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A Trophic Theory of Neural Connections

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Contents

ONE

Introduction

THIS book explores the proposition that the changing size and form of the bodies of mammals and other vertebrates elicit corresponding changes in the connectivity of the nervous system. For reasons that will become apparent, I refer to this general idea as the trophic theory of neural connections. Because it is conventional to think of the nervous system as an organ that monitors and motivates the body rather than as an organ controlled by the body, the perspective of the trophic theory may appear unusual. Nevertheless, the body's influence on the nervous system is as important for the organism as is neural dominion over the body.

As theories about the nervous system go, the trophic theory of neural connections is decidedly biological, providing no insight into consciousness, intelligence, free will, or other psychological phenomena whose explanation is popularly considered to be the proper objective of a neurological theory. Moreover, there is as yet little evidence that the concepts expressed in the theory apply to animals other than vertebrates, which are, after all, a tiny subset of the animal kingdom. These limitations notwithstanding, the trophic theory is of fundamental importance to topics as diverse as neural development, the response of the nervous system to the inevitable injuries that arise in the course of life, the way in which information is stored in the nervous system, and the manner in which the nervous system adjusts to the somatic changes that occur during the course of evolution.

Definitions

The meaning of most specialized terms used in this book can be found in the glossary. Several key words and phrases, however, need to be defined in detail at the outset. Preeminent among these are the term *trophic* and the general concept of *trophic interaction*.

The word trophic is taken from the Greek *trophē*, which means, roughly, nourishment. Trophic interactions have been operationally defined over the years as long-term dependencies between neurons and the cells they innervate (non-neural cells or other neurons, as the case may be). By long-term, neurobiologists generally mean effects that can be observed over weeks or months; by dependency, they refer to the deleterious effects observed when one cell or the other in the partnership is removed or incapacitated. The indexes of trophic dependence range from neuronal death to a myriad of electrophysiological and metabolic effects taken to be signs of cellular ill health. The agent of these effects is generally envisioned as intercellular signals. In most accounts, these signals are a molecular message that passes between the two cells involved (in addition to whatever neurotransmitters may operate between the cells in question). Historically, the phrase trophic interaction has been applied both to long-term dependencies of nerve cells on their targets and to dependencies of targets on the nerve cells that innervate them.

The sustenance provided to neurons in the course of trophic interactions is not the sort derived from the ordinary metabolites that neurons use to generate the energy and structural elements essential for any cellular activity. Although the agents of trophic interaction may be equally important (neurons deprived of trophic support may die), trophic effects are specific: the requirement of one kind of nerve cell is qualitatively different from that of another. Specific cellular interactions are by no means unique to trophic agents; neurotransmitters and hormones are other classes of molecular signals that influence specific sets of cells in ways that are now well understood.

Some other terms that require definition concern the structure of the nervous system. These include *axon, dendrite, neural target,* and *neural connections*. Axons are usually defined as neuronal processes that traverse a substantial distance and carry a regenerative electrical signal (the action potential) to a distant target. Dendrites are neuronal branches, usually short and profuse compared to axons, that passively receive innervation from other neurons. These conventional definitions are ultimately inadequate because they do not fully describe the complex reality of neuronal processes and their functions. Thus, some neuronal processes which by one criterion appear to be axons also have functional characteristics of dendrites. In other instances, neuronal processes that have the typical appearance of dendrites support action potentials. Indeed, it would be difficult to classify the processes of some neurons. In short, axons and dendrites are usually distinct in

both their anatomy and their function; in some cases, however, the differences between them are blurred.

Some nerve cell axons innervate muscles, glands, sensory receptors, and other organs directly. Other neurons innervate the nerve cells that innervate these somatic structures. Still other neurons—the majority—establish their connections entirely within the central nervous system. Thus the *targets* of innervation can be cells outside the nervous system or other nerve cells within it. For the most part, the evidence which supports the trophic theory of neural connections has been drawn from observations of the first-order nerve cells that innervate the body directly and the second-order neurons that innervate or are innervated by the primary motor and sensory neurons. However, every neuron in the vertebrate nervous system is ultimately linked to the body by a chain of neural connections. It is therefore axiomatic that the concepts expressed in the trophic theory apply in some measure to all nerve cells and their connections.

