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NDN, VOLUME TRANSMISSION, AND SELF-ORGANIZATION IN BRAIN DYNAMICS

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Fields of neural activity are seen in synchronized oscillations that are detected at mesoscopic scales in syntheses of multicellular recordings of action potentials and electroencephalograms (EEGs) over broad areas of cerebral cortex. The waves often have large-scale, highly textured spatial patterns of cortical activity that form in the context of associative learning under classical and operant conditioning in rabbits. The patterns show spatial amplitude modulation of shared oscillations of carrier waves in the beta and gamma ranges of the EEG, with recurrence at frame rates in the alpha and theta ranges. The frames also show spatial phase modulation that is inconsistent with driving of the oscillations by focal pacemakers. The hypothesis is developed that the synchronization manifests continuous distributions of activity in cortical neuropil that modulate firings of selected neural networks embedded in the neuropil. Five interactive agencies have been postulated to explain the mechanism for the field synchrony: electric fields; magnetic fields; electromagnetic fields (radio waves); diffusion chemical gradients; and order parameters that control self-organization of large populations of neurons by widespread synaptic interaction constituting negative and positive feedback. Only the last fits the data. The points are emphasized that these field patterns in frames require interactive neural dynamics that is modulated in respect to global operations mediating arousal, attention, selective emotional stance, wake, sleep, learn, habituate, dishabituate, *etc*., and that these operations require differing but complementary fields that form by massive parallel feed-forward architectures of brainstem neuromodulatory nuclei. An example is given using histamine of the neural discharges of brainstem nuclei that do not require fine spatiotemporal texturing of their firing; they operate by nonsynaptic release of neuromodulators that effect changes in background state, such that textured patterns of cortical activity can form and update in flexible adaptations of brains to their environments. These systems instantiate volume transmission by nonsynaptic diffusion transmission, in concert with the self-organization of the textured neural activity that supports cognition.

Keywords: EEG; field theory; neurodynamics; neuromodulators; nonsynaptic diffusion neurotransmission; oscillation; self-organization; synaptic transmission; synchronization.

1. Introduction

1.1. *20th century origins of neural field theory*

Behavioral studies in the first half of the 20th century by neuropsychologists, among them Wolfgang Köhler [33] and Karl Lashley [36], established neural field theory as a conceptual basis for explaining how brains make and control behavior. Their theory was founded on the existence of a continuous medium, the cortical neuropil, which contrasted with neural network theory as proposed by Hebb in his 1949 classic *The Organization of Behavior* where he introduced the neuroscience community to "nerve

cell assemblies [28].” Köhler in 1940 had summarized his studies of chimpanzees as follows: “Our present knowledge of human perception leaves no doubt as to the general form of any theory which is to do justice to such knowledge: a theory of perception must be a field theory. By this we mean that the neural functions and processes with which the perceptual facts are associated in each case are located in a continuous medium [33].” Köhler was led by Hans Berger’s discovery a decade earlier to identify his perceptual fields with the electric fields of the electroencephalogram (EEG). This was a classic instance of what philosopher Gilbert Ryle called a “category mistake:” confusing a phenomenon with one of its properties [12]. Roger Sperry in 1958 [57] tested Köhler’s hypothesis in cats and monkeys by cross hatching the visual cortex with mica strips, and by threading silver wires through the cortex to block or distort the electric fields. His animals revealed no losses in perceptual performance (see also [37]). Most physiologists abandoned field theory and Gestaltism along with it.

Lashley in 1929 [35] sought to localize specific memories in the cerebral cortices of his trained rats by systematic ablation of numerous cortical areas. He concluded that memory storage must be distributed, and that memory loss was proportional to the area of cortical destruction, leading to his hypothesis of “mass action” in the storage and retrieval of memories in support of behavior. This field conception brought him to a problem that he stated as follows: “Generalization [stimulus equivalence] is one of the primitive basic functions of organized nervous tissue. … Here is the dilemma. Nerve impulses are transmitted ... from cell to cell through definite intercellular connections. Yet all behavior seems to be determined by masses of excitation. ... What sort of nervous organization might be capable of responding to a pattern of excitation without limited specialized paths of conduction? The problem is almost universal in the activities of the nervous system (pp. 302-306 [36]).” Despite half a century of experimental study, Lashley found no resolution beyond ill-defined field properties of “resonance” and “cerebral interference patterns [37].”

