ORDERLY PATTERNING OF SYNAPTIC ASSOCIATIONS IN REGENERATION OF INTRACENTRAL FIBER TRACTS MEDIATING VISUOMOTOR COORDINATION

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TWO FIGURES

The manner in which the integrative circuits of the nervous system became organized in development is still conjectural. For many years Kappers' ('32) electrical theory of "neurobriotaxis" was favored as the most likely explanation of how the synaptic associations become arranged in appropriate patterns. The timing of nerve discharges he supposed to be the crucial factor in determining the adaptive selectivity of neuronal interconnections. This interpretation was in accord with the widespread conviction that the refined precision, complex organization and functional adaptiveness of the underlying neural structures required for mediation of central nervous integration could hardly be attained independently of function.

A recent series of experiments on the inherent patterning of synaptic connections in the amphibian central nervous system (Sperry, '43-'48) prompted by an entirely different working hypothesis which puts no dependence upon functional factors has repeatedly yielded results consistent with the alternative view and incompatible with the neurobriotatic interpretation. In brief, without reference to the supporting evidence which has been reviewed at length elsewhere (Sperry,

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rnative hypothesis assumes that the developing
continue to undergo a refined biochemical differ-
ing themselves far beyond that which becomes
ibly and which closely approaches in degree the
entiation attained in their inherent structural
It is postulated further that selective affinities
abilities of a physico-chemical nature develop
ious neuron types as a result of their differenti-
synaptic linkages are formed in a discrimina-
only between cells which have special affinity for
the advancing tips of the developing nerve fibers
ly to bypass many of the nerve cells which they
their outgrowth forming synaptic endings only
with particular neurons the chemical properties
specially matched to those of the growing fibers.
ments thus far have been concerned with the
ich appropriate connections become established
and periphery and accordingly have dealt only
formation in the primary sensory and motor
uestion has therefore arisen as to whether the
ynapses deeper in the nervous system, involving
and higher order association neurons, might not
a quite different and more functional type of
was to investigate this possibility that the
iments were undertaken.
ations are concerned with the reestablishment of
ative relations in regeneration of central associa-
towing brain transection near the caudal end of
lalon. Although regeneration of many different
both descending and ascending, was included, at-
centrated primarily upon the descending tracts
motor coordination. These tracts were singled
he differential adjustment and organization of
ctions are comparatively easy to measure, and
the factor of functional adaptation in recovery
y tested in the case of vision by surgically re-
tating or inverting the eyes or by cross-uniting the optic
erves.

EXPERIMENTAL PLAN AND METHODS

All the descending intracentral fiber tracts which link the
primary visual centers with the medulla and spinal cord were
severed by transecting the brain posterior to the optic lobes.
The object was to find out if the divided fibers would regen-
erate and restore functional associations with the lower cen-
ters of the spinal cord and medulla, and, if so, whether the
central synaptic associations would be restored in a haphaz-
ard, indiscriminate fashion or in an orderly, selective manner.
Finally, the experiments were designed, in the latter case, to
determine whether the adjustment of the central connections
might be dependent upon functional types of adaptation like
learning or whether it was regulated by factors intrinsic to
the regeneration process itself.

If the central course and termination of the regenerate
ting fibers were determined merely by mechanical guidance, one
would anticipate only confusion and disorder in the recovered
function because of the inevitable admixture of regenerating
fibers of different functional types. With division of all the
tracts which link cord and medulla to the higher brain centers,
ascending as well as descending, there would be opportunity
for intermixing of fibers not only within those tracts subserv-
ing vision but also between these and many nearby tracts of
various other functions. Furthermore, even if a few fibers
should chance to be directed across the cut into their original
channels, they would not necessarily be guided to their former
terminals because the final portion of their course within the
neuropil, where the synaptic connections are made, remains
unchanneled. This latter factor alone would cause much con-
fusion in fiber termination were it dependent entirely upon
mechanical guidance. Any orderliness in the recovery of
function under the experimental conditions would thus nec-
ecessarily indicate the action of discriminative organizing
agencies of some sort.
they might conceivably be the "conditioning" process by which adaptive synaptic connections were forced and maladaptive ones eliminated on the functional effects. Surgical rotation of the eyes degrees was carried out in some of the animals in which the divided central tracts were for the purpose of testing this possibility. If recovered normal visuomotor responses despite immobile nature of the eyes, it would certainly imply a degree of adjustment. On the other hand if the visuomotor associations were restored in the one result would be a recovery of systematically adaptively assortments, highly maladaptive-in increased, '43-'45). In view of the detrimental function in this latter case the orderliness of recovery has been ascribed to any functional process of adaptively guidance and functional adjustment. Regenerating fibers would have no means of representatively arranged relations in the fibers were all alike in character. Accord- ing of reversed vision would constitute evidence of specificity among the regenerating fibers and the idea that the formation of synaptic con- nected by selective affinities between the regen- rate and lower level neurons.

