ESSAYS ON APS CLASSIC PAPERS

Roger Sperry: pioneer of neuronal specificity

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This essay looks at the historical significance of two APS classic papers that are freely available online:


When Roger Sperry (Fig. 1) received the Nobel Prize in 1981 for his work on functional specialization of the cerebral hemispheres, some of his admirers felt that the prize had been awarded for the wrong body of work. Or even that he deserved a second prize! How the organization of the nervous system manifested itself in behavior was always at the forefront of his interests, but the split-brain studies for which he received the Nobel Prize represented only a fraction of the avenues by which he chose to explore this subject. Another approach that figured importantly in his career was to examine the behavioral effects of perturbing the nervous system, especially in lower animals, where both the brain structure and the behavioral repertoire were apparently simpler to interpret. These experiments led him to hypotheses about basic mechanisms regulating the wiring of the nervous system, hypotheses that even today influence our thinking about neuronal organization, particularly in development.

Some of Sperry’s classic experiments appear in two papers in the *Journal of Neurophysiology* in 1944 and 1945. The object of the experiments in the first of these papers (Sperry 1944) was to confirm in adult and immature anuran amphibians what he himself had previously observed in the more primitive newt (Sperry 1943a,b): when severed, optic axons reconnected to the optic tectum (the principal visual center in these animals) and visual function eventually returned, indicating that reflex relations in the brain had been correctly restored. To test how the restored vision had come about, regeneration was combined with a perturbation of the visual field produced by rotation of the eye (Sperry 1943b).

Sperry tested vision in his experimental animals using flies impaled on a thin wire as a food lure for the adults and rotary optokinetic stimulation in the case of the tadpoles. He found that after a few weeks had been allowed for regeneration of the optic nerve, the animals showed persistently reversed responses. Neither development of the tadpoles nor repeated exposure of the adults to the stimuli produced any correction of the responses. On the other hand, control animals that had undergone regeneration of the optic nerve without rotation of the eye always showed correct responses under the same conditions. Thus the incorrect responses from the rotated eyes could not be attributed to any inherent defect in the regeneration process itself, and they could not be corrected by any functional process such as learning, even if they were of a maladaptive nature.

Moreover, by testing visual responses after having made lesions in various regions of the optic tectum, Sperry showed that in the regenerated animals these regions still retained their appropriate correspondence with the original retinal sectors, even when the eye had been rotated. Histological examination of the regenerated optic nerves showed that axon outgrowth in the region of the lesion was quite disorderly, but it was not possible to determine whether the axons might at some point have sought out an appropriate pathway, or whether the only axons that survived were the ones that had by chance reached their appropriate termination sites. It was also not possible to assess the precision of the retinal projections.

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FIG. 1. Roger Sperry in 1973. (Photo courtesy of Dr. Robert W. Doty.)
Sperry inferred from these experiments that “the ingrowths of optic fibers must possess specific properties of some sort by which they are differentially distinguished in the [brain] according to their respective retinal origins” (Sperry 1944, p. 67). Moreover, “a basic embryonic specification [may arise] through central self-differentiation of the nuclear [i.e., neural?] mass itself” (Sperry 1944, p. 68) to account for the likelihood that the central neurons to which the optic axons connected were likewise differentially specified, in order for appropriate connections to be made.

In his second paper in the *Journal of Neurophysiology* (Sperry 1945), Sperry set the regenerating optic axons a more difficult task by excising the optic chiasma and rerouting the optic nerves (which are usually completely crossed in the amphibians that he used) to connect each eye to the ipsilateral lobe of the optic tectum. He tested these animals by optokinetic stimulation and directed food presentation, as before, but also made detailed examination of their spontaneous movements and escape reactions. Again he observed inverted responses to stimulation, made more difficult by the fact that these animals showed prominent spontaneous circling. Some of these animals were studied over a period of several months, with no qualitative change in their reactions.

Another approach he used was to transplant one eye to the opposite side, thus reversing its dorsal-ventral orientation without changing its nasal-temporal orientation, or vice versa. This operation in previous workers’ hands had not led to restoration of vision, but Sperry nevertheless found good visual recovery in urodeles and in metamorphosing frog tadpoles at the stage of forelimb emergence. In these animals, the visuomotor responses were altered from normal in the direction that would have been predicted from their eye orientations. No correction of these abnormal responses was seen even 2–3 mo after recovery. Histological studies showed a disorderly progression of the optic axons along the nerve, with almost all of them crossing to the contralateral tectum and only a scattering selecting the route to the side to which they would originally have connected. Thus it was evident that the regenerating axons were not passively following their old trajectories, and hence their final orderly reconnection to the optic tectum must have been determined by an intrinsic property reflecting the specific location of their cell bodies in the retina. Sperry inferred that the specific local properties would have been produced originally in the embryo “through a field differentiation of the retina” (Sperry 1945, p. 15). This process would be analogous to the establishment of polarity in the developing limb bud, with two differentiation gradients, corresponding to the anteroposterior and dorsoventral axes, determined separately.