The idea that the body influences the nervous system by affecting the concatenation of neurons linked to somatic structures is discussed in terms of *neural connections*. This phrase refers to the number and disposition of axonal and dendritic branches as well as to the synaptic relationships they establish. The emphasis on the regulation of neural connections admittedly minimizes consideration of other ways in which the body influences the nervous system (for example, by inductive influences on neural differentiation) and other important aspects of synaptic relations (such as the formation of synapses according to intercellular recognition). The short shrift given these issues is intended not to diminish their importance or to obscure the true complexity of the neurosomatic relationship, but simply to maintain a sharp focus on the theme of the changing anatomy of neural connectivity.

In some uses, the phrase *neural connections* refers primarily to synapses, the highly specialized junctions that occur at the points where one nerve cell contacts another. There are good reasons, however, for defining neural connections to include the axonal and dendritic branches that link nerve cells and their targets. One reason is that a good deal of evidence supports the action of trophic signals on neuronal branches. Whether such signals have a *direct* effect on synaptic specializations is for the most part not known. Another reason is that connections between nerve cells and targets do not always involve anatomically discrete synapses. An example is the innervation of viscera by autonomic neurons, in which case the release of transmitter by

the presynaptic cells occurs at some distance from the postsynaptic smooth muscle cells (which in turn show no specialization that is confined to the vicinity of the nerve terminal). The innervation of body surfaces by free nerve endings (in the skin and other surface epithelia, for instance) deviates still further from the norm in that no synapses of any type are involved in the association of neuron and target. Trophic action is therefore discussed in terms of effects on axonal and dendritic branches rather than on synapses *per se*.

In the light of these definitions, it is possible to formulate a working definition of the trophic theory itself. The theory holds that patterns of nerve cell connections—which is to say, the number and disposition of axonal and dendritic arbors and the connections they make—are subject to ongoing regulation by interactions with the cells that they contact.

Historical Background

Until ten or fifteen years ago, it was widely supposed that the nervous system is hard-wired, meaning that neural connections form according to a precise plan which remains fixed thereafter, in the style of electrical circuits. There were, and to some extent still are, good reasons for this consensus. The early differentiation of neurons, the paucity of direct evidence for anatomical change in the adult nervous system, and the inability of the mammalian nervous system to compensate effectively for neural injury all argue for a relatively static organization of neural connections. A corollary of this view is that the principal purpose of neural development—with respect to the connections between nerve cells—is to establish such circuits with great accuracy.

The first evidence that nerve cells are endowed with qualities which allow them to generate precise patterns of connectivity was provided by the English physiologist J. N. Langley. In his pioneering work between 1875 and 1925, Langley defined the autonomic nervous system of mammals and many of its properties. The autonomic system is that part of the nervous system primarily concerned with the functions of smooth muscles and glands; as a consequence, it is also referred to as the visceral or involuntary division of the nervous system. The part of this system investigated most thoroughly by Langley was the superior cervical ganglion (Figure 1.1). Neurons in this most rostral of the segmental sympathetic ganglia innervate the gamut of visceral end-organs in the head and neck (the blood vessels, iris, salivary glands, and piloerector muscles, as well as some targets within the brain). Langley

