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30 Years Later: On the Problem of the Relation Between Structure and Func- tion in the Brain From a Contemporary Viewpoint (1966), Part II

Lev P. Latash, Mark L. Latash, and Onno G. Meijer

In the first half of the present paper, which appeared in vol. 3, issue 4 issue of *Motor Control*, the authors elaborated on Bernstein's (1935/1967) idea of the ambiguity of the relationship between the central command and the peripheral effect. The authors presented maybe the strongest statement so far: It is because the means are variant that the results can be invariant. As in Bernstein's 1935 paper, this was taken as evidence that there is no one-to-one relationship between structure and function in the brain. The authors discussed the history of localization theories, pointing out that neither strong localizationism nor strong anti-localizationism (as in Lashley's equipotentiality) would help understand the relation between brain structure and function. In order to understand the nature of a "brain center" for a function, the authors argued, one has to understand the concept of "function" itself. The development of "function" does not imply that the organism learns to (re)act in a stereotyped fashion, but that a control matrix is established, with non-single-valued relationships, allowing the organism to (re)act differently every time, in accordance with the need and actual situation. At the end of the first part of the paper, the authors emphasized the importance of a new basic logic of neurophysiology. In that sense, there are certain parallels between neurophysiology in the 60s (and also today, the present editors would add) and physics around the turn of the century, when Maxwell, Boltzmann, Planck, and others, created a completely new framework for theoretical physics.

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On the Problem of the Relation Between Structure and Function in the Brain From a Contemporary Viewpoint (Continued)*

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Key Words: motor control, invariance, localization, reflexes

Beyond Functional Systems³⁵

To solve the problem of the relationship between brain structure and function, it is important to take into account contemporary knowledge of the formation of a brain mechanism for function realization (a functional system), of the relations of this process to the phenomena that occur at the level of the elements (neurons and synapses), and of the notions that can be used to describe the functioning of such a brain mechanism.

It is well-known that the formative process of a functional system was not so long ago viewed as a process of establishing relations between the future elements of the system in order to allow for the possibility of conducting neural impulses along these elements. This is how the importance of “beating the trail” (“Bahnung”) and “closing” was understood. Hence, the idea emerged of an exceptional role played by the processes of cellular excitation, of the creation of connections between the elements of a functional system, and a similarly crucial role of inhibition in the elimination of old connections.

However, this system of concepts is contradicted by a large number of facts from electrophysiological, particularly microelectrode studies of different brain reactions. Findings by Jasper, Ricci, and Doane (1962), Burns (1958), Granit (1964) and many other investigators have demonstrated that there is always a possibility of transferring an impulse from one part of the brain to another, and

*The chapter was originally published in: Grastschenkov, N.I. (Ed., 1966). *Physiology in clinical practice* (pp. 38-71). Moscow: Nauka. It was translated by Mark L. Latash and edited for clarity.

³⁵At the time of writing this paper, the authors continued to use the notion of “functional system,” as is evident in the text that follows. It is only with hindsight that one can recognize that the idea of whole-brain involvement in function (cf. Latash, 1998) renders the notion of “functional system” superfluous. Of course, this may have caused some of the estrangement from Luria or, for instance, Anokhin. It may also be relevant to note that at approximately the same time, Gel’fand and Tsetlin (1966) were elaborating a notion of a “structural unit” as a function-specific organization of elements within a multi-element system that appears to have much in common with the “functional system.”

that this possibility is being realized all the time. As pointed out by Morrell (cited by Wells, 1963), a response to a conditional stimulus can be seen anywhere in the brain where one cares to place a microelectrode.

It follows that a functional system does not simply emerge to ensure the possibility to conduct impulses along different parts of the brain. The main factor in the process of organizing a functional system (under the influence of a certain set of stimuli and the interaction between these stimuli with the regulating brain systems) is the creation of a certain spatio-temporal distribution of excitations ensuring that an adequate command is sent by the system to the effectors.

This view on the formation of a functional system, attaching crucial importance to the spatio-temporal distribution of excitations (and inhibitions), is supported by numerous findings, particularly from studies of the electrical activity of single neurons in the visual cortex in response to moving objects, as performed recently by Hubel and Wiesel (1962),³⁶ Lettvin et al. (1959), and many others. It has been found that these neurons form vertical columns united by their response to the direction of object motion in the visual field. This fact clearly demonstrates that excitation of one and the same area of the retina induces certain spatio-temporal structures of excitation at the level of the neurons of the corresponding projection area of the brain cortex that depend on which retinal areas were excited before and which will be excited after it (i.e., depending on the spatio-temporal structure of excitation in the periphery).

All the aforementioned information about the organization of brain functions shows that the particular neuronal makeup of a functional brain system is never stable, as was emphasized some time ago by A.A. Ukhtomsky (1950), this being the only way to achieve stability of a desired ultimate outcome of a reaction. The statistical representation of elementary neural brain processes, reflecting the numerous neural elements with their connections as well as the vast number of incoming influences, only³⁷ allows for a probabilistic determination of which particular neurons participate in a brain functional system. This was demonstrated, in particular, in experiments by Werner and Mountcastle (1963), by M. Livanov (1965), and others. This factor defines the variability of the spatio-temporal distribution of excitations within a brain system which, at the same time, is organ-

³⁶At first reading, such a specific functional role of single cortical neurons appears to run against the general argument of the present paper. Note, however, that this reference to the work of Hubel and Wiesel allows the authors to introduce the element of time: A clear plasticity of cortical organization is implied because the organization of the cortex develops in a specific environment, depends on the specific experience of an individual (see Edelman, 1987, pp. 127-133; Held & Hein, 1963; Uttall, 1978, pp. 466-474).

