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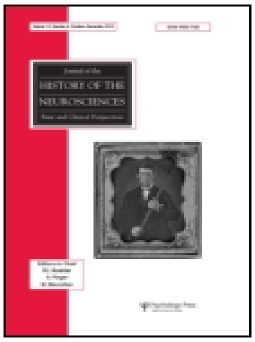

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Revisiting the 1981 Nobel Prize to Roger Sperry, David Hubel, and Torsten Wiesel on the Occasion of the Centennial of the Prize to Golgi and Cajal

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In 1981 the Nobel Prize for Medicine or Physiology was awarded to Roger Sperry for his work on the functional specialization of the cerebral hemispheres, and to David Hubel and Torsten Wiesel for their work on information processing in the visual system. The present paper points to some important links between the work of Sperry and that of Hubel and Wiesel and to their influences on neuroscience in the best tradition going back to Cajal.

Keywords Roger Sperry, David Hubel, Torsten Wiesel, neuroembryology, visual Cortex, corpus callosum, Cortical Columns, nature and nurture and the nervous System, history of neuroscience

The First Nobel Prize to the Neurosciences

When Santiago Ramón y Cajal delivered his Nobel Lecture on the 12th of December one hundred years ago, he kept strictly to his neurohistological findings and did not venture into a discussion of a general theory of the nervous system (Ramón y Cajal, 1906). Perhaps he had decided that the sole exposition of solid facts was the best response to the ill-conceived attack that Camillo Golgi had launched on the neuron theory in his Nobel Lecture of the previous day (Golgi, 1906). Or perhaps Cajal felt that he ought to limit himself to illustrate his anatomical discoveries in accordance with the motivation for which he and Golgi had been awarded the prize: "in recognition of their work on the structure of the nervous system."

Today Cajal is regarded as a giant in the history of the neurosciences not only for his extraordinary contributions to our knowledge of the morphology of the nervous system but also and above all for his amazing intuitions about the functional meaning of the structures that he saw under the microscope. Twelve years before receiving the Nobel Prize, when he was invited to give the Croonian Lecture at the Royal Society in London (Ramón y Cajal, 1894), Cajal concluded his talk with "various more or less probable physiological or even psychological interpretations" of the anatomical facts, admittedly, as he recounted in his autobiography, in order to satisfy "the practical and didactic demands" of the English physiologists and medical men who predominated in the audience (Ramón y Cajal, 1991). To all effects, those more or less probable interpretations constituted a general theory of the organization of the nervous system that placed evolutionary, embryological, maturational, and adaptive aspects of neural function in a proper context of behavioral and

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Figure 1. Torsten Wiesel, Roger Sperry, and David Hubel in Stockholm in December 1981 for receiving the Nobel Prize for Physiology or Medicine (From Hubel and Wiesel, 2005).

cognitive significance. With subsequent appropriate extensions and qualifications by Cajal himself and others that theory continues to inspire contemporary neurological thinking to a major degree.

In looking at the Nobel Prizes for Medicine or Physiology, which since 1906 have been bestowed on scientists working on the nervous system, it seems to me that the persisting influence of Cajal's ideas on modern neuroscience is best illustrated by the 1981 prize to Roger Sperry, David Hubel, and Torsten Wiesel (Fig. 1). As the motivation for the prize reads, they received it for apparently unrelated discoveries: one half of the prize went to Sperry "for his discoveries concerning the functional specialization of the cerebral hemispheres," and the other half went jointly to Hubel and Wiesel "for their discoveries concerning information processing in the visual system." It is my opinion that behind those apparently unrelated discoveries there are many factual and theoretical commonalities between the contributions to neuroscience of Sperry and those of Hubel and Wiesel, and that some of Cajal's visionary concepts of how the brain might function have found confirmation in these works. I will present here some examples of such implicit or explicit links.

Sperry and Neuroembryiology

It has been argued by many that Sperry would have deserved a Nobel Prize for his neuroembryological studies as well as or better than for his studies on the split brain (for extensive reviews see Hunt and Cowan, 1990; Meyer, 1998). With his chemoaffinity hypothesis, he single-handedly resurrected Cajal's concept of neurotropism at a time when it was commonly believed that the developing nervous system was a random, diffuse, unstructured, and essentially equipotential transmission network, a blank slate to be molded and shaped into a functionally adaptive communication system by use, experience, practice and learning.

