Review

Reflections on the specificity of synaptic connections

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The principal focus of this treatise is the specificity of synaptic connectivity in the mammalian central nervous system. The occurrence of stereotypical patterns of connection at the macro level (e.g., the general consistency with which axonal pathways impinge on and originate within specific cortical areas and layers) implies that the cerebral cortex is a highly ordered structure. Order is seen also at the more micro level of synaptic connectivity, for instance, in the contrasting synaptic patterns of spiny vs. non-spiny neurons. Quantitative electron microscopic studies of synapses between identified neurons and correlative anatomical/electrophysiological investigations indicate that the high degree of order characterizing many aspects of cortical organization is mirrored by an equally ordered arrangement of synaptic connections between specific types of neurons. The recognition of recurring synaptic patterns has generated increased support for the notion of synaptic specificity as opposed to randomness, and we have begun now to understand the role of specificity in cortical function. At the core of cortical processing lie myriad possibilities for computation provided by the wealth of synaptic connections involving each neuron. Specificity, by limiting possibilities for connection, imposes an order on synaptic interactions even as processes of dynamic selection or synaptic remodeling ensure the constant formation and dissolution of cortical circuits. Collectively, these operations make maximal use of the richness of cortical synaptic connections to produce a highly flexible system, irrespective of the degree of hard-wiring, mutability, randomness or specificity that obtains for cortical wiring at any particular time. A brief, historical account of developments leading to our current understanding of cortical synaptic organization will precede the presentation of evidence for synaptic specificity.

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1. Introductory paean to Santiago Ramón y Cajal

This treatise is written within the framework of a volume dedicated to the memory of Santiago Ramón y Cajal. The principal focus is the specificity of synaptic connectivity in the mammalian central nervous system, primarily within the cerebral cortex. Most of the data presented were obtained using quantitative electron microscopy or multiple neuron recording, approaches unavailable in Cajal’s day. Despite the technical limitations of the methods available to Cajal, and even more so, in view of them, it is incumbent on every investigator of the brain to recognize the great debt we all owe to his magnificent investigator. I begin, therefore, with a brief description of how Cajal’s work, and his conclusions on the specificity of synaptic connections, provide a firm basis for our current concept of synaptic specificity.

Cajal’s tenacious, and ultimately, successful support of the Neuron Theory rested largely on his observations of intimate spatial relationships between specific axonal fibers and the dendrites or cell bodies of particular morphological types of neurons. In fact, in his final publication (Neuron Theory or Reticular Theory? Cajal, 1954), Cajal begins his discourse on the evidentiary basis of the Neuron Theory with a listing of specific connectional relationships. Later on, in the same treatise, Cajal refers to an earlier paper in which he states explicitly that the hypothesis of impulse transmission by contiguous fibers was “favored” by the existence of specific connectional relationships (Cajal, 1888a).

Cajal observed in several avian and mammalian species, that the axons of cerebellar stellate cells contribute to pericellular nests or baskets arrayed around the somata of Purkinje cells (Cajal, 1888a). Shortly thereafter, he reported that climbing fibers wind like vines along Purkinje cell dendrites (Cajal, 1888b). Throughout his long career, these and similar examples of specific interneuronal associations in a wide range of areas in various species formed an inseparable component of Cajal’s and others’ thoughts on the validity of the Neuron Theory (Cajal, 1954; see Shepherd, 1991 for an in depth treatise on the foundations of the neuron doctrine).

By careful observation, Cajal was able to observe the separation between what we now know as pre- and postsynaptic elements: as stated on p. 12 in Cajal (1954) “there always exists between both synaptic surfaces an intervening frontier”, but in his time, it was not possible to visualize fine structural details on a regular basis and so, in effect, he lacked the means to assess the quantitative aspects of the specific synaptic relationships that he discovered. However, it is clear from a consideration of Cajal’s work produced over a 50-year period that he succeeded in providing the necessary substrate upon which have crystallized our current views on the specificity of synaptic connections.