³⁷Logically, this "only" appears to be an overstatement. Note, however, that recent developments suggest that the authors may have been correct (cf. Edelman, 1987; Sporns & Edelman, 1998). Of course, this is one of the central issues of the paper (cf. note 7 to the first part of the present paper). The authors claim that the brain can only be functional, can only have adaptive value, if it makes use of stochastic mechanisms. This not only marks a clear break from *Gestalt* but is revolutionary in and of itself. In 1966, the claim was not unique (cf. Burns, 1958; Fessard, 1963, on metastability) but still very unusual, reminiscent of developments of immunology at the time.

ized in such a way that the output of the system can only be received by a pre-defined effector apparatus. Hence, the biological significance of a functional system is revealed by processes at the output side.

These specific factors determine both the exceptional flexibility (plasticity) of functional brain systems and their reliability due to the existence of functional backups. Together with the aforementioned data on the spatio-temporal distribution of excitations forming the functional system, these factors imply, in particular, that attempts at finding some kind of special brain areas that would be specific to a process of “closing” neural connections are flawed.

Besides, the whole previous discussion leads to the conclusion that it would be inadequate to describe the whole, active, functional brain system in terms of cellular excitation and inhibition, unrelated to the particular structural elements of the system. A simple quantitative analysis of the number of excited and inhibited elements, even if it were to reveal dominance of one of these two forms of activity, also fails to characterize the particular spatio-temporal structure of excitations and thus cannot be used for conclusions concerning the abilities, purpose, and level of activity of the functional system as a whole.³⁸ Correspondingly, it is true that one cannot draw conclusions on the state of the elementary cellular processes on the basis of an external³⁹ characterization of a function which only allows for conclusions on the activity of the brain system as a whole.⁴⁰ Anyhow, descriptions of activity of a whole functional system in terms of the dynamics of basic neuronal processes, their mobility, magnitude, etc., appear to be unfounded.

The State of Sleep

A convincing example, providing support for the above conclusions, is given by the state of sleep, viewed for a long time as a state of inhibition of most neuronal brain elements based on indices of external activity of the organism.

Detailed studies of brain electrical activity in clinical observations (Grastchenkov, Latash, & Vein, 1965) and animal experiments (Hess, 1964) have revealed the exceptional variety of EEG patterns during sleep, with their specific sequences, that cannot be reduced to changes in the number of inhibited neurons. An analysis of the so-called paradoxical phase of sleep (“fast sleep”) by Jouvet (1962) and others have shown that the beginning of this sleep stage may be accompanied by changes in brain activity which look indistinguishable from those during alert wakefulness.

Investigations of the behavior of single neurons during falling asleep have revealed particular changes in the structure of their firing patterns (Jasper, 1961;

³⁸Note that this was suited before the invention of imaging techniques such MRI, PET, and so on, which by now have revealed the validity of the argument.

³⁹This is an important part of the argument. The way in which any externally defined function (such as vision) can be divided into components does not map one-to-one to any subdivision of the internal mechanisms to realize that function.

⁴⁰In 1965, “Synergetics” was on its way, presenting a formal basis for stability at the macro-level, notwithstanding changes at the micro-level (cf. Haken, 1983). In the neurophysiological literature of the 1960s, the term *metastability* was just emerging (cf. Fessard, 1963).

Verzeano, 1961) but have not produced any convincing evidence that would suggest a quantitative dominance of inhibitory over excitatory processes different from the ratio that is typical of wakefulness in the same neurons (Jasper, 1961; Evarts, 1963). All these findings allow one to conclude that sleep is not a state of “spreaded inhibition” of cortical neurons, not a mere cessation of the activity of a “wakefulness system,” but rather the result of the activity of a special functional brain system directed at destructing the spatio-temporal pattern of excitations that is typical of brain activity during wakefulness. This conclusion is corroborated by demonstrations of a decrease in evoked neuronal activity during sleep while the spontaneous activity of the same neurons is increased.

Finally, a third⁴¹ point that we would like to emphasize is that both the cessation of activity of a functional system, and its emergence, are always related to changes in the spatio-temporal structure of excitations and to elements of a given system that are also involved in other functional systems. As a particular example, we mention the possibility of the annihilation of a functional system by the activation of an antagonist system (for example, the relations between a system of “appetite maintenance” and a system of “satiation,” as described by Brobeck and others, representing, according to Konorski (1962), a general principle of brain activity). The destruction of a functional system may also result from the activity of a deactivating brain system including, first of all, the already mentioned system of sleep, as well as some others.

All this suggests that the description of the activity of a brain system, for many reasons cannot rely on notions of cellular neurophysiology. It appears to be necessary to elaborate new systems of concepts and analytical tools, an important future task of physiology.

The Whole Brain Is Involved

Earlier, we discussed, in general terms, contemporary understanding of the problem of the organization of brain function and some principles of the formation of the neuronal ensembles that form a functional system. Now, we can move directly to the analysis of the problem of the interrelation between brain function and structure in its narrow sense, i.e., to an analysis of the problem of brain function localization taking into account how these functions are organized and formed.

To understand better how the contemporary treatment of the structure of a function is reflected in the localization theory, one needs to remember a number of points, known in neurology since the times of Hughlings Jackson, but still not always taken into consideration as they deserve.

Without doubt, the notion of a function “center” emerged on the basis of numerous clinical and experimental surgical brain studies, and carries a negative rather than a positive message, not implying a structure that realizes a function, but a structure whose destruction prevents the function from being realized, which

⁴¹The first two arguments in the present section concern the spatio-temporal patterns that are characteristic of function and the statistical nature of their elementary processes.

then leads to the corresponding syndrome of functional deficiency.⁴² The non-equivalence of such “positive” versus “negative” understanding was convincingly shown in a whole series of investigations, particularly those that compared the loss of activity induced by surgical interventions to the bioelectrical changes observed in different brain areas during unimpeded progression of corresponding brain processes. For example, such studies revealed that a crude destruction of a function can be induced by an injury to neural structures that play an important role in the conduction of impulses to the effector without being particularly significant for the preceding, most significant phases of function organization.

