Glutamatergic Mechanisms of Perceptual Learning: an Essay in Neuroepistemology

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Abstract Introducing the project of an area of study called *Neuroepistemology*, I argue that perceptual learning - the presentation of an attended stimulus eliciting the register of a corresponding informational pattern in the brain - is supported by glutamatergic synaptic and post-synaptic structures receiving afferent signals from thalamic projections. Glutamate membrane receptors (AMPA, NMDA and metabotropic) control signaling pathways, targeting a molecular computing device in dendritic spines that registers the relevant afferent patterns. From the study of these biological structures and functions, I criticize the neuroepistemological version of Transcendental Idealism proposed by Behrendt (2003), and suggest - following the classical Empiricist hypothesis - that the building-blocks of our mental universe are *impressed* in the brain following the presentation of attended stimuli.

Key-Words: Perceptual Learning, Neuroepistemology, Empiricism, Glutamate, Dendritic Spine.

Introduction

In this essay I describe molecular mechanisms that compose synaptic and post-synaptic functions supporting perceptual learning. The description is accompanied by a discussion of the possible implications of such mechanisms for the classical philosophical debate of Idealism and Empiricism. Contemporary philosophers of science would possibly agree that such a kind of philosophical debate is underdetermined by scientific findings. However, neuroscience does contribute to the understanding of brain information-

processing architectures. The existence of such architectures lend (or not) *inductive* support to philosophical views about mental functions.

I propose this essay to be part of a new, transdisciplinary area of research, to be called *Neuroepistemology*. This area is aimed to clarify the neurobiological basis of knowledge acquisition and (re)construction. The project of Neuroepistemology can be compared with the developments of contemporary Genetics. Gregory Mendel created the laws of Genetics without any knowledge of the biophysical structures involved in the process of inheritance, such as the DNA, RNA and transcriptional factors. Similarly, John Locke, David Hume and Emmanuel Kant - among other important philosophers - elaborated on theories of knowledge, without knowing neurobiological mechanisms responsible for mental functions as learning, thinking and linguistic processing.

The Mendelian laws of genetic inheritance were largely corroborated by Molecular Genetics, while at the same time the latter has furnished a richness of details absent in the original theoretical formulation. For instance, while Mendel postulated an independent combination of genes, Molecular Genetics has shown that the independence is not absolute. In the vertical line (from gene to protein) each gene is autonomous in the determination of the aminoacid sequence of the respective protein, but when considering the horizontal plane (the relations between genes) several interactions were discovered, as the existence of regulatory genes (genes that control the expression of other genes) and DNA segments (called "introns") that edit the genetic sequences to be expressed into proteins.

The relation between philosophical theories of knowledge and neuroscience is more complex, since it is not merely the rapport of two scientific approaches to the same subject, but a relation between philosophical

and interdisciplinary scientific approaches. A full introduction to Neuroepistemology would have to encompass deep issues, as the relation between physical stimulation and brain activity, and the relation of brain activity with mental functions. Considering the complexity of such relations, methodological simplifications are necessary in order to approach a specific topic. In this essay, I restrict myself to one single question about the role of stimuli patterns in perception.

Making a reasonable assumption that brain activity is *necessary* to generate mental functions, the question is: do stimuli patterns *determine* perceptual patterns or do they *only activate* previously existing, internal brain patterns (that generate perceptual patterns)? The first alternative is closer to Empiricism (in the line from Locke to Hume), while the second is closer to Kant's Transcendental Idealism.

Considering the complexity of neuroepistemological discussions, I am aware that I cannot attempt to demonstrate that Empiricism is true or Idealism is false. Since the Kantian position was benefited by a recent defense in a neuroepistemological context (Behrendt, 2003; see a brief review and discussion below), the objective of this paper is *to provide neuroscientific support for* the Empiricist position.

The modest goal of this essay is, in summary, *to show that Empiricism is neurobiologically possible*. My effort to accomplish this task is divided in five sections. The first one approaches some epistemological issues involved in this kind of project. The second one reviews Behrendt´s defense of Transcendental Idealism. The third one describes a model of neurobiological structures and functions that could possibly support perceptual learning. The fourth section is devoted to the discussion of the explanatory power of the

presented model, and the Concluding Remarks show an implication of the model for Neuroepistemology.

Some Epistemological Issues

In recent philosophical literature, the classical epistemological debate of Idealism and Empiricism has transmuted to a dispute of *Internalism* (briefly, the claim that the brain/mind generates and individuates mental content from internal sources) and *Externalism* (briefly, the claim that mental content is influenced or determined by the world external to the brain/mind).

The existence of a larger proportion of cortico-thalamic (than thalamo-cortical) *cholinergic* projections has suggested to some theoreticians (Llinás and Ribary, 1990; Behrendt, 2003) that knowledge construction is internal to the brain. Contrary to this proposal, I claim that *glutamatergic* thalamo-cortical projections and their post-synaptic machinery can account for *perceptual learning*, i.e. the presentation of an (external) attended stimulus eliciting the register of a corresponding informational pattern in the brain. The corollary Empiricist thesis - also assumed in this essay - states that such informational patterns constitute the building blocks for the construction of conscious episodes, including dreams, hallucinations and intentional representations.