2. Picking up the torch

If anyone can be considered the immediate inheritor of Cajal’s scientific, theoretical and technical approaches, it is Lorente de Nó (1922, 1938), whose observations of Golgi impregnated material confirmed and extended Cajal’s findings with respect to connectional specificity. Lorente de Nó’s maps of cortical circuits provide a graphic depiction of his recognition that the nervous system contains stereotypical patterns of interneuronal connections. Much as did Cajal, Lorente de Nó was able by careful observation of anatomy to depict accurately, if only in a qualitative way, aspects of brain circuitry that would be established with certainty only 50 years later consequent to the application of electron microscopy to the study of synaptic organization.

3. The visualization of synapses by electron microscopy

Within a few years of the first observations of synapses in thin sections (DeRobertis and Bennett, 1954; Palay, 1956; Robertson, 1953), efforts were begun to unravel the circuitry of the cerebral cortex (e.g., Cipolloni and Peters, 1983; Garey and Powell, 1971; Jones and Powell, 1970; Peters and Feldman, 1977; Peters et al., 1976; Sloper and Powell, 1979). Initial findings indicated that any neuronal type having a dendrite within a particular layer would receive input from pathways terminating within that layer, and additionally, that a high degree of interconnectivity obtains between different morphological types of cortical neurons (Tables 3.2 and 3.1, respectively, in White, 1989b), observations consistent with contemporary statistical analyses of cortical connectivity (Braitenberg, 1978). The plethora of cortical synaptic connections and the inability for the most part to identify consistently in a single preparation the cell types of pre- and postsynaptic elements, rendered cortical synaptic connectivity nearly indecipherable and helped promote the impression that cortical wiring was unorganized or “random” (e.g., Braitenberg, 1990; Peters, 1979). This impression was reflected in anatomical constructs of cortical organization prevalent at the time and for some years afterward (e.g., Szentagothai, 1969, 1978a), and was a prominent feature in theories of cortical function ( Eccles, 1984) based on these constructs. The idea was that any type of neuron may synapse with any other type with no particular order, a line of thought that excluded from consideration any meaningful differences in the relative numbers of various types of synaptic connections; in effect, a view that left little room for quantitative specificity in synaptic circuitry.
4. Early theories

Cognizant of the large gaps in knowledge of cortical connectivity, but undeterred by them, Szentagothai addressed head-on the issue of “specificity” vs. randomness in cortical connectivity. He concluded that “a high degree of specific wiring prevails in most distant connections of the cerebral cortex (Szentagothai, 1978b).” Szentagothai’s reference was primarily to the projection of extrinsic axonal pathways to specific cortical areas and layers. He did not discern a comparable degree of specificity for the local axonal ramifications of pyramidal and “Golgi type II” neurons, and described the organization at this level as “quasirandom.” By extending and misinterpreting these comments one could find support for the thesis that synaptic connectivity, at least of intrinsic pathways, is random, but Szentagothai did not state this, concluding only that a certain amount of “randomization” of cortical connectivity is necessary to support the plasticity of connectivity observed during development and after (Szentagothai, 1978a). In more recent times, the concept of randomness of cortical connectivity has played a significant role in neural network theory, primarily because randomness has been viewed as a “simplest assumption” (see e.g., Amit, 1989); the necessity for such speculation related in part to the large gaps in our knowledge of cortical connectivity.

