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Nonsynaptic Diffusion Neurotransmission and Some Other Emerging Concepts

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This paper is dedicated to Keith Killam. Keith was a wonderful pharmacologist, teacher and friend, who died recently. I had the privilege of working with him at UCLA in the i950's, studying the newly discovered GABA neurotransmitter and other fascinating topics. One of our papers was published in volume 3 of these Proceedings [1]. With Keith, I learned about diffusion, which later led to the concept of nonsynaptic diffusion neurotransmission. Our Science paper [2] may have been the first ever to demonstrate the selective (and contrasting) action of pharmacological agents on different parts of the brain. For this, Keith should have received much more credit than he has.

In the exciting environment of his laboratory, Keith loved to play with ideas. In that spirit, this paper will reflect emerging and possibly overly optimistic concepts of mechanism of brain function, especially those related to space and energy conservation, brain plasticity and recovery of function. I think Keith would have liked it.

Portions of the following have appeared in a number of publications.

NONSYNAPTIC DIFFUSION NEUROTRANSMISSION: Nonsynaptic diffusion neurotransmission (NDN) has emerged as a mechanism of information transmission that may play multiple roles in the brain, including normal and abnormal activity, brain plasticity and drug actions [3,4]. NDN, also called volume transmission [5], includes the diffusion through the extracellular fluid of neurotransmitters released at points that may be remote from the target cells, with the resulting activation of extrasynaptic receptors, as well as intrasynaptic receptors reached by diffusion into the synaptic cleft. NDN also includes the diffusion of substances such as nitric oxide (NO) and carbon monoxide (CO) through both the extracellular fluid and cellular membranes,

NDN may play a role in learning. The demonstration [6] of spreading potentiation, extended by Schuman and Madison [7], strongly suggests that a principal mechanism of brain plasticity (long-term potentiation; LTP) involves both selective synaptic changes as well as distributed potentiation by means of diffusion to nearby cells. News report, "Learning by diffusion,, in Science has called attention to this mechanism [8].

Early studies on regional distribution of enkephalin in the brain pointed out discrepancies, or "mis-matches", between opiate peptide distributions and opiate receptors, such as those between dense enkephalin-containing terminals and sparse opiate receptors [9]. These were initially considered to be exceptional instances. However, Herkenham [10] has reviewed the evidence for mismatches for various neurotransmitters, including peptides, monoamines and amino acids, He concluded that, in the brain, mismatches are the rule rather than the exception (which could mean that synaptic transmission may not be quantitatively the principal neurotransmission mechanism). Studies from Basbaum's laboratory have demonstrated that mismatches in substance P receptors and sites of release (only 15% synaptic apposition was noted). This has been interpreted, in the presence of electron microscopic evidence of widespread (70%) coverage of the cell surface by substance P receptors, as supporting that "much of the surface of substance P receptor- expressing neurons can be targeted by substance P that diffuses a considerable distance from its site of release"[11].

Recent studies on the extracellular space, calculating the diffusion of ions in the brain stem microenvironment in the living brain [12,13), confirm the conclusions of van

Harreveld [14] and others that about 20% of brain tissue is extracellular space. Furthermore, work carried out in Routtenberg's laboratory in the late 1960s demonstrated that transmitters could readily more in the extracellular space [15]. Microdialysis studies show that virtually all the neurotransmitters are found in the extracellular fluid [16,l7], confirming that the conditions exist for NDN.

The comparative efficiency of diffusion and "wiring" (synaptic) transmission in the massive, sustained activity with which the locus coeruleus is associated, has recently been discussed [18]. The coerulean system can activate over a long period of 'time at a relatively low energy cost. The varicosities are generally not part of a junction, and so release of norepinephrine must take time to diffuse through the extracellular fluid to extrasynaptic receptors. Activity induced in the distant dendritic tree takes con-siderable time to reach the soma, where the influence is maintained over a period of time. In the absence of a junction, inactivation of the norepinephrine is slowed: the synapse has a full panoply of degradation enzymes and re-uptake mechanisms, while nonjuctional receptor sites posses few if any of these inactivating devices. Glial mechanisms provide still another mechanisms for affecting the time course of norepinephrine activation. We concluded, therefore, that the effect of nonjunctional norepinephrine is likely to be both more massive and longer lasting than a similar quantity of norepinephrine released at synapses [18]

