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A Survey

EDITED BY EDWARD HUTCHINGS, JR.

WITH EDITORIAL COMMENTARIES BY

L. A. DuBRIDGE, GEORGE W. BEADLE,

HARRISON BROWN, AND HUNTER MEAD

ALL OF CALIFORNIA INSTITUTE OF TECHNOLOGY

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R. W. SPERRY

Brain Mechanisms in Behavior

SOME EXPERIMENTAL OBSERVATIONS ON THE WORKINGS OF THAT BAFFLING MECHANISM—THE BRAIN.

The vertebrate brain, with an organizational complexity far surpassing that of any other natural or man-made system and possessing in certain of its parts the puzzling property of conscious awareness, will probably continue to remain a challenge to man's understanding for many decades to come. At the present time, the cerebral events underlying even the simplest forms of mental activity remain quite obscure. Although it should someday be possible to start correlating subjective experience with the corresponding brain process—perhaps even to comprehend the basis and derivation of the "mental" properties—we have to be satisfied, for the present, to work at many removes from this ultimate goal.

How *far* removed can be judged from the following series of experimental observations that will serve to illustrate some of the things our psychobiology group has been doing and will also serve to indicate the general status of some of the current problems in brain organization.

I will start with some early work dealing with nerve growth and regeneration, the results of which have been interpreted broadly to mean that brain function in the vertebrates generally is predetermined by inheritance to a much greater degree than

formerly had been supposed. The findings also give us some ideas about how the inherent patterning of the brain circuits is achieved in embryonic development.

Our information on the developmental patterning of brain pathways has been obtained mainly from fishes and amphibians because the early developmental stages in these lower vertebrates are accessible to surgery and because the central nervous system, in the larval and adult stages, retains a capacity for regrowth after surgical intervention that is almost entirely lacking in higher forms.

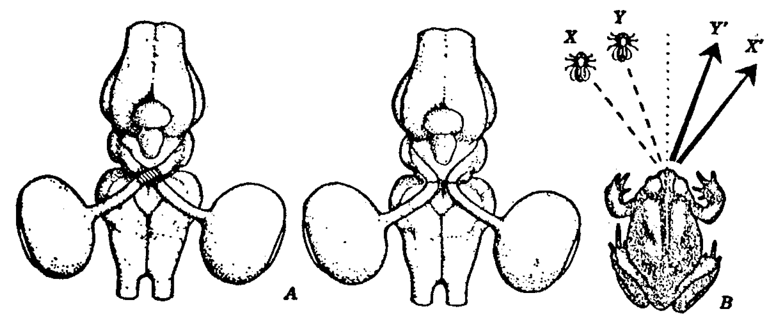

Fig. 1.—Connecting eyes to wrong side of brain results in an illusory right-left reversal of visual field. However, the relationships of *X* to *Y* and of *X* to any and all other points within the same visual field are restored to normal patterns.

As shown in Fig. 1, it is possible in these animals to cut the nerves of the eye where they cross and to reunite them surgically in such manner that, when they regenerate, the eyes become connected to the wrong sides of the brain. Under these conditions, the animals respond thereafter as if everything seen through one eye were being viewed through the opposite eye. For example, when a fly moves within the field of view of a frog's left eye, the frog will strike out at a corresponding point in the right field of view. This right-left reversal of visual reactions persists indefinitely, with no evidence of correction by re-education.

The sensory surface or retina of the eye in all vertebrates is projected through the optic nerve fibers onto the brain in an orderly, topographic, or map-like fashion. In the foregoing experiment the behavioral tests (and other evidence) indicate that this orderly topographic projection is restored with systematic precision in the regeneration process—despite extensive intertangling of the regenerating fibers. In Fig. 1, for instance, the the relationships of X to Y and of X to any and all other points within the same visual field are restored to their normal patterns. The fact that this occurs, despite the maladaptive functional effect produced by crossing the optic nerves, means that learning, or any other kind of functional readjustment, is not responsible for the orderly topographic patterning of the central hook-ups.

The fact, also, that this orderly restoration occurs in the face of random intermixing and intertangling of the regenerated fibers—particularly in the region of the nerve transection—has forced us to conclude that the optic fibers must differ from one another in quality.

In the lower vertebrates the optic fibers number around 25,000 (there are over a million in the optic nerve of man), and we have to infer that these individual fibers differ from one another in their biochemical constitution according to the particular points of the retinal field from which they arise. The further inference here is that the ingrowing fibers, on entering the brain, establish their central hook-ups in a selective, discriminative manner, governed by specific chemical affinities between the different types of ingrowing fibers and the central cells on which they terminate. This inference requires the corollary conclusion that a similar topical specificity exists among the nerve cells of the optic centers.