Cajal had argued, on purely hypothetical grounds, that the orderly growth and selective connections of neurons during embryonic life are brought about principally because neuroblasts possess a chemotactic sensitivity to attractive substances secreted by epithelial and mesodermic cells or by other neuroblasts or neurons (Ramón y Cajal, 1909). Sperry's deceivingly simple and extremely ingenious experiments led him to conclude that the functionalistic views of brain development prevailing in the 1940s were totally incorrect, and that Cajal's old ideas on chemical selectivity were surprisingly close to the truth. He offered strong support to the idea that the complicated neuronal nets of the brain do indeed grow, assemble, and organize themselves through the use of intricate, genetically controlled codes that are as yet incompletely understood but can only be chemical in nature. According to Sperry, early in development the billions of nerve cells of a mammalian brain acquire and retain individual chemical identification tags by which they can be recognized and distinguished from one another, such that lasting functional synaptic connections are established only between neurons that are selectively matched by inherent chemical affinities (Sperry, 1951).

Hubel and Wiesel and Connection Selectivity in the Visual System

Sperry's most eloquent anatomical and behavioral results were obtained by examining the retino-tectal connections of fish and amphibia. He showed that the orderly retinotopic projection of the retinae on the optic tecta could be precisely reestablished after section and regrowth of the optic nerves so as to mediate highly organized visuomotor behaviors, even when such behaviors were rendered maladaptive by appropriate experimental manipulations (see Hunt and Cowan, 1990; Meyer, 1998).

Electrophysiological evidence from Maturana et al. (1959) in the late 1950s furnished support to Sperry's chemoaffinity hypothesis and to his claim that after cutting the optic nerve the retinal map in the midbrain was reconstituted by selective regeneration of each retinal fiber to its normal depth and locus in the tectum. The work of Lettvin and Maturana on the coding of patterned visual stimuli by single optic fibers (Maturana et al., 1960) forms a clear conceptual link between the histological and behavioral work of Sperry on retino-tectal connections and Hubel and Wiesel's work on the mammalian visual cortex.

The papers in collaborations by Hubel and Wiesel have been recently reprinted in a collection with extensive a posteriori comments by Hubel (Hubel and Wiesel, 2005). In the following, I will refer the reader to that book for all relevant papers of Hubel and Wiesel. They published their first paper on simple cells with spatially oriented receptive fields in the cat primary visual cortex (Hubel and Wiesel, 2005, pp. 58–82), at about the same time as Lettvin, Maturana et al. described different types of edge detectors in the frog retina (Maturana et al., 1960). The electrophysiological evidence for single neurons specialized in the representation of discrete features of the visual environment obviously suggested a very selective arrangement of excitatory and inhibitory connections conveying visual information to these neurons.

Hubel and Wiesel's diagrams for the neural connections giving rise to simple receptive fields in the cat visual cortex, and those developed after their further discovery of complex and hypercomplex (or end-stopped) visual cortical cells in cats and monkeys (Hubel and Wiesel, 2005, pp.104–192 and 244–272), and called for a refined connection selectivity of the kind envisaged by Sperry. The big question that remained open was whether such patterns of selective connections underlying the specialization of different types of visual neurons are organized primarily by developmental mechanisms or are acquired through functional use.

Hubel and Wiesel's Experiments on Visual Development and Deprivation

When trying to conciliate his conviction of a strict, development-dependent selectivity of neural connections with the self-evident reality of an environment-dependent plasticity of the nervous system, Sperry called attention to the possible contributions of the early visual deprivation experiments to the assessment of the cooperative role of function in the attainment of adaptive neural structures. However, in his attempt to interpret the defective vision of chimpanzees reared in the dark from birth (Riesen, 1947), he acknowledged the extreme difficulty of disentangling the relative influences exerted on stable visual connections by three interrelated factors: inherent maturation, function as a specific organizing agent, and function as a nonformative but necessary condition (Sperry, 1951).