NDN may be the primary information transmission mechanism in certain normal mass. Sustained functions, such as sleep, vigilance, hunger, brain tone and mood [19] and certain responses to sensory stimuli, as well as several abnormal functions, such as mood disorders, spinal shock, spasticity, shoulder-hand and autonomic dysreflexia syndromes, and drug addiction [3,4,20-22], Very recent evidence that the serotonergic system may play a role in cocaine addiction [23] opens intriguing questions about the role of up-and down-regulation of nonsysaptic receptors, and possible opens an avenue for studies on addiction prevention and treatment.

Even before the era of molecular biology, the exclusivity of the synapse as a means of transmitting information had been questioned, when results obtained from intra- and extracellular microelectrode studies of polysensory brain stem neurons could not be fit into the prevailing connectionistic theory of

brain function[24]. I interpreted the result as suggesting the presence of diffusion neurotransmission. Having worked in Keith Killam's laboratory with neuroactive substances injected into the ventricles that must have diffused through the brain to reach their sites of action (e.g.,[25]), the concept of diffusion neurotransmission followed naturally. Thus, I have Keith to thank for preparing me to develop the concept of NDN.

Following their demonstration of neurotransmitter filled varicosities distant from synapses. Beaudet and Descarries [26] suggested that the biogenic amines released form non-synaptic varicosities may act not only upon adjacent post-synaptic surfaces, but also in tissue of more distant receptor elements. More recent studies have confirmed and extended those findings [27-29]. These and other early diffusion neurotransmission studies have been summarized [4,5].

Individual movements of functions, such as playing the piano, or watching a tennis game, require great selectivity, synaptic action is essential. However, for mass sustained functions (e.g., sleep, mood, hunger), sustained, widespread activity (rather than speed and selectivity9 is required, which appear to be largely mediated by NDN [4,19]. Many functions may be produced by combination of both types of neurotransmission.

In the piano playing example presented above, in addition to the relevant synaptic mechanisms, the finger movements can be more precise in the presence of adequate preparation including changes in brain tone (probably mediated by norepinephrine). The visual perception of the tennis game may require neuronal receptivity to be set at a high level, probably involving several neurotransmitters, including nitric oxide [30] and dopamine [31] in the retina, serotonin and histamine in the lateral geniculate nucleus [32,33] and norepinephrine in the visual cortex [34,35]. These effects appear to be primarily non-synaptically mediated. Some of them have been called modulation; the modulation of synaptic activity by diffusion outside the synaptic gap is also a nonsynaptic, diffusion-mediated activity.

NDN may play a role in the actions of neuroactive drugs, many of which may not act primarily on synapses, although only synaptic action is usually considered. For example, Barondes [36] discussed the changes n psychiatric practice that have occurred with the widespread use of prozac, and he commented on the possible mechanisms of action of prozac. These were considered strictly in terms of synaptic information transmission. Similarly, a Nature news and views commentary on the recent report of the role of serotonin in cocaine addiction refers only to synaptic transmission [37]. However, serotonin, which Barondes pointed out is involved in the action of prozac, is among the most highly nonsynaptic monoamines in the central nervous system; it may be as much as 96 % nonsynaptic in some systems [29,38-40]

Thus, other than the conceptual limitations imposed by the present synaptic-dominated model of brain function, there is no reason to consider that prozac or any of the drugs used in psychopharmacology operate exclusively via synaptic mechanisms [41]. In fact, accumulating evidence suggests the contrary [3,4]; the primary mechanisms may be by NDN.

Within the context of the above discussion of NDN, this should not be a surprise. Mood is a mass sustained function [19]. It is more comparable to hunger, pain and sleep than it is visual perception and fine motor movements, which require synaptic activity (but which also have important NDN components at all levels [4]. Thus disorders of mood (and other psychiatric disorders) may be disorders of NDN mechanisms.