Further development of brain field theory has been overshadowed in the second half of the 20th century by exploitation of the technologies for microelectrode recording of trains of action potentials of single cortical neurons in behaving animals, by genetic and developmental control of specific connectivities in sensorimotor pathways, by biochemical analyses of the molecular basis for synaptic modification in Hebbian and non-Hebbian learning; and by the mathematical theory of neural networks implemented with their offspring, digital computers.

Now in the 21st century new interest in brain field theory is aroused by the growth of two new technologies. One is brain imaging with EEG, magneto-encephalogram (MEG), and various methods for measuring cerebral blood flow and related metabolites (*e.g.*, functional magnetic resonance imaging (fMRI), positron emission tomography (PET), Single Photon Emission Computed Tomography (SPECT), and Blood-Oxygen-Level-Dependent (BOLD). The other is the development of prostheses for sensory substitution as described in several reports in this volume. Remarkable successes in these endeavors have proven four important and inter-related properties of neocortex: the exchangeability of its ports for sensory input, its ability to adapt rapidly and flexibly to short- and long-term changes, its reliance on large-scale organization of patterns of neural activity that mediate its perceptual functions, and the incredibly small amounts of information entering each port in brief behavioral time frames that support effective and efficient intentional action and perception.

1.2. *Five proposed agencies in the formation of brain fields*

These properties have all pointed to the importance of neural fields of activity and raised the question of what might be the agency by which the neurons in these fields might be induced to cooperate. The feature in Köhler's view [33] that distinguished a neural field from a neural network was the continuum for the field, not only in space but also in time and in scale from the subatomic through the molecular, neural and modular levels to the whole brain and beyond. The concept of the continuum restricts the class of agency to processes involving large populations of neurons in varying degrees of synchronized discharges, contrasting with selected modules or netlets embedded in cortical neuropil, as a means to resolve Lashley's dilemma. Five candidates for the agency of synchronization have been proposed and are being explored.

(1) Electric fields are revealed by the extracellular flow of dendritic current across the resistance of brain tissue [9], which is shown to be relatively fixed by simultaneously passing kiloHertz (kHz) currents across the tissue and measuring the amplitudes of externally imposed voltages [19]. The passive potential differences are measured as the EEG. Weak extracellular electric currents have been shown to modulate the firing of neurons *in vitro*, and have been postulated as the agency by which neurons are ephaptically linked together [58]. The current densities required *in vivo* to modulate cortical firings exceed by nearly two orders of magnitude those sustained by extracellular dendritic currents [9, 19].

(2) The intracellular current in palisades of dendritic shafts in cortical columns generates magnetic fields of such intensity that they can be measured 4-5 cm above the scalp with MEG. The earth's far stronger magnetic field can be detected by specialized receptors for navigation in birds and bees [64], leading to the search for magnetic receptors among cortical neurons (*e.g.*, [4, 8]), so far without positive results.

(3) The agency of electric and magnetic fields combined in propagating radio waves has also been postulated [1]. Radio transmission is unlikely owing to the 80:1 disparity between electric permittivity and magnetic permeability of brain tissue and to the low frequencies (<100 Hertz) and kilometer wavelengths of electromagnetic radiation at EEG frequencies.

(4) Chemical fields of metabolites provide manifestations of widespread coordinated firing; they have been estimated indirectly by measures of unit activity in studies of spike timing among multiple pulse trains (*e.g.*, [3, 42, 53]), of cerebral blood flow using fMRI or BOLD (*e.g.*, [52, 61]), and of spatial patterns of the distributions of radio-labeled neurotransmitters and neuromodulators as measured with PET, SPECT, and optical techniques. Answers to the question, how it is that broad and diffuse chemical gradients might induce phase locking of neural pulse trains at ms intervals, have been proposed in several essays in this volume in terms of nonsynaptic diffusion neurotransmission [5] as the mechanism for implementation of volume transmission. In my view nonsynaptic transmission is essential for neuromodulation, as I describe in Section 4 below, but diffusion is much too slow to explain the highly textured patterns and their rapid changes as described in Section 3 below.

(5) As an alternative to these four types of field I propose a fifth type, which is the emergent population activity of immense numbers of synaptically interactive

cortical neurons. This emergent patterning resembles in some respects the behaviors of swarms of insects, flocks of birds, and schools of fish. The agency that supports the emergent neural activity is neither the electric field of extracellular dendritic current nor the magnetic fields inside the dendritic shafts, which are much too weak, nor is it long-range diffusion, which is much too slow. It is Haken's "order parameter" [27] generated by the immense numbers of neurons and synapses, which creates and sustains a field that "enslaves" the neurons that generate it. Haken described this form of interaction as "circular causality" as distinct from "upward" and "downward" causation, because simultaneously the collective of particles (neurons) generated the field, and the field organized and modulated the collective.

