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Biomolecular Information, Brain Activity and Cognitive Functions

Alfredo Pereira Jr[1] and Fábio Augusto Furlan[2]

[1] Department of Education, Institute of Biosciences, São Paulo State University (Unesp), BRAZIL
[2] Faculty of Medicine and Nursing, University of Marilia, BRAZIL

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Abstract

Pereira Jr A, Furlan FA. Biomolecular Information, Brain Activity and Cognitive Functions. ARBS Annu Rev Biomed Sci 2007;9:12-29. Molecular neurobiology has provided an explanation of mechanisms supporting mental functions as learning, memory, emotion and consciousness. However, an explanatory gap remains between two levels of description: molecular mechanisms determining cellular and tissue functions, and cognitive functions. In this paper we review molecular and cellular mechanisms that determine brain activity, and then hypothetize about their relation with cognition and consciousness. The brain is conceived of as a dynamic system that exchanges information with the whole body and the environment. Three explanatory hypotheses are presented, stating that: a) brain tissue function is coordinated by macromolecules controlling ion movements, b) structured (amplitude, frequency and phase-modulated) local field potentials generated by organized ionic movement embody cognitive information patterns, and c) conscious episodes are constructed by a large-scale mechanism that uses oscillatory synchrony to integrate local field patterns.

Keywords: biomolecular information, molecular neurobiology, brain function, cognition, local field potentials

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[1] **Correspondence**
Alfredo Pereira Jr. Departmento de Educação, Instituto de Biociências, Universidade Estadual Paulista (UNESP), Campus de Rubião Jr., CEP 18618-000, Botucatu, SP, Brazil. E-mail: apj@ibb.unesp.br

1. Introduction

A large number of findings in scientific disciplines as neuropsychology, biological psychiatry, neurology, molecular neurobiology, cognitive and affective neuroscience suggest that cognition and conscious experiences depend on brain activity. Lesions of specific areas in the brain lead to specific cognitive and/or affective deficits; imbalance of neurochemical systems lead to altered states of consciousness, and brain anesthesia produces a loss of consciousness. Although most neuroscientists and cognitive scientists agree that brain activity is necessary for cognition and consciousness, knowledge of brain science has not been regarded as sufficient to explain these phenomena.

For instance, the identification of *brain areas* activated during cognitive and emotional processes is not sufficient to explain *the experiences* (*e.g.*, pain) supported by these areas. In order to elucidate the role of biomolecular mechanisms in the generation of mental life, we argue that they are responsible for *the tuning of cellular activity into large-scale patterns that support cognitive processes*. In the above example, the tuning of neuronal membrane activity by means of molecular effectors (*e.g.*, neuropeptides) would define the difference between pain and pleasure.

Our reasoning assumes the existence of prototypical cognitive patterns, such as hunger, thirst, sensations of hot and cold, pain and pleasure; visual features as color, shape and movement, auditory features as tone, intensity and timbre, etc.. We adopt a view of prototypes as informational patterns emerging from the activity of a cognitive system interacting with the environment, as proposed by Rosch (1975), Lakoff (1987), Johnson (1987) and Gärdenfors (2000, 2004).

Prototypes are organized (or self-organized) into complete mental episodes by means of a non-linear combinatorial process, making room for the emergence of new properties. Emergentism is the assumption that the result of a combinatorial process can be richer than the sum of the combined elements (see Stephan, 1999) For instance, molecules are not alive, but the interaction of molecules forming a cell constitues a living system. In this example, life is conceived as an emergent property. This is the general strategy we use to explain how properties of molecules control brain activity, and how brain activity support cognitive processes.

2. Biomolecular Information and Brain Activity

Before discussing the meaning of *information* at the molecular level of analysis, and its possible relations with cognition, we review important aspects of biological information processing.

Proteins are biophysical agents operating as "Maxwell Demons" (Monod, 1970; Loewenstein, 1999). In open systems like the living cell, they are able to reduce entropy locally, at the cost of increasing it in their environment. In this sense, proteins are mechanisms, generated by evolution, able to keep living systems at low entropy states while obeying the Second Law of Thermodynamics. They possess the capacity of producing *metabolism*, the physiochemical transformations that enable and control life processes.

Two models describe the work of enzymes, the proteins that catalyze physiochemical interactions: the *lock-and-key*, and the allosteric interaction models. The *lock-and-key* model illustrates how enzymes interact with their substrates. It refers to a matching mechanism composed of two factors: spatial three-dimensional (3D) conformation and electrostatic field patterns. Proteins are linear chains of amino acids that fold in a self-organized manner into 3D configurations, forming spatial structures able to select other molecular interacting partners by their shape. This selection process is well depicted by the matching of lock-and-key.

Besides conformational compatibility, the interaction among molecules also depends on electrostatic charges: molecules with equal charges repel each other, while molecules with opposite charges attract each other. The formation of covalent bonds occurs when atoms composing molecules share electrons. However, there is a large class of biological molecular interactions that does not involve a chemical exchange, only a transfer of information by means of electrostatic fields (Loewenstein, 1999).

How is molecular information encoded in electrostatic fields? The spatial distribution of positive and negative charges along the contact surface (active site) of a molecule composes an informational pattern. The positively and negatively charged, sequentially ordered microsites form a surface pattern at the active site of a protein. Each charged microsite can in principle determine a binary choice (bit) and consequently each sequence of **n** charged microsites can encode a message of **n** bits. Therefore, each molecule can contain a piece of information that is derived from its structure, as well as from transitory

arrangements of its flexible parts.

In order to store information for long periods of time, it is better to use stable macromolecules, as the DNA. To perform metabolic transformations, molecules with a flexible structure are more appropriate. Since the pioneering work of Monod et al. (1963), the flexible structure of proteins is called "allosteric". In the original allosteric model, enzymes have a flexible structure limited to two mutually exclusive states, relaxed and tense. Enzymes in the relaxed state bind substrates more readly than those in the tense state. More recently, intermediary states have been proposed (see Changeux & Edelstein, 2005).

The transition between the states is determined by the interaction with other molecules, called *ligands* or *effectors*. The lock-and-key binding of effectors with one or more active microsites of the protein generates a transition of states. The protein can also act as an effector to produce a change in another molecule, called the *substrate* (Fig. 1).

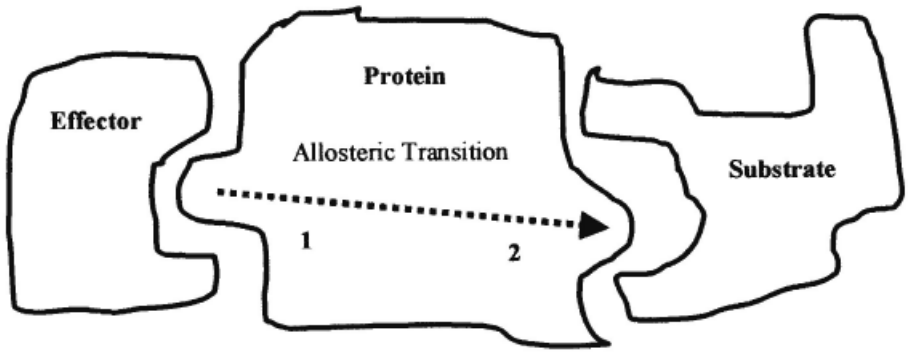

Figure 1. The binding of an effector with a protein at the active site 1 causes an allosteric transition and then site 2 of the protein binds with the substrate.

