ELSEVIER

Restorative Neurology and Neuroscience 10 (1996) 1–3

Restorative Neurology
and
Neuroscience

Guest editorial

Conservation of space and energy in the brain

Paul Bach-y-Rita*

Department of Rehabilitation Medicine, University of Wisconsin, 1300 University Ave, Room 2756, Madison WI 53706, USA

Keywords: Neurotransmission; Brain plasticity; Non-synaptic diffusion neurotransmission; Functional localization; Neurologic rehabilitation

There appears to be a law of conservation of space and energy in the brain. Many cells (e.g., [2]), as well as axons [17] are multiplexed, neuronal connectedness may be constrained resulting in minimal brain volume for the tasks performed [13], and neural coding may optimize information transmission [14]. Furthermore, wiring (synaptic) transmission appears to be held to a minimum in those systems that can function with less space and energy-consuming information transmission methods [4]. The parsimonious nature of its use of energy and space allows the brain to accomplish all of its myriad tasks with a small mass and with low energy consumption.

A number of studies have demonstrated multiple sensory (e.g., [2,11]) and motor (e.g., [8]) 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. [7], and the expanded finger motor cortex representation in piano players as well as in the sensorimotor cortex in Braille readers, reported by Pascual-Leone and Torres [12]. As yet unpublished human functional magnetic resonance imaging studies from Burnod's laboratory in Paris (Burnod, personal communication) have strongly suggested that in the 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 [9,15], which may be mobilized in motor and sensory recovery following peripheral nerve or brain damage. The non-visual (auditory and tactile) sensory representation demonstrated in primary visual cortex [11] has been shown to be very active in the visual cortex of adult congenitally blind persons [16].

Saberi and Hafter [14] demonstrated a 'neurally economical solution to how the auditory system encodes (FM and AM) sounds'. Most naturally occurring sounds are modulated in amplitude or frequency. The authors interpreted their results as demonstrating an FM to AM transduction, leading to a common neural code for frequency and amplitude modulated sounds, thus avoiding dual neuronal systems in the brain.

Bach-y-Rita [4] has recently examined the evidence for low energy, sustained activation of cell assemblies by non-synaptic diffusion neurotransmission (NDN). He noted that this may represent the majority of information transmission in the brain, especially for mass, sustained functions such as pain, mood and hunger. A detailed discussion of the issues raised here appears in that book. Below, two examples of space and energy conservation will be presented:

1. Multiplexed Pontine sensory cells

Sensory convergent cells were demonstrated in the Pontine brain stem [2]. A large number of those neurons showed both early and late responses, with latencies of up to 4 sec and more. The late response latencies were essentially the same to all types of stimuli to which

* Corresponding author, fax: +1 608 265 3757.

0922-6028/96/$15.00 © 1996 — Elsevier Science Ireland Ltd. All rights reserved
PII S0922-6028(96)00330-X

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.

The experimental 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 block the responses from various types of sensory receptors in various parts 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 1964 study [2], 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 [18]. The authors consider the distant heterosynaptic effects to be mediated by dynorphin diffusing in the extracellular fluid.

2. The coerulean system

The comparative efficiency of diffusion (NDN) and 'wiring' (synaptic) transmission in the mass, sustained activity with which the locus coeruleus (LC) is associated, has recently been discussed [5]. The very few (approximately 13 000 cells per hemisphere in the human; [6]) LC cells innervate many hundreds of millions of cells by means of long axons that meander through the brain. Apparently, selective regional release of noradrenaline occurs.

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 noradrenaline must take time to diffuse through the extracellular fluid to extrasynaptic receptors. Activity induced in the distant dendritic tree takes considerable time to reach the soma, where the influence is maintained over a period of time. In the absence of a junction, inactivation of the noradrenaline is slowed: the synapse has a full panoply of degradation enzymes and re-uptake mechanisms, while non-junctional receptor sites have few if any of these inactivating devices. In view of the largely non-synaptic nature of noradrenaline innervation of the brain (c.f., [5]), glial mechanisms provide still another mechanisms for affecting the time course of noradrenaline activation.

We concluded therefore, that the effect of non-junctional noradrenaline is likely to be both more massive and longer lasting than a similar quantity of noradrenaline released at synapses. Furthermore, in the absence of synapses, many fewer nerve fibers are required. Thus, the LC-noradrenaline system appears to be an excellent example of space and energy conservation in the brain.

3. Relevance to restorative neurology

The ability of individual cells and neuronal systems to subserve more than one function, and the multiple representation of functions, appear to be mechanisms of developmental and learning plasticity, but they also offer alternate neural systems that can serve as the basis for reorganization after brain damage. However, the existence of these alternatives does not mean that the reorganization will automatically occur after brain damage, although some 'spontaneous' recovery occurs that may be related to plastic changes such as neurotransmitter receptor up- and down-regulation. In fact, it would appear from studies reviewed elsewhere [4], that appropriate rehabilitation is required to obtain optimal reorganization, both in the early stages and in late neurologic rehabilitation. Thus, patients who have reached a sustained plateau lasting for years have been shown to regain important functions after initiating late rehabilitation programs.