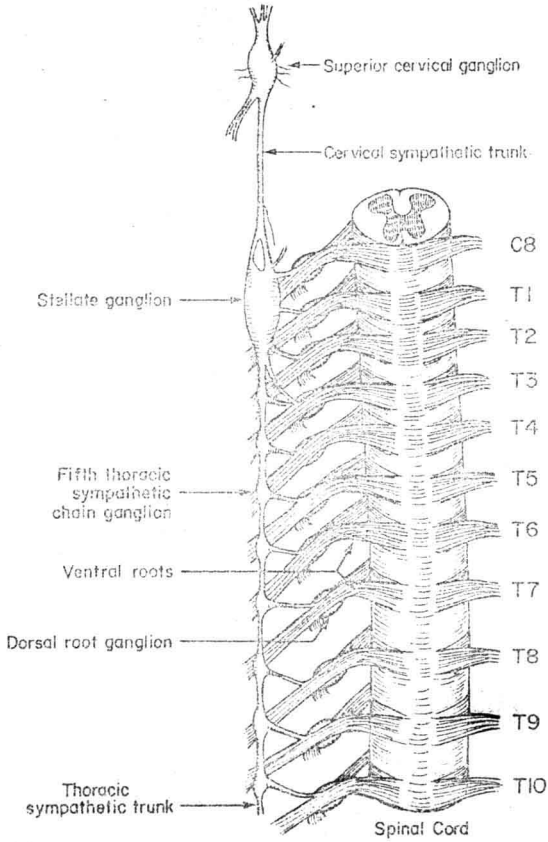

Figure 1.1. Overall arrangement of the cervical and thoracic portion of the sympathetic nervous system in mammals (ignoring minor differences among species). The sympathetic ganglia, each comprising thousands of neurons, receive innervation from preganglionic neurons that reside in the spinal cord; the axons from these spinal cord neurons reach the ganglia by way of the ventral roots. The axons that arise in turn from ganglion cells innervate smooth muscles, glands, and other targets at corresponding segmental levels (indicated on right; C = cervical, T = thoracic). The peripheral part of the sympathetic system is attractive because of both its accessibility and the simplicity of its anatomical organization compared to pathways wholly within the spinal cord and brain.

found that the preganglionic axons arising from different spinal cord segments innervate superior cervical ganglion cells in mammals in a highly stereotyped way (Figure 1.2; Langley, 1892, 1921). When he stimulated the most rostral thoracic ventral root (T1), thereby stimulating all of the preganglionic axons emerging from that spinal segment, Langley observed a particular constellation of end-organ effects: the pupil dilated, but other sympathetic responses, such as constriction of blood vessels in the ear or piloerection, were weak or absent (Langley, 1892; see also Langley, 1895, 1897). Conversely, stimulation of a more caudal thoracic segment, such as T4, revealed a different set of end-organ effects: the blood vessels of the ear became constricted and the hair in part of the territory of the superior cervical ganglion stood on end, but pupillary dilation was weak or absent. These findings led to the supposition of a special affinity between preganglionic axons arising from different spinal cord segments and different subsets or classes of superior cervical ganglion cells.

In Langley's day, an investigation of the formation of these connections in embryonic or neonatal animals was not technically possible (although it is now). Therefore, studies of reinnervation were a reasonable alternative in seeking to understand the general rules of neuronal connectivity. A few weeks after cutting the preganglionic nerve to the superior cervical ganglion in adult animals (the cervical sympathetic trunk; Figure 1.1), Langley found that the end-organ responses were restored by nerve regeneration and reinnervation of the ganglion cells (Langley, 1895, 1897). Moreover, the end-organ responses after nerve regeneration were organized as before. Thus, stimulation of T1 once again elicited a particular constellation of peripheral effects that did not overlap with those generated by stimulation of T4 (Figure 1.2). In summarizing these experiments, Langley concluded: "The only feasible explanation appears to me to be that the [preganglionic] sympathetic fibres grow out along the peripheral piece of nerve . . . spreading amongst the cells of [the] ganglion, and that there is some special chemical relation between each class of nerve fibre and each class of nerve cell, which induces each fibre to grow towards a cell of its own class and there to form its terminal branches" (1895, p. 284).

This straightforward expression of what is now called the chemoaffinity hypothesis was eclipsed for several decades by another conception of how neural connections develop. Why Langley's results and lucid interpretation were ignored for the next fifty years or more is not clear. In any event, a quite different view of neural connectivity was

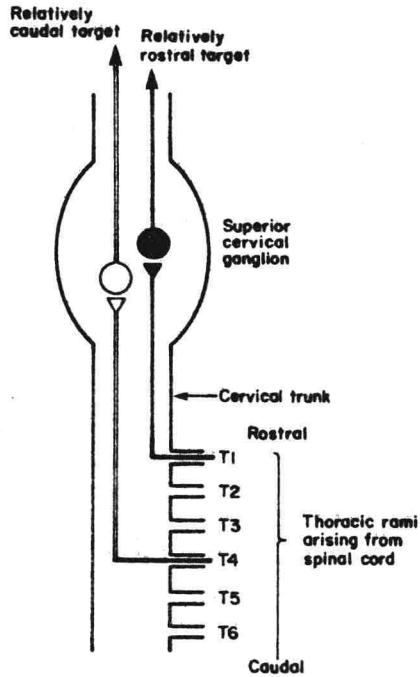

Figure 1.2. Evidence that neural connections form according to specific affinities between different classes of pre- and postsynaptic cells. In the mammalian superior cervical ganglion, preganglionic neurons located in particular spinal cord segments (T1, for example) innervate ganglion cells that project to particular peripheral targets (the eye, for example). The re-establishment of these preferential relationships in adult animals after interruption of the cervical trunk suggests that selective affinities are a major determinant of neural connectivity.