The above usage of "molecular information" refers to structural properties of molecules, such as three-dimensional conformation and distribution of charges along surfaces. Although displaying a similarity with the Weaver & Shannon (1949) mathematical concept of information (which is about the quantity of information transmitted by a communication channel), molecular information has a different nature. The mathematical concept refers to a *probabilistic structure* relative to an abstract channel defined in the context of a system composed of a source of signals, a receiver and a code (the latter being a set of correspondence rules to match the states of the source with the states of the receiver). The molecular concept refers to an ordered *physical structure* that interacts with other physical structures, producing several kinds of phenomena (for a discussion of this concept, see Stonier, 1990).

In biological systems, signaling molecules are suitably positioned to control cellular and tissue activity, according to the molecules' informational properties. For instance, the displacement of calcium ions initiate the contraction of muscular fibers. Such an understanding of molecular information is provided by a *cybernetic* concept of information as a low energy signal (the calcium ions, in the above example) that controls (relatively) higher-energy processes (the muscle fiber contraction, in the same example).

Would such low energy signaling chains in the brain participate in cognitive processes? In order to answer this question, it is necessary to consider the role of molecular information in brain activity. The brain, as any complex system, is characterized by the occurrence of dynamic patterns and self-organizing processes (see Kelso, 1995). These patterns can be compared to a ripple that is generated by the meeting of fluxes of water and continues to exist as long as it is sustained by them.

Brain activity is co-determined by several factors: genetic information, epigenetic influences, and signal exchanges with the entire body and the external environment. The latter kind of exchange is necessary for normal brain development and functioning. The important notion of *neuroplasticity* is related to this dynamical nature of brain activity. This term implies that the dynamic patterns of brain activity of an individual are shaped by his/her history of interactions, and that the resulting patterns of activity determine important aspects of brain structure. For instance, an animal raised with sensory deprivation does not develop functional perceptual subsystems, whereas under normal conditions the patterns of activation determine part of the architecture of the perceptual systems.

Brain activity is located at the intersection of two cycles (Fig. 2): the *Epigenetic Cycle*, a circular flux of information, composed of genetic expression into proteins and regulatory feedback from

proteins to genes, and the *Functional Cycle*, a circular flux of efferent and afferent processes, originally proposed by von Uexküll (1957). When the functional cycle is formed, the brain motor system, besides controlling behavior, also sends signals to the perceptual system; these signals are called "efferent copy" or "corollary discharge" (see *e.g.* Gilbert, 2001). By means of both kinds of feedback, external and internal to the brain, an "inner world" (the *Umwelt*, also proposed by von Uexküll, 1957) emerges from an active functional cycle.

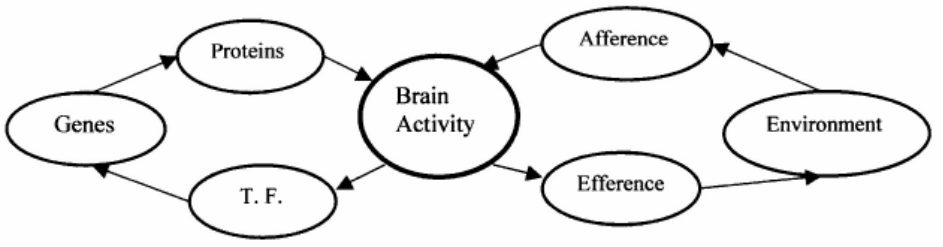

Figure 2. Epigenetic and Functional Cycles Meet in the Brain. The Epigenetic Cycle: genes are expressed into messenger RNA and proteins, which control brain activity. The patterns of brain activity feedback on the genes by means of transcriptional factors (T. F. in the figure), the signaling molecules that trigger gene expression. The Functional Cycle: in perceptual processes, information from the brain's environment (the entire body and the external environment) is captured by sensors and sent to the brain; it then helps to shape brain activity. The results of brain activity control efferent processes, the action of the organism in the environment.

The above cycles involve several spatial and temporal levels of description. Genes and proteins are macromolecules. Changes in their molecular conformation occur in the temporal scale of picoseconds. The interaction with the environment is usually mapped at the macroscopic level. The entire body mediates the interaction of the brain with the environment, which can be described in the temporal scale of seconds. There are also other relations between the brain, the body and the environment that take part in processes that occur in cosmic scales. For methodological reasons, these scales will not be considered here.

The complex circuits generated by the intersection of epigenetic and functional cycles in the brain are described in more detail in the diagram shown in Fig. 3. The signaling pathways depicted in this kind of diagram are called *Signal Transduction Pathways* (STPs). Technical terms that appear in the diagram are explained below.

Transmission of stimuli messages from cell to cell involves more than one encoding strategy. In afferent (from stimulus to the brain) processes, the connections between sensors, thalamic relays and cortical receptors are in some cases"hardwired" (*i.e.*, the destination of the signal is determined by a specific connection), and therefore the afferent signal (the sequence of pulses originated by the presence of the stimulus and transmitted from neuron to neuron) corresponds to a *frequency code*. When the channel is not hardwired, the afferent signal must carry information about its origin, corresponding to a *temporal code*: as each pulse has approximately the same amplitude, information is encoded in the relative timing of the pulses.

Stimuli messages are carried by sequences of neuronal pulses called *spike trains*. These pulses trigger the opening of transmitter vesicles at the axon terminal of neurons, releasing the transmitters at the synaptic cleft. The transmitters bind to receptors located in the membrane of the post-synaptic neuron. These receptors, as allosteric proteins, control molecular gates that allow the flux of ions through membrane channels.

The flux of ions across the channels determine the electromagnetic (EM) activity of the membrane, producing *excitatory post-synaptic potentials* (EPSPs) and *inhibitory post-synaptic potentials* (IPSPs). EPSPs are membrane *depolarizations*, a decrease in the difference of electric potential between the inner and the outer sides of the membrane that can generate membrane *oscillations* (variations of the EM field) and *action potentials* (the *firing* of the neuron, propagated by its axon to other neurons) when it reaches a capacitive threshold. Even not reaching such a threshold, it also has biological functionality, being able to activate signaling pathways in the neuron. IPSPs are membrane *hyperpolarizations* that inhibit the generation of action potentials.