As the experiments were carried out on adult *Periplaneta americana*, during the winter months from March. After the animals had been deeply etherized, the ventral wall of the cranium was sharp-pointed watchmakers' forceps and broken at the junction of midbrain and medulla. After this had been reflected rostrally the brain was approximately the level indicated in figure 1, time, by repeated crushing with an extremely forceps, the points of which had been especially sharpened and ground to blade-like thinness. The division of the brain substance by this method was clearly visible. It was thought that separate section of each side of the brain in bilateral cases might help reduce the misalignment of fibers across the median raphe. This is important because other experiments (Sperry, '45, '48) have indicated that some neuron types, if given a chance, readily form their characteristic associations on the opposite as well as on the normal side of the brain or cord.

A transection was performed unilaterally in 10 cases and bilaterally in 19 cases, only 11 of the latter of which survived. It was found that the mortality of the bilateral cases could be greatly reduced by keeping the animals first in cold (approxi-

![Fig. 1 The level of transection, diagrammatic.](image-url)
RESULTS

effects of transection. In the unilateral cases the responses toward the side opposite the hemisection were normal or exaggerated whereas the responses on the side were extremely weak or lacking. Rotation of the visual field on the longitudinal and body axes were distorted by the persistent tendency and turned to the side opposite the lesion. The ability to localize small objects in space also underwent great improvement until no conspicuous defects remained on either side. The best cases were indistinguishable from normal with the tests employed. The bilateral cases recovered optokinetic responses correctly directed in all three planes. Responses in the frontal plane were roughly normal in character. Those in the transverse and sagittal planes, however, which normally are less pronounced, were noticeably weak in most cases. In one case the responses seemed to be lacking entirely in the transverse plane and in another no reliable optokinetic reactions could be elicited in either vertical plane.

The localizing reactions of all but three of the bilateral cases were made consistently toward the proper quadrant of the visual field for all quadrants on both sides after the eyes had been returned to normal position. There was a range in the degree of recovery, however, from the best case which responded with roughly the normal speed and accuracy to the worst cases which were obviously slower to react and less certain of the precise direction and distance of the lure. In one of the exceptional cases no localizing responses could be elicited on one side. In the second exception, distinct erroneous reactions toward the corresponding quadrant of the visual field on the contralateral side were made consistently when the lure was presented in the dorsal quadrants on either
as the animal in which the vertical optokinetic nystagmus was lacking. Apparently regenerating fibers which crossed the midline had failed to do so, or vice versa. Rare exception frequently displayed crossed responses to those of the preceding case when the lure was presented in the dorsal quadrant of the left visual field. The optic acuity gave no information on visual acuity and it is at least the case that at least a degree of directional precision of gross quadrant discrimination. One got the feeling that the responses of most of the animals, particularly in bilateral cases, were not aimed as precisely after as before. Nevertheless, correct optokinetic movement of the visual field around the three main body axes could be performed even though it was the extent of turning to the proper quadrant of the body. There was together a high degree of selectivity and underlying neural mechanisms.

Visual functions likewise appeared to have undergotten recovery. The various abnormalities of movement had almost completely disappeared in all cases and had been largely disappeared in the final tests.