Vizi [42-45] noted that drug have difficulty reaching the receptors intrasynaptically. He noted that the sensitivity of nonsynaptic receptors is higher, and they are much more accessible to drugs. Receptors located presynaptically or prejunctionally (and thus by definition, outside of the synaptic cleft) must be reached by means of diffusion through the extracellular fluid. Vizi suggested that diffusion neurotransmission may be the primary means of activation of receptors by externally applied or administered drugs.

Thus, concepts of the effects of dugs on the CNS have progressed form a consideration of the effects of specific agents on the brain; to a consideration of their differential effects on specific regions of the brain [2], to an understanding of their effects on specific neurotransmitter systems, to knowledge of their specific intra- and extra-cellular mechanisms. The addition of an understanding of the mechanisms of transport within the brain and activation of synaptic and extra-synaptic receptors (as well as intracellular activation following diffusion across membranes, such as by NO; Synder [46] has referred to NO as "one of the main neurotransmitters in the brain") should aid in the development and in the evaluation of the mechanisms of action of effective drugs, such as prozac, for psychiatric disorders.

LATE BRAIN PLASTICITY: Experimental design and experimental methodology mcthod01ogy is limited by the conceptual boundaries of thc then— dominant paradigm (discussed extensively in Chapter l of [41]). The still-dominant localizationist concept of brain function is not compatible with adult brain plasticity, and even developmental plasticity fits with difficulty into that model. An example is thc study by Nobel laureates Hubel and Viesel [47] of the "permanent" amblyopia that results from eyelid suture during the critical period of visual development in kittens. Their conceptual framework evidently was thc prevailing connectionist-localizationist model that did not include brain plasticity. They noted some recovery of vision in the deprived eye, especially when the normal eye was sutured, and one cat showed further progress during thc 4 1/2 years of testing. However, they concluded: " The effects of monocular deprivation for the first three months of life tend to be permanent, with very limited morphological, physio1ogical or behavioral recovery"

Furthermore, instead of considering the behavioral recovery (that occurred even in the absence of specific training) to be of importance, Dews and Wiesel [48] stated: "The partial recovery from the effects of deprivation should not be a1lowed to obscure the essentially permanent changes in thc visual system..." Thc fact that they did not interpret their findings as supporting evidence for plasticity is consistent with the observations of Fleck [49]: "Evidence conform to conceptions just as often as conceptions conform to evidence. After all, conceptions are not logical systems.... They are stylized units which either develop or atrophy just as they are or merge with their proofs into others. Analogously to social structures, every age has its own dominant conceptions as well as remnants of past ages and rudiments of those of the future".

Studies such as the excellent experiments of Hubel and Wiesel on the critical period emphasize the importance of the

"conceptual substance" [50] of the neurosciences. Hubel and Wiesel [47] had concluded that, if the eyelids of one eye of a kitten are sutured closed for the duration of the critical period of normal visual development, that eye is permanently amblyopic following the removal of the sutures-even if the cat lives for 5 years or more with the eyelids functioning normally. However, Chow and Stewart [51] asked the critical plasticity question: can recovery of vision be obtained with an appropriate training (rehabilitation) program? Not only were they were able to demonstrate that it is possible to obtain some function (vision), but they also recorded concomitant physiologic changes (increased numbers of binocular cells in the visual cortex) and morphologic changes (in the lateral geniculate body). In addition to the brain plasticity findings, the description of procedures is pertinent to human rehabilitation. For example, it was noted that commonly used rewards were insufficient; the cats required periods of "gentling" and petting (to establish an affectionate bond with the experimenters), and the experimenters' approach to developing a demanding and intensive rehabilitation program while avoiding frustration is of particular interest.

In a pioneering rehabilitation study. Weiss and Brown [52] transposed the biceps femoris muscle (a flexor) to the extensor side of a knee joint to substitute for the weakened or lost action of a paralyzed quadriceps muscle (an extensor). Initially the muscle contracted only in the flexor phase, but "surprisingly few trials were required to make the transplant suddenly contract in the extensor phase." After further trials the muscle operated only in the extensor phase. Even then, however, temporary lapses into the old flexor pattern occurred repeatedly, even years after the operation. These relapses seemed to be favored by fatigue, lack of concentration, automaticity of movement, etc. Weiss and Brown [52] suggested that the adjusted use of the transplant is based not on the substitution of a permanent extensor association for its former flexor association, but rather on the development in higher centers of a new type of action that can effectively override the innate coordinative associations without abolishing them.