In other studies, it was shown that a function may suffer under an action (surgical or electrical) in brain areas which most likely contain important pathways of intracerebral impulse propagation (or, possibly, some other yet unknown tone generating brain structures), while the function is certainly realized by a much larger set of brain structures. Such situations were observed, in particular, by Penfield in his studies of the specificities of speech localization, and formed the foundation for the identification in the cortex of a whole system of so-called secondary speech zones.

All studies of this type thus demonstrated a much wider involvement of brain structures in the realization of a function than could be expected on the basis of the topography of the areas which can be used to destroy the function. Such an understanding has certainly not been unexpected. It was prepared by earlier experimental work, in particular studies of P.K. Anokhin (1958) which demonstrated unusually wide responses within the central nervous system, even to the lightest and most local stimuli. As shown by accurate experiments by Soviet and foreign scientists, responses to single stimuli applied to the skin or mucosa can be detected not only in different cortical areas but also in the trigeminal nucleus, the visual colliculus, Ammon’s horn, in the striatum, at different levels of the brainstem reticular formation, and even at the level of spinal structures. With respect to this problem of the wide distribution of responses to stimulation, Granit (cf. 1964) once said that if one had a sufficiently sensitive gauge, a response to a stimulus even when applied to a single receptor, or to activation of a single motor unit, could probably be detected in each of the hundreds of millions of cells that compose the central nervous system.

Polysensory Neurons

The wide spread of reactions to stimulation never created the impression of a simple diffusion of excitation but, on the contrary, revealed a clear differentiation of the reactions of different neural structures and, therefore, a similar differentiation of the role of these structures in responses. For a while, this phenomenon helped to avoid seeing the contradiction with the traditional understanding of function localization. One was able to hypothesize that the wide distribution of reactions to stimuli of a certain modality was simply due to a considerably wider than expected representation of the “distributed elements” of the corresponding analyzer. Such a soothing interpretation, allowing to disregard the signs of the inevitably approaching necessity to radically reconsider the existing views, sur-

⁴²This logical mistake is still prevailing in many textbooks and research papers.

vived for a short time only.

This conservative scheme was destroyed by blows from different directions: Studies revealing the peculiar fact of the convergence of impulse volleys induced by stimuli of different modalities to the same neurons, the analysis of secondary or irradiating potentials, and finally, the ultimate proof of the existence of neurons of the so-called polysensory type, not only in the reticular formation, as had been admitted earlier, but also in many cortical structures.

Let us briefly review some of the conclusions from these new experimental findings.

About 10 years ago, researchers who investigated the spread of excitation in the brain stem reticular formation, discovered the phenomenon of impulse convergence induced by the stimulation of different central structures and receptors from different sensory modalities within the same areas of the brain stem. Such facts were described in 1952–1954 by Bremer and Terzuolo (1954), French, Van Amerongen, and Magoun (1952), French, Verzeano, and Magoun (1953), and many others. During stimulation of reticulopetal projections, with stimuli following each other at different intervals, one could observe different forms of mutual influence among the incoming excitations (facilitation, blocking, etc.) in the target areas of the impulses. Later microelectrode studies have shown that, in such cases, there is a genuine convergence of impulses of different modalities on single neurons of the reticular formation (Baumgarten, Mollica, & Moruzzi, 1954; Rossi & Zanchetti, 1960; and others).

At the same time, it was shown that the wide responsiveness of the reticular formation to stimuli of different modalities and intensities cannot be interpreted as a simple diffusion of excitatory waves spreading indiscriminately over an unstructured functional substrate. The convergence of afferent impulses onto a single reticular formation cell turned out to be a common phenomenon, but not a universal rule. A study by Scheibel with coauthors (Scheibel et al., 1955), performed at a very high level, has shown different degrees of convergence of heterogenic afferent impulses in different reticular neurons. These authors found cells responding to a polarization of the cerebellum, to tactile stimuli, tendon taps in the extremities, and electrical stimulation of the sensorimotor cortex, but showing absolutely no response to vagus stimulation or to sounds. Similar phenomena of differential responsiveness of reticular neurons to stimuli of different types were revealed by many other authors. It is of interest to note that a large number (up to 50% in the pons and up to 65% in the midbrain) of “relatively mute” reticular cells were described, i.e., neurons whose electrical activity did not change during adequate sensory stimulation, cortico-reticular and cerebello-reticular impulse inflow, or even during strong electrical stimulation of afferent nerves (Mancia, Mechelse, & Mollica, 1957; and others).

As a result of all these studies, two major points have been emphasized: First, the very peculiar character of the spread of heterosensory excitations in the reticular formation using, in appropriate conditions, the same conducting and processing neuronal structures; and, second, the selective responsiveness of different reticular neurons to incoming excitations, reflecting their different roles in the processes of neural integration. Further, it has been shown that similar relations of neurons to impulses of different modalities exist in other brain structures

(subcortical nuclei, limbic system, and neocortex). Therefore, they reflect a general principle of the organization of brain systems. Main studies leading to these more general interpretations are linked to the name of Fessard (1964).⁴³ In recent years, they have exerted a deep influence on the science of localization.

Electrophysiological studies have established that heterogenic signals of both sensory and central origin converge in the neocortex over rather large territories. This important fact was established, in particular, in studies of so-called secondary or irradiating evoked potentials in response to the stimulation of a certain modality, far beyond the corresponding projectional field.

Buser and Imbert (1964) have shown that neurons of the sensorimotor cortex in cats (under narcosis or without it), besides bioelectrical reactions to somesthetic stimuli, show regular responses to visual and auditory stimuli (during extracellular microelectrode recording). Neurons responding to all the used forms of stimulation (somatic, visual, and auditory) were considered as "polysensory." Neurons responding only to somatic stimuli, independently of the area of the body to which the stimuli were applied, were termed "polyvalent" or "atopic." Finally, neurons whose activation occurred only in response to somatic stimuli in strict relation to the classical principles of the organization of somatic conduction pathways, were viewed as "spatially specific." A detailed study of the topography of these functionally heterogenic cells was undertaken. The analysis revealed that up to 92% (!) of the neurons within the anterior sigmoid and the rostral section of the posterior sigmoid convolution belonged to the polysensory type, 8% to the polyvalent type, and 0% to the spatially specific type (in other, more caudal areas, these relations were somewhat different).

