ELSEVIER

INTERNATIONAL JOURNAL OF PSYCHOPHYSIOLOGY

International Journal of Psychophysiology 35 (2000) 179–187 www.elsevier.com/locate/ijpsycho

Hierarchical neuronal modeling of cognitive functions: from synaptic transmission to the Tower of London

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Abstract

Recent progress in the molecular biology of synaptic transmission, in particular of neurotransmitter receptors, offers novel information relevant to 'realistic' modeling of neural processes at the single cell and network level. Sophisticated computer analyses of two-dimensional crystals by high resolution electron microscopy yield images of single neurotransmitter receptor molecules with tentative identifications of ligand binding sites and of conformational transitions. The dynamics of conformational changes can be accounted for by a 'multistate allosteric network' model. Allosteric receptors also possess the structural and functional properties required to serve as coincidence detectors between pre- and post-synaptic signals and, therefore, can be used as building blocks for a chemical Hebb synapse. These properties were introduced into networks of formal neurons capable of producing and detecting temporal sequences. In more elaborate models of pre-frontal cortex functions, allosteric receptors control the selection of transient 'pre-representations' and their stabilization by external or internal reward signals. We apply this scheme to Shallice's Tower of London test, and we show how a hierarchical neuronal architecture can implement executive or planning functions associated with frontal areas. (Académie des sciences/Elsevier, Paris.)

1. Introduction

Any attempt to integrate, within a single causal model, anatomy, activity and a defined behavior hinges upon several difficulties (see Changeux and Dehaene, 1989 for discussion). The first one is the definition of nested hierarchical levels of organization (from the molecular cellular circuit to the higher circuit levels) at which a given behavioral performance can be assigned; a classical source of error, indeed, is the attempt to relate a given cognitive function to an organization which does not exhibit the required structural complexity and vice versa. A second issue is the 'style' of information processing postulated for the artificial organism under modeling; in many instances, the standard information processing input-output scheme of the cybernetics and of classical physiology has to be abandoned in favor

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0167-8760/00/$ - see front matter
PII: S0167-8760(99)00052-5

of a projective style, according to which the organism constantly anticipates and tests the outside world (as its own private world) by producing a diversity of 'pre-representations'. Last, many of the elementary building blocks currently utilized in model building are taken from physiological and often phenomenological experiments; the recent progress in the molecular biology of synaptic transmission offers additional elementary mechanisms particularly relevant to 'realistic' modeling at the single cell and network levels.

2. Modeling synaptic transmission and its regulation at the neurotransmitter receptor level

In recent models of formal neurons (Amit, 1989, see also Churchland and Sejnowski, 1992; Arbib et al., 1998), the basic synaptic units are viewed as transmitting devices in which pre-synaptic penetrating ionic currents specify the amount of neurotransmitter release and, accordingly, the 'efficacy' of the synapse. Quantal analysis of neurotransmitter release mechanisms and their regulation has indeed produced important sets of data which have been modeled on computers, thus offering new tools for the formalization of neural networks and for the depression/facilitation of their connections (Korn and Faber, 1993). On the other hand, fast and/or slow receptor mechanisms (excitatory or inhibitory) at the post-synaptic level on the output neuron as on the nerve endings at the terminal and/or preterminal level do contribute, in a significant (or sometimes dominant) manner, to the regulation of synaptic 'efficacies' (review in Andersen et al., 1993; Fuxe et al., 1998).

The 'fast' channel-linked receptors, and the 'slow' metabotropic G-protein-linked receptors are composed of two major families of neurotransmitter receptors with distinct three-dimensional organizations (Changeux, 1996). The archetype of the first one is typified by the nicotinic acetylcholine receptor, with four transmembrane spanning segments (glutamate receptors may compose a separate family) (review Galzi and Changeux, 1994; Changeux and Edelstein, 1998). The second follows the pattern of the bacteriorhodopsin-β-adrenergic receptor with seven transmembrane spanning segments (Henderson et al., 1990; Lefkowitz et al., 1993). In the absence of three-dimensional X-ray crystallographic data, sophisticated electron microscopy at high resolution yields, after extensive computer treatment, images of single receptor molecules down to atomic resolution. Moreover, affinity labeling and site-directed mutagenesis experiments have resulted in the identification of amino acids from a variety of critical sites. Progress in the understanding of these receptor molecules and of their regulatory properties is thus expected from the computer reconstruction of their three dimensional functional organization.