With eyes rotated. When visual responses reappearance 7 animals in which the eyes had been rotated, with the same systematic reversal observed after rotation of the eyes in animals otherwise normal (a). Reversal of the optokinetic responses in the transverse plane, spontaneous optokinetic nystagmus, movements of the head, most pronounced in the transverse plane, and erroneous localization of small objects appeared in characteristic fashion to a degree that was the subsequent display of normal reactions described above. These maladaptive coordinations persisted correction longer than a month in all cases in which were reset in the normal orientation.

Central Nervous Regeneration

Effect of optic lobe lesions. It was possible that regeneration had taken place at random and that by "induction" effects via the efferent connections a reorganization of synaptic relations had occurred in the higher centers to suit the new patterns of connections at lower levels. There was no indication of this in the functional results of destruction of the median part of the optic lobes in 5 of the bilateral cases after the eyes had been reset. The effects of these lesions were found to be similar to those obtained in normal cases, namely, an elimination of all responses to the lure when it was presented anywhere in the dorsal part of the visual field plus retention of normal reactions to the lure when it was presented in the ventral portions of the visual field. Had there been a functional readjustment in the optic lobe to suit random connections in the lower centers, the above operation should have impaired vision in the ventral as well as in the dorsal quadrants and also might possibly have left some residual vision in the dorsal quadrants. Apparently, however, the afferent system had retained its original organization and the efferent relations had been adjusted accordingly.

![Photomicrograph of a parasagittal section through the optic tract showing the deafferentation and internervous of the regenated fibers despite which occurred an orderly recovery of function. (473 X.)](image)
tively. Presumably the formation of synaptic connections in the spinal and medullary centers is regulated by differential affinities between the various types of regenerating fibers and the different kinds of lower-level neurons. The regenerating fibers in their descent into the cord may be pictured as giving off numerous collaterals which arborize profusely in the central grey and superficial neuropil zones encountering many types of nerve cell bodies, dendrites, axons, glia cells, and capillaries with only a few of these contacts, limited to specific neuron types, resulting in the formation of synaptic endings.

had already been inferred indirectly from the results of regeneration of spinal limb nerves and of the 11th, 11th, 11th, and 11th cranial nerves (Sperry, '48) that the secondary central neurons connected with these various nerves must be qualitatively specified. The present results are entirely in accord with those obtained on synaptic formation within the primary nuclei and lend additional support to the "biochemical affinity" hypothesis of synaptic organization outlined above.

The only other possible basis of interpretation recognizable at present lies in the "resonance" and "specific nerve energy" concepts formulated by Hering ('13) and elaborated more recently by Weiss ('26, '41). It could be supposed that the visuomotor coordination of these animals is independent of selectivity among neuronal interconnections and is regulated instead through the emission of specific frequencies or modes of excitatory energies plus selective sensitization to these on the part of the different neuron types. Ordinarily recovery of function might be possible on this basis despite a diffuse and indiscriminate reestablishment of synaptic connections. Reasons discussed elsewhere (Sperry, '48) for continuing at this time to favor the connectionist interpretation are applicable to the present observations.

The misdirection of localizing responses toward the corresponding quadrant of the contralateral visual field clearly detectable in two of the bilateral cases indicated that the fibers of these intracentral neurons, like those of the optic
Spinal sensory roots (Sperry, '45a; '48) are able to maintain a characteristic pattern of synaptic connections on either side of the neuraxis. Since such connections are maladaptive from the functional aspect, this suggests that the patterning of these synaptic relays is regulated on a functional basis. The fact that fibers were sufficiently to terminate in the wrong side also provides further evidence that there was some extent of mixing of fiber types.

**SUMMARY**

Intracranial fiber tracts subserving visuomotor function were transected in adult newts slightly posterior to the mid-brain, the divided fibers regrew and established functional relations with the diencephalon and spinal centers in an orderly systematic manner. The mechanical guidance of the regenerating fibers and the function of the nerves were both eliminated as factors regulating the orderliness of recovery. It is suggested that biochemical affinities exist between the higher and lower neurons and that the selective patterning of synaptic connections is regulated by these affinities in accordance with the correlated chemotactic interpretation of the development of neuronal interconnections.

**LITERATURE CITED**