Many other researchers have indicated the wide spread of convergence effects among heterosensory impulse inflows in cortical neurons (Amassian & Woller, 1962; Jasper, Ricci, & Doane, 1962; Li, 1962; and others). All these data lead to the hypothesis that the specific functional features of the sensorimotor

⁴³At the time, Alfred Fessard was the leading French neurophysiologist. He often met with Russians in international conferences. Unfortunately, we have been unable to retrieve the Russian text of the 1964 Moscow Symposium on "Connection Theory in Sensory Systems." Reading Fessard's work (e.g., Fessard, 1963, 1969, 1974; Fessard & Gastaut, 1958; Fessard & Szabo, 1974) immediately reveals that he was astonishingly modern and inspiring. He was early in rejecting strong localizationism without jumping to general equipotentiality. His network theory of the organization of the brain was stochastic, emphasizing metastability. Of the concepts presented so far in the present paper, the spatio-temporal distribution of impulses may derive from Fessard. In the present section, he is mentioned for his understanding of polysensoryity. In the next section, the notion of "operator" will be introduced. This notion derives directly from Fessard. At the time of the present paper, French science was to be reorganized, no longer centered around relatively independent laboratories with their own continuity (plus a rather high degree of interaction with different groups). The system became much more focused on fashionable topics (such as, at the time, "motor program"). And relatively soon, Fessard was forgotten, notwithstanding the existence of an *Institut Alfred Fessard* in Paris.

cortex, as well as the specificities of the functioning of the reticular formation, are due to their neuropile⁴⁴ structure.

We have discussed the problem of the polysensoryity of cortical and reticular neurons in detail because this problem is of particular significance for the present reconsideration of ideas on the principles of localization of brain function.

Undoubtedly, our understanding of the regularities and, particularly, of the physiological significance of neuronal polysensoryity is very poor. For example, one study emphasized qualitative parallelism and synchronicity of the changes in potentials that were induced by two heterotopical somatic stimuli in a neuron of the medial thalamic nucleus and in a cortical neuron. This allowed Fessard to suggest the existence of a special projectional connection between polysensory structures, whose mechanism, however, is still absolutely unclear. One could assume that convergence of different stimuli on one neuron could be particularly important for the associative process but it is certainly impossible to claim that this assumption is correct. Nevertheless, the proven fact of the existence of polysensory neurons in different cortical and brain stem formations, allows for the introduction of important details with respect to the problem of the specificity of the localization of brain functions.

Stochastically Organized Neuronal Nets

The heterogeneous excitability of polysensory neurons in response to very different stimuli, together with their wide representation within the central nervous system, certainly forces one to reject the idea that each of these neurons has a special system of links with all of the mind-boggling number of receptors that can potentially be connected to this neuron. It may be possible to prove mathematically that such a humongous, absurdly uneconomical communication system, consisting of numerous linear, functionally specialized neuronal tracts (i.e., nonintersecting pathways, each one dedicated to the transmission of excitations that are induced by stimuli of only particular modality), would have a volume far exceeding the limited volume of the skull and the spine. There is, however, only one alternative, that is a neuronal net scheme⁴⁵ involving a large enough number of relays of impulse volleys.

Within such a net, heterogeneous impulses can spread at different times along both the same or different neural tracts (i.e., it eliminates, to a considerable degree, the functional specificity of conducting neuronal chains, a selective relation of each of the neuronal tracts to impulses of a certain functional category, observed as the leading principle at more peripheral levels of the nervous system). As a result, within such a net, each impulse of excitation has numerous

⁴⁴For the distinction between neuropile and connecting channels, see the paragraph that contains notes 22 and 23 in the first part of this paper (in vol. 3, issue 4 of *Motor Control*).

⁴⁵In 1986, Parallel Distributed Processing (PDP) was proudly announced (Rumelhart, McClelland, & the PDP Research Group, 1986; McClelland, Rumelhart, & the PDP Research Group, 1986). The present paper not only precedes that event by 20 years but is also much more biologically realistic than early forms of PDP.

potentially accessible tracts that lead in a required direction (consequently, there is an enormous increase in the reliability of the functioning of the whole mesh-like system).⁴⁶ And finally, it is important that the design of the neuronal net depends not only on genetically predetermined specific factors but also on factors of a “random” origin (i.e., details, whose design is determined by unforeseeable environmental factors acting during embryogenesis; as a result, the design has the appearance of “random” growth and distribution of neuronal branches and synapses).⁴⁷

This last specific aspect of the design of neuronal nets represents a particular case of a more general, uniquely biological regularity, exemplified, as already been mentioned in our literature (Bernstein, 1963), by the extreme “resistance” of the organism with respect to basic, “essential” features of its design, and, vice versa, its extreme “compliance” with respect to “non-essential” features which, as a result, are very individual and show high variability.⁴⁸ In the case of a neuronal net, this combination of genetically fixed and “random” features has a very special physiological meaning.