But how are the alternate systems mobilized by the rehabilitation? Proposed mechanisms [4] include the following: following cell loss from brain damage, surviving cells that have been totally or partially denervated may have one or more of three responses: (a) the 'strengthening' of synapses from secondary connections, which should involve changes in the sizes of the synapses and an increased neurotransmitter release

from the presynaptic cell; (b) the development of extrasynaptic receptors on the membrane of the surviving cells, which respond by means of NDN mechanisms; or, (c) receptor development related to the new synapses formed by the sprouting of processes from surviving cells. Physical and occupational rehabilitation, and psychosocial (e.g., social and environmental) factors influence these mechanisms in as yet unknown ways. However, to obtain long-term functional changes, cellular protein changes must occur. Agnati et al. [1] have recently reviewed some of the early immediate gene actions that are stimulated by neurotransmitters in the extracellular fluid that could produce lasting changes, and Bach-y-Rita [3] has noted that the actions of neuroactive medications appear to operate largely on the NDN systems.

An understanding of the neural mechanisms underlying brain reorganization after damage should lead to improved rehabilitation procedures, to the optimal timing of the introduction of the various procedures, to the efficient attention to the psychosocial issues that can influence the reorganization, and to the rational use of medications that affect specific neurotransmitter systems.

4. Conclusion

The conservation of space and energy appears to be a guiding principle of brain organization and function. The evidence discussed above is consistent with the view of Mitchison [10], who has recently noted that it would be reasonable to expect that the cortex has been organized so as to keep the 'wiring', axons and dendrites, which take up 30% of the mass of the mouse brain (and more in larger brains; [13]), to a minimum. A wasteful arrangement of neural processes could significantly increase the volume of the cortex. 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.

Acknowledgements

Partial support was obtained from the National Institutes of Health, National Eye Institute Research Grant 1-RO1-EY 10019, the CNRS unité URA 316 (Université Paris V) and the Fondation pour la Recherche Medicale (Paris). The warm hospitality of the Maison Suger, Maison des Sciences de L'Homme, Paris, is greatly appreciated.

References

[1] Agnati, L.F., Zoli, M., Strömberg, I. and Fuxe, K., Intercellular communication in the brain: wiring versus volume transmission, *Neurosci.*, 69 (1995) 711–726.

[2] Bach-y-Rita, P. Convergent and long latency unit responses in the reticular formation of the cat, *Exp. Neurol.*, 9 (1964) 327–344.

[3] Bach-y-Rita, P., Psychopharmacologic drugs: Mechanisms of action (Letter), *Science*, 264 (1994) 642–644.

[4] Bach-y-Rita, P., *Non-synaptic Diffusion Neurotransmission and Late Brain Reorganization*, Demos, New York, 1995.

[5] Bach-y-Rita, P. and Smith C.U.M., Comparative efficiency of volume and synaptic transmission in the coerulean system: relevance to neurologic rehabilitation, *Scand. J. Rehab. Med.*, 25 (1993) 3–6.

[6] Foote, S.L. and Morrison, J.H., Extrathalamic modulation of cortical function, *Annu. Rev. Neurosci.*, 10 (1987) 67–95.

[7] Jenkins, W.M., Merzenich, M.M., Ochs, M.T., Allard, T. and Guic- Robles, E., Functional reorganization of primary somatosensory cortex in adult owl monkeys after behaviorally controlled tactile stimulation, *J. Neurophysiol.*, 63 (1990) 82–104.

[8] Leyton, A.S. and Sherrington, C.S., Observations on the excitable cortex of the chimpanzee, orangutan and gorilla, *Quart. J. Exper. Physiol.*, 11 (1917) 35–222.

[9] Merzenich, M.M., Kaas, J.H., Wall, J.T., Nelson, R.J., Sun, M. and Felleman, D., Topographic reorganization of somatosensory cortical areas 3b and 1 in adult monkeys following restricted deafferentation, *Neurosci.*, 8 (1983) 33–55.

[10] Mitchison, G., Axonal trees and cortical architecture, *Trends Neurosci.*, 15 (1992) 122–126.

[11] Murata, K., Cramer, H. and Bach-y-Rita, P., Neuronal convergence of noxious, acoustic and visual stimuli in the visual cortex of the cat, *J. Neurophysiol.*, 28 (1965) 1223–1239.

[12] Pascual-Leone, A. and Torres, F., Plasticity of the sensorimotor cortex representation of the reading finger in Braille readers, *Brain*, 116 (1993) 39–52.

[13] Ringo, J.L., Neuronal interconnection as a function of brain size, *Brain Behav. Evol.*, 38 (1991) 1–6.

[14] Saberi, K. and Hafter, E.R., A common neural code for frequency- and amplitude-modulated sounds, *Nature*, 374 (1995) 537–539.

[15] Wall, P.D., Mechanisms of plasticity of connection following damage in adult mammalian nervous systems. In P. Bach-y-Rita (Ed), *Recovery of function; theoretical considerations for brain injury rehabilitation*, Hans Huber, Bern, Switzerland, 1980, pp. 91–105.

[16] Wanet-Defalque, M.C., Veraart, C., DeVolder, A., Metz, R., Michel, C., Dooms, G. and Goffinet, A., High metabolic activity in the visual cortex of early blind human subjects, *Brain Res.*, 446 (1988) 369–373.

[17] Waxman, S.G., Regional differentiation of the axon: a review with special reference to the concept of multiplex neurons, *Brain Res.*, 47 (1972) 269–288.

[18] Weisskopf, G.P., Zalutski, R.A. and Nicoll, R.A., The opioid peptide dynorphin mediates heterosynaptic depression of hippocamoal mossy fiber synapses and modulates long-term potentiation, *Nature*, 662 (1993) 423–427.