2. Two Types of Architecture Underlying Two Types of Neural Fields

I propose that the contents of cortical activity that we experience subjectively as thought and observe objectively as behavior are created and executed in emergent neural fields of self-organized activity. Yet the order parameters are not by themselves sufficient to explain brain dynamics in behavior. Chemical fields from specialized nuclei in the brain stem are also necessary, although alone they are not sufficient either. My intent in Section 2 is to describe the unique contributions made by these two types of field in terms of their relevant architectures.

2.1. *Arthropods, cephalopods, and vertebrates*

The architectures of the central nervous systems of intelligent invertebrate animals differ markedly from those in vertebrate animals. The basic ground plan of bee and octopus is formed by two parallel chains of neurons resembling a ladder located ventral to the digestive system, from which and to which the axons of motor and sensory nerves extend. Typically eyes are located in the front of the animal above the mouth, which are serviced by large collections of neurons forming the dorsal cerebrum. Axons form bidirectional connections with the ventral nerve cords around the gut, so that the esophagus runs through the brain. Perhaps this is why all higher invertebrates are restricted to a liquid diet, lest they rupture their brains by swallowing solid food.

The brains of vertebrates do not encounter this limitation, because the central nervous system forms by invagination of the dorsal surface and creates the neural tube. The posterior part forms the spinal cord while the most anterior part forms the brain. Yet vertebrate nervous systems share the ladder-like architecture of invertebrates in two ways. One is the chain of sympathetic and parasympathetic ganglia that runs anteroposteriorly outside the spinal cord, servicing the adrenergic and cholinergic parts of the autonomic nervous system. The other is a paired collection of ganglia inside the ventral half of the anterior brainstem, that service the cerebrum with neuroamines, including noradrenaline, acetylcholine, serotonin, dopamine, and histamine, and several of the neuropeptides. This internal architecture is found in the brain stem and forebrain of all vertebrates [46], despite enormous variations in the forms taken by the dorsal forebrain and hindbrain, particularly in the mantles formed in the cerebral and cerebellar cortices.

These two structures – the ladder-like neuromodulatory chain and the cerebral cortex – both contribute to the creation of brain fields in differing but complementary ways. The characteristic topology of cortical neurons is feedback. Each pyramidal cell transmits to roughly ten thousand other neurons and receives input from a comparable number of others in its surround. Yet such is the density of cells and synapses that a neuron connects with less than one percent of neurons within its dendritic arbor, and the

likelihood of a direct reciprocal connection between pairs is extremely small, about one in a million. The excitatory postsynaptic potential evoked in any one neuron by any other single neuron is 30-fold too small to reach threshold for firing [4]. These numbers mean that every cortical neuron interacts with its neighborhood in a continuum and not with a few neurons in discrete neural networks formed by privileged synapses. The distributed feedback to every neuron from very many other neurons in large neighborhoods is the basis for the emergence of brain fields, primarily by mutual excitation that supports stable, long-term "spontaneous" background activity of the brain, and secondarily by negative feedback interactions of pyramidal cells with inhibitory interneurons that support the oscillations observed in the EEG and MEG [9, 13, 15].

2.2. *Feedforward divergence vs. feedback recruitment in the creation of brain fields*

All neurons form initially as spheres and then grow extended filaments of cytoplasm that become axons and dendrites. In cortex the short-axon neurons predominate in the formation of neuropil, which is the dense collection of cell bodies, dendrites, axons, glia and capillaries constituting "grey matter." Long-axon neurons are far less numerous than short-axon neurons, but even in low density their actions are important by introducing what are called "small-world" effects [68]; local activity is seeded broadly, so that no cortical neuron is more than a few synapses from any other neuron. This topological proximity by synaptic connections enables rapid changes in states of neuron populations over large areas of cortex [21, 67], the diameters of which exceed the mean length of cortical axons by two or more orders of magnitude.

Another topological property of neocortex is the power-law distribution of synaptic connection densities. This property results when very few cortical areas are connected with many other areas, while the majority of areas are connected with few other areas. The connectivity pattern has been analogized to the fractal connectivity patterns of airlines and the Internet [66]. Examples of high-density areas are the entorhinal cortex and the frontal poles, as well as the subcortical interconnections to the thalamic and midbrain reticular formation and cortical feedback to the brain stem neuromodulatory nuclei. In brains the putative fractal distribution gives rise to patterns of neural activity that are "scale-free," meaning that large spatial patterns form and dissolve as quickly as small patterns [15-17], which enables new patterns to form repeatedly at rates in the theta and alpha range over large areas of human cortex [21, 22] and presumably over the cortices of mice and whales despite the enormous difference in scale.