5. Synapse quantification applied to brain circuitry: methods and approaches

The development of methods and approaches for labeling single neurons or neuronal populations (e.g., Fairén et al., 1977; Fairén, 2005; Keller et al., 1985; Leranth and Pickel, 1989; Papadopoulos and Dori, 1993; Peters et al., 1977; Van den Pol, 1988; White et al., 1980) made possible the study of synapses involving identified cells (e.g., DeFelipe and Fairén, 1993; Del Río and DeFelipe, 1997; Fairén et al., 1981; White, 1978; White et al., 1993; White and Hersch, 1981; White and Hersch, 1982). Combined with methods to reconstruct neurons from serial thin sections, these advances in cell labeling spurred efforts to determine the distribution of synapses over relatively large surfaces of identified neurons (Fairén and Valverde, 1980; Fariñas and DeFelipe, 1991a; White et al., 1994; White and Rock, 1980, 1981) and underpinned the blossoming of quantitative studies of cortical synaptic connectivity during the last two to three decades of the 20th century (e.g., Beaulieu et al., 1994; Czeiger and White, 1997; DeFelipe and Fairén, 1988; Elhanany and White, 1990; Fariñas and DeFelipe, 1991b; Hersch and White, 1981; Hersch and White, 1982; Keller and White, 1987; White, 1989b; White and Czeiger, 1991; White and Keller, 1987). An important result of these efforts was the recognition of recurring synaptic patterns between specific neuronal types and the consequent diminution of the notion of randomness in cortical synaptic connectivity (see e.g., White and Keller, 1989). Quantitative electron microscopy has provided irrefutable evidence of synaptic specificity in the cerebral cortex, but clearly, the basis for these findings must be attributed to earlier light microscopic studies. In fact, there is precious little regarding the qualitative aspects of synaptic connectivity in the cerebral cortex that escaped the observations of the Golgi masters such as Cajal and Lorente de Nó despite their inability to visualize synaptic details with the tools and approaches at their disposal.

6. Synapse quantification applied to brain circuitry: support for the concept of synaptic specificity

Quantitative analyses of data obtained by electron microscopy (EM) of serial thin sections through tissue containing labeled pre- and postsynaptic elements have proven to be a crucial factor in shaping our current concept of synaptic specificity. A few details from several studies combining quantitative EM and cell labeling with the making of 3D reconstructions are offered here as an example of the kinds of data provided by these approaches. In one study, the distribution of thalamocortical synapses was determined over essentially the entire cell body and dendritic tree of a layer IV spiny stellate cell (White and Rock, 1979, 1980). An intriguing finding was that the majority of spines receiving thalamocortical input were attached to their parent dendritic shafts at regular intervals of about 5 μm or multiples of this distance. In contrast, intervals between thalamocortical synapses were generally less than 2 μm for dendrites of a second neuron, a non-spiny bitufted cell (White and Rock, 1981). The observation that thalamocortical synapses may be spaced regularly along dendrites is consistent with the view that cortical circuitry is highly ordered. Additional support for this thesis has been inferred also from comparisons of the spatial distributions of other synaptic types observed in reconstructions of dendrites. For example, different types of synapses were distributed similarly along each of the different dendrites of a single non-spiny neuron. This was true also for the distribution of synapses along the dendrites of the spiny stellate cell; however, the synaptic arrangements observed for each cell type differed markedly from each other (cf., Figs. 3.6 and 3.7 in White, 1989b).

The distribution of thalamocortical synapses onto neurons identified by their morphology and/or by the targets of their distant axonal projections has been studied extensively in layer IV of the large barrel region of mouse primary somatosensory cortex. The results of this work demonstrate that the proportions and distribution of thalamocortical synapses are characteristically different for different neuronal types (e.g., Keller, 1995; White, 1986; White, 1989b; White and Hersch, 1981; White and Rock, 1979, 1981; and see Fig. 6, Keller, 1995, and pp. 73–78, White, 1989c). For example, corticostriatal, corticohypothalamic and corticocortical projection cells in mouse barrel cortex, are all infragranular (deep) pyramidal cells, but the proportions of their asymmetrical synapses that each group receives in layer IV from thalamic afferents fall within markedly different ranges having little or no overlap (White and Hersch, 1982, and see p. 78, White, 1989b). The various thalamocortical synaptic patterns observed were shown to be unrelated to any corresponding difference in the concentration of thalamocortical synapses in the surrounding neuropil which was determined to be similar in all instances. Specific synaptic patterns involving callosal afferents and identified
postsynaptic neurons have been observed also in mouse motor cortex (Porter and White, 1986).

These indications of specificity in synaptic circuitry were formulated into a set of general rules that emphasize the quantitative aspects of cortical synaptic organization (p. 82, White, 1989b). Functional studies have elucidated additional rules that reflect the specificity of cortical connectivity (Reid and Alonso, 1995). Later studies of the synaptic output patterns of individual, labeled thalamicocortical axons confirmed that specific synaptic output patterns are laid down early in development and are maintained into adulthood (Lev et al., 2002; White et al., 2004).