successfully promoted by P. A. Weiss in the context of muscle innervation in vertebrate limbs. In this scheme, put forward at about the time of Langley's death in 1925, specific matching between nerve cells and their targets had an operational rather than an anatomical-chemical basis. The experiments that led to this conclusion involved limb transplantation in amphibians. When an extra limb was placed near the normal appendage in a host animal, the two limbs moved in exact synchrony and with obvious coordination (Weiss, 1924, 1928; see also Weiss, 1936, 1968). Because Weiss could not imagine that the same axons correctly innervated the homologous muscle in both the normal

and the supernumerary limb, as later proved to be the case (Stephenson, 1979), he interpreted the result in terms of what would now be called systems matching. Motor axons were thought to ramify more or less indiscriminately in the limb; the manifestly appropriate responses of muscles were taken to represent a matching process based on patterns of neural impulses (Weiss, 1924, 1928). Thus a given muscle was thought to contract when it "picked up" a particular pattern of neural activity that was present in the nerves to the limb. Because this conception embodied the idea that neural targets are somehow tuned to specific patterns of nerve activity, in much the same way that a taut string can be made to vibrate by a tone of a specific frequency, it was referred to as the resonance hypothesis.

When this proposal was disproven by the advent of electrical recording in biology and the demonstration that each motor nerve branch carries a unique pattern of activity to specific muscles (Wiersma, 1931), the original notion of resonance was modified. Although Weiss continued to maintain that specific activation of particular muscles by spinal motor neurons arises from a developmental strategy that involves a largely random outgrowth of motor axons to the limb, he subsequently suggested that appropriate function reflects a reorganization of haphazard projections through information provided by the neural targets (Weiss, 1936, 1941, 1942, 1965). Because the target muscles in the vertebrate limb were thought to dictate the central connectivity of motor neurons that contacted them at random, this revised hypothesis was referred to as myotypic specification. Thus, by the 1930s the groundwork had been laid for a dialectic between the view that the nervous system is wired according to preexisting cellular identities and the alternative belief that neural connections are shaped interactively according to the functional properties of the pre- and postsynaptic elements.

The idea of highly malleable connections capable of being reorganized according to functional criteria was challenged in the late 1930s by R. W. Sperry, a graduate student of Weiss's at the University of Chicago. Sperry revived Langley's original theory in a new context, the retinotectal system, in which axons arising from nerve cells in the retina make an orderly topographic map in the tectal region of the midbrain. He took advantage of the fact that the severed optic nerve regenerates over a period of several weeks in some fish and amphibians, restoring normal vision; indeed, such animals see again even after an eye has been removed and reimplanted, or transplanted from one individual to another (Stone and Zaur, 1940; Stone, 1941; Stone and

Farthing, 1942). To investigate the validity of Weiss's notion of functional plasticity, Sperry cut the optic nerve in newts (and later frogs) and rotated the eye 180° (Figure 1.3; Sperry, 1943a,b; see also Stone, 1944). After the nerve had regenerated, animals with rotated eyes behaved as if their visual world had been inverted and shifted left for right. This outcome—like the outcome of reinnervation in the superior cervical ganglion—suggested that nerve cell axons grew back to approximately the same target cells they contacted originally, in spite of the fact that the regenerated connections in the frog were maladaptive (since they produced nonsensical behavior). This interpretation was confirmed by showing that regenerated fibers, visualized by histochemical staining, appeared to ignore large areas of denervated neural tissue to contact the part of the optic tectum in which they had normally terminated (Attardi and Sperry, 1963; see also Fujisawa, 1981; Fujisawa et al., 1981). Sperry summarized 25 years of work on this issue in the following way: "It seemed a necessary conclusion from these results that the cells and fibers of the brain . . . must carry some kind of individual identification tags, presumably cytochemical in na-