The great merit of Hubel and Wiesel was that they succeeded in the task that Sperry had regarded as nearly impossible. They showed that the complex wiring underlying the receptive field organization of visual cortical neurons is present in immature cats and monkeys before any exercise of visual function, and therefore must be innately determined. However such innately determined functioning of the visual system is disrupted by lack, reduction, or distortion of normal visual experience during critical postnatal periods. Similar limitations or manipulations of visual experience occurring after the critical periods have little or no damaging effects on visual behavior, attesting the essential participation of early visual experience in the maintenance of the selective connections laid down by developmental factors alone. Moreover, Hubel and Wiesel provided definitive evidence that the damaging absence of early visual experience can operate, as expected, because of disuse but also, and even more effectively, because of a competition between deprived and nondeprived portions of the visual system (Hubel and Wiesel, 2005, pp. 369–454 and 480–591).

Hubel and Wiesel's discovery of the respective roles of development and experience in the organization of the visual cortex not only opened a still growing field of investigation but also laid to rest the old philosophical nature-versus-nurture controversy. For enlightened scientists like Cajal and Sperry the idea that the nervous system depends crucially on both had always been a truism, but it was the factual evidence provided by Hubel and Wiesel that at last forced extremely strict nativists and empiricists alike to concede that neither the genes plus development alone nor experience alone can give rise to and maintain functioning neural structures.

Cortical Columns

The histological studies of the cerebral cortex with the Golgi method by Cajal and Lorente de Nò (Ramón y Cajal, 1911; Lorente de Nò, 1949) had indicated that intracortical connections are established chiefly in the vertical direction, from the surface to the white matter and the reverse, whereas horizontal connections appear to be limited in spread and density, suggesting a greater vertical than horizontal functional coupling of cortical neurons. The concept of cortical columns was introduced into neurophysiology by Mountcastle based on his findings of recurrent patterns of vertical chains of neurons with selective response properties in the somatosensory cortex of cats (Mountcastle, 1957).

Hubel and Wiesel's extensive analysis of functional citoarchitecture in visual cortical areas of cats and monkeys subsequently revealed a striking pattern of neuronal columns marked by consistency of receptive field orientation, nested into larger neuronal columns marked by consistency of ocular dominance (Hubel and Wiesel, 2005, pp. 595–704). It is now thought that throughout the cerebral cortex, regardless of regional specialization, essentially similar vertical arrays of neurons form the basic discrete units for intracortical information processing and input-output operations.

Sperry largely anticipated the notion of the vertical anatomo-functional parcellation of the cortex with his typical experimental approach, combining precisely aimed neural lesions with ingenious behavioral testing. He made multiple vertical cuts in the somatosensory and motor cortices of monkeys and in the visual cortex of cats, so as to interrupt most intracortical horizontal connections while leaving most vertical intracortical connections undisturbed. He found that these lesions, when restricted to the depth of the cortical gray matter, failed to disrupt refined motor control in monkeys and difficult visual pattern discriminations in cats. Both kinds of performance were known to require a normal functioning of the respective cortical areas submitted to the multiple intragriseal slicing. It was only with deeper cuts entering the white matter that functional deficits began to emerge (Sperry, 1947; Sperry and Miner, 1955; Sperry, Miner, and Myers, 1955).

Sperry was led to do these experiments primarily for defending a straightforward connectionistic view of the nervous system against implausible but then fashionable electrical field models of cortical functioning. He took pains to rule out any functional importance of the spread of mass electrical potential and field forces across the cortex by further demonstrating maintained normal performance after the insertion of conductors and insulators into the cortical cuts (Sperry and Miner, 1955; Sperry, Miner, and Myers, 1955). Many years later Hubel argued that if a man of the scientific stature of Sperry was forced to do experiments for disproving ideas that even then could not be taken seriously, those had to be disgraceful times for the neurological thinking about the cortex (Hubel, 1982). However from those experiments Sperry drew other conclusions that were quite relevant to the interpretation of the orthodox connectivity of the cortex, such as the greater functional importance of vertical over horizontal cortical connections, and the preferential course of the latter connections through the white compared to the gray matter. The impact of such conclusions on the understanding of cortical functioning was eventually recognized by Hubel in his obituary of Sperry, where he wrote that those experiments had allowed Sperry to foresee the existence of cortical columns well before Mountcastle discovered them (Hubel, 1994).