Recent, preliminary results indicate that parvalbumin reactive cells in deep layer IV of mouse barrels consistently make 20% of their asymmetrical synapses with thalamic afferents (personal observation). These cells thus occur at the highest end of the wide range of values (1 to 21%) observed for the percentage of asymmetrical synapses received by non-synaptic stellate cells from thalamic afferents (p. 78, White, 1989b). This finding, a clear example of quantitative specificity of thalamocortical synapses, suggests that the parvalbumin reactive subgroup of non-synaptic stellate cells are equivalent to the fast spiking (FS) cells described by Sun et al. (2006) that, strongly excited by thalamic afferents, go on to provide powerful feedforward inhibition of spiny stellate cells.

This discussion on synaptic specificity focuses on chemical synapses, but it is becoming increasingly clear that electrical synapses or gap junctions also provide specific links between neurons. Parvalbumin cells in several primary sensory areas of mouse and rat cerebral cortex are linked by dendrodendritic gap junctions as well as by chemical synapses (e.g., Fukuda and Kosaka, 2003; Galarreta and Hestrin, 2002). In a review of electrical synapses in the mammalian brain, Connors and Long (2004) note that inhibitory neurons of the same type communicate with each other through electrical synapses, in effect, forming “nearly independent”, electrotonically coupled networks. Possible contributions to cortical function of networks of inhibitory cells are discussed in their paper and in a subsequent review by Hestrin and Galarreta (2005).

Combinations of electrophysiological and anatomical approaches have confirmed and broadened the evidence for the specificity of synaptic connectivity in the cerebral cortex. For example, Kossoski et al. (2001) demonstrated that the local axon collaterals of a homogenous population of pyramidal neurons synapese preferentially with only a few morphological neuronal types that display stereotypical physiological and synaptic responses. Markram (1997) has identified highly interconnected networks of pyramidal cells that include reciprocal feedback arrangements that are not randomly organized. Gupta et al. (2000) concluded that groups of GABAergic neurons synapse specifically with functionally related neurons; it is worth considering this finding within the context of the inhibitory, electrotonically coupled networks mentioned above. Combining intracellular labeling with electrophysiological recordings of interconnected neurons has shown that both projection cells and interneurons are targeted by “feedforward” projections between laminae, but that interneurons are selectively targeted by interlaminar “feedback” projections (Thomson and Bannister, 2003). By combining patch-clamp recording and caged glutamate photolysis with the reconstruction and morphological analysis of biocytin labeled neurons, Schubert et al. (2003) have shown in barrels, that regular spiking layer V pyramidal cells are preferentially involved in processing within single cortical columns, whereas intrinsically bursting pyramids integrate excitatory inputs across several columns. Additional studies, combining electrophysiological approaches with electron microscopy, have adduced examples of specific interneuronal connectivity that provide a functional context for the findings that go well beyond what either approach used alone can provide (e.g., Feldmeyer et al., 2002; Lübke et al., 2000). Finally, Yoshimura et al. (2005) have demonstrated that superficial pyramidal cells connected to each other share similar inputs originating within layers II/III and IV, but that even adjacent pairs of superficial pyramidal cells that are not connected with each other do not share inputs from these sources. I see in their statement: “relatively independent subnetworks of excitatory neurons are therefore embedded within the larger-scale functional architecture…” a most beautiful expression of the pervasiveness of specificity in all aspects of cortical synaptic organization.

The existence of specific synaptic patterns contrasts sharply with the concept of nonselectivity that is often, and erroneously, equated with randomness of synaptic connections. An example of apparent nonselectivity, is the synapsing of thalamic afferents to the cortex with dendrites belonging to a wide variety of different cell types in different species (e.g., see Reference White, 1989b, pp. 65–68). The “randomness” one might see in these data is more apparent than real; the specific nature of these synaptic connections is evident, but only when accurate methods for synapse quantification are employed.