Because such a net has numerous possible ways of transmitting impulse volleys, and a huge number of neuronal contacts and branches, special, statistical regularities of the distribution of possible patterns of excitation spread emerge. These regularities spontaneously, if such a metaphor is possible, assure the existence of certain types of neuronal interaction which are important for communication, inevitably following the laws of the theory of large numbers and probability theory. That is why the inevitable “chance” element in the structure of dendrites and axons cannot become an obstacle for the normal functioning of a stochastically organized neuronal net. On the other hand, within a linear, rigidly fixed system, consisting of functionally specific connections with no statistical determination, a minor element of randomness in the distribution of branches and contacts is doomed to become a menacing source of unavoidable functional disorders.⁴⁹

The Ambiguous Relation Between Structure and Function

The above ideas on the specificities of excitation neurodynamics within a neuronal net have penetrated deeply into contemporary neurophysiology. They force

⁴⁶This may be viewed as another example of the shift from the notion of “redundancy” as a nuisance feature that needs to be eliminated by the central nervous system to the notion of “abundance” as a useful factor increasing the system’s reliability and flexibility (cf. Kugler, 1986).

⁴⁷Compare with Edelman, 1987. Moreover, such nets are robust against minor structural damage and may allow for quick and efficient relearning after major damage (Hinton & Sejnowski, 1986), while the general pattern of activity may even be robust against changes in grammar (Kauffman, 1993).

⁴⁸[Note in the original paper:] An example of this universal regularity is the fact that any two leaves on the stem of a plant are always similar to each other with respect to certain basic, species specific features, while they never form perfect structural copies of each other. (Mathematically speaking, they are not mutually congruent).

⁴⁹This is the first place in the paper where a logically compelling argument is offered for the necessity of the existence of stochastic brain mechanisms.

researchers to pay attention to two factors that are very important for the future development of the doctrine of localization and, at first sight, look contradictory.

On the one hand, such phenomena as the convergence of heterogenous excitations onto the same neural elements, and the polysensority of brain neurons have revealed how over-simplified the old views were, according to which specific features of excitation spread were unambiguously determined by the specificities of the morphological organization of the brain.

On the other hand, thanks to the same phenomena it has become clear that the design of morphological connections in the brain, allowing for numerous potentially accessible routes for the spread of impulse volleys, implies the existence of qualitatively different principles and regularities of excitation spread, specific to each neuronal net. The morphological substrate of a function of a neuronal net type does not determine unambiguously the dynamics of excitation. However, it does not cease to be a factor which affects the dynamics, while acting in a much more complex, probabilistic, and indirect way.

Recently, this aspect of the problem has attracted special attention. It has motivated many researchers to undertake more thorough theoretical studies of the neurodynamic properties of neuronal nets with a particular design. During the first attempts, the performance of logical operations was studied in obviously artificial neuronal nets (with rigidly fixed deterministic connections—McCulloch & Pitts, 1956, and others; vice versa, with a purely probabilistic nature of determination—Rapoport, 1950; Shimbel, 1950, 1952; Beurle, 1956; and others). These schemes were rather far away from real neuronal nets. Only most recently, there have been attempts at studying the specificities of excitation spread in neuronal nets that can be assumed to resemble actual brain structures in their general design and types of branching (Fessard, 1964; Scheibel et al., 1955). In these studies, it was shown that there exists a whole set of lawful relations between the type of design of connections that conduct excitations and the type of processing of these excitations. One may assume, as pointed out by Fessard and others, that one particular design of neuronal branches and connections facilitates the synchronization of spreading excitations; another design induces contrast effects (an amplification of differences) among specific features of different impulse volleys; a third type exerts a specific amplifying effect on impulse characteristics counteracting the tendency for inhibition and attenuation of rhythmical activity; a fourth type (reverberating neuronal nets of Lorente de No and Forbes) is responsible for maintaining certain long-lasting functional states of neurons, etc.⁵⁰

Major difficulties in this analysis are primarily related to our insufficient knowledge of the exact specific features of the relative location of neurons and their elements. We therefore regard as particularly important recent so-called histonomic studies in a number of laboratories, i.e., investigations that use electrophysiological and optical methods in attempts to refine the present understanding of mathematically formulated regularities of the structure and mutual location of cells in the real neuropile (Sholl, 1956; Bok, 1959; Braitenberg, 1963; and others). There are good reasons to expect these particular histonomic studies to create, in the nearest years, a methodologically adequate foundation

⁵⁰Compare with Fessard and Gastaut, 1958, in particular Figures 17 and 18, discussing “operant nervous structures.” See also Burns, 1958.

for more successful modeling of the structural and functional specificities of real neuronal nets.⁵¹

Localized Operators for Global Functions

The characterized relations between structure and function in neuronal nets pose a number of tough problems for the localization concept. We are forced to introduce serious corrections into the traditional view of the functional specificity of neuronal pathways and constellations, the view that specific features of integration, in their relation to different functions,⁵² were predefined by the localization of excitations within a given system of neurons. Even the prevailing relation between the excitation in one or another projectional cortical area (i.e., input or output “gates” of the cortex) and the corresponding brain function, turns out to be less than conventional: Let us remind ourselves of the fact that 90% of neurons in the somatosensory cortex of the cat participate in the perception of somesthetic, visual, and auditory signals.

On the other hand, we have a much clearer understanding of the dependence of the dynamics of excitation on the topics, i.e., on the specificities of the morphological structure of the neuronal nets along which the excitations spread.

The whole experience of the investigation of the brain foundation of a physiological function (its main results have been presented above) points at the inadequacy of identifying a limited complex of neural elements as such a brain foundation for any physiological function. After the phenomena of neuronal polysensory were discovered, any attempts at imposing strict limits on brain areas responsible for the realization of a function meet practically insurmountable difficulties.

Nevertheless, the elementary features of the spread of impulse volleys and, consequently, the elementary forms of processing of the information carried by these volleys, become deeply dependent on the specific local features of the structure of the neuronal net that carries the volleys. These local morphological characteristics are an important factor which defines local neurodynamic characteristics, as well as the type of excitation transformation occurring in different brain microzones. For structures, whose design strictly defines the type of their activity, contemporary control theory uses the special notion of an “operator.” Therefore, one may say that particular designs of neuronal nets play the role of operators, defining the character of neurodynamic processes within particular brain zones and, by doing so, specific features of information processing within these zones. Only these specific features of neurodynamic processes can be viewed as a truly local, predefined manifestation form of brain activity.