There is good reason to think that the qualitative specificity of the optic fibers is achieved in development through a polarized chemical differentiation of the retina. First, a naso-temporal, or front-back gradient of differentiation is laid down, and later—superimposed at right angles on top of this—an up-down gradient. This would mark each retinal locus with a latitude and longitude, so to speak, expressed as a unique ratio of chemical

properties. We don't know the exact chemical or physico-chemical nature of these neuronal specificities as yet any more than we know the chemical basis for most of the cellular differentiations that occur throughout the organism during development.

By rotating the eye surgically in the orbit, or by transplanting the eyeball from one orbit to the other, with different degrees of rotation, one may produce various other types of visual inversion and distortion. These inversions and distortions are always correlated directly with the orientation of the eyeball in the orbit; and, like the right-left reversal, they too persist without functional correction.

Leon Stone at Yale and George Szekely in Hungary have since carried these eye transplantations into prefunctional embryonic stages and have found that inverted vision results in just the same way as it does in the later stages. It would appear that the perception of visual direction is built into the vertebrate brain and, contrary to earlier opinion, does not have to be learned.

In some related work on cutaneous sensibility it was found that if one crosses the major nerve trunks of the left hind foot in the rat into the opposite leg and reunites them with the corresponding nerves of the right hind foot, then, after regeneration of the fibers into the skin of the opposite foot, all sensations aroused in the right foot are falsely referred to the left foot, from which the nerves originally came. For instance, an electric shock applied to the sole of the right foot causes the animal to withdraw the left foot.

The surgery was done in these rats during the fourth week after birth—before the animals could have had much experience in localizing cutaneous stimuli. The resultant reversal of reflex-reaction with the false reference of cutaneous sensibility persisted indefinitely, despite prolonged efforts to retrain the reactions by conditioning techniques and other methods. The results suggest that the mechanism for locating points on the body surface, like that for sensing visual direction, is built into the nervous system and, common assumption to the contrary, is not a product of experience and training.

This interpretation received further support in later experiments like the one carried out by Dr. Nancy Miner in which a flap of skin was peeled off the trunk region of a frog, lifted, and cut completely free of all nerve and other connections, rotated 180 degrees, and reimplanted (Fig. 2). The operation was done in early larval stages. When the tadpoles had grown up and undergone metamorphosis into the adult, we found that tickling these frogs on the back, within the graft region, caused them to scratch the belly with the foreleg. Conversely, stimulating them on the belly caused them to swipe at the back with the hind leg.

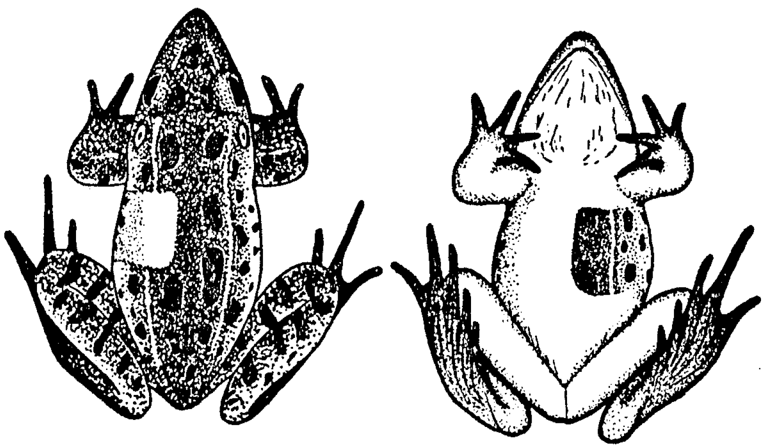

Fig. 2.—Skin grafts, rotated 180 degrees, result in a reversal of localizing reflexes. When back is stimulated in graft region, frog rubs belly—and vice versa.

These and related experiments have confirmed the preceding inference that the mechanism for locating points on the body surface is organized in the growth process itself—ultimately, of course, under genetic control. This neural apparatus for locating points on the skin is not a simple thing: I am told that our engineering is not yet developed to the point where we could build a machine to do nearly so well—particularly one in which the points to be localized are on its own mobile parts.

The further interpretation of how the neural mechanism is put together and developed in the growth process—based on the foregoing, and similar, studies—goes something like this: The skin, like the retina of the eye, must undergo a refined local differentiation during development—probably also on a basic, biaxial plan. The local specificity of the skin is then stamped or imprinted upon the nerve fibers at their terminal contacts. This induced chemical specificity in the nerve fibers, after spreading centrally along the fibers into the spinal and cranial nerve centers, then determines the type of reflex hook-ups formed —again, presumably on the basis of specific affinities between the peripheral fibers and central cells with which they connect.