In a comparable context, we have studied the development of sensory substitution in blind persons (see be1ow) and of coordinated face movements in patients who have had the XII cranial nerve (genetically programmed to control tongue, not face, muscles) connected to the peripheral portion of the VII nerve, following loss of facial nerve function, and following an appropriate rehabilitation program which can be initiated even many years after the damage [4].

Comparably, persons with brain damage due to stroke, tumor or trauma have, in selected studies, shown the capacity to recover functions with appropriate rehabilitation even many years after the damage has occurred. As under the classical connectionist-localizationist model of brain function recovery is not usually expected, it is not pursued with sufficient effort in most cases. Recovery from brain damage is one of the most dramatic examples of the limiting effects of the existing conceptual framework on clinical treatment, A more plastic model of brain function creates opportunities for studies of the contributions of psychological, behavioral and pharmacologist interventions (in general, beyond the critical periods of development, the reorganization does not occur spontaneously) to the process of reorganization and recovery [4,53,54].

SENSORY SUBSTITUTION: As the first model of late brain plasticity, we have previously developed tactile vision substitution systems (TVSS) to deliver visual information to the brain via arrays of stimulators in contact with the skin of one of several parts of the body (abdomen, back, thigh, finger-tip). Optical images picked up by a TV camera are transduced into a form of energy (vibratory or direct electrical stimulation) that can be mediated by the skin receptors. The visual information reaches the perceptual levels for analysis and interpretation via somatosensory pathways and structures.

After sufficient training with the TVSS, our blind subjects reported experiencing the images in space, instead of on the skin. They learned to make perceptual judgments using visual means of analysis, such as perspective, parallax, looming and zooming, and depth judgments. Our studies with the TVSS have been extensively described [4,55]

After training, our blind subjects using the TVSS system do not feel anything on the skin on which the interface is placed; rather they perceive it out in three dimensional space they control the camera movement. Although the TVSS systems have only had between 100 and 1032 point arrays, the low resolution has been sufficient to perform complex perception and "eye"-hand co-ordination tasks. These have included facial recognition, accurate judgment of speed and direction of a rolling ball with over 95% accuracy in batting the ball as it rolls over a table edge, and complex inspection-assembly tasks.

The tactile system is as capable as the visual and auditory systems for information transmission [4,55,56], but it has largely been ignored. One reason may be man machine interface problems; we have developed a tongue interface, which overcomes many of those problems [57]. In addition to vision substitution, this approach may also have, applications to deaf persons, persons with high quadriplegia or limb prostheses, and for augmented communications systems in aviation, perception in dark environments, robotics, and underwater exploration.

For the brain to correctly interpret information from devices, it is not necessary that it be presented in the same form as in natural sensory information systems. We do not see with the eyes [55]; the visual image does not go beyond the retina, where it is turned into patterns of pulses along nerves. Those individual pulses are not different from the pulses from the big toe. it is the brain that recreates the image from the patterns of pulses. We have demonstrated that the brain is able to recreate "visual" images that originate in an artificial receptor (a TV camera), are transduced into a tactile display (the TVSS system), and carried to the brain via tactile nerve pathways. Thus, it is only necessary to present the information from a device in a form of energy that can be mediated by the receptors at the man-machine interface, and for the brain, through a motor system (e.g., a head-mounted camera under the motor control of the neck muscles), to know the origin of the information.

ASSEMBLLES OF NBURONS: ln i949 Hebb [58] developed the concept of the "cell-assembly", with enormous numbers of individual cells simultaneously aroused by extensive activity, and with every point connected to every other point. It has had an impact on later brain scientists [59-61]. Its impact continues unabated after almost 50 years. Hebb wished to lay the foundations for a theory of the mental values of behavior (such

as thought. expectancy, interest, volition, emotion and attention) that would also comprise the main facts of perception and learning, and would relate to neurosis, psychosis and recovery from brain damage.