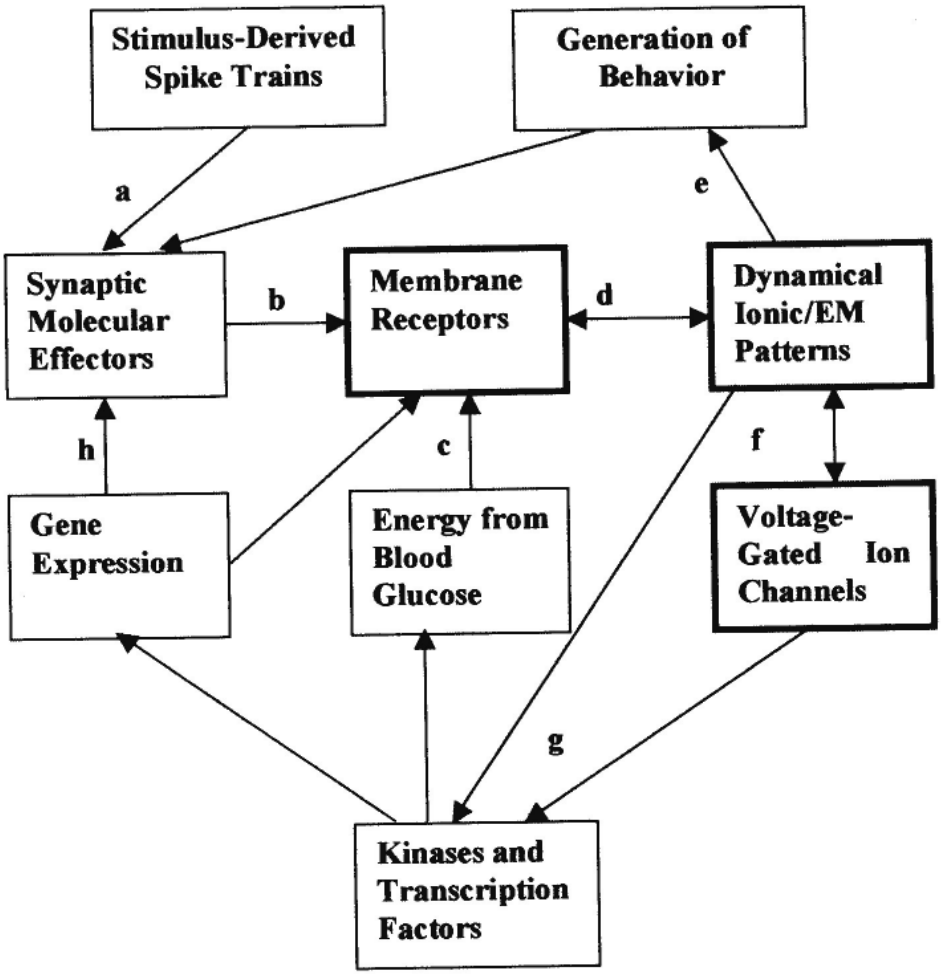

Figure 3. Diagram of Brain Signaling Mechanisms. a) Stimulus-Derived Spike Trains trigger the release of Synaptic Molecular Effectors (Neurotransmitters, Neuromodulators and Gliotransmitters); b) Molecular Effectors bind to Membrane Receptors. One class of these receptors, called "Ionotropic", directly controls the flux of ions across the neuronal membrane (the other class, called "Metabotropic", only activates STPs inside the cell); c) Energy in the form of ATP, produced in mitochondria (or elsewhere) from blood glucose, is broken into ADP and cAMP and then supports the phosphorylation of proteins; d) Ionotropic Receptors are ion channels which, when activated, generate Dynamical Ionic Patterns with their respective EM fields and action potentials; e) Ionic Patterns provide intercellular communication by means of neural pulses and synaptic transmission in brain circuits. Reaching the motor system, these patterns generate overt and covert Behavioral Patterns. The motor commands are also sent to sensory Synaptic Molecular Effectors and modulate incoming stimulation; f) Ionic Patterns control the activity of Voltage-Gated Ion Channels, which control ionic activity and also activate intracellular STPs; g) Ionic Patterns, by means of calcium ions entering neurons, activate proteins from the Kinase Family and Transcriptional Factors; h) Gene Expression produces signaling molecules and their respective receptors, which maintain, amplify or inhibit the previous cycles of activity.

Both EPSPs and axonal pulses present in a neuronal population are measured by the EEG and similar tools (*e.g.*, single-cell electrodes) that meaure brain electroactivity. Therefore, membrane receptors activated by low-energy, informational processes, are able to control higher energy processes, the EM waves recorded by the EEG, and the resulting behavior of the organism.

Since cellular EM oscillations are accompanied by microscopic vibratory activity (see Panagopoulos *et al.*, 2002), the higher energy processes are in fact *electro-magnetic-vibratory*. The depolarization/hyperpolrization processes, besides generating an electrical potential with

the corresponding electromagnetic field, also produces membrane channel vibrations ("twitching"), physically described as phonon patterns (the phonon being the quantum of energy present in molecular and ionic vibrations and in thermal agitation). Mosbacher *et al.* (1998, p.65) have suggested that "electrically induced motility will cause twitching during action potentials, and may have physiological consequences".

EM activity is supported by biochemical processes that use energy from glucose to sustain the low entropy states of the cells. The phosphorylation of proteins, necessary to sustain them in active states, is a distribution of the energy obtained from blood glucose that is controlled by the family of protein kinases. The kinases are enzymes that control other proteins. They can organize cellular processes and eventually activate transcriptional factors. The activity of kinases and other proteins that transform and distribute energy in the cell can sustain or abolish the EM patterns.

In summary, molecular information in the brain controls the movements of ions across the neuronal membrane, generating EM activity (and a corollary production of microscopic vibratory patterns), supported by energy obtained from blood glucose.

3. Evolution of Molecular Mechanisms Supporting Cognition

Consciousness-generating mechanisms possibly evolved from simpler molecular processes, such as those involved in the signaling of hunger and thirst. Denton *et al.* (1999) propose that thirst sensations have an interoceptive origin, being a reaction not to an external stimulus (as the dry mouth) but to a change in the sodium concentration detected by molecular sensors in the blood-brain barrier. The sodium-level detection system is a rudimentary example of a signaling unit that supports cognition.

This rudimentary model of molecular interaction would approximately cover the main features of initial and intermediary (between peripheral sensors and the final cortical destination) processes in the chemical senses. A study of odor perception by Leon & Johnson (2003) illustrates perceptual processes based on molecular signaling. Olfactory signal transduction in the rat begins with the activation of a thousand of receptors in the olfactory epithelium. There are many more odorants to which the animals respond, so "it is therefore likely that most odorants are coded by a unique combination of receptors such that a unique combination of responses would describe any particular molecule (*i.e.*, its odor – APJ/FAF). One way this could occur is by simple feature extraction in which different receptors independently recognize different parts of the same odorant molecule" (Leon & Johnson, 2003, p. 24).

The rat olfactory system is composed of groups of epithelium receptors projecting to glomeruli (dense synaptic bundles) in the bulb, which project to a small number of mitral cells, which in turn project to the olfactory cortex. Leon & Johnson (2003, p. 26) found that "each odorant stimulated a unique combination of glomerular clusters that we call *modules*. The modules describe a group of glomeruli in which we reliably find responses to a particular odorant feature". Their experiments showed the possibility of predicting both the neural response from the structure of the odorant molecule and the odor perception from the neural response to the molecular structure. These findings demonstrate the existence of information transmission from the molecular structure of the olfactory stimulus to conscious content (the experienced sensation of odor). It is important to note that, according to the same authors, "if there are odorants with differences in molecular structure, but without differences in their evoked glomerular activity, then these odorants should not be discriminated" (Leon & Johnson, 2003, p. 28). Therefore, from a molecular information transmission perspective, we can only perceive the features that our neural receptors are able to discriminate.