### 7. Specificity is Ubiquitous

Specificity in synaptic connectivity has also been evidenced for regions of the brain other than the cortex. For example, in the lateral geniculate nucleus, single retinal afferents are highly selective for the numbers and distribution of the synapses they form (Hamos et al., 1987), in the spinal cord, Ia-afferents project preferentially to the alpha motoneurons that innervate their muscles of origin (Burke, 1981), different types of axon terminals target specific regions of motoneurons (Rose and Neuber-Hess, 1991), and in the cockroach, particular types of axon synapse with specific regions of particular neurons (Blagburn, 1989). These findings suggest that the occurrence of specific patterns of synaptic connection is a general organizational principle of the nervous system.

It has been shown in a variety of cortical areas and species, that different extrinsic and intrinsic excitatory pathways form specific proportions of their synapses with spines vs. dendritic shafts. These proportions are unrelated to the concentrations in the neuropil of axospinous vs. axodendritic synapses (see Fig. 16, Elhanany and White, 1990; Figs. 7.1 and 7.2, White and Keller, 1983; and Fig. 13, Czeiger and White, 1993). Neurons whose axonal output is excitatory (e.g., pyramidal and spiny stellate cells in cortex) receive nearly all their excitatory input onto their spines; rarely are their dendritic shafts or somata postsynaptic at excitatory synapses. In contrast, cells whose output is inhibitory (e.g., in cerebral cortex, stellate cells that...
possess few or no spines) receive their excitatory input directly onto their dendritic shafts and cell bodies (White, 1989a). Thus, the relative proportions of synapses made by excitatory pathways onto spines vs. onto dendritic shafts and somata indicate the degree to which the axons of a particular pathway terminate selectively onto excitatory vs. inhibitory neurons. Illustrations of selective output patterns of identified axonal pathways both in cortex and elsewhere, surfaced in quantitative analyses of synaptic connectivity published mainly during the 1980s (see pp. 192–196 in White and Keller, 1989). However, these synaptic arrangements were foreshadowed by much earlier descriptions of stereotypical patterns of synapses provided by Cajal (1954) and Lorente de Nó (1922, 1938).

8. Stereotypic patterns of synapses

Stereotypic patterns of synapses are a general feature of the cerebral cortex where they serve as a constant reminder of the high degree of specificity that characterizes cortical synaptic organization. Perhaps the most basic expression of this is the contrasting patterns of synapses on the surfaces of spiny vs. non-spiny neurons mentioned above. Briefly, the dendritic shafts and cell bodies of cortical neurons whose dendrites have many spines, such as pyramidal and spiny stellate cells, are postsynaptic nearly exclusively at symmetrical, presumed inhibitory synapses; whereas, the spines of these neurons are targeted preferentially by asymmetrical, presumed excitatory synapses. In contrast, all types of non-spiny neurons display both asymmetrical and symmetrical synapses on all parts of their cell bodies and dendritic shafts (see Fig. 2.8 in White, 1989a).

A second example of a commonly encountered pattern of synaptic connection is the “triad”. As applied originally to a synaptic pattern common in subcortical structures, a triadic synaptic relationship consists of excitatory afferent input to excitatory and inhibitory neurons that interact with each other via reciprocal, dendrodendritic synapses (e.g., Fagioli and Peters, 1972; Shepherd, 1979). Triadic arrangements in the cerebral cortex differ from those in other regions of the brain in that the synaptic interactions of cortical triads are mediated by axonal pathways and not by dendrodendritic synapses (Keller and White, 1989; White and Keller, 1989). The ubiquity of triadic circuits indicates that different regions of the brain in diverse species are characterized by similar, ordered patterns of synaptic circuitry, i.e., stereotypic patterns of synapses are a basic feature of brain organization.

Stereotypic patterns are not restricted to synaptic connections in the brain. The term, “Network motifs” was coined by Shen-Orr et al. (2002, and see Alon, 2006), to describe recurring circuit elements in biological networks. The second most common motif observed in gene transcription networks, the incoherent type 1, closely resembles a synaptic triad: one gene (X) turns on two other genes (Y and Z), and Y turns off Z. Alon compared the role of this genetic triad to that of a pulse generator, in effect, an oscillator, and it may well be that synaptic triads play a similar role in synaptic circuits, providing alternately for feedforward excitation and for the subsequent dampening of it.