In the case of the ligand-gated ion channels, the introduction of chemical kinetics methods where binding of agonist and channel opening were measured directly and in parallel, in vitro on membrane 'microsacs' (Changeux, 1981), has given the opportunity to evaluate new parameters and by consequence to test new theoretical models. Extension to membrane-bound receptors of the two-state Monod-Wyman-Changeux scheme for allosteric transitions, initially designed to account for the structural and kinetic properties of cytoplasmic regulatory enzymes, has lead to the demonstration that the nicotinic receptor may undergo a 'cascade' of discrete conformational transitions between resting (low affinity, closed) state, active (medium affinity, fast, open) state and desensitized (high affinity, slow, refractory) state. Formal models of such allosteric network mechanisms (Changeux and Edelstein, 1998) offer simple explanations for the remarkable pleiotropic phenotypes observed with acetylcholine nicotinic, glycine and serotonine receptors (such as the simultaneous loss of desensitization; the enhanced affinity, the alterations of channel properties, the spontaneous opening of the channel, the switch of some antagonists to agonists) as a consequence of single mutations within the channel domain M2 (Galzi et al., 1996). Similarly, point mutations within G-protein-linked receptors may stabilize constitutively active conformations of G-protein-linked receptors in the absence of ligand (Lefkowitz et al., 1993).

An important assumption of the allosteric

model is that at variance with sequential models these different conformations may spontaneously exist, in equilibrium prior to ligand binding. Accordingly, the physiological effect of agonists/competitive antagonists is viewed as the selective stabilization of the particular conformation of the receptor to which they selectively bind. Moreover, physiological effectors such as divalent cations, neuropeptides, voltage, phosphorylation/dephosphorylation modulate the response of these receptors without directly interacting with the agonist binding site but via the differential regulation of 'activatable' vs. 'refractory' conformations of the receptors, thus determining the efficacy of the synapse at the post-synaptic level. Depending on the initial balance between conformations the regulation might either be a potentiation or a depression (see Changeux and Edelstein, 1998).

3. An 'allosteric' Hebb rule and the concept of synaptic triad

A popular model for near coincidence detection between pre- and post-synaptic excitation has been suggested in the recent years for the glutamate-NMDA receptor on the basis of the voltage-dependent block of the ion channel by Mg^{2+} (see Wigstrom et al., 1993). The pre-synaptically released glutamate activates the NMDA receptor channel only if, at the same moment, the post-synaptic membrane is sufficiently depolarized to release the Mg^{2+} block of the channel. This model is indeed parsimonious: only two states (R and A) are required. However, the voltage-sensitive Mg^{2+} block (or homolog) is rarely encountered in other species of ligand-gated ion channels (cationic or anionic).

On the other hand, a large majority of ligand-gated ion channels display desensitization and/or potentiation with kinetics which may be fitted by allosteric models. In addition, because of their transmembrane disposition these receptors carry sites on both their synaptic and cytoplasmic sides letting the molecule integrate within a given time window multiple convergent pre-and post-synaptic signals. A time coincidence detection mechanism may then be built from the discrete all-or-none mechanism of the slow allosteric transitions between, for instance, the R and D states. Simulation experiments, indeed, show that, using the values of the parameters determined with Torpedo AChR, changes of synaptic efficacy following a Hebbian rule can be obtained which may, in theory, last seconds or even minutes. Moreover, a distinctive property of neuronal nicotinic receptors is their high Ca^{2+} to Na^{+} permeability ratio (Mulle et al., 1992; Vernino et al., 1992; Bertrand et al., 1993) which approaches that of the glutamate-NMDA receptor. As a consequence, in nicotinic brain receptors (as in other brain receptors), Ca^{2+} influx through the open channel may elicit second messenger cascades, resulting in long-term modulations. It is thus expected that a better knowledge of the actual contribution of the neurotransmitter receptors to these processes, as their modeling, will directly contribute to the understanding of elementary learning mechanisms at the synaptic level.

Moreover, incorporation of allosteric receptors into networks of formal neurons may further contribute to the modelization of interactions between synapses, for instance, at the post-synaptic level. On the basis of observations on the acquisition of song by birds, a model of neural networks that learn temporal sequences by selection was proposed (Dehaene et al., 1987) which relied upon allosteric receptors, included within a device made up of three neurons, the synaptic triad. In a triad the efficacy of a synapse of neuron A on neuron B is influenced by a third neuron C, called a modulator. If the synapse A-B is excitatory and its post-synaptic receptor spontaneously in a 'refractory' conformation, then, synapse C-B will be able to switch the post-synaptic receptor of synapse A-B into an 'activatable' state by releasing a diffusible chemical messenger. As a consequence, synapse C-B has to be active before synapse A-B and with a determined time delay for signals to be transmitted by synapse A-B. This short-term modification of synaptic efficacy thus creates a mechanism for time-sequence detection and production (Dehaene et al., 1987).