Hebb considered his cell-assembly theory to be a form of connectionism, with the individual cells joined by means of nerve fibers and synapses. This does not appear to be materially possible. Our calculations revealed that in a cell-assembly of 100,000 cells, to connect every cell to every other cell with just one fiber of the shortest possible length with a single synapse (in contrast to exclusive NDN innervation which would have no fibers connecting the cells), would require 8000 km of nerve and would increase the volume of the cell-assembly by 200 times [62]. The energetic costs would be unreasonably large, leading to excessive heat production (Aiello and Bach-y-Rita, submitted). We also analyzed the role of the extracellular space (ECS), and of changes in neuronal excitability with ECS reduction accompanying neuronal swelling with activity [63]. We have suggested in those publications that cell assemblies are connected by a combination of nerve fibers and NDN.

The dependence on timing that Hebb considered to be necessary for optimal function of the cell-assemblies was difficult for him to explain in his synaptic model. However, delays are a characteristic of NDN models of cell-assemblies. The initial NDN studies revealed delays of up to 4 s, which were considered to be related to multi-plexing of polysensory pontine cells that could have the effect of reducing the numbers of cells needed for sen- sory messages [24,64]. NDN has been proposed for mass sustained functions such as mood, wakefulness, and sustained pain [19]. These are comparable to the cell assembly-related functions mentioned by Hebb: thought, expectancy, interest, emotion and attention. NDN would easily provide for the 0.5-1.0 s time delay, which Hebb related to perception.

Delays in NDN systems can be due to: the size and irregular geometry of diffusion channels in the ECS (tortuosity); extracellular matrix molecules (ECM); fine neuronal and glial processes; changes in the extracellular volume fraction, such as due to astrocyte and cellular swelling ions, and to other ECS constituents [12,13,65]. Sykova [66] noted that large molecules in the ECS can slow down the movement (diffusion of various neuroactive substances through the ECS...(and) can hinder diffusion of molecules so that they are confined to certain places, while diffusion to other brain regions will be facilitated".

A strong role for NDN does not in any way diminish the importance of synaptic connectivity, which is essential and possibly exclusive for some functions, although even in such synaptic-dominated functions as vision, there are many NDN mechanisms in the retina, lateral geniculate nucleus and visual cortex [41. Mitcheson [67] suggested that connectivity appears to be minimized in the brain. Cell-assemblies that are a combination of synaptic and NDN connectivity would be consistent with that view.

MULTIPLEXING: Multiplexing in the brain consists of the multiple uses of neurons and fibers so that they participate in various functions. Studies have demonstrated multiple sensory [24,68,69] and motor [70] representations of a single brain region, and overlap of representation. This may provide the neural substrates for plastic changes with training. Examples include the greatly increased cortical representation of a fingertip area in monkeys following training in haptic exploration reported by Jenkins et al.[71],and the expanded finger motor cort representation in piano players and in the sensorimotor cortex in Braille readers [721. Human functional magnetic resonance imaging studies [68] have Strongly suggested that in thc primary hand region around the central sulcus, the same neuronal population is active in the three tasks studied (active finger apposition, texture on fingers, and haptic exploration).

Lesions or temporary suppression of a sensory input can unmask multiple sensory inputs to a cell [73,74]、which may be mobilized in motor and sensory recovery fo1lowing peripheral nerve or brain damage. The nonvisual (auditory and tactile) sensory representation demonstrated in primary visual cortex [69] has been shown to be active in the visual cortex of adult congenitally blind persons [75]. This may represent the unmasking of previously week tactile and auditory inputs to the primary visual cortex demonstrated by Murata, Cramer and Bach-y-Rita [69]. Almost half of the primary visual cortex cells that responded to visual stimuli also responded to tactile and auditory stimuli, but with longer latencies, and those nonvisual inputs were more easily blocked.

The nonvisual pathways to the visual cortex may also be unmasked in Braille readers, in whom transcranial magnetic stimulation has shown a robust tactile representation in the visual cortex [76], In the normal cat visual cortex, in addition to visual inputs, weak auditory somatosensory responses can be recorded [69]. These appear to be unmasked by the loss of the visual input [75], resulting in significant PET scan activity in response to auditory and tactile inputs in blind persons.