It was shown further by Dr. Miner that if an extra hind limb

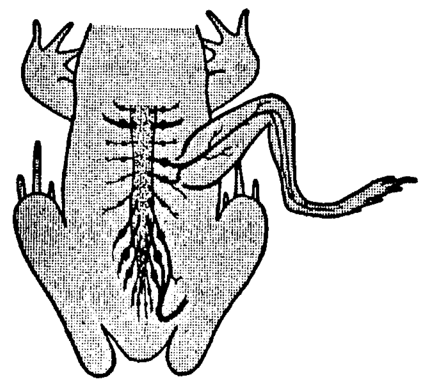

Fig. 3.—Trunk nerves growing into transplanted limb form limb reflex connections instead of normal trunk reflexes.

bud is transplanted into the trunk region of the frog (Fig. 3.), the same trunk nerves that were involved in the preceding graft experiment—and which normally form belly, back, and side-wiping reflex patterns—now form entirely different patterns of central connections, suited in each case to the particular patterns of the transplanted limb with which the fibers connect. By stimulating different points in the extra limb we get knee-wiping, thigh-wiping, and various types of kicking reactions. This means that cutaneous nerve fibers destined normally to form central hook-ups appropriate for the belly, flank, and back skin of the trunk formed instead connections appropriate for the digits, heel, and knee of the limb.

All these responses, incidentally, are made by the normal limb on the same side as the transplant; the transplant itself has no motor function. The important point is that here again the local quality of the skin with which the fibers connect in the periphery, and not the functional effects for the organism, determines the patterns of synaptic hook-ups formed in the central nervous system.

It used to be thought that the nervous system was first laid out in embryonic development pretty much as a random equipotential network that was gradually channelized through experience and training. The training effects were presumed to start way back in the early movements of the fetus in utero. Now our picture is quite different. We think that the great bulk of the neural circuits are laid down in precise, predetermined patterns in the growth mechanism itself. The effects of learning are presumably confined to the highest association centers, particularly the cerebral cortex, and are so minute a part of the total central nervous structure that they have thus far eluded any direct morphological demonstration.

Another part of our work deals with a brain theory of perception that developed out of the Gestalt school of psychology and is perhaps most commonly referred to as the "electrical field theory of cerebral integration." Proponents of field theory have ascribed a primary role in brain function to gross electric currents that spread through the cortex *en masse;* that is, through the cortical tissue as a volume conductor. Most aspects of perception appear to be more readily correlated with these gross electric currents in the brain than with the more orthodox type of nerve impulses that travel in scattered discontinuous patterns along discrete fiber pathways.

In an experiment aimed at testing this electrical field theory, the visual area of the cortex in the cat was filled with metallic inserts of tantalum wire. The aim here was to short-circuit, and hence to distort, the normal patterning of DC current-flow in the cortex during visual form perception. These numerous metal-

lic inserts, which are biologically inert and remained in the brain for months without any deleterious effects, proved to have no measurable effect on any visual reactions—including previously-trained high-level pattern discriminations.

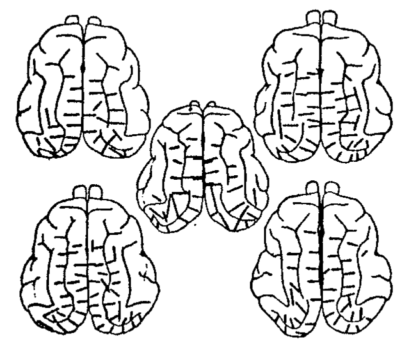

Fig. 4.—Dielectric mica plates inserted in visual cortex to distort the patterning of brain currents during perception.

In another experiment aimed at testing the electrical field theory the approach was just the opposite. Dielectric or insulating plates of mica were inserted vertically into the cortex, in the patterns shown in Fig. 4, in an attempt to distort—this time by blocking instead of by shorting—the postulated patterns of DC flow in the visual area during pattern perception. Although some functional impairment was found in this series, it was shown in controls to be correlated with the tissue damage produced by the inserts rather than with their dielectric effects, and the conclusion was the same as in the previous experiment.

The outcome of these two studies has rather discouraged any inclination, on our part at least, to forsake the traditional fiber conduction doctrine of brain function in favor of the newer electrical field hypothesis.

