the conditioned reflex were also without success. Looking for synaptic connections responsible for a definite conditioned reflex is like looking for a needle in a haystack. Up to this day we have failed to observe "conditioned" synaptic connections through an electronic or a light microscope.

Although direct information concerning the neuronal mechanism of the conditioning process was absent, from a long time, owing to the advance of knowledge of brain structure and growth, there suggested itself a hypothesis that a synaptic reorganization, and particualarly a formation of new synaptic connections, is the material basis of conditioning. This hypothesis was formulated by Konorski already in 1948 (10, p. 89).

Strategy II: deprivational strategy

This strategy won popularity in the nineteen sixties. To its pioneers belong D. Hubel and T. Wiesel.

For technical reasons, deprivation usually affects visual stimuli. Mostly, three methods of deprivation are in use: the animal is kept in darkness, its eyelids are sutured, or it wears a linen hood on its head. Deprivation can affect one eye or both.

In contrast to strategy I, the chief impact of research is directed to electrophysiological analysis of the obtained changes. Nevertheless, there has been achieved a general picture of behavioral changes characteristic for deprived animals. Let us consider them on the example of animals deprived visually at an early age. Two important groups of results were obtained:

1. In these animals some responses to visual stimuli are abnormal. For instance, cats reared under conditions of deprivation have later a disturbed depth perception. Particularly dramatic symptoms are observed in deprived humans. After an operation of a congenital cataract the human patient is unable to recognize, with his recovered eyesight, the faces of his close relatives (18).

2. Some forms of learnig based on visual stimuli progress in a very slow manner. For that reason animals, and especially humans, find it difficult to make up arrears from the deprivation period. In cat, for

example, post-deprivational disturbances of depth perception are of a permanent nature, and to humans operated for cataract learning that certain faces belong to their relatives comes with the greatest difficulty (18). These data show that in the post-deprivational period the plasticity of the visual system and its connections with other analyzers is weakened. It may by presumed that the lack of "key" synaptic connections which can be formed only in early life makes difficult or even impossible the formation of other connections.

The effects of visual deprivation proved convenient for the morphological, electrophysiological and biochemical analysis (1, 5, 14). It has been found for instance, that in the visual cortex of deprived animals there is a smaller number of dendritic spines than in normals and many of these spines have an abnormal shape (4). As an example of electrophysiological results may be quoted a marked decrease in the deprived visual cortex of the number of binocular neurons, i.e., those activated by stimulation of the right and the left eye. This result explains the above-described disturbances of depth perception in deprived cats. In some cases post-deprivational effects can be so considerable that one can even speak of brain lesions of a sensory origin. The above results answered our expectations — the growth of synaptic connections actually proved to be dependent on sensory stimulation.

So far, we have examined the strategy of total deprivation within a given sensory modality. The visually deprived animals could not see the light, or at least objects. But deprivation can be partial. In such instance the animal lives in an impoverished sensory environment. For example, it is reared single in a cage isolated from other cages (16). It should be noted that all animals reared under artificial conditions, among them domesticated or laboratory animals, are subjected to a partial sensory deprivation. In such animals brain weight gets reduced (7, 12) and they are less efficient in resolving behavioral tests (21).

Finally, it should be said that the animal can be subjected to a procedure which is opposite to deprivational, i.e., it can be reared in an enriched sensory environment. For instance, it can be kept together with many other animals in a large cage furnished with various objects, among them playthings (16). However, though such an enriched environment contrasts to advantage with the laboratory animal's usual environment, it is inferior to the wealth of the natural environment where the animal lives free.

Strategy III: abnormal sensory stimulation

Like in the strategy of deprivation, investigations are performed mainly on the visual system. There are three major procedures of producing plastic changes:

1. The animal can see only one definite stimulus. For instance, the cage where the cat is reared is painted in vertical stripes and the animal wears on its neck a vertically striped collar that conceals its body and extremities. Except for that one stimulus, the animal is visually deprived. The first studies of that character appeared in the sixties.

2. Abnormal stimulation is obtained by surgery. For instance, the animal's eyeball is turned by 180°. For technical reasons, such studies are carried out mostly on amphibians. They were started in the nineteen forties by R. Sperry.

3. Abnormal stimulation is obtained when a man wears specially constructed goggles which change the external vision, e. g., from right to left or *vice versa*. The first studies of that kind appeared in the fifties.

Let us now consider briefly the major results achieved with this strategy. Although results obtained with the use of procedure 1 are not uniform, electrophysiological data suggest that the visual stimulus applied engages a great number of neurons in the visual cortex (1, 5). With procedure 2, electrophysiological investigation showed a regrouping of certain central connections. In the frog, for instance, turning the eyeball at an early period of life brings about a reorganization of intertectal connections (8). Finally, it was found that with the use of procedure 3 a relatively quick behavioral adjustment and, moreover, a related psychical adjustment, takes place in adult humans (9). After the period of training in goggles the subjects start not only to respond correctly, but also to see correctly.

Strategy IV: the lesion strategy

This research strategy appeared already in the end of the 19th century. It consists in the observation of effects of brain lesion (surgical or chemical) over a longer time period.