Corpus Callosum and Vision

Sperry's contribution to the definitive affirmation in the neurosciences of orthodox circuit theory, including functional specialization and connection specificity, reached its best in his studies on the role of the corpus callosum in interhemispheric transfer and communication. His "split-brain" work, which culminated in the analysis of the separate and independent specializations of the right and left hemispheres of the human brain and was recognized with the Nobel Prize (Sperry, 1982), has been amply reviewed in several publications (see e.g. Trevarthen, 1990). Here I will restrict my consideration to an aspect of the functional significance of the corpus callosum that has been investigated from different but complementary viewpoints by both Sperry and Hubel and Wiesel.

Sperry proposed his principle of supplemental complementarity to account for the callosal unification of the representation of sensory and motor maps in the cerebral cortex of the two hemispheres (see Berlucchi and Antonini, 1990). For example, since the cortical representation of the visual field is split down the middle because the optic pathways convey to each hemisphere only the projection of the contralateral half field, it is one of the functions of the corpus callosum to bring together the two projections in visual perception. Hubel and Wiesel recorded from the visual part of the cat corpus callosum and found that visual callosal fibers are mainly concerned with the representation of the central vertical meridian of the visual field in both hemispheres (Hubel and Wiesel, 2005, pp. 231–243). This finding is in agreement with the proposed role of the corpus callosum in interlocking the half maps of the two hemispheres into a continuous map of the entire visual field. The participation of the corpus callosum to the building up of bilateral receptive fields in visual cortical areas of cats and monkeys has been confirmed in different laboratories (Stryker and Antonini, 2001). In a recent comment on his old experiment with Wiesel on the cat corpus callosum, Hubel has argued that the visual fibers of the corpus callosum perform in the representation of the central visual field region in both hemispheres the same function that the connections between neighboring cells carry out in the representation of a peripheral visual region in a single hemisphere. While in the latter representation all cells would be in the same hemisphere, for the representation of the vertical meridian some cells would be in one hemisphere and some in the opposite hemisphere, so that connections between them would have to cross from one hemisphere to the other. Delays caused by the greater distance to be traveled could be made up for by the greater conduction velocity of myelinic callosal axons (Hubel and Wiesel, 2005, p. 232). This interpretation is fully in line with Sperry's general view of topographic cortical maps as reflections of the developmental processes of corticogenesis rather than the bases for an isomorphic representation of the external world on the brain. In his words, "if topographic projection could be eliminated by random displacement of neurons, at the same time maintaining all the original synaptic connections and the conduction time intervals … little or no disturbance would be expected from the standpoint of orthodox circuit theory" (Sperry, 1952). In nature, the displacement in different hemispheres of neurons concerned with the same part of the visual field can be compensated by linking such neurons through fast conducting callosal connections.

The Mind-Brain Problem

Believing that no general theory of the nervous system can be complete without attacking the mind-brain problem, Cajal was not afraid to offer some cautious speculations about it (Ramón y Cajal, 1911). Cajal's belief was constantly shared by Sperry who early in his career proposed a very ingenious and stimulating view of conscious perception as the ensemble of the potential motor reactions to the perceived object. He went further to argue that conscious perception has evolved just to provide complex organisms with an operational knowledge of their environment, favoring an adaptive control of motor coordination and overt behavior (Sperry, 1952). Later on, his split-brain experiments challenged the dogma of a unitary consciousness with the demonstration of parallel conscious processes in the two disconnected hemispheres of the human brain (Sperry, 1982). He devoted the last part of his life to spelling out a conception of consciousness as an emergent or supervenient result of neural activity. In his opinion, such conception avoids the traps of dualism while maintaining the possibility of a two-way interaction between the mental and the physical (Sperry, 1998).

Sperry regarded his speculations at the border between neuroscience and metaphysics as his best work, far superior to his neuroembryiological and split-brain discoveries. Posterity does not seem to agree with his assessment. Contrary to Sperry, and perhaps more wisely, Hubel and Wiesel have always stayed away from speculating on the mind-brain problem. That the brain is the sole generator of consciousness is an obvious truth, but the problem of how the brain generates consciousness appears intractable today and may turn out to be intractable for ever.

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