Wherever tested, the peaks and valleys in AM potential, corresponding to maxima and minima of dendritic current densities, also correspond to high and low pulse densities in the local neighborhoods, owing to the control of firing probabilities by the dendritic currents [10, 14]. The negative feedback formed by interactions of pyramidal cells with inhibitory interneurons provides not only for oscillations of activity in the beta and gamma ranges but also for spatial contrast enhancement that supports spatial patterns of amplitude modulation (AM) of shared carrier waves in the beta and gamma ranges [6, 17]. The widespread gap junctions among cortical neurons promote the shared oscillations by fixed positive feedback, while the modifiable excitatory synaptic connections between pyramidal cells provide by variable feedback the fine-grain textures of AM patterns that form during learning [23, 24, 34].

The architectures of the brainstem nuclei in contrast to cortex are characterized by dominance of forward projections. The axon of each ganglionic neuron has comparatively few local collateral branches within its ganglion; its axon extends far into the cerebrum, branches repeatedly and widely, and yet forms no synapses [5, 26]. Its

action potentials release its neuromodulator broadly and concomitantly with other axons in parallel, thereby creating a chemical field that is overlapping and superimposed on the emergent activity fields generated by populations of pyramidal cells. Herein lies the topological distinction between the neurotransmtters released by the pyramidal cells locally at specific synapses versus the neuromodulators released by the internal ganglionic chain that diffuse among the pyramidal cells and modify their synaptic transmissions nonsynaptically [5], thereby achieving volume transmission. In brief, the local and long-range synaptic interactive fields enable the emergence of highly textured spatial patterns of amplitude and phase modulation of neural firings in frames, and the global feedforward fields enable the state transitions by which sequences of patterns are continually updated with respect to changes in the internal and external environments of brain and body controlling affect and emotion [46].

3. Emergent Neural Population Fields with Contents at High Spatial Resolution

3.1. *Bistability of cortical populations*

The single neuron has the all-or-none property of bistability; it is either at rest or generating an action potential. The transition between states is induced by depolarization of the membrane. When a depolarizing current is applied in very small steps far from threshold, the neural dynamics is linear; responses to current steps are additive and proportional to input in correspondence with the principle of superposition. As threshold is approached, a nonlinear domain is encountered in which local responses occur that are greater than expected by proportionality, yet are still below threshold for a propagated action potential. In this domain an excitatory input not only produces depolarization; it sensitizes the neuron to further excitation.

The neuron population has a comparable bistability that is revealed by calculating the probability of firing of its neurons conditional on the amplitude of the dendritic currents as revealed by measuring the EEG amplitude [9]. The conditional probability is revealed by an asymmetric sigmoid function [13]. The derivative of the curve reveals the asymmetry as a peak that is displaced to the excitatory side of the resting state. This asymmetry shows that the population is sensitized by input, so that further input yields larger responses. This nonlinear property imposes a threshold on the dynamics of the population, so that if input to cortex exceeds the threshold, the mutual excitation among pyramidal cells leads to an explosive growth of activity by positive feedback. The result is a state transition by which cortex jumps abruptly from a resting, receiving state to an active transmitting state [13]. Spatial AM patterns form during the active state and dissolve as the cortex returns to its resting state after transmission. These state transitions in cortex form frames of AM patterns in a few ms, hold them for 80-120 ms, and repeat them at rates in the alpha and theta ranges of the EEG [15-17, 22]. These high rates of field modulation are not compatible with mediation by diffusion, yet are fully accounted for by known properties of self-organization in complex media [27].