There is a serious limitation to the rudimentary molecular model: it is restricted to direct molecular contact and diffusion processes. Evolution overcame this limitation by using *ions* as carriers of energy and information in cellular and inter-cellular processes, while keeping the ion movements under the control of proteins. Ion movements across the membrane generate local EM fields that broadcast the locally generated content to the tissue level. The expansion from prototypical patterns into an integrated, episodic form of consciousness would correspond to the evolution of the mammalian brain, leading to human consciousness.

4. Molecular Tuning of Electromagnetic Patterns

The combination of molecular informational processes with ionic transmission, integrating several cells into a functional unit, gave rise to a complex mechanism, corresponding to what is traditionally called a *feature detector* (FD) in visual, auditory and somatic perception studies. FDs are complex mechanisms present in perceptual neuronal networks, responding to specific characteristics of stimuli (for a more complete definition, see Bickle & Mandik, 2002). Among the important structural components of FDs is the architecture of the dendritic tree of neurons, and the pool of proteins that control the activation threshold of ion channels. Based on these properties, each FD, in each perceptual, emotional and/or cognitive modality, responds selectively to a narrow range of stimuli. The *functional signature* of a FD lies in the pattern of EM activity that it generates and/or resonates with.

In a dendritic network, when EM patterns are *appropriately tuned* by the underlying molecular mechanisms, they *resonate* to the incoming spike trains that display a similar spatio-temporal structure, forming a *local EM signature*. Molecularly tuned EM patterns are good candidates to generate prototypical cognitive patterns. This view is similar to that of Phibram (1991) and Woolf (1999b) regarding the central role attributed to dendritic excitatory fields for consciousness. This view is an alternative to models based on axonal firing (see Crick & Koch, 1994).

This proposal also has affinity with the idea (Gabora, 2002) that conscious patterns derive from physical information, being amplified into subjective consciousness in the brain. We understand that such a derivation process occurs in two steps: a) molecular information controls ionic movements, inducing prototypical patterns to emerge; and b) prototypical contents are integrated, composing conscious episodes. The compositional process is based on several mechanisms discussed in the next sections, such as astroglial communication and electrical synapses providing collective oscillations, synchronization of oscillations, and calcium waves flowing in the astrocytic syncytium.

We do not agree with McFadden (2002) about the existence of a unitary conscious magnetic field, since local fields are too weak to support a whole-brain magnetic integration. On the other hand, we also disagree with the *micro-consciousness* hypothesis defended by Zeki (2001), since a prototypical pattern is not considered to be an isolated, self-contained experience. Zeki (2001, p.57) claims that "the primate visual brain consists of many separate, functionally specialized processing systems, each consisting of several apparently hierarchical stages or nodes…activity at each node reaches a perceptual end point at a different time…consequently, activity at each node generates a micro consciousness". In our proposal, prototypical patterns do not become conscious until they are integrated in a conscious episode; otherwise, they remain unconscious.

In so far as consciousness is generated by molecular information and incoming spike trains modulating local EM fields, some of the properties of conscious content should be detected by techniques that measure local fields and the metabolic activity necessary to sustain them. Besides the classical evidences obtained with EEGs (*e.g.*, event-related potentials that indicate conscious semantic processing of language), recent results with fMRI are highly relevant to this proposal. Current understanding of fMRI is that it measures arterial blood oxygen consumption reflecting increased metabolic demand that corresponds to local field activity (*e.g.*, Logothetis & Pfeuffer, 2004). Therefore, it is expected from high-precision fMRI experiments to reveal some aspects of conscious content, a task that is beginning to be accomplished. For instance, Kamitami & Tong (2005) investigated the perception of edge orientation, an important visual feature. Using statistical algorithms to classify brain states, they found that "ensemble fMRI signals in early visual areas could reliably predict in individual trials which of eight stimulus orientations the subject was seeing" (p. 679).

5. Ionic Dynamics

The movement of ions is central to the physiology of many kinds of cells. In the brain, the flux of Sodium (Na^+), Potassium (K^+), Chloride (Cl^-) and Calcium (Ca^{2+}) ions is controlled by proteins located in the neuronal membrane. While the first three ions are mainly a vehicle for energy processes (their movement across the membrane determines the electrical excitation or inhibition of the neuron), the calcium ion is mainly an informational vehicle.

A key feature of membrane physiology is that EPSPs and the corresponding axonal firings are produced mainly by the movement of Na^+ and K^+ in and out of the membrane, generating the electric potential. Ca^{2+} has several functions in the brain, such as carrying a message from the synaptic cleft to

the interior of the postsynaptic cell, and activating intracellular processes (in the role of a "second messenger", when it is called *intracellular calcium* - abbreviated iCa^{2+}). The Ca^{2+} that is available in the synaptic cleft, following a previous EPSP that opens Ca^{2+} channels, enters the membrane and binds with intracellular proteins, while some of the results of iCa^{2+} intracellular signaling processes feedback on the membrane.

The hypothesis of Ca^{2+} activity as a vehicle for consciousness was originally raised by Beck & Eccles (1992). They raised the possibility of consciousness influencing synaptic activity by means of Ca^{2+} action in the axon terminal, where it contributes to the opening of vesicles and transmitter release in the synaptic cleft. Another possible role of iCa^{2+} in conscious processing was discussed by Christof Koch: "it is possible that the NCC [Neural Correlates of Consciousness – APJ/FAF] are not expressed in the spiking activity of some neurons but, perhaps, in the concentration of free, intracellular calcium ions in the postsynaptic dendrites of their target cells" (Koch, 2003, p.17).

In our proposal, the main contribution of Ca^{2+} dynamics for consciousness refers to its function in the glutamatergic synapse. Glutamate (Glu) is the main excitatory transmitter in the brain. It binds to three kinds of protein receptors, called AMPA (*alpha-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid*), NMDA (*N-methyl-d-aspartate*) and metabotropic Glu receptors (Fig. 4 - the name of the first two receptors was drawn from the name of substances that bind with them).

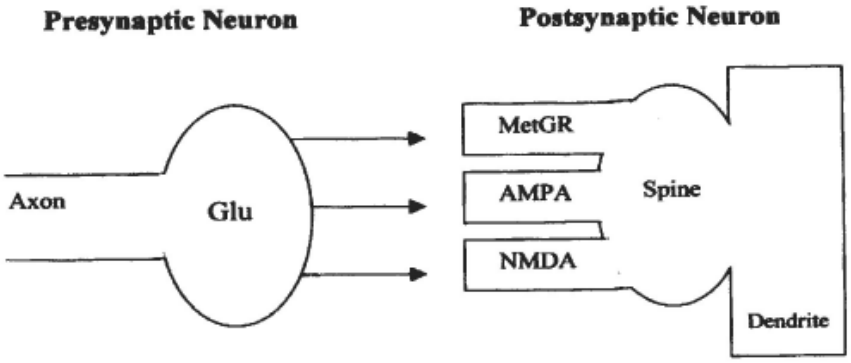

Figure 4. The Glutamatergic Synapse. Glu released from the pre-synaptic neuron's axon terminal spreads through synaptic space and binds to three different kinds of receptors (AMPA, NMDA and Metabotropic Glutamate Receptors – MetGR) located in the post-synaptic neuron membrane. The three kinds of receptors activate signal-transduction pathways that converge into the dendritic spine, a morphological structure that contains molecular mechanisms involved in the processing of the information transmitted by the glutamatergic synapse (adapted from Krystal el al., 1999).