⁵¹Compare with the later development of methods of neuroanatomical tracing based, in particular, on horseradish peroxidase transport.

⁵²This “in their relation to different functions” is essential to the argument. The authors develop a view with a distributed set of localized neuronal nets, each contributing to the non-localized execution of functions. So, “specific features of integration” may be dependent on localization, but these features can now be used in this, and then in another (externally defined) function.

We have already noted that one weakness of the system concept consisted in its easy acceptance of the idea of the rigid localization of the components⁵³ of a function, whereas the idea of rigid localization of the function as a whole was rejected. Are we making a similar mistake by rejecting the idea of rigid localization of a function while accepting rigid localization of specific features of neurodynamics defined by operators? It would be so, if the notion of operator were equivalent to the notion of function “component.” However, this is not so, in particular because the functioning of an operator is not linked to any single function and can be involved in the realization of very different brain functions. Therefore, there is no logical contradiction in accepting the idea of rigid localization of operators and rejecting a similar type of localization of functions.

This conceptual system requires a clarification of such traditionally used notions as “a center” and “function being localized.” An image of a rigidly defined “center” of a function identified on the brain map may certainly remain useful in studies of clinical syndromes, i.e., in the localization of zones whose injury leads to a disorder of function. However, such an image loses its significance if one tries to identify the totality of mechanisms forming the foundation of such a function. Moreover, relating the notions of “function” and “localization” meets with difficulties even in the area of semantics. It is sufficient to consider the problem of identifying “function localization” in any mechanism (for example, that of a watch) to appreciate these difficulties.⁵⁴ To illumine the emerging inconsistencies, one needs to involve an area of mathematics that deals with the problems of notion incompatibility and logical paradoxes. However, we are not going to venture into this area now.

Thus, we are arriving at the general conclusion that only data on patterns of changes, proceeding differentially in different brain structures, and reflecting the role of these structures as operators in the processes of information transformation, can form a concrete foundation for an understanding of the localization of any brain function. Hence, the main task of the localization doctrine is to define the character of these patterns for each individual brain function, their significance for the time development of the functions, and their dependence on the external conditions of its development. There absolutely cannot be any other meaning of the notion of a brain substrate for a function.⁵⁵

Such are the answers contemporary knowledge provides to questions regarding the relation between the structure and the functional activity of the brain. In many aspects, these answers differ from traditional views, but this should not be a major source of concern to us since many factors suggest that the differences are well based and represent signs of progress.

⁵³Since function is externally defined (cf. note 39), these “components” are what can be seen from the outside. The authors argue that the underlying structures do not map one-to-one onto externally defined components

⁵⁴Again, these difficulties appear if one attempts to subdivide an externally defined function and then proceeds to map the subdivision onto the internal structure of the watch.

⁵⁵This is the second climax of the paper. The powerful statement in the last phrase remains challenging with respect to recent studies using contemporary techniques in attempts to localize a whole variety of functions ranging from movement to memory to speech and so on.

*Forthcoming Biological Chapters of Mathematics*⁵⁶

In conclusion, let us say a few words regarding the possible help that can be expected from mathematics in solving crucial contemporary problems of brain physiology.

The current stage of development is characterized by an increasing complexity of the methods, and a striving towards a common language⁵⁷ and a common understanding among scientists working in different areas. In particular, this process is reflected in the increased attention of mathematicians to biological problems and their mathematical modeling.

Mathematicians who are addressing biological problems took time to understand that their wonderful apparatus developed for the analysis of problems pertaining to inanimate nature, which worked impeccably for problems of physics and chemistry, is inadequate⁵⁸ to address the new realm of questions which they tried to tackle with a degree of arrogance.

Now, this initial phase of misunderstanding is over, and the best mathematicians have been able to appreciate that their arsenal is still unable to reflect adequately the specificity of biological processes.

It has become obvious that the route to making biology “more mathematical” should not imply an application of mathematics to biology from outside but a development of new, “biological” chapters of mathematics that originate from inside, i.e., from the essence of the problems posed by the life sciences. Then, equipped by an adequate mathematical apparatus, biology and biocybernetics will probably merge into a synthetic discipline which will become their new, supreme stage.⁵⁹ This emerging discipline looks particularly promising for concepts on brain structure and function.

There are two major classes of mathematical relations that look particularly promising for modeling and analysis of brain functions: (a) the class of mappings or images;⁶⁰ and (b) the class of functions of dispersion. A third, similarly important class, embracing the functions of control and regulation in living organ-

⁵⁶This last section was written by Bernstein himself. It is clearly inspired by his cooperation with Gel'fand and Tsetlin.

⁵⁷Although the development of a theoretical neurophysiology, and thus of a new “common language,” is central to the paper, ascribing this search for a new, common language to neurophysiologists at large is overoptimistic. In a way, it still is—many still are convinced that it is too early to develop such a new language. Bernstein, however, knew there were several important seminars going on in Moscow—Gel'fand on a new mathematical language for biology, Gurfinkel on physiology, and Lyapounov on the mathematical foundations of cybernetics. This certainly led to an atmosphere of optimism.

⁵⁸This was, and still is, an important point of Gel'fand (cf. Gel'fand & Latash, 1998). One is reminded of: “Biologists understand the problem but lack the mathematical skills, and mathematicians have the skills but don't understand the problem” (Bernstein, 1965/1988, p. 246, quoted from Bongaardt, 1996, p. 42).

⁵⁹This unified mathematical understanding, however (un)realistic, was Bernstein's dream in his last years (cf. Bongaardt, 1996, pp. 42–43).