We shall note its two properties. First to a some degree it resembles, the deprivational strategy. A lesion causes isolation (deprivation) of some brain structures from the afflux of nervous impulses from the damaged structures. Second, as aforesaid, the action of the damaging factor is generally irreversible. In other words, when we proceed to testing stage of the experiment (investigation of plastic changes), the factor producing plastic changes is still active.

About a hundred years of research conducted with the use of this strategy brought a number of important results. They mostly concern the recovery of function (based on compensation processess) and of its neuronal mechanism. Generally speaking, the behavioral compensation is considerable. A good illustration is the absence of obvious behavioral and intellectual deficits in adult humans whose cortex became paper-thin in result of hydrocephalus progressing from early infancy.

Compensation effects were studied successfully with the use of morphological, electrophysiological and biochemical methods (6). The most convenient to investigate are the effects of damage of a definite nervous pathway. As an example can serve the elegant studies by Rais man (15), who analyzed with an electronic microscope the effects of cutting the tracks leading from the hippocampus and hypothalamus to the septum.

A number of results indicate that two types of synaptic reorganization are mainly responsible for the process of compensation. First, synaptic connections with the neurons deprived of a normal afflux of impulses from the cut axons are formed by the neighboring neurons (15, 17). Second, the cut axons start growing below the point of lesion and seek new neurons for a destination (17). As we know, in the central vervous system a post-lesion scar prevents a direct regeneration of the severed axon. However, recent studies show that regeneration can be facilitated by implanting other tissue in the place of lesion (2). It would be tempting to assume that the first type of reorganization occurs also in sensorily deprived animals, but we lack direct evidence to confirm this thesis.

Future research

It is possible that a new strategy of brain plasticity research will appear in laboratories within the next few years. Yet the existing strategies will doubtless continue to be used for a long time to come. Moreover, the use of strategies II to IV is probably still in its early phase.

Strategy I. The future of the conditioned reflex strategy seems to lie in the development of new and further application of such already existing research models as enable the analysis of conditioning mechanism. As an example can serve the conditioning of ocular reflexes in the awake isolated cerebrum in the cat, where the electrical brain activity can be analyzed with convenience (22).

Strategy II. There is no doubt that plastic changes achieved through sensory deprivation are, so far, analyzed to a large degree unilaterally. Certain important research aspects mentioned below are being almost completely omitted.

1. Electrophysiologists, anatomists and biochemists have concentrated on studying a deficite in the plastic changes within the system which is undergoing deprivation, i. e., mostly the visual one, omitting as a rule other systems, like limbic, motor, auditory etc. And yet, as aforesaid in visually deprived animals it is also not utilized the plas-

ticity for association of the visual system with other systems. Besides, in result of compensatory processes, the plasticity of other systems, including the associative plasticity, is being used more than in normal animals.

2. Research deals almost exclusively with the stimuli's gnostic aspect with the omission of their drive (motivational) aspect (see 11, p. 42). This one-sidedness results from the "visual" model of this method. Visual stimuli are primarily of a gnostic nature, and their drive aspect is generally not original, but acquired through conditioning, which is not possible under conditions of deprivation.

Therefore a research model would deserve consideration where the animal would be deprived of stimuli eliciting definite primary drives (pain, for instance). Such model is important for two reasons. First, these drives are a decisive factor responsible for the animal's behavior. Second, presumably these very drives are "plastic" to a considerable degree. The pilot results of Melzack and Scott (13) showed that deprivation of dogs from pain stimuli in the early period of life decreased their later sensitivity to pain. Let us give an everyday-life example to illustrate the importance of the problem of drive plasticity. Two individuals reared in entirely different environments differ between themselves not so much in gnostic perception, as in the drives they possess. For instance, two such men will both describe a tree or a motor car which they have seen in a similar way, but they can make use of their efficient visual system for totally different purposes.

3. Investigations are conducted mostly in the post-deprivation period. Consequently, so far we do not know much of the dynamics of plastic processes taking place during deprivation.

Strategy III. Our comments will be limited to the procedure where the animal is subjected to the action of only one definite stimulus (it always is the visual stimulus). As already mentioned, the results obtained are not uniform. It seems they would be clearer if the stimulus had not only a gnostic, but also a drive importance. From this viewpoint, two new research models deserve attention.

1. The stimulus would not be presented continuously, but would serve as a signal of a definite unconditioned stimulus, e.g., it would be food-reinforced. In other words, conditioned plastic changes would then occur.

2. A stimulus evoking an "unconditioned" drive would be used, a food stimulus being most convenient. As already mentioned, the emotional taste appreciation is very "plastic". Wyrwicka (20) showed that young kittens can easily learn to eat a food not acceptable by normal cats. We have also plenty of information from everyday life on the

plasticity of food drive. The fact that our preference for certain foods and drinks changes in the course of life is a convincing example. Besides, the animal's taste environment is fairly easily controlled. For instance, in the early period of life the animals would be given food only with a given flavor, which would be different in different group of animals. Thereupon one would compare changes of preference with regard to these flavors, the speed of developing conditioned reflexes with these flavors used as reinforcement, etc.