The activity of the glutamatergic synapse involves:

a) *Glu binding to AMPA and NMDA receptors*, leading to a conformational change in the AMPA receptor that opens the channel to Na^{+} entry, depolarizing the membrane and then facilitating Ca^{2+} entry through NMDA and voltage-dependent calcium channels (VDCCs; these are Ca^{2+} channels that are controlled exclusively by changes in the voltage of the membrane);

b) *Glu binding to G-protein-coupled metabotropic receptors*, activating STPs that lead, among other actions, to an activation of enzyme adenylyl cyclase (AC), leading to an increase in the production of cAMP (the abbreviation for *cyclic adenosine monophosphate*, which serves as an energy component to activate intracellular proteins supporting several functions).

Therefore, the Glu activation of post-synaptic machinery occurs either by means of Ca^{2+} entry in the neuron (through NMDA and VDCC), or by the activation of metabotropic receptors and their coupled G-proteins.

The NMDA receptor is an allosteric protein with three or more active sites, controlling Ca^{2+}

entry in the post-synaptic neuron by means of a gate that in its resting state is blocked by magnesium. The *coincidence detection* function of the NMDA channels refers to the opening to Ca^{2+} entry only when two excitatory pulses activate at least two sites of the protein in a hundred-millisecond time window.

Flohr (1995) was possibly the first author to relate Ca^{2+} entry in NMDA channels with consciousness. This suggestion was based on pharmacological studies. The coincidence detection function assures the reliability of perceptions, whereas NMDA blockage by drugs such as ketamine causes perceptual distortions and hallucinations (Pereira Jr. & Johnson, 2003). In normal functioning, NMDA activity can sustain excitatory membrane activity by activating the retrograde messengers nitric oxide and arachidonic acid, which help to increase arterial blood flow (see Bliss & Collingridge, 1993).

The Ca^{2+} that enters through NMDA or VDCCs binds with several intracellular receptors. With some of them (calbindin, parvalbumin; see Jones, 2001), the forms of interaction are still poorly understood. Calmodulin (CaM), the better studied Ca^{2+} intracellular receptor, can adopt hundreds of different conformations, depending on the properties of the Ca^{2+} population that binds with it (Gerstein & Krebs, 1998; Wilson & Brunger, 2000). Ca^{2+} interacts strongly with proteins, both as an effector and as a substrate, to the point of being compared to a hormone (Loewenstein, 1999).

The informational capacity of Ca^{2+} (see, *e.g.*, Loewenstein, 1999; Jaiswal, 2001; Carafoli, 2002; Bast, 2004) is derived from its electronic structure. The calcium atom has 20 electrons, having an orbital distribution of 2-8-8-2. The Ca^{2+} loses two electrons of the outer orbital, being attracted to molecules with a negative charge. While attracted, it can also carry information in its flexible electronic structure. The information is embodied in the distribution of electrons in the shells and sub-shells of the electronic structure.

There are two, non-exclusive possibilities for informational exchanges between macromolecules and Ca. The first one is by lock-and-key binding, as in the case of Ca^{2+} binding with CaM. The second possibility is that the membrane channel transfers to the entering Ca^{2+} a vibratory pattern. This information transfer would have an important function. When the incoming spike train induces the release of transmitters that promote the flow of Na^{+} and K^{+} across thousands of channels in the post-synaptic neuron, the *global* EM pattern generated in the dendritic network of the neuron is likely to be chaotic (in the sense of *inharmonic*). The feedback of Ca^{2+}-activated intracellular molecular mechanisms on membrane ionotropic receptors and voltage-gated channels possibly *tunes* the membrane EM patterns, inducing *a harmonic structure* that defines the signature pattern of the neural assembly (see Yeung *et al.*, 2004). Such a tuning would also be related to the informational coherence formulated by Tononi *et al.* (1998). In this view, the generation of prototypical cognitive patterns would depend on the tuning by intracellular feedback mechanisms such as those activated by Ca^{2+} entry.

6. Cellular Cycles Modulated by Metabotropic Receptor and Neuropeptide Signaling

In this section we extend the role of tuning neural activity to metabotropic receptors exerting feedback on the membrane, and neuropeptides that bind with these receptors. Membrane metabotropic receptors are allosteric proteins activated by transmitters and modulators available in the synaptic space. These receptors do not control an ion channel, but they activate intracellular effectors forming signaling chains that control many cellular functions. Glutamatergic, as well as cholinergic (referring to *Acetylcholine*) and other monoaminergic (as *Dopamine* and *Serotonin*) neurotransmitter binding with metabotropic receptors activate intracellular STPs directed to several targets, including feedback on membrane ionotropic receptors.

These pathways - when situated in their proper neural and glial networks in the limbic system - are likely to be involved with the setting of mood, affective/emotional states, and with the action of drugs that modulate these kinds of states. For instance, it has been found that both caffeine (see Lindskog *et al.*, 2002) and lithium (Williams *et al.*, 2002) act on the inositol pathway, one of the signal pathways controlled by metabotropic receptors. This pathway exerts feedback on the synapse (*e.g.*, by modulating AMPA activity and K^{+} channels) to control membrane activity.

Metabotropic receptors bind to a class of proteins called *G-proteins*, which are activated by Guanidine Triphosphate (GTP), a phosphor-releasing molecule that is - like ATP - a source of energy for protein activity. For this reason, metabotropic receptors are also called G-Protein-Coupled-Receptors (GPCRs). When a GPCR binds to a G-protein, an active subunit of this protein translocates along the internal membrane surface to bind with adenylyl cyclase (AC),

an enzyme that transforms ATP into cAMP.

There are at least 11 kinds of AC enzymes in the mammalian brain. Like the NMDA protein, they have been conceived as molecular coincidence-detectors (Anholt, 1994), since they link metabotropic receptors and G-proteins to cAMP signaling pathways essential for many brain functions. AC can be activated by iCa, leading to cAMP release and activation of transcriptional factors (Alkon *et al.*, 1998). AC1 and AC8, the two major isoforms of AC sensitive to iCa, are highly expressed in the anterior cingulate cortex. For instance, Ca^{2+} activation of AC in the proper brain circuits is a central component in the generation of chronic pain (Wei *et al.*, 2002).

The activation of metabotropic receptor STPs, leading to an increase in the activity of ACs, can also produce feedback cycles that tune membrane EM patterns, by means of feedback on ionotropic receptors (*e.g.*, nicotinic receptors) and voltage-dependent channels (*e.g.*, K^+ channels). For instance, citochrome oxidase (CO) is an enzyme present in mitochondria, which is important for the metabolism of the glucose carried in the blood. ATP production from CO impact on AC production of cAMP. A possible molecular factor participating in the modulation of membrane EM activity is the quantity of cAMP available in the neuron. The level of energy possibly correlates with the pattern of EM activity of the membrane. This conjecture would explain the different distribution of CO in the mitochondria of neurons in the visual cortex areas responsible for the recognition of colors (for this distribution, see Dow, 2002; Gegenfurtner & Kiper, 2003).