Any brain theory of perception, we believe, must square also with the following observation: The visual area of the cortex, in the cat again, was sliced with numerous subpial knife cuts in crisscross patterns, as shown in Fig. 5. When these cuts—in the top two cases—proved to have only negligible effects upon pattern perception, we decided—in the third case—to carry this slicing procedure to an extreme, making the cuts as numerous and as close together as possible. After four weeks, this third animal was performing again on our test scales at a level only one or two notches below its preoperative standard.

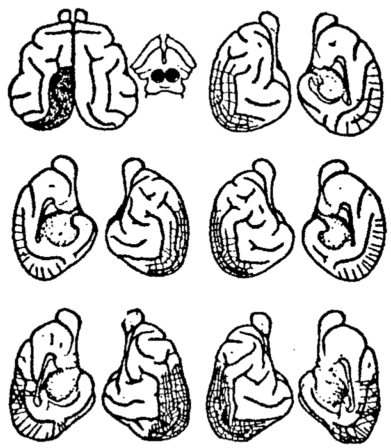

Fig. 5.—Visual area of cortex, partitioned with numerous subpial cuts to test effect on pattern perception.

The best discriminations that this animal was able to perform several months later are shown in (A) of Fig. 6. It could discriminate the central triangle when paired with any of those surrounding it. And the animal also readily learned the size discrimination shown in (B). The lack of any marked functional disturbance after such slicing of the cerebral cortex seems to eliminate as an important factor in perceptual integration any tangential or horizontal spread of nervous conduction within the cortex itself—that is, on any scale large enough to mediate so-called relational or structuring effects in the perception of pattern.

In another group of studies we have been concerned with the function in perception of long fiber connections in the mammalian cortex. The largest of the fiber bundles in the brain of higher mammals is the corpus callosum which unites the two cerebral hemispheres. It has been somewhat embarrassing to our concepts of brain organization that complete surgical section

of this largest fiber tract has consistently failed in human patients to produce any clear-cut functional symptoms. In checking this observation in animal experiments, however, we have been able in recent years to demonstrate definite integrative functions for this structure.

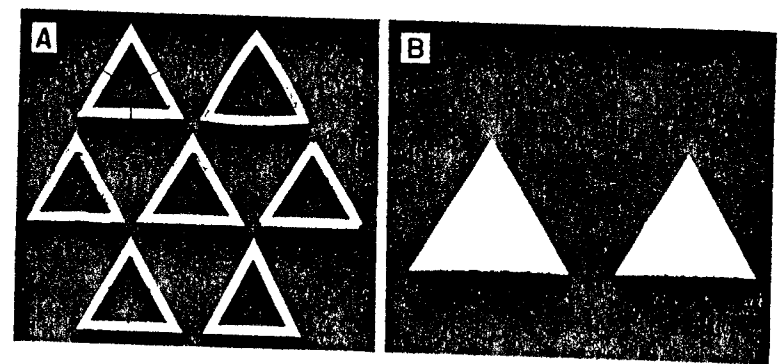

Fig. 6.—With its visual cortex subdivided by multiple crisscross cuts, test animal could discriminate central triangle in A, above, when it was paired with any of those surrounding it—and also learned size discrimination in B.

In these experiments, carried out mainly in cats, we first section all crossed optic fibers at the chiasma, in order to restrict the input from each eye to the same side of the brain. The animal is then taught a few simple visual discriminations with a mask covering one eye. After the habit has been stabilized by overtraining, the mask is shifted to the other eye.

With this procedure it was shown originally by Dr. Ronald Myers that the trained performance transfers readily to the untrained eye, if the corpus callosum is intact; but if the corpus callosum has been sectioned prior to training, there is no transfer at all. Without the callosum, such animals apparently have no recollection with one eye of what they have been doing with the other eye. In fact, it is possible to train opposing incompatible discriminations to the separate eyes concurrently without getting any interference. Work in progress shows the same to be true in the monkey.

In collaboration with Dr. John Stamm, we have obtained similar results for the contralateral transfer from one forepaw to the other of tactile discriminations. Cats are trained to push the correct one of two pedals which they can reach with only one forepaw and which they are unable to see and must distinguish entirely on the basis of touch. One gets 70 to 80 percent transfer of learning upon shifting to the untrained paw in unoperated animals. When the callosum is sectioned, the transfer is zero.

Perceptual learning and memory thus seem to proceed independently in the two hemispheres of the brain in the absence of the corpus callosum. It is interesting that, in spite of this independence, the learning curves for the two separated hemispheres are remarkably similar in character, suggesting that the individual variability in perceptual learning is predetermined to an unexpected degree by the intrinsic structural and functional organization of the cerebral hemisphere. This was found to be true in cats for both tactile and visual discriminations, but seems to be much less characteristic of the monkey, the difference here reflecting perhaps an important species difference in learning.