Strategy IV. As we have mentioned before, morphological, electrophysiological and biochemical investigations are highly effective in the analysis of plastic changes brought about by brain lesions. However, many researchers use these techniques exclusively, to the neglect of behavioral tests. The absence of a systematic analysis of behavioral correlates of the neuronal processes is always a disadvantage. As an example may serve the situation when, years ago, the quickly developing electrophysiological research of brain activities, conducted almost exclusively under anesthesia, was not correlated with the animal's behavior.

Combined strategies. A simultaneous use of more than one method controlling the formation of plastic changes is rare. An instance of such combined strategy is to perform a lesion and to place the operated animal in an enriched sensory environment (19). Another example would be the mentioned developing of a conditioned reflex to a definite visual stimulus in a situation of the otherwise total visual deprivation of the animal.

To conclude, it should be stressed that in recent years brain plasticity is being intensively studied worldwide in numerous laboratories. It seems likely that within the nearest decades its properties will be fully described and mechanism explained.

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REFERENCES

1. BLAKEMORE, C. 1978. Maturation and modification in the developing visual system. *In* R. Held, H. W. Leibowitz and H.-L. Teuber (ed.). Handbook of sensory physiology. Vol. VIII. Springer-Verlag. Berlin, p. 377–436.
2. DAVID, S. and AGUAYO, A. 1981. Axonal elongation into peripheral nervous system "bridges" after central nervous system injury in adult rats. Science 214: 931–933.
3. GANZ, L. 1978. Innate and environmental factors in the development of visual form perception. *In* R. Held, H. W. Leibowitz and H.-L. Teuber (ed.). Handbook of sensory physiology. Springer-Verlag, Berlin, p. 437–488.

4. GLOBUS, A. and SCHEIBEL, A. B. 1967. The effect of visual deprıvation on cortical neurons: a Golgi study. Exp. Neurol. 19: 331–345.
5. HIRSCH, H. V. B and LEVENTHAL, A. G. 1978. Functional modification of the developing visual system. *In* M. Jacobson (ed.). Handbook of sensory physiology, Vol. IX. Springer-Verlag, Berlin, p. 279–335
6. VAN HOF, M. W. and MOHN, G. (ed.) 1981. Functional recovery from brain damage. Developments in Neuroscience. Vol. XIII. Elsevier/North-Holland Biomedical Press, Amsterdam, 449 p.
7. JACOBSON, M. 1978. Developmental neurobiology. Plenum Press. New York, 562 p.
8. KEATING, M. J. and GAZE, R. M. 1970. Rigidity and plasticity in the amphibian visual system. Brain Behav. Evol. 3: 102–120.
9. KOHLER, I. 1962. Experiments with goggles. Sci. Am. 206: 62–72.
10. KONORSKI, J. 1948. Conditioned reflexes and neuron organization. Cambridge Univ. Press, Cambridge, 267 p.
11. KONORSKI, J. 1970. Integrative activity of the brain. An interdisciplinary approach. Univ. Chicago Press, Chicago, 530 p.
12. KRUSKA, D. and RÖHRS, M. 1974. Comparative-quantitative investigations on brains of feral pigs from the Galapagos Islands and of European domestic pigs. Z. Anat. Entwicklungsgesch. 144: 61–73.
13. MELZACK, R. and SCOTT, T. H. 1957. The effects of early experience on the response to pain. J. Comp. Physiol. Psychol. 50: 155–161.
14. NIEMIERKO, S. 1980. Biochemical changes in cat cerebrum produced by visual deprivation and specific stimulation. Acta Physiol. Pol. 31, supl. 20: 43–56.
15. RAISMAN, G. 1969. Neuronal plasticity in the septal nuclei of the adult rat. Brain Res. 14: 25–48.
16. ROSENZWEIG, M. R., BENNETT, E. L. and DIAMOND, M. C. 1972. Brain changes in response to experience. Sci. Am. 226: 22–29.
17. SCHNEIDER, G. E. 1979. Is it really better to have your brain lasion early? A revision of the "Kennard principle". Neuropsychologia 17: 557–583.
18. VON SENDEN, M. 1960. Space and sight. The perception of space and shape in the congenitally blind before and after operation. Methuen, London, 348 p.
19. WILL, B. E. 1981. The influence of environment on recovery after brain damage in rodents. *In* M. W. van Hof and G. Mohn (ed.). Functional recovery from brain damage. Develop. Neurosci. 13, Elsevier/North-Holland Biomedical Press, Amsterdam, p. 167–188.
20. WYRWICKA, W. 1981. The development of food preferences. Charles C. Thomas, Springfield, 102 p.
21. ZABŁOCKA, T. and ŻERNICKI, B. 1978. Object discrimination learning in cats deprived on pattern vision from birth. Acta Neurobiol. Exp. 38: 63–70.
22. ŻERNICKI, B. 1974. Isolated cerebrum of the pretrigeminal cat. Arch. Ital. Biol. 112: 350–571.
23. ŻERNICKI, B. and ZIELIŃSKI, K. (ed.) 1980. The Warsaw colloquium on instrumental conditioning and brain research. Martinus Nijhoff, Hague, 736 p.

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