The activation of intracellular STPs by metabotropic receptors, besides the proposed function of supporting consciousness, also leads to gene transcription processes, production of new proteins and growth factors controlling the architecture of the dendritic tree. A classical example is the process of formation of long-term memory, elucidated in the pioneering work of Eric Kandel and associates with Aplysia (see Bailey & Kandel, 1995). Serotonin binding to a metabotropic receptor modulates an ionotropic receptor controlling Na^+-K^+ fluxes. The cAMP released by AC activates a kinase (Protein Kinase A) and then transcriptional factors, leading to the disinhibition of a regulatory gene. This gene disinhibits another one, which is expressed and then produces a neural growth factor (a molecule that controls dendritic growth).

An interesting aspect of metabotropic receptor activation, in the context of a theory of consciousness, is that it can be made by *sub-threshold* EPSPs, *i.e.*, membrane depolarizations that do not reach the firing threshold. An interesting experimental study demonstrated the importance of sub-threshold potentials in the development of the cortical structures necessary for perceptual feature detection in the somatosensory cortex of rats (Moore *et al.*, 1999). The possibility of sub-threshold EPSPs producing sustained self-organizing cycles has an impact on the interpretation of neuronal data, using current techniques as single-cell electrodes. "Silent" cells (*i.e.*, cells that are not firing during a given time interval) may in fact be participating in cognitive processing.

Another class of signaling molecules that is important for the support of conscious processing is the neuropeptide. A neuropeptide is a macromolecule produced in the brain that is smaller than a protein and has - like other hormones - the role of a biomolecular informational effector in STPs. Neuropeptides are released by the pre-synaptic neuron together with transmitters and bind with membrane receptors, then modulating the EPSP.

Panksepp (1998) suggested the participation of neuropeptides in the generation of affective/emotional states and reviewed the correlations between neuropeptide molecular activity and kinds of affective/emotional experiences (Table 1). It is remarkable that the functions activated by neuropeptides are very specific, a fact that suggests that *they carry information relative to a specific content* to be generated. While modulating STPs in the limbic system, neuropeptides can contribute to generate specific kinds of membrane EM pattern signature, corresponding to affective/emotional prototypical contents.

In summary, the biomolecular informational factors that contribute to tune local EM patterns, generating prototypical conscious contents, would include:

a) faster Ca^{2+} information transmission, possibly supporting perceptual processes in the sensory neocortex;
b) metabotropic transmission, forming sustained molecular cycles of activity based on cAMP production by AC, activating several STPs that feedback on membrane activity;
c) neuropeptide modulation of STPs in the limbic system, hypothesized to sustain sub-threshold potentials generating mood and affective/emotional states.

Table 1. Neuropeptide modulation and affective/emotional contents: discoveries from 1935 to 1985.

NEUROPEPTIDE	ELICITED CONTENT
Substance P	Pain and Anger
Angiotensin	Thirst
Oxytocin	Orgasm, Maternal Feelings
ACTH	Stress
Insulin	Energy
Vasopressin	Male Sexual Arousal, Dominance
Bradykinin	Pain
CCK	Saciety, Panic
Prolactin	Maternal and Social Feelings
TRH	Playfulness
LH-RH	Female Sexual Arousal
Bombesin	Saciety
Neurotensin	Seeking
Enkephalin	Pain, Pleasure
Endorphin	Pain, Pleasure
DSIP	Sleepiness
Dynorphin	Hunger
CRF	Panic, Anxiety
NPY	Hunger

Adapted from Panksepp (1998).

7. Constructing Integrated Conscious Experiences

According to our hypothesis above exposed, the building-blocks of cognitive processes and conscious experiences - the prototypical contents - are related to local field EM pattern signatures, which are heavily dependent on the molecular structure of the cells.

These patterns are activated over baseline through a matching with the spatio-temporal structure of incoming spike trains. The matching function has been modeled in neural networks using Adaptive Resonance Theory, a theoretical tool that is useful for the understanding of neural mechansms underlying conscious perception and learning (see Grossberg, 1999).

Human consciousness is composed of complete episodes that dynamically combine a large number of prototypical patterns. As local fields are too weak to allow direct magnetic interaction of all regions of the brain, biological evolution led to the development of several forms of intercommunication able to produce integrated whole-brain spatio-temporal patterns.

There are several mechanisms of integration in the brain, some of them related, in the neuroscientific literature, to *attention* processes. Their function is both to select the local fields that participate in the composition of the conscious episode, in a hundred-millisecond time interval, and to bind the fields' informational content into an integrated focus.

Axonal firing is, of course, the main form of long-range communication in the brain, but it has limitations. Axonal transmission it is not able to directly transmit the waveform signature of each neuron, because the firing threshold is determined by constant parameters (Edwards, 2005). In other words, the amplitude modulation that characterizes each EM signature pattern is lost in axonal transmission; only the frequency and phase information is effectively transmitted. Therefore, axonal transmission operates with a system of discrete pulses, usually described as a binary code in the artificial neural network literature.

Axonal firing is also limited by the point-to-point architecture of axon-dendrite connections. This architecture does not support the integration of distributed information, since there is not a brain center where all circuits converge. There are limited convergence zones (Damasio, 1990) that integrate brain activity regionally. Supplementary mechanisms, such as electrical synapses, astrocytic calcium waves, nitric oxide spread and hormonal signaling are likely to help to integrate local fields into a whole-brain spatio-temporal EM pattern that crosses neuro-glial tissue in several ways (carried in blood flow, crossing neuronal membranes sequentially, etc.).

In this approach, local fields, besides the function of feature detector - whether matching an incoming spike train or not - also exert the function of an "emission antenna" that broadcasts the local

field signature to other brain regions. The emission function implies that the local field has to be activated above baseline, but the excitation cannot be excessive. The balance of excitation and inhibition, essential for preserving the signal-to-noise ratio, cannot be disturbed (on the importance of the balance of excitation and inhibition for cortical function, see Marino et al., 2005).

In the next sections, we analyse the selection and integration mechanisms involved in perceptual consciousness. Other modalities of human consciousness (abstract thinking, planning the future, aesthetic and moral judgment, self-consciousness) will not be discussed here, but they can be accounted for by the consideration of higher-order relations between brain systems, specially the "executive system", involving large brain networks connecting the hippocampus and frontal cortex with the parietal and temporal associative areas.

8. Amplification Mechanisms

The expression of a content begins with the stimulation of the respective specialized neuronal assembly by means of an afferent spike train or an endogenous brain signal that matches with the assembly's EM signature and excites it beyond baseline. Departing from this initial excitation, *recurrent circuits*, widely present in the brain, promote the amplification of the assembly's EM signature. In recurrent circuits, *excitatory loops* are formed: initial EPSPs generate spike trains that activate EPSPs in other neurons that generate spike trains that reinforce the initial EPSPs.