Attempts to localize in the brain the memory traces for particular habits have generally failed. The memory traces, or engrams, appear to be extremely elusive and diffuse and so far have not been specifically localized or demonstrated. In the case of the memory traces ingrained for the visual discriminations in the foregoing experiments, it was possible to show that they are not confined to the directly trained hemisphere. One can remove the visual and the neighboring association cortex on the trained side in these animals before switching the mask and still get the transfer to the untrained eye through the callosum. Further, one can still get this transfer even if the entire callosum is sectioned after the completion of training but before testing for the transfer. Some kind of mnemonic carryover into the opposite hemisphere is evidently effected via the corpus callosum.

At the present time we are investigating the functional capacities of small islands of cerebral cortex. In these studies we put to use the above-mentioned functional independence of the

two hemispheres in what we have come to call the "split-brain preparation." This is an animal in which the brain has been split down the middle by sectioning the corpus callosum, hippocampal commissure, and the optic chiasma and, frequently also, some of the lower-level connecting systems. To casual examination, these split-brain animals after recovery are indistinguishable from normal in their general cage behavior.

In such animals the brain-lesion analyses can be carried out in one hemisphere alone, the other hemisphere being kept intact to maintain generalized background functions. In the test hemisphere, instead of the customary small lesions in the critical area, it becomes possible in such preparations to use the opposite approach—that is, to remove the greater part of the cortex and to leave intact only the small critical area, the functions of of which one wishes to investigate.

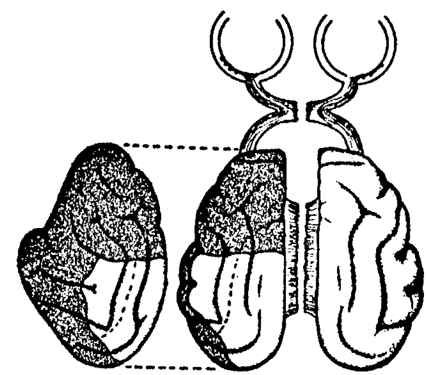

Fig. 7.—Removal of nonvisual cortex with preservation of visual area abolishes visual functions for reasons still undetermined.

To what extent would visual perception be possible, for example, if all parts of the cerebral cortex were removed excepting just the visual area itself? We have found that vision is practically absent on the test side when the visual area is isolated in cats to the degree shown in Fig. 7.

If the nonvisual parts are removed in two or three separate operations, starting with the cortex immediately surrounding the sector to be preserved, it is not until the final removal of frontal or temporal lobes, as the case may be, that we get the really severe visual impairment.

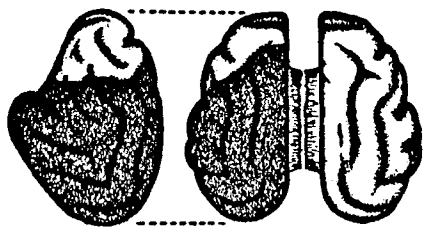

Fig. 8.—Small island of intact cortex retains capacity to remember and to learn new tactile discriminations almost as well as the whole hemisphere.

Similar isolation of the cortical area for touch perception, as shown in Fig. 8, has yielded quite different results. In this case the cats, after operation, are still able to perform, at a high level, previously-trained tactile discriminations. They also are able to learn new discriminations with the isolated area almost as well as with the whole hemisphere. If circumscribed lesions are subsequently placed in the forepaw tactile area in the opposite, intact hemisphere, it is possible to abolish all discrimination with the affected paw without significantly impairing the performance of the paw that is controlled through the isolated remnant of cortex.

It would appear that the processes of cortical integration and reintegration involved in the learning and memory of these tactile discriminations are localized within the intact cortical island. Under normal conditions it is entirely possible that the integrative processes are much more widespread through the cerebral hemisphere, but it is important to know at least that these unknown cerebral mechanisms are of such a nature that they *can* be handled with a rather small, isolated sector of the cortex.

This is about where we stand on these projects at the moment. As can be seen, we are still a very long way from being able to blueprint the circuit diagrams for perceptual integration, learning, or memory. Nor have we the vaguest notion of the general type of circuits needed, for example, to build into a machine so simple a thing as pain sensation. We don't know enough to say in theory even that it can—or ever could—be done.

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Edited by ANNE ROE *and*

GEORGE GAYLORD SIMPSON

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