9. The future

This section is written in response to Dr. Swanson’s charge that the authors in this volume should discourse on the future of their particular subfield. In my case this would be the realm of quantitative synaptic organization as elucidated by serial thin section reconstruction. I do not pretend to be a prophet, but it is easy enough to read the recent past and see that the future does not bode well for analyses of synaptic circuitry using serial thin sectioning and the making of 3D reconstructions. This would be an unfortunate future, for it would arrive despite the recognized value of serial thin section analyses, as a stand-alone approach or in combination with electrophysiology, for understanding neuronal interactions that lie at the basis of brain function.

A persistent disadvantage of reconstructing neurons or their processes from serial thin sections revolves around the problem of “low N”. Simply put, making serial reconstructions is tedious, exacting, time-consuming, and consequently of low yield with respect to the numbers of cells or processes that can be reconstructed in whole or in part. For example, there exists for mammalian cerebral cortex, only a single neuronal reconstruction that provides data on synapses over the entirety of a cell body and its dendritic tree (White and Rock, 1980), lending itself to realistic computational analysis (Segev et al., 1995).

Publications based on serial thin section reconstructions have provided information on the numbers, types and spatial distributions of synapses that could not have been obtained in any other way, but truth be told, the reconstructions that have been produced to date have resulted in a small number of publications relative to the time and effort invested. Therein lies the problem—it is not a scientific problem per se, but given the value of the approach, it is a problem for science.

There was a time when aspiring candidates for research positions or for promotion were subjected to having their papers counted, an activity particularly popular with evaluation committees composed of people who were ignorant of the work they were judging. Personally, I have always had the good fortune to have been judged by prospective employers and evaluation committees that appreciated the value of serial electron micrographic reconstruction and I have not suffered at all from having had, at every stage of my career, a relatively small number of publications. However, times have changed. Neuroscience has become a very large field both with respect to the number of its subdisciplines and with regard to the increasingly large number of workers in the field; few neuroscientists are familiar with areas beyond their own. Counting papers has gone out of fashion, and good riddance, but in its place is the Citation Index and the associated Impact Factor for journals. Perhaps because of their reliance on popular, modern technology, the Citation Index and Impact Factor are finding increasing use as criteria for hiring and promotion. But are they not just a slightly more sophisticated version of old-fashioned counting? A paper that is widely cited may be very important, or it may be that there are simply a large number of workers in that particular subfield of Neuroscience, and they cite each other’s papers. Numbers matter. Moreover, a paper may be widely cited because the findings are striking, but this does not necessarily mean that
the work is of long-lasting impact (for a discussion of this aspect of the Impact Factor, see Saper, 1999).

Making three-dimensional reconstructions from serial thin sections is a low volume business boasting few practitioners; technical difficulties that constrain the publication of large numbers of reports are appreciated by few non-practitioners. These features are guaranteed to cause difficulty with the hiring and promotion of practitioners of the approach, especially given the increasing reliance on the Citation Index and Impact Factor. In my opinion – no scientifically valid poll having been taken – the disadvantage of working in an area where “low N” could be taken to refer not only to sample size, but also to number of publications, is a prime factor discouraging young investigators from devoting more time to the serial section/3D reconstruction approach. If I am correct, then in this and perhaps in other instances as well, the use of the Citation Index has taken the credo of “publish or perish” to a damaging extreme.

Although I am not sanguine regarding the future of serial reconstruction as applied to synaptic organization, neither am I unalterably pessimistic. Graham W. Knott (Knott et al., 2006) of the University of Lausanne has done much to increase the efficiency and affordability of the approach by crafting a computer-assisted, 3D reconstruction method using widely available software. Taking a different tack, several investigators (Bruno et al., 2005; Denk and Horstmann, 2004) in Bert Sakmann’s Laboratories at the Max Planck-Institute in Heidelberg are developing an approach to serial electron microscopic reconstruction that relies on scanning rather than transmission electron microscopy to increase the efficiency of tissue analysis. I close this paper with the hope that these, or some other talented investigators, will solve the problem of low N and in so doing brighten the future of investigation into the complexities of synaptic circuitry.

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References