Multiplexing of sensory convergent cells was demonstrated in the pontine brain stem in 1964 [23]. A large number of those neurons showed both early and late responses, with latencies of up to four seconds and more. The late response latencies were essentially the same to all types of stimuli to which the cell responded, although the latency of the early responses were dependent on the conduction distance to the cell (e.g., longer to tail or hind limb stimulation than to anterior limb or Whisker stimulation). Analysis of the data from ablation and other destructive lesion studies did not support the possibility that the late responses were due to conduction along slow pathways.

The interaction of the responses to stimulation of more than one modality or area demonstrated occlusion in many highly convergent brainstem cells. Furthermore, repetitions of the same stimulus during the silent period between the early and late responses not only failed to modify the original late response, but failed to evoke further late responses.

These results suggested a mechanism with a long time course that allowed the convergent cell and its related structures to elaborate the information from the original stimulus and temporarily to block the responses from various types of sensory receptors in various part of the body for a period of time that, in those studies, ranged from hundreds of milliseconds to several seconds. Although this class of cells is convergent, this would allow serial rather than simultaneous responses to the various potentially activating inputs, thus allowing the same cell to be involved in information analysis and transmission from many inputs, but to only one input at a

time. This could greatly reduce the number of cells required to process the sensory information; instead of separate cells for each sensory input from each part of the body, a small number of highly convergent cells could perform the same operations. However, such cells would require the temporary blockage of other sensory information while elaborating the sensory information from one modality from one body locus.

In that early study [24], diffusion (NDN) mechanisms were considered to play a role in the inhibition of the sensory responses. A comparable inhibitory diffusion mechanism has recently been demonstrated in the hippocampus: dynorphin, which is co-stored with glutamate in mossy fibers, can cause a long-lasting inhibition of mossy fiber synaptic responses by decreasing glutamate release [77]. The authors consider the distant heterosynaptic effects to be mediated by dynorphin diffusing in the extra-cellular fluid.

Some nerve fibers may also be multiplexed, and thus rather than simple conductors of information, at least some of them appear to be complex computational structures [61].

EXTRACELLULAR SPACE VOLUME FRACTION: The extracellular space (ECS) in the brain plays a role in many functions, including nonsynaptic diffusion neuro-transmission. In an assembly of cells in the brain, the distance between neurons can be reduced by 50% with neuron activity that causes them to swell. This has an effect on the excitability and metabolism of the cells by means of changes in the distance between the neurons and, which produces, among other things, changes in ionic concentrations and dynamics [63].

Changes in the size of the extracellular compartment (volume fraction; VF) may play a role in membrane excitability in pathological brain states such as brain damage, epileptiform discharges and pain, and in the survival of partially denervated neurons during the post-injury period of receptor up-regulation that can lead to reorganization of brain function by unmasking and other mechanisms. Glial cells, which have receptors and release sites for neurotransmitters, play a role in neurotransmission via diffusion through the extracellular space [4].

Under pathological conditions, such as anoxia and spreading depression, the EVF is reduced [78-80], and it is also reduced (by up to 50%) in hyperexcitability, changes in the concentration of potassium, and with epileptiform discharges [81,82]. Hochman et al. [83] noted that the neuronal synchronization involved in epileptiform activity can be disassociated from synaptic excitability, and proposed that the nonsynaptic mechanisms that underlie the action of furosemide(a chloride cotransporter antagonist) are related to cell volume regulation and in particular to glial swelling.

Brain cell swelling due to anoxia and brain trauma, leading to a decreased EVF, may aid in the survival of partially denervated neurons during the post-injury period of receptor up-regulation (shown to follow damage to the brain in animal models [84] and in humans [85]). Those cells may respond to previously sub-threshold stimuli, either synaptically, or by NDN, which generally involves activation of membrane surface receptors [4]. However, it is also possible that hyperexcitability due to a volume fraction decrease, either independently or in combination with excitotoxic activity, may increase secondary cell death following brain damage [63].