⁶⁰Compare with Meijer and Bongaardt, 1998.

isms, unlike the former two, has already been significantly developed in theories of automatic regulation, of the behavior of limit automata, of so-called “games with nature,” etc. The former two classes have not been as lucky yet. As it is clear from the names of these classes, the first one—the class of mappings—is intimately tied to processes and results of active generalization, i.e., ultimately, to “essential” variables as they were described earlier. The second class—the class of dispersion functions—clearly includes problems of adaptive variability and the concrete realization of processes and actions, i.e., problems of “non-essential” variables.⁶¹

The class of mapping functions includes all types of functional mathematical relations, expressing projections of similarly organized sets of elements onto other sets of elements organized according to a different (even stochastic) principle.

It is easy to imagine the breadth of the area occupied by functions of the mapping class within the field of biology; this area includes many vitally important relations between the organism and its environment. Information reception and processing by the organism, at all the stages of its progression—from the receptor, through the afferent pathway with its relay nuclei, to the highest integrating apparatuses of the brain—represents a whole chain of events which belong to this class. Every synthetic afferent process is mapped (certainly, far from unambiguously) onto a responding motor action (in its wide meaning). Most importantly, every generalized program⁶² of actions is founded on intrinsic processing in systems of mapping, so-called “models of the present and of the future.”⁶³

A particular version of mapping relations can be found in the relation between the program of a motor act (or of any other active process), formed as a “model of the future,” and the actual execution of the act. The latter may be viewed as a particular reflection of the former, i.e., an active projection of a programmed brain code onto reality with a corresponding time delay. To date, it is clear that mathematical categories adequate to the relations within this class are yet to be found; nevertheless, there are reasons to expect that the creation of these new mathematical tools will contribute to the development of perceptrics, whose problems until now have not found precise solutions.⁶⁴

The profound specificity of the mapping class in biological objects becomes particularly clear when contrasted by the class of dispersion functions.

⁶¹Studies of patterns of motor variability (“dispersion functions”) have recently been used by several groups (Haggard, Hutchinson, & Stein, 1995; McIntyre, Stratta, & Laquaniti, 1997; Scholz & Schöner, 1999) to test hypotheses regarding different “essential variables.”

⁶²Nine years after the appearance of the present paper, the notion of a “generalized program” was reintroduced by R.A. Schmidt in one of the most frequently cited papers in the whole history of psychology (Schmidt, 1975).

⁶³Although this paragraph is very close in spirit to the notion of action-perception coupling originating from works by Gibson (e.g., 1979), contrary to Gibson (or *Gestalt*), the mapping is “far from unambiguous.”

⁶⁴This is vintage Bernstein. The very fact that there is no solution yet allows him to speculate about the applications of the solution-to-come. To Bernstein, unsolved problems are so much more interesting than solved ones.

All human motor acts, in particular skilled repetitive motor acts such as locomotion, writing, simple labor movements, etc., have a characteristic variability of the kinematic patterns, or of the parameters of corresponding kinematic equations which describe the movements. Very rarely can one reveal an adaptive purpose of these variations among cycles of a movement (for example, due to the uneven surface of the road, wind blasts, resistance of a material or of an opponent, etc.). The considerable “residual” scatter across movement repetitions, observed under conditions of ideally reproducible external conditions, cannot be viewed as a result of the action of unobservable factors that escape the attention of the experimenter. If we also take into consideration that variability, both adaptive and stochastic,⁶⁵ always applies only to non-essential components and parameters of the movement, and never affects its essential, goal-related characteristics, we naturally come to the conclusion that this group of phenomena reflects a particular subordinated structure of control, inherent to the motor apparatus.

During the last years, the idea of such a subordination has been expressed in a mathematical model and has received experimental support in a series of studies by I.M. Gel’fand and his coauthors (Gel’fand & Tsetlin, 1962, 1966; Gel’fand, Gurfinkel, & Tsetlin, 1962) and by M.L. Tsetlin (1963). According to the model of these authors, the higher controlling brain apparatus does not send detailed commands along efferent pathways to lower (spinal) structures, that is to say, to muscles.⁶⁶ Rather, it sends commands for the recruitment of working matrices,⁶⁷ developed earlier and localized, according to many findings, in the segmental apparatus of the spinal cord including alpha- and gamma-motoneurons, afferent neurons of different types and modalities, and the so-called interneuronal medium. When recruited, each functional matrix possesses enough autonomy in assuring the execution of corresponding elements of a motor act. Each matrix switches its components—either following commands from brain systems that detect errors, or, possibly when the situation becomes too complicated for a given matrix, bringing about some kind of SOS signal from the corresponding segmental system to higher brain organs.

Presently, it is important to emphasize two aspects of the functioning of these subordinated systems. First, we are forced to assign to the lower matrix apparatuses not only the ability to accumulate experience, i.e., to form their own connections and develop their own “tactics” based on the experienced interaction with the environment, but also the active search for optimizing the “games with nature,”⁶⁸ into which these apparatuses are involved. From this view, the aforementioned “residual” dispersion, which probably cannot be assigned a reactive-adaptive meaning, should be characterized as a search dispersion, i.e., as active forms of testing the situation, its gradients, optimal directions of actions, etc.⁶⁹

⁶⁵Earlier in the text (cf. note 7), adaptive variability was also regarded as stochastic.

⁶⁶It is interesting to note that Bernstein now ascribes his own 1935/1967 idea to Gel’fand and Tsetlin.

⁶⁷Compare with the subsection on Matrix Control in Part I (in vol. 3, issue 4 of *Motor Control*).

⁶⁸It was in particular Tsetlin who emphasized the importance of studying such “games.”

⁶⁹For Bernstein on search variability, see 1965/1988. The present argument is close to Gel’fand and colleagues, 1963. For relevant contemporary ideas, compare with note 10 and Bongaardt, 1996.