In addition, since the post-synaptic receptor of synapse A-B may follow the 'allosteric Hebb rule',

then a longer term modification of synaptic efficacy may take place at its level. Introduction of this rule leads to the differentiation of sequence detecting neurons and to the stabilization of ongoing temporal sequences.

It is of interest that trials, composed of a dopamine terminal and of a presumed excitatory input together with a spine of a pyramidal cell have been identified in pre-frontal cortex by electron microscopy (Goldman Rakic, 1995). Similar devices have also been assumed for elementary learning in simple networks such as in Aplysia (Kandel) or cerebellum (Ito), though in a different conceptual network (see (Changeux and Edelstein, 1998) for discussion).

4. Levels of organization and selection by reward in formal networks performing delayed response tasks

Attempts have been made to build more elaborate formal models of neural architecture which are able to perform cognitive tasks such as delayed response (Changeux and Dehaene, 1989) and Wisconsin Card sorting task (Dehaene and Changeux, 1991) which both tax the prefrontal cortex. Pre-frontal cortex has expanded at the fastest rate in the course of mammalian evolution and its lesions cause profound cognitive disorders in humans. Pre-frontal areas, together with the anterior cingulate, may collectively function as a 'central executive' or 'working memory' system controlling and maintaining on line information from and to other brain areas. Our network simulations provide concrete examples of how this system may operate (see Fig. 1).

The basic units of the network have been defined as clusters of synergic neurons, the state of activity of which is assumed to code for an elementary neural representation. Each cluster is formalized as a set of (possibly) hundreds of neurons densely interconnected by excitatory synapses which may exist in at least two self-sustained states of activity (with either a high or a low frequency of discharge). As a consequence, they are able to store memories through short delay periods. In the models, clusters are linked together by axon bundles. In order to carry out learning tasks, some of these links have to be modulated. The local synaptic organization that we have postulated for the modulated links is the above mentioned synaptic triad (Dehaene et al., 1987).

The global architecture of the networks is assumed to encompass two distinct levels of organization: (a) a low level (no. 1), which governs the orientation of the organism toward an object with a defined feature and would correspond to a visuo-motor loop including visual areas and the premotor cortex; and (b) a high level (no. 2), which controls the behavioral task according to a memory rule and would be homologous to the pre-frontal cortex or closely related areas.

A key feature of the model is that level two contains a particular category of clusters referred to as rule coding, which each code for a single dimension (position, color, shape, etc.) of the environment. Their connectivity is hierarchically organized in such a way that they 'globally' regulate the efficacy of bundles of connections, involved in the processing of particular features of the environment (input-output and memory clusters from the lower level). This second level gives the organism the opportunity to abstract 'categories' from the environment which are more general, though more 'complex' than particular features of the cues.

During the acquisition step, the layer of rule-coding neurons is assumed to play the role of a generator of diversity. According to the model: (a) the rule-coding clusters are active spontaneously, but because of lateral inhibition, only one cluster will be active at a time; and (b) the activity of this particular cluster changes at random with time in such a way that the organism is able to test successively one (or the other) of the dimension rules upon its environment. In other words, a search by trial and error takes place, until a positive reward is received. Then, the particular cluster active at this precise moment is selected. At present, the postulated mechanism of production of pre-representations is too simple to be fully realistic. First the range of variability to which the generator has access is very small: one among few possibilities. Moreover, the rule-coding clusters are assumed to be pre-established in