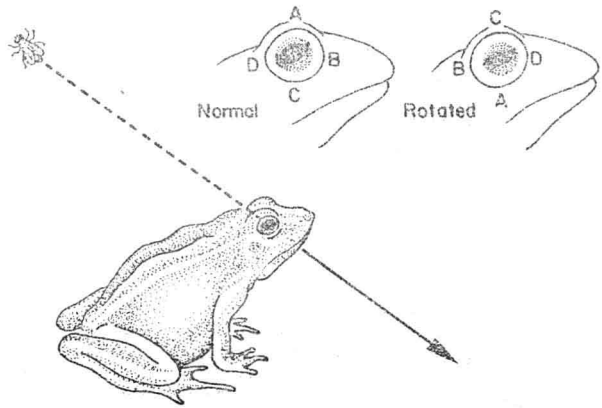

Figure 1.3. Experiment that revived the chemoaffinity theory. The right optic nerve of the frog was cut some weeks earlier, and the eye was rotated through 180 degrees and fixed in place (enlarged above). Although the frog could see perfectly well through the experimental eye, its attack on prey was consistently misdirected. This observation indicates that the regenerating axons of the optic nerve establish connections with their *original* target cells in the brain and that these connections are not reorganized in the face of the functional requirements imposed by new circumstances. (After Sperry, 1956)

ture, by which they are distinguished one from another almost, in many regions, to the level of the single neuron; and further, that the growing fibers are extremely particular when it comes to establishing synaptic connections, each axon linking only with certain neurons to which it becomes selectively attached by specific chemical affinities" (1963, pp. 703–704).

The renaissance of the chemoaffinity theory had a profound effect on the subsequent generation of neurobiologists, leading to a wealth of further experiments after Sperry had retired from the field in the 1960s to concentrate on studies of interhemispheric communication. The hegemony of the chemoaffinity theory, which persists to this day, is justified by the fact that in virtually every system in which this issue has been explored, evidence of selective synaptic connections between pre- and postsynaptic cells has been observed. Nevertheless, important qualifications of the chemoaffinity theory have been required by more recent evidence.

One problem with the theory is the implication that each neuron is unique and can therefore receive only a complementary set of synaptic connections. Although it must in some sense be true that every neuron *is* unique, it is now clear that the distinctions between vertebrate neurons of a given class (for example, tectal neurons) are not terribly rigid. That chemoaffinity is less restrictive than originally imagined was shown by further experiments in the retinotectal system. Thus, if either the retina or the tectum is quantitatively mismatched to its counterpart by surgically removing a portion of the target or a part of the innervating population, adjustments of neural connections are observed over time which belie any rigid preordination of connectivity (Figure 1.4, Gaze and Sharma, 1970; Horder, 1971; Yoon, 1971, 1972, 1976; Schmidt et al., 1978). In general, the retinal projections adjust to occupy the space made available by the particular surgery. This result indicates that retinal neurons can contact target cells other than the ones they innervated originally. The same conclusion has been drawn from experiments in which eyes with duplicate half-retinas have been created at an early stage of development (Gaze et al., 1963, 1965) and in which the pattern of retinotectal connections has been studied during the course of normal development (Chung et al., 1974; Gaze et al., 1974, 1979; Longley, 1978; Meyer, 1978; Easter and Stuermer, 1984; Reh and Constantine-Paton, 1984; Grant and Keating, 1986; O'Rourke and Fraser, 1986). In the case of surgically constructed compound eyes, the axons from both retinal halves project to the entire tectum. Since the experimental eyes comprise duplicate half-retinas, this result again im-