3.2. *Formation of novel spatial AM patterns by learning*

AM patterns are measured with arrays of electrodes that are sufficiently closely spaced in the pial surface of cortex that the texture of the patterns can be observed and displayed in contour plots of the amplitudes of oscillations in the beta and gamma ranges [6, 17]. Each AM pattern is expressed as a 64x1 column vector that specifies a unique point in the 64-space, which is a finite projection from infinite brain state-space provided by the 64 electrodes. The degrees of similarities or differences among the spatial AM patterns of successive frames are calculated by Euclidean distances among

sets of points in 64-space in any of a variety of unsupervised clustering algorithms. Similar AM patterns form clusters each with its center of gravity; differing AM patterns form multiple clusters with centers, and classification is by finding the shortest distance of each point (frame) to the nearest center. This technique of multivariate analysis and classification has revealed the sensitivity of AM patterns to behavioral manipulation using classical Pavlovian conditioning [23] and operant conditioning [24]. On presentation of conditioned stimuli (CS) with either aversive or appetitive reinforcement, new AM patterns form that are expressed by new centers of gravity. The AM patterns were first found in the olfactory bulb and have since been identified in the prepyriform, visual, auditory, somatic, and entorhinal cortices [6, 17, 23].

The formation of each AM pattern in the EEG is by a state transition, which is manifested by a discontinuity in the EEG phase at a frequency in the beta or gamma range, followed by rapid resynchronization of the oscillations and then maintenance for a period of about a tenth of a second [6, 16]. The AM pattern emerges and stabilizes, followed by a brief dramatic increase in the analytic amplitude of the pattern. Each AM pattern is accompanied by a spatial pattern of phase modulation (PM) best seen at the peak frequency of the frame. The isophase contours of the PM pattern display the form of a cone. The location and sign of the apex of the cone (lead or lag) vary randomly, but the slope in radians/mm when converted to m/s by use of the frequency in Hz conforms to the conduction velocities of the intracortical axons running parallel to the pial cortical surface [18, 20] and not to the rate of diffusion in cortical neuropil.

I interpret the phase cone as the manifestation of a state transition in a distributed medium, which does not occur everywhere simultaneously but starts at a site of nucleation and spreads radially, in the manner of formation of a raindrop or a snow flake from a grain a dust. The PM patterns provide evidence that the state transition is mediated by the long axons in the cortical neuropil, which determine the limiting velocity and therefore the surface area of the frame of coordinated activity. Yet the amplitudes of the oscillations within the area of synchrony are not constrained and can express the AM patterns independently of the phase locking.

Simulations of the formation of AM patterns with networks of nonlinear differential equations have shown that the synapses that are modified during Hebbian and non-Hebbian learning are located between pyramidal cells [13] and give rise to attractor landscapes in each of the sensory systems [56]. The action of a CS is to select the proper basin of attraction that elicits the AM pattern governed by the selected attractor [17].

4. Modulatory Neural Fields at Low Spatial Resolution

The genesis of an AM pattern with its attendant PM pattern requires that the cortex be in a state that has been prepared by prior conditioning and learning. That preparation in turn depends on the operations of neuromodulators that operate broadly in correspondence to and presumably exceeding the breadth of the emergent fields of AM patterns. These global operations include sleeping, waking, arousal, selective attention, imprinting, associative learning, habituation, and normalization [34], which are carried out by the neuroamines (*e.g.*, norepinephrine [26]) and neuropeptides (*e.g.*, oxytocin [29, 32] that are widely distributed by brain stem ganglia with low spatial resolution.

4.1. *The example of histamine*

I concentrate my remarks on the example of the putative function of histamine as a nonsynaptic neuromodulator, because it is the least understood and the most in need of experimental study, yet it is representative of the feedforward dynamics of other

modulatory neuroamines and neuropeptides. I believe that its functions take place by modulation of the actions of gamma-amino butyric acid at gamma-aminobutyric acid (GABA)-A synapses. Few myths are more firmly entrenched in neurobiology than the view that GABAergic neurons are only inhibitory, despite the facts that both slow and fast excitatory actions have been demonstrated repeatedly in a broad range of invertebrates. A counter-example in mammals comes from the olfactory bulb, which has two main populations of GABAergic interneurons [50]. The internal granule cells have dendrodendritic reciprocal synapses with mitral cell basal dendrites, and the external granule (periglomerular) cell have axons synapsing onto each other and onto mitral cell apical dendrites in the glomeruli.

A neural network model of periglomerular function predicted more than thirty years ago that, whereas the internal granule cells inhibited the mitral cells, the external cells excited each other and mitral cells as well [9]. The model indicated that the periglomerular cells generated an excitatory bias that was essential to "turn on" (arouse) the olfactory system. This proposal was vigorously disputed [25], in part owing to confusion between presynaptic [62] and postsynaptic [54] inhibition. Experimental evidence has since accumulated [7, 40, 45, 48, 49] largely driven by the logic of mathematical models [10, 13], that the main action of periglomerular cells is excitatory. The most compelling histochemical evidence thus far is the recent finding, based on a technique pioneered 40 years ago by van Harreveld and Schadé [59], that periglomerular dendrites and probably mitral cell apical dendrites as well, accumulate intracellular chloride [55]. The finding implies that activated GABA-A receptors depolarize these cells by an outflow of chloride ions from their dendrites.