In the awake state, inter-neuronal communication in thalamocortical networks is boosted by tonic (*i.e.*, pulsed) spiking provided by cholinergic activation. The dependence of amplification on cholinergic mechanism makes acetylcholine one of the major transmitters involved in conscious processing (see Perry *et al.*, 1999).

Excitatory loops are counterbalanced by the activation of inhibitory interneurons, which are part of the selective mechanisms. Inhibitory neurons release neurotransmitter GABA (abbreviation for *gamma-aminobutyric acid*) to other neurons. This transmitter and its membrane receptors contribute to inhibit membrane activity by controlling the flux of Cl^- ions.

The amplification of prototypical contents by recurrent circuits involves the following operations:

a) neuronal assembly A, which generates EPSPs corresponding to an prototypical content, sends spike trains to other assemblies B;
b) reentrant signaling (see Edelman, 1989; Damasio, 1990) - *i.e.*, reentrant spike trains - from B to A releases transmitters that bind to membrane receptors to sustain the original EPSPs.

Therefore, a recurrent circuit neural population amplifies its EM pattern signature using recurrent circuits that activate, in each neuron belonging to the circuit, the same mechanisms involved in generating the original pattern:

a) the action of metabotropic receptors on the ionotropic ones; the effect of this activation is membrane depolarization, which also controls the opening of voltage-dependent channels;
b) the action of hormones/neuropeptides and other molecular effectors sustaining the feedback pathways;
c) Ca^{2+} entering on NMDA and VDCC, activating cellular STPs that feedback on the membrane.

9. Broadcasting Mechanisms

According to Freeman's (2003) analysis of brain activity, sensory processing involves the formation of *wave packets* - spatially distributed dynamical EM patterns affecting large populations of neurons. This process can be analysed as resulting from the reciprocal broadcasting of excitatory patterns from interconnected local fields located at several brain regions. Each local field produces spike trains that modulate the assemblies with which they are connected.

Broadcasting requires neuronal communication by means of spiking activity and other complementary mechanisms, as information transmission by calcium waves along the astroglial syncytium (Fig. 5). Astrocytes are currently considered to be a third party in the synapse (besides pre and post-synaptic neurons; see Perea & Araque, 2005). They communicate with neurons, receiving information from pre-synaptic neurons during synaptic transmission, and sending information to post-synaptic neurons

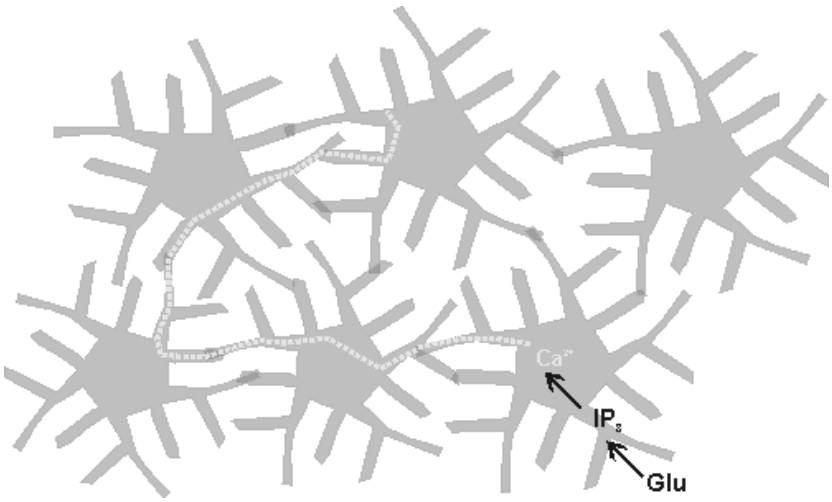

Figure 5. The Astrocytic Syncytium (http://synapses.mcg.edu/). Calcium waves are induced by the binding of Glutamate (Glu) with metabotropic receptors and activation of the inositol (IP) signaling pathway in astrocytes.

by means of gliotransmitters. Calcium waves are the physiological response of astrocytes to neuronal excitation. Although being too slow to support the broadcasting of sensory signals, these waves can possibly support mechanisms of conscious short-term/working memory (Robertson, 2002).

Understanding large-scale integration in the brain requires the consideration of a combination of effects generated by cables (axons) typical of input-output systems - such as communication between basal ganglia and hippocampus, to and from polymodal cortical areas - as well as integrative mechanisms operating by means of diffusion - such as hormones carried by blood flow and calcium waves in astrocytes. The resulting portrait is composed of *interference patterns* of EM signatures of all the neuronal assemblies involved in the wave packet. These patterns are second-order phenomena derived from the *interaction* of EM patterns. Possibly, the content of cognitive and conscious processing is correlated to such interference patterns, instead than the underlying EM patterns alone.

Two of the most important mechanisms that affect broadcasting processes and contribute to the formation of interference patterns are *collective oscillations* and *synchrony* (*i.e.*, phase cross-correlation). High-frequency oscillations are based on electrical transmission through gap junctions (LeBeau *et al.*, 2003; Bennett & Zukin, 2004). Gap junctions are regions of contact of neuron membranes (contrasting with chemical synapses). Synchrony is dependent on inhibitory neurons in the thalamocortical system (Steriade, 2005). Both mechanisms are coupled, since GABA-releasing inhibitory interneurons communicate by electrical synapses (Galaretta & Hestrin, 2001).

Both oscillations and synchrony possibly contribute to the *binding* of distributed neuronal activity. Singer (1990) showed the relation between oscillatory synchrony and the physiology of the NMDA receptor, one of the major players in the determination of local field signatures. Engel *et al.* (1992) suggested that oscillatory signals may carry a temporal code. Recently, the relation of synchrony and oscillatory activity in the propagation of local field signatures in the visual system was clarified by Samonds & Bonds: "the reliable synchrony at response onset could be driven by spatial and temporal correlation of the stimulus that is preserved through the earlier stages of the visual system. Oscillation then contributes to maintenance of the synchrony to enhance reliable transmission of the information for higher cognitive processing" (Samonds & Bonds, 2005, p. 223). Another important result is that gamma oscillations can be generated from an endogenous source (Hermann *et al.*, 2004).

10. Selection Mechanisms

Selective mechanisms operate on the amplified and broadcasted EM patterns, to determine the participants in the interference patterns that support conscious episodes. Selection processes possibly occur in successive hierarchical steps, beginning at primary sensory areas and progressing to associative areas, including the interplay of frontal and posterior areas and inter-hemispheric rivalry.

These hierarchical mechanisms provide "top-down" control from higher to lower hierarchical

levels, stabilizing brain-wide interference patterns, in spite of the existence of continuous changes at the lower levels of activity. Patterns that do not reach consciousness in a given moment may remain activated at lower processing levels and achieve a future cognitive impact by the priming of the system.

Opponent-processing circuits is a key mechanism present in all modalities (Schluppeck & Engel, 2002; Seymour *et al.*, 2005; Stecker *et al.*, 2005). Two groups of neurons in an opponent process circuit are tuned by long-term potentiation due to past learning. When stimulation disinhibits one group, homeostasis is disturbed and changes from baseline settings; after the external afferent is inactive the group returns to baseline.