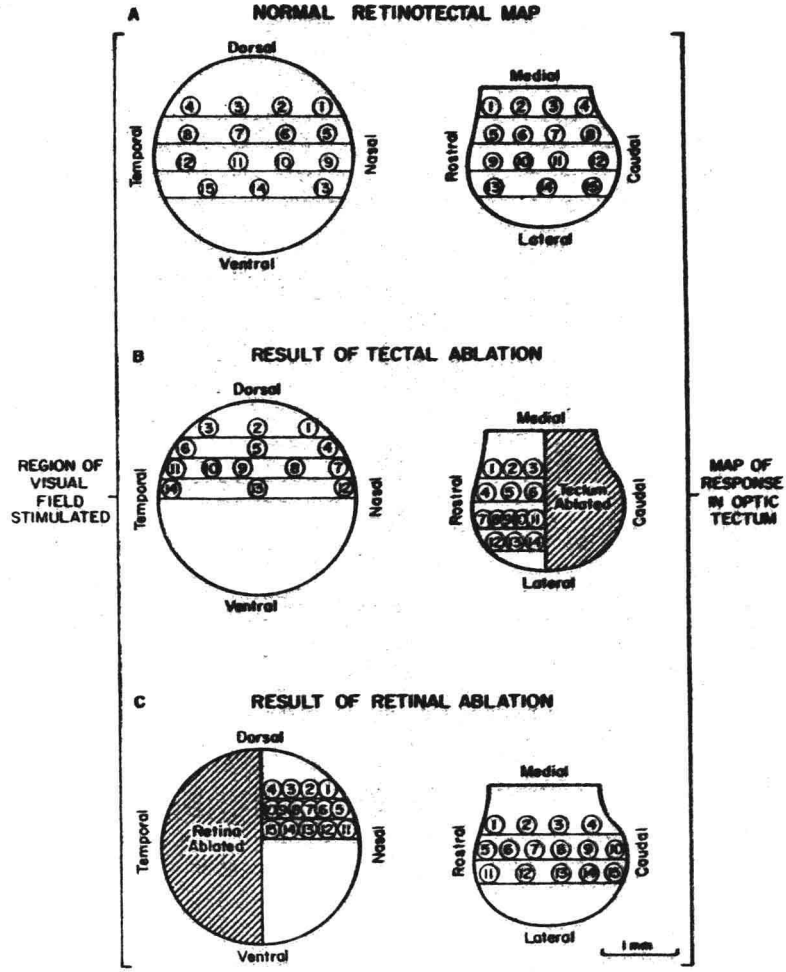

Figure 1.4. Experiments that create size disparities between the retina and its target in the midbrain, the optic tectum, used to test the rigidity of matching during synaptogenesis. (*A*) The normal retinotectal map in a goldfish. The numbers indicate the region of the tectum activated by stimulation of the corresponding point in the visual field. (*B*) A complete, but compressed, retinotectal map several months after the optic nerve was cut and about half of the optic tectum removed. Over time, axons arising from the retina reorder their connections so that the remaining tectal territory is divided among them, in spite of the fact that this entails many abnormal connections. (C) The result of a complementary experiment in which half of the retina was removed at the time the optic nerve was cut. The remaining part of the retina maps over the full tectum. Such compensatory changes suggest that retinotectal connections form according to preferences rather than rigid restrictions. (After Yoon, 1971; Schmidt et al., 1978)

plies that many neurons have projected to target cells that they would not ordinarily contact. During normal development, axon terminals also show evidence of onging rearrangement which apparently compensates for the differential growth of the retina and the tectum. Such "shifting connections," as they have been called, indicate that pre- and postsynaptic elements associate according to the changing circumstances of development, in addition to obeying the dictates of their inherent identities.

Support for the assertion that connections are less rigidly specified than originally thought has also come from studies of the mammalian autonomic nervous system, in which Langley first adduced evidence for chemoaffinity at the end of the last century. Langley, like Sperry, emphasized the restrictive aspect of his observations on autonomic connectivity. However, intracellular recordings from individual ganglion cells have shown that each neuron in the superior cervical and thoracic chain ganglia is actually innervated by a number of axons arising from several different spinal cord segments (Figure 1.5; Njå and Purves, 1977a). As expected from Langley's behavioral observations, each ganglion cell is innervated most strongly by axons arising from a particular spinal cord segment within this set (Njå and Purves, 1977a; Lichtman et al., 1980; see also Yip, 1986). However, axons from the spinal segments contiguous to the dominant one also innervate each cell, the average strength of innervation from adjacent segments falling off as a function of distance from the dominant one. The same arrangement is observed in adult animals after regeneration of the cervical sympathetic trunk (Njå and Purves, 1977b, 1978b; Purves et al., 1981).

On the whole, these findings confirm Langley's inference of selective affinities between pre- and postsynaptic neurons; indeed, they reveal the cellular basis for the end-organ responses that he observed upon stimulation of various spinal nerves in the 1890s (Figure 1.2). However, the results of recording from individual neurons indicate that the affinities between pre- and postsynaptic neurons, as in the retinotectal system, are not terribly restrictive; connections from neurons of a particular spinal level are preferred, but terminals arising from neurons at other levels are not excluded. This interpretation has been further strengthened by quantitative mismatch experiments, similar in principle to those carried out in the retinotectal system. Thus, if a portion of the innervation to the superior cervical ganglion is surgically removed (analogous to experiments in the retinotectal system in which part of the retina is removed), then recordings from individual ganglion cells indicate that new connections are established