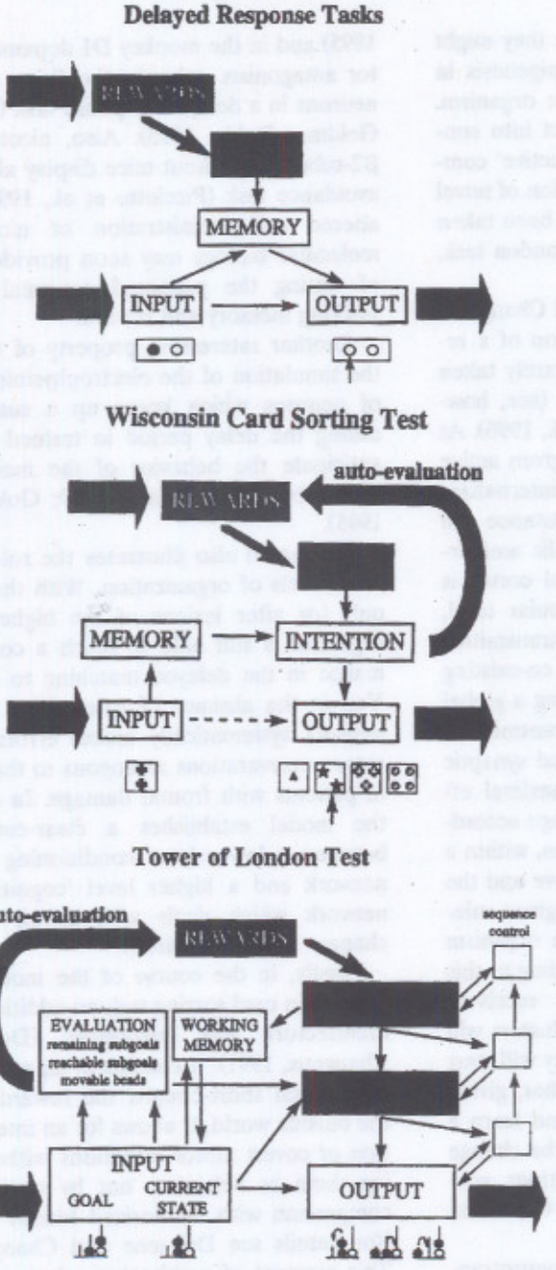

Fig. 1. Schematic description of the architecture of three models for distinct functions related to pre-frontal cortex. For details, see refs. (Changeux and Dehaene, 1989; Dehaene and Changeux, 1991, 1997). All three models embody a top-down hierarchy of neuronal assemblies whose activity is modified in a selective manner by reward signals. Reward unit activity can be specified by a teacher external to the organization, as in the delayed response tasks used with animals, or it can be internally generated by an auto-evaluation loop. In the latter case, the network becomes a critic of its own activity.

the initial state of the organism while they might plausibly be established via active epigenesis in the course of the development of the organism. Future models should take this aspect into consideration and introduce more 'productive' combinatorial mechanisms for the generation of novel behaviors. Steps in this direction have been taken with a new model of the Tower of London task, detailed below.

The model suggested (Dehaene and Changeux, 1991) offers an original implementation of a reward mechanism, a process which is rarely taken into account by connectionist models (see, however, Barto et al., 1983; Montague et al., 1996). At the network level, the selection of a given active rule-coding cluster is viewed as an 'internalization' of the outside world via, for instance the limbic system and/or the mesencephalic aminergic neurons with which the pre-frontal cortex is densely interconnected. At the molecular level, the reward signal would be a neurotransmitter such as dopamine, acetylcholine or a co-existing messenger (Hokfelt et al., 1992) exerting a global modulatory action e.g. via volume transmission (Fuxe and Agnati, 1991) or via targeted synaptic triads (Goldman-Rakic, 1995). The maximal efficacy of the synaptic triads would change according to an allosteric Hebb rule as long as, within a given time window, the reward is positive and the post-synaptic neuron is active. Once a given rule-coding cluster has been stabilized, the organism will continue to perform the task according to this rule, unless a negative reward is received. Destabilization of all the rule-coding clusters will then take place, the spontaneous activity will start to vary again from one cluster to another, giving the organism the chance to discover and learn a new rule. The speed of recovery from the change of receptor efficacy, under these conditions, governs the memory span of the generator (Dehaene and Changeux, 1991).

In the formal model, receptors for neurotransmitters and/or neuro-modulatory signals thus play a crucial role. Indeed in the rat, a nicotinic receptor antagonist neuronal bungarotoxin decreases the working memory performance of a delayed matching to sample task (Granon et al., 1995) and in the monkey D1 dopaminergic receptor antagonists enhance the firing of the delay-neurons in a delayed response task (Williams and Goldman-Rakic, 1995). Also, nicotinic receptor β2-subunit knockout mice display altered passive avoidance task (Picciotto et al., 1995) as well as altered self-administration of nicotine. Thus, molecular biology may soon provide new means of testing the proposed neuronal circuits for working memory and reward.