Second, if indeed variability and dispersion emerge because of the functional properties of segmental matrices, playing an important role in the adaptation of essential action components to external conditions, qualitative mathematical characteristics of observed dispersions should directly depend on the structure and pattern of the purposeful interrelationships between the two subordinatively linked levels. This means that, in each particular case, the function of dispersion is a reflection of these structures and patterns. If this idea is correct, processes of control of actions, that are difficult for both registration and direct mathematical interpretation, can find an interpretation in their reflections in functions of dispersion, in all their wide qualitative variety and specificity. It is less crucial which particular algorithms will link these functions to corresponding actual patterns and whether it will be possible to express these algorithms with presently available notions and symbols of mathematics.

We are not going to try to further develop all these ideas (such attempts are presented in one of the last works by N.A. Bernstein). We would only like to state that we-biologists-are to address the problem of formulating requirements and axioms of the emerging field of biomathematics of tomorrow which promises to develop and spread widely. It is possible to solve this problem, however, only in a close symbiosis between biologists and mathematicians, a symbiosis not in the form of formal contacts, but in a true natural merging of their creative thinking. The perspectives of such a symbiosis are truly without limits.⁷⁰

Epilogue

Lev P. Latash, Mark L. Latash, and Onno G. Meijer

Are we closer now to the “biomathematics of tomorrow” than Bassin, Bernstein, and L.P. Latash were 30 years ago? Of course, this is in part a matter of opinion. Nevertheless, most researchers would probably agree that an adequate formal language for biological problems (“biomathematics”) does not exist, yet, and that all the attempts at importing a language from areas of physics and mathematics have failed to remedy the problem. In our opinion, this statement includes applications of the theory of dynamical systems, however fascinating, because these attempts fail, at least so far (e.g., Kelso, 1995), to connect with the specificity of the *structures* that underlie the *functions*.

So, again we find ourselves emphasizing the need for a theoretical neurophysiology—for the development of an adequate language to capture the problems of motor control. In this respect, the late 60s were quite inspiring, both globally and locally.

⁷⁰This is the third and last climax of the chapter. The first (note 25) was that we have to define the notion of a “brain center” for a function, that is, that we have to understand “function” before we can understand localization. The second (note 55) stated that understanding “function,” and thus localization, implies characterizing the spatio-temporal patterns that pertain to a function. These two are now linked with Bernstein’s (and Gel’fand’s) dream of a really new biomathematics.

Globally, attempts to create theoretical biology were popular in the 60s because at least one coherent set of notions had been found for biology (Judson, 1979): The four DNA-bases are complementary to each other (explaining self-multiplication), and triplets of such bases code for the 20 amino acids (explaining protein synthesis). Moreover, the recognition of somatic mutations (e.g., Burnet, 1959) had changed immunology from an instruction-oriented to a selection-oriented field, much more in agreement with other developments in biology. So, in the late 60s, theoretical biology seemed to be within reach, with authors such as Waddington, Kauffman, Pattee, Szent-Györgi, Prigogine, and Fessard (e.g., Marois, 1969; Pattee, 1973).

Still, if we look at what happened afterwards, the promises were not fulfilled. To date, much of the theoretical studies in biology are applying existing mathematics to biological problems, rather than having biologists present their problems to mathematicians so that a new mathematics can be developed in cooperation—as Bassin, Bernstein, and L.P. Latash wanted in 1966.

Also locally, the late 60s in Moscow were an inspiring period for physiology and the study of movement. Part of this appears to be due to coincidence: The right people (such as Bernstein, Gel'fand, Tsetlin) happened to be at the same place at the same time. But of course, more can and should be said about that coincidence.

The terror of the system forced most researchers to pursue their own program in relative isolation. It was said at the time that “the Russians survive because the government is lazy” (G. Orlovsky, personal communication). Scientific controversies with one’s friends were often preferred over those with real enemies. So, counterbalancing the isolation, there were frequent interactions in more or less informally organized seminars. Not only would friends and students meet with Bernstein at his home, but there also was a biomathematical seminar around Gel'fand and Tsetlin (with a special winter event in Komarovo, part skiing, part debating), a seminar on biocybernetics around A.A. Lyapounov and A.I. Berg, and a physiological seminar organized by Gurfinkel. Overall, this was an incredibly stimulating set-up.

Still, when Bassin presented the paper, in Erevan, 1964, not much really happened. Not only were the traditional adversaries, the neo-Pavlovians, clearly against the whole framework of ideas that was presented, but also some of the friends were offended, in particular Luria. Tsetlin’s remark that the paper was “untimely” (see our introduction) because it was too early for the idea of a “theoretical neurophysiology” may be seen as testimony to his polite, tactical, and stimulating demeanor.

The paper was finally published in a source with a neurophysiologically rather uninspiring title: “Physiology in Clinical Practice.” And so, the paper succeeded in “disappearing,” so to speak, for another 30 years. Of course, the preparation for Bernstein’s own selection of his work (1967) had been finalized already, but the Bassin et al. paper was offered for separate translation—and wasn’t translated until now.

Fairly often, we witness (or fail to consciously witness) new attempts to establish a “theoretical neurophysiology.” Some of these attempts attract considerable attention (e.g., Edelman, 1987), but a large majority is ignored for a long time. Ashby’s (1954/1952) “Design for a Brain” is a case in point. The clearest case

we met in editing the present paper is that of Alfred Fessard who was the leading neurophysiologist in France in the 1950s and wrote in 1958 (!) about stochastic neural networks with specific functional capacities (Fessard & Gastaut, 1958; cf. Burns, 1958). The present paper reveals how much of a source of inspiration Fessard really was. To date, his work is all but forgotten.

There may be an important message in this aspect of the history of neurophysiology. Many researchers may feel that *even now* it is too early to create a “theoretical neurophysiology” because we don’t sufficiently understand the basic facts. However true this may be, we argue that relevant discussions and attempts in the past may have received insufficient attention. So, by editing the present paper, we hope that we not only contribute to the historiography of our science, but also add relevant ideas to contemporary debates.

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In the following, the original references, the editors’ references, and the acknowledgments are combined for Parts I and II.

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