The selection of patterns that dominate large-scale brain activity involves a dynamical balance of excitation and inhibition (see Marino *et al.*, 2005). This balance is involved in the homeostasis of brain activity, habituation and shifting the focus of attention. Glutamate-GABA is the major opponent pair for the fundamental balance of excitation and inhibition. Cholinergic modulation of the network – psychologically described as *attention* processes - shapes the dominant focus and maintains open relays from peripheral signals. Dopamine and serotonin are higher-order controllers of large neuronal networks, influencing the balance of excitation and inhibition related to the selection of patterns. Neuropeptides such as orexin A can control sustainment via action at multiple loci in thalamocortical, corticothalamic and corticocortical circuits.

The selective processes involve large recurrent circuits such as the thalamocortical (see Jones, 2001) and the striatum-thalamo-cortical (see Gilbert, 2001) ones; *e.g.*, the basal ganglia pathway to the thalamic reticular nucleus and the hippocampal pathway to cortical layer 1 are involved in gating tonic recurrent loop circuits.

11. Binding Mechanisms

The *Binding Problem* is about the explanation of how features processed in several areas of the brain bind into integrated conscious contents. The discussion of this problem touches upon the Hard Problem of Consciousness (Chalmers, 1995, 1996), since the unity of content is a central feature of phenomenal experience.

Information integration has been proposed as a central condition for the existence of consciousness (Tononi, 2004). The binding process involves a modality of information integration that possibly goes beyond the explanatory possibilities of classical information transmission. Ordinary transmission of information occurs from a source to a receiver, but the binding problem refers to the integration of several sources without a definite receiver.

The being that experiences the conscious content is a complex self-organizing system existing in the domain of the interaction of brain, body and environment. The production of conscious content is possibly a stage in the system's self-organizing process. Quantum theory is a good approach for this kind of system, since it overcomes the classical separation between the receiver and the source of information, replacing it by an interactive process where the reception of information by the receiver (as the act of measurement) interferes with the dynamics of the source. This interference can be understood as a special case of a broader property of quantum systems, called *entanglement*. It refers to the formation of dynamical correlations between spatially separated parts of a quantum system, such that the interference with one of the entangled parts immediately implies a corresponding change on the other.

Considering the limitations of the physical background of neuroscientific theories, several philosophers (see Lockwood, 1989; Herbert, 1993; Chalmers, 1996) and scientists (King, 1991,1997; Phibram, 1991; Beck & Eccles, 1992; Hameroff, 1998; Loewenstein, 1999; Woolf, 1999a; Rocha *et al.*, 2001; John, 2001) have raised the possibility that conscious processing in the brain includes properly quantum or quantum-like mechanisms, supplementary to the classical ones.

Leading scientific journals, such as Nature and Science, have recently paid attention to experimental realizations of quantum computers, mainly the models of Ca^{2+}-trapped quantum computation (*e.g.*, Cirac & Zoller, 2000; Kielpinski *et al.*, 2002). Inducing from artificial to biological systems, it is possible that protein-trapped Ca^{2+} in the brain could perform quantum communication and computation supporting consciousness (Rocha *et al.*, 2001, 2005). While trapped in dendritic spines or astroglial gap junctions, Ca^{2+} ions in an active neuroglial assembly would get entangled and then interchange information.

Although the first experimental realizations of Ca^{2+}-trapped quantum computers used ions cooled to their ground state, a procedure that makes easier the use of the system as a binary mechanism, models of ion-trap quantum computing in hot temperatures have been recently proposed

(see Poyatos *et al.*, 1998; Molmer & Sorensen, 1999; Milburn *et al.*, 2000; Zheng, 2003). These efforts approximate the ion-trap quantum computing model to biological reality, furnishing with tools for the advancement of experimental research to prove (or disprove) the existence of quantum coherence in the brain.

12. Philosophical Issues in the Explanation of Consciousness

The subjective or "first-person" experience of each conscious being emerges from contingent conditions: the singular history of interactions of several dynamical processes and cycles of activity. The Hard Problem of Consciousness (Chalmers, 1995, 1996) refers to an explanation of subjective experiences from an objective of "third-person" perspective. As subjective experiences are singular, solving this problem would imply a scientific revolution towards the explanation of singular histories.

However, in the subjective experience of every conscious being there are common features that enable intersubjective agreement. We usually agree about the color and size of visible objects, intensity and tonality of sounds, properties of food such as tastes and odors, etc.. These are the prototypical contents (called 'qualia' in the philosophical literature) composing integrated conscious episodes.

Understanding how the brain encodes prototypical contents and composes conscious episodes addresses a segment of the Hard Problem. The idea of an isomorphism of brain processing mechanisms, the structure of awareness and the structure of consciousness was advanced by Chalmers' "Principle of Structural Coherence" (Chalmers, 1995). Edelman also claims that "differences in qualia correlate with differences in the neural structure and dynamics that underlie them. Thus, for example, olfactory neurons and their circuits differ from retinal neurons and circuits, and such differences seem sufficient to account for differences in their respective qualia" (Edelman, 2003).

If the hypotheses presented in this essay turn out to be true, they can solve one small part of the problem, by *providing a neuroscientific explanation of how the contents of consciousness are produced and integrated* in the brain. However, it does not solve the largest part of the Hard Problem, which refers to explaining why conscious experiences exist at all, and/or explaining the subjective, first-person and intentional character of phenomenal experiences. Possible advances in this direction may be achieved by *Neurophenomenology*, a transdisciplinary area of study aimed to describe the structure of phenomenal experiences and to compare it with descriptions of brain activity made in the context of cognitive neuroscience (see Varela, 1996).

Dennett (1988) argued for an eliminativist position about qualia, denying that conscious experiences have "special properties". This position limits his later proposal of "heterophenomenology" (Dennett, 1991): if there is nothing special in first-person conscious experiences, heterophenomenology is limited to exercising the "intentional stance" (Dennett, 1991, p. 76), *i.e.*, the elaboration of hypotheses about mental states in order to explain observed behavior. Varela's (1996) neurophenomenology seems to have broader conceptual foundations, possibly allowing a better performance in phenomenological analyses.

Although we assume, with Edelman, Dennett and Varela, a naturalist framework, in our view conscious experiences *do* present special properties, when compared to the rest of the natural world. Current evidence is that these special properties emerge from the multiscale, brain-centered dynamical processes and self-organizing cycles reviewed in this paper.

13. Concluding Remarks: Brain Activity and Conscious Cognition

The hypotheses presented in this essay suggest that the scientific study of consciousness should focus on brain spatio-temporal waves and interference patterns composed of local fields activated by incoming spike trains, tuned by molecular mechanisms and integrated by collective oscillations. From this standpoint, molecular neurobiology is important for consciousness research, in that it enables an improved understanding of the EM signature pattern of each specialized local field.

On the other hand, a bridge between molecular neurobiology and consciousness research implies viewing neurobiological findings from a new perspective. Besides the biological role of molecular signals, the cognitive/affective content that they elicit in the brain should also be considered.

The explanations afforded by this approach do not cover the entire range of questions raised in the philosophy of mind, but is able to make sense of many results from molecular neurobiology. In this approach, molecular neurobiology has the benefit of having its results organized and made useful for human self-understanding.

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