Another interesting property of the model is the simulation of the electrophysiological activity of neurons which keeps up a sustained firing during the delay period in trained animals and anticipate the behavior of the monkey (review Watanabe, 1986; Fuster, 1989; Goldman Rakic, 1995).

The model also illustrates the role of two distinct levels of organization. With the lower level only (or after lesions of the higher level), the organism is still able to reach a correct performance in the delayed matching to sample task. Yet, in the absence of rule-coding clusters, the network systematically makes errors. It displays error perseverations analogous to those observed in patients with frontal damage. In other words, the model establishes a clear-cut difference between a lower level conditioning or 'routine' network and a higher level 'cognitive' memory network which deals with novel, non-routine, changes in task demands.

Finally, in the course of the modeling of the Wisconsin card sorting task an additional piece of architecture was introduced (Dehaene and Changeux, 1991). It consists of an auto-evaluation loop which short-circuits the reward input from the outside world. It allows for an internal evaluation of covert motor intentions without actualizing them as behaviors but by testing them by comparison with memorized former experiences (for details see Dehaene and Changeux, 1991). This element of architecture gives access to enhanced rates of learning via an elementary reasoning process. Still, the 'mental experiments' authorized by this autoevaluation loop are rather simple minded. For a more complex behavioral paradigm where the above neural architectural

principles could be applied, we turned to a classical test of pre-frontal function, the Tower of London (Shallice, 1982).

5. A Hierarchical network for the tower of London test

The Tower of London (Shallice, 1982) is derived from the classical Tower of Hanoi test. It consists in moving three colored beads, mounted on vertical rods of unequal length, from an initial position to a pre-specified goal. Patients with pre-frontal cortex lesions experience difficulties in achieving a coherent solution (Shallice, 1982; Owen et al., 1990; Goel and Crafman, 1995). Solving the problem calls for mentally planning, by trial and error, a series of moves that successively brings all of the beads to their desired location. We recently developed a network model, described in greater detail elsewhere, that implements this planning process (Dehaene and Changeux, 1997). The key elements used in our previous models were used. First, the model spontaneously generates tentative solutions to the problem at hand in a top-down, projective manner. Second, such 'generation of diversity' occurs at multiple hierarchical levels. Third, auto-evaluation is used to evaluate whether each tentative move brings the problem closer to a solution or not, and the unfolding plan is amended or accepted through selection by an internal reward system.

The schematic architecture of the model is shown on the figure. The model is divided into two main components: a descending planning system (right) and an ascending evaluation system (left). In the descending planning system, the current plan unfolds internally at each of three hierarchical level: plans, operations and gestures. Activation of plan units causes a series of activation's at the lower operation level, with a fringe of variability. Each activation of an operation unit in turn causes the sequential activation of two units at the lower gesture level, one for pointing to a bead and another to point to its new location. Hence, the descending planning generates a variable, 'embedded' hierarchical sequence of internal moves.

This sequence, however, is not entirely random, but is limited by constraints provided by the ascending evaluation system. Based on the given of an initial state and a goal state, this system computes which beads are movable, which subgoals (misplaced beads) remain to be solved, and which subgoals are directly reachable. When a bead can be placed directly at its final location, the corresponding operation is activated and executed immediately, without calling for plan unit activation. Only if no such move is available are plan units needed to activate the 'generator of diversity' of operation units and to generate a tentative move.

As in the Wisconsin Card Sorting model, a key element of the network is the internal reward and auto-evaluation system. In the Tower of London test, no external feedback is received at all about the correctness of tentative moves. Hence, in our model, reward units are now exclusively activated by an internal auto-evaluation loop. The total activation of remaining goal units is used to compute an internal estimate of distance to the goal: when this total activation decreases, it means that the last move brought the problem closer to a solution. Hence, in our network, the temporal derivative of total remaining goal unit activity is used to activate positive or negative reward units. The latter in turn activate dedicated plan units that either validate the previous move and store it in working memory, or reject it and return to a previous memorized state.