Subsequently, data that would be necessary to support this hypothesis were obtained in Sperry’s laboratory by demonstrating the detailed connection pattern of the regenerating axons (Attardi and Sperry 1963). A series of histological studies in the visual system of fish showed that after localized lesions in either the tectum or retina, or after surgical rerouting of the optic tracts into foreign regions of the tectum, the regenerating axons were seen inevitably to have grown back to their appropriate end-zones, bypassing, if necessary, more readily accessible but inappropriate synaptic regions. Studies in other systems, such as innervation of skin (Miner 1956) and muscles (Sperry and Arora 1965), likewise showed preferential connections to the correct targets despite various surgical perturbations of the neuron-target pathways. Sperry was led to define this specificity as arising from “each axon linking only with certain neurons to which it becomes selectively attached by specific chemical affinities” (Sperry 1963, p. 704).

Despite this accumulation of evidence, however, Sperry’s hypothesis was not readily accepted. One factor undoubtedly was that virtually all his experiments were carried out in lower vertebrates and hence failed to immediately attract the attention of the community of neuroscientists oriented to “real,” i.e., mammalian, organisms. Hence progress in this area fell to a relatively small number of workers, who perceived the importance (and convenience) of lower animals for establishing basic biological principles that might prevail throughout the animal kingdom.

Historical factors also worked against the acceptance of hypotheses that apparently did not adhere to the principle of Occam’s razor, namely that “one should not increase, beyond what is necessary, the number of entities required to explain anything” (http://pespmc1.vub.ac.be/OCCAMRAZ.html). Sperry’s original experiments were undertaken at a time when the idea that physical and chemical forces governed the form of biological structures, particularly as espoused by D’Arcy Thompson (1917), was still an important illuminating principle. Paul Weiss’s now-classic textbook on development (Weiss 1939) and J. Z. Young’s essay on axonal morphology (1945) strongly emphasized this view in relation to the dynamics of growth in the nervous system. Weiss exerted a powerful influence with his demonstration that the outgrowth of axons in tissue culture was determined more by the physical properties of the substrate than any positive attraction by target tissue (Weiss 1934) and that regenerating axons, given their choice of pathways, showed no preference for the direction in which their target lay (Weiss and Taylor 1944).1 If Occam’s razor was to be applied, the view that axon growth was essentially determined by mechanical factors left little room for Sperry’s postulates of specific chemical affinities and attractive forces.

On the other hand, numerous observations that restoration of motor function might occur even with apparently random reinnervation of muscles (reviewed by Weiss 1936) had given rise to explanations that required that motor neurons could undergo functional modification subsequent to their contact with the muscles (reviewed by Grafstein 2001a). These views posed a particularly difficult problem for Sperry himself. He had been a graduate student of Weiss’s and had shown that incorrect innervation of muscles, at least in mammals, led to incorrect movements that were not subject to any functional modification or learning (Sperry 1941). In interpreting his studies on the visual system he initially tried to leave room for Weiss’s concepts of functional modulation (Sperry 1944) but finally chose to regard them as unimportant in the face of his own ideas (Sperry 1963).2

At the present time, of course, the resistance to Sperry’s ideas has vanished (see review by Meyer 1998). Indeed, these

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1 It is ironic that this demonstration of the absence of attraction factors in regenerating nerve was eventually found to have been invalid due to an ingenious but incorrect choice of substrate: nerve growth was tested in an arterial sleeve that may have nullified the trophic influence of the degenerating nerve stump (Politis et al. 1982).

2 But not without retaining a lifelong antipathy to Weiss and his ideas (reviewed by Grafstein 2001a, b).
ideas may be seen as the embodiment of many principles that we now regard as fundamental to nervous system development and regeneration. Diffusible signals for attraction and repulsion of growing axons and factors involved in selective synapse formation have been identified and are being explored in great detail (e.g., see Purves et al. 2004). A postulate that worried Sperry no longer seems unreasonable—that there might not be enough distinct chemical labels available to account for so many different neurons and so many different neuronal interconnections in the nervous system. Now we have no qualms about whether there is enough information available—there are plenty of genes, plenty of time-dependent regulators of gene expression, and plenty of posttranslational mechanisms for modification of gene products.

REFERENCES