4.2. ***Open questions regarding the operations of neuromodulatory fields***

The significance of the findings extends beyond experimental pharmacology, because they offer a new perspective on possible roles of histamine in brain function. The histaminergic system suffers unjustified neglect, as demonstrated by a review article in *IBRO News* [51] on arousal systems of the brain, covering four amines - norepinephrine, dopamine, serotonin and acetylcholine - but failing to mention histamine. There is substantial histochemical evidence for the wide distribution in the forebrain of histaminergic axons arising from nuclei in the posterior hypothalamus [47, 63, 65], and there is equally compelling evidence for a substantial role of histamine in arousal reactions [38, 41].

The targets of these histaminergic projections include the olfactory bulb. Our model generates the hypothesis that histamine increases the chloride uptake of periglomerular cells, which increases the depolarizing action of GABA through A receptors and thereby the sustained excitatory bias that activates the olfactory neural networks, leading to arousal. There are major unanswered cellular questions. Do the periglomerular cells have an inwardly directed chloride pump? If there is a pump, is it activated by histamine? Is there any similarity between chloride transport in cortex and in the stomach? Are the EPSPs and the excitatory bias of the periglomerular cells augmented by histamine? Is the concentration gradient of chloride sufficient to explain the physiological effects? Are there other GABAergic populations in the forebrain that provide excitatory bias under histamine control for arousal?

Major pharmacological questions arise. Do peripherally administered antihistamines decrease or reverse the putative chloride transport? Is the rate of inward chloride transport in periglomerular cells augmented during anxiety states, and is it reduced by anxiolytics and sedatives? An obvious inference is that centrally acting antihistamines,

phenothiazines and benzodiazepines may have a common thread of action through chloride channels and GABA and histamine receptors. Conversely, is the rate of chloride transport abnormally low in clinical depression, as a part or even a main aspect of diminished arousal? The bulbectomized rat has been described as the best available animal model for clinical depression [30, 60]. Might a search among agents that promote chloride transport reveal new ways of treating clinical depression?

The literature on the pharmacological actions of behaviorally neuroactive substances relating to chloride transport and GABA (*e.g.*, [43, 60, 69]) reveals lack of full understanding of the actions of these agents on the complex synaptic systems involving GABA and the modulator amines. Excitatory actions of GABA have been explained at the cellular molecular levels by synaptic changes [2, 31] without reference to histamine, and with no impact as yet on the belief that diazepam acts to enhance an inhibitory action of GABA. There has been little change in this belief for nearly four decades, owing to widespread agnosia about the multifaceted actions of GABA, but also to experimental difficulties: intracellular chloride concentrations are extremely labile and very difficult to measure.

As induced by van Harreveld and Khattab [59] using asphyxia, massive shifts of chloride ions from neurons into glia occur with experimental trauma to brain tissue. This tendency should greatly concern researchers, because a normal excitatory action of GABA might be reversed to an inhibitory action in standard laboratory assays, owing to a substantial change in the direction of transmembrane chloride concentration gradients for which the GABA-A channels are opened. The questions should be asked, especially for *in vitro* studies of cortical slices and slabs, what is the direction of the chloride gradient normally, and what is it when the physiological measurements are made?

5. Conclusions

These and related questions arise with all other neuromodulators, brought on by complexity in the forms of proliferating receptor subtypes [44], nonlinear feedback regulatory mechanisms [30], ionic concentration dependencies [2], and multitransmitter interactions [69]. Evolutionary pressures for selection act on behavior, not on single genes or molecular receptors, and the effects of shaping will be seen in the performance of densely interactive populations of neurons. A molecular approach one receptor at a time may further confuse rather than enlighten investigators. Mathematical models that encompass interactive wholes [9, 14, 39] can give broad pictures that may prove necessary for informed development of more theoretically oriented neuropsychopharmacology [14]. Central to this effort will be the recognition of broad, non-topographic, nonsynaptic actions of neuromodulators on the populations of neurons that use synapses to do the work of generating specific goals, the behaviors needed to achieve them, and the specific sensory feedback necessary for evaluation of behaviors. Nonsynaptic neural transmission should form an essential component of brain models, such as those that depend on synaptic interaction for self-organization, that purport to simulate and explain the genesis of animal and human behaviors.

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