When simulated, the model generates solutions in a manner remarkably similar to normal subjects. In particular, it shows a gradient of difficulty similar to humans. Simple problems that call only for one, two or three direct moves are solved without trial-and-error. For more difficult problems, the network generates a complex internal sequence of trial-and-error that often rapidly converges to a valid solution. Measurement of the networks error rates and solution times indicate a close match to data from normal human subjects (Morris et al., 1988a; Ward and Allport, 1997). When plan or reward units are deteriorated in the simulation, however, the resolution of com-

plex problems becomes selectively impaired, as observed in actual experiments with pre-frontal patients (Shallice, 1982; Fuster, 1989; Owen et al., 1990; Goel and Crafman, 1995; Granon et al., 1995; Picciotto et al., 1995; Williams and Goldman-Rakic, 1995). The lesioned networks generate random trajectories that wander aimlessly in problem space. Their planning deficit can be attributed to an inability to guide the selection of motor operations by an internal evaluation of their relevance to reaching the goal, a characterization which also applies to human frontal patients (Goldman-Rakic et al., 1992; Sirigu et al., 1996).

The model makes several novel behavioral, neuropsychological and physiological predictions for experiments. One crucial concern is the role of internal reward systems in guiding and selection reasoning processes. Diffuse catecholaminergic projections systems are predicted to be active and to play an important role in problem solving. Lesions of dopaminergic neurones may be simulated in the model by removing the reward units, while alterations of dopamine action on its receptors and/or related signal transduction mechanisms (Picciotto et al., 1995) may be mimicked by altering the parameters determining the impact of reward units on plan units. In both cases, a severe planning deficit similar to that caused by plan unit lesions is observed, in good agreement with the deficits of Parkinsonian patients in the Tower of London test (Morris et al., 1988b; Owen et al., 1992; Owen et al., 1995).

6. Conclusion

We have described how a consideration of basic principles of architectural, cellular and molecular organization of the brain can guide the development of simple models of brain function. While these models may appear simplistic compared to the complexity of actual cerebral networks, we believe that they capture significant aspects of cerebral function: its projective nature, its organization in multiple parallel circuits, and its constant modification through selection by internal reward signals. Through computer simulation, the known molecular properties of receptor channels intervening in reward and working memory circuits can then be tentatively related to specific functional roles.

References

Amit, D.J., 1989. Modeling Brain Functions. Cambridge University Press, Cambridge.

Andersen, P., Hvalby, O., Paulsen, O., Hokfelt, B., 1993. Memory Concepts; Basic and Clinical Aspects. Novo Nordisk Foundation Symposium no. 7.

Arbib, M., Erdi, P., Szentágothai, J., 1998. Neural organisation. The MIT Press, Cambridge, Mass., USA.

Barto, A.G., Sutton, R.S., Anoerson, C.W., 1983. Neuron like elements that can solve difficult learning control problems. IEEE Trans. Syst. Man. Cyber SMC. 13, 834–846.

Bertrand, D., Galzi, J.L., Devillers-Thiéry, A., Bertrand, S., Changeux, J.R., 1993. Mutations at two distinct sites within the channel domain MII alter calcium permeability of neuronal alpha 7 nicotinic receptor. Proc. Natl. Acad. Sci. U.S.A. 90, 6971–6975.

Changeux, J.P., Dehaene, S., 1989. Neuronal models of cognitive functions. Cognition 33, 63–109.

Changeux, J.P, 1981. The acetylcholine receptor: an 'allosteric' membrane protein. Harvey Lectures. Acad. Press Inc.

Changeux, J.P., 1996. Neurotransmitter receptors in the changing brain signal transduction, gene expression and pathology at the molecular level. In: Magnusson, D. (Ed.), The Lifespan Development of Individuals Behavioral Neurological and Psychological Perspectives – A Synthesis, pp. 107–133.

Changeux, J.P., Edelstein, S., 1998. Allosteric receptors after 30 years. Neuron 21, 959–980.

Churchland, P., Sejnowski, T., 1992. The Computational Brain. MIT Press.

Dehaene, S., Changeux, J.P., 1991. The Wisconsin card sorting test: theoretical analysis and simulation of a reasoning task in a model neuronal network. Cereb. Cortex 1, 62–79.

Dehaene, S., Changeux, J.P., 1997. A hierarchical neuronal network for planning behavior. Proc. Natl. Acad. Sci. U.S.A. 94, 13293–13298.

Dehaene, S., Changeux, J.P., Nadal, J.P., 1987. Neural networks that learn temporal sequences by selection. Proc. Natl. Acad. Sci. U.S.A. 84, 2727–2731.

Fuster, J.M., 1989. The Prefrontal Cortex, 2nd Ed. Raven Press, New York.

Fuxe, K, Agnati, L., 1991. Volume Transmission in the Brain: New Aspects for Electrical and Chemical Communications. Raven, New York.

Fuxe, K., Grillnei, S., Hölsfelt, T., Olson, L., Agnati, L., 1998.