LOW THRESFIOLD PATHS FOR TRANSIUISSION OF NEURAL ACTIVITY CREATED RONAL AND GLIA SWELLING DURING ACTIVITY: VF studies [63] suggest a role for glial cells in the- NDN studies showed how glia could participate in neurotransmission by diffusion of neurotransmitters through the extracellular fluid [4]. The VF studies suggest that changes in the volume of glial cells may alter the extracellular space volume fraction, thus influencing membrane excitability. Change in the volume of glial cells (and neurons) that alter the ECS-VF in specific areas of the brain may provide a pathway for information transmission. Thus, if cells in a particular region of the brain swell, they will facilitate the direction taken by neural activity, and thus messages can be directed through those swollen cells. This offers the possibility of another, biophysical, mechanism of neurotransmission in addition to those that have been described. It may also be a mechanism of selective regional activation.

SPACE AND ENERGY CONSERVATION IN THE BRAIN: There appears to be a law of space and energy conservation in the brain [57]. A wasteful arrangement of neural processes could significantly increase the volume of the cortex. Some of the mechanisms discussed above such as NDN and multiplexing, appear to save space; and in a recent study we have calculated the enormous energy utilization differences with synaptic versus nonsynaptic diffusion neurotransmission (Aiello and Bach-y-Rita, submitted). The plastic mechanisms that subserve space and energy conservation are among those that appear to provide the neural substrates for recovery of function (with appropriate rehabilitation) following brain damage.

EARLY EXPERIENCE, VESTIGIAL PATHWAYS AND ADULT PLASTICITY: A recent report that late plasticity in the adult owl auditory system is dependent upon early exposure to similar experiences, which leave enduring traces [86] raise interesting questions as to the nature of the factors that provide the basis for the adult plasticity.

Studies demonstrating the absence of polyneuronal innervation of the multiply-innervated extraocular muscle fibers in adult cats, in spite of evidence of polyneuronal innervation of muscle fibers from embryonic state though early infancy [88], led to speculation that the pruning back of the polyneuronal nerve fibers may leave trace, or “vestigial” pathways that could be accessed by future functional demands [89]. In the case of muscle innervation, polio produces the loss of motor neurons, which leads to giant muscle units; the surviving motor neurons develop pathways to the denervated muscle fibers. Could the new innervation use these “vestigial” pathways? Could pruning back, a common event in the developing brain, leave traces that can be beneficial when plasticity is required?. –

We have analyzed the possible microenvironment mechanisms for specific neural activity, due to volume fraction changes and changes in cellular excitability [63]. Other factors that merit exploring include the “traces” left in the form of up- or down-regulation neurotransmitter receptor sites on nerve cells, and glial changes.

Knudsen's results are important for an understanding of the mechanisms of plasticity. However, laboratory animals with

limited early experiences may not be appropriate for studies of adult function and plasticity [87]. They may have fewer such traces than animals raised in their natural habitat, where multiple experiences and stimuli may produce more “trace pathways” and opportunities for adult brain plasticity. Indeed, these studies could provide a rationale for Head Start and other human early intervention programs.

CONCLUDING COMMENTS: In the neurosciences, the absence of a formal structure for theoretical studies, in contrast to physics and chemistry where theoreticians form a well-accepted branch of the specialty, has led to the persistence of mainstream concepts well beyond the time when accumulating experimental evidence demands a change.

Since the beginning of this century, the synaptic model of information transmission has been firmly established, and has virtually excluded other concepts of neurotransmission in the brain. The connectionist-Localizationist model of brain function has led to a concept of a rigidly wired brain that has virtually excluded plasticity concepts.

However, there is increasing evidence that extra-synaptic diffusion may be a major space and energy conserving mechanism of information transmission, especially for mass sustained functions such as vigilance mood and pain, and may play a role in pathological state such as the shoulder-hand syndrome and drug addiction. Furthermore, accumulating evidence demonstrates malleable brain, able to reorganize at all stages of life. Thus, recovery of function following brain damage becomes more achievable, and the contributions of psychological, behavioral, physical, and pharmacological interventions in the process of recovery can be extensively explored.

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