The very idea of perceptual learning implies the possibility of informational patterns from attended stimuli being *impressed* in the brain and eventually appearing in the composition of conscious episodes. Of course, unconscious perceptions are also possible, as in the cases of subliminal perception of briefly presented or unattended stimuli. The term “impression” was used, by the Empiricist philosopher David Hume, to refer to *vivid*

perceptions, distinguished from abstract ideas created by the mind. Konrad Lorenz used a similar term, "imprinting", in his classical study of the innate learning mechanism of the greylag goose. In the context of this essay, both terms are used to refer to a biophysical process that occurs in glutamatergic post-synaptic structures.

My use of "imprinting" is close to Lorenz' with regard to the effect of the external stimulus on the perceptual system, but it is different in two important aspects:

a) In Lorenz' theory, imprinting triggers a fixed behavioral pattern, while perceptual impressions do not; and
b) In Lorenz' observations of the greylag goose, the object being imprinted is also innately defined - as pointed by Wimsatt (1986) - while the objects of perceptual impressions are totally learned.

I propose that perceptual imprinting occurs every time that we perceive objects and processes from the brain's external environment, *registering* and eventually *recording* the stimulus pattern in post-synaptic structures. It provides the basic patterns, or building-blocks, from which we can construct complex thoughts, intentional representations and the content of dreams and hallucinations.

It is important to note that my defense of Empiricism is restricted to the thesis that impressions are the building blocks of mental life. The *Associationist* theory of knowledge is not assumed here. Associationism refers to the process of *concept formation*, a cognitive stage that operates *after* impressions are obtained. One of the reasons why I would not like to assume Associationism is that it does not account for "top down" effects, as attentional control driving the interaction of the perceptual system with the environment. Another important reason is the combinatorial 'modus operandi' of

Associationism, which does not account for generative procedures (as *parsing*) studied in Chomskyan grammars, or for context-dependence, as in the conceptual space approach (see Gärdenfors, 2000).

The theme of this essay is also related to the debate between Representationalist and Direct Perception views. For several outstanding Cognitive Science theoreticians, the notion of *representation* could bridge the gap between external stimulation, the corresponding brain activity and mental content. In this view, the explanation of perceptual processes is directed to the explanation of the formation of mental representations related to external stimulation. On the other hand, Direct Perception theorists, following the influential work of J. J. Gibson, explain perception by means of an active interaction of the perceptual system with the environment, refusing to consider brain mechanisms or mental representations as central to the explanation.

My proposal refers to neurobiological mechanisms located at an intermediary stage that is not focused by both kinds of theory. They are located between the domain of the interaction of organism and environment, and the domain of internal brain operations that (putatively) support mental representations. Such neurobiological mechanisms are proposed to be responsible for the *transmission and register of sensory information* from external receptors (eyes, ears) to cortical networks.

Disagreeing in this subject with Dretske (1981, 1995), I note that such a transmission and register of sensory information is better described as *presentational*, instead of a *representational* process (for a philosophical distinction of presentational/representational, see Shanon, 1993).

The reasons why I do not consider perception as a representational process were advanced in a previous work (Pereira Jr., 1999). I recognize the impossibility of verifying if our knowledge is truly isomorphic with physical

objects and processes. We only know that some kinds of attended patterns appear in our consciousness, following the presentation of some kinds of stimuli. This kind of epistemological view was called “blind realism” in the context of philosophy of science (Almeder, 1991), thus differing from classical, Aristotelian varieties of realism.

On the other hand, I would not like to assume an anti-representationalist position, since the brain effectively generates abstract constructs from perceptually learned elementary patterns. The *executive system*, based on frontal cortical functions (see D’Esposito and Grossman, 1996), is responsible for second-order operations on sensory patterns to construct representations. Perceptual processes can be conceived as first-order presentations supported by imprinting processes, while representations are second-order constructs that use imprinted patterns as building-blocks. This kind of neurocognitive architecture was used in the Working Memory model (see Jonides, 1996), where prefrontal networks - the working memory processor - operate on the results of temporal and parietal networks - the auxiliary buffers - cognitive processing.

In summary, I understand that *concepts* - including those present in philosophical and scientific theories - *are intentional representations*, while their building-blocks are *presentations*. Although I cannot discuss these issues deeply here, they stand as good examples of themes to be approached in future neuroepistemological studies.

A Criticism of Behrendt's Defense of Transcendental Idealism

In a scientifically well-informed paper, R. P. Behrendt (2003) examined thalamocortical functions to provide a defense of Transcendental Idealism

(TI). As the brain is a biophysical system, neuronal patterns cannot, in principle, be identified with Kant's mental forms and categories, which belong to the other side of the dualistic divide proposed by Descartes. In spite of this ontological issue, Behrendt's work presents an appealing claim for a brain-internalist view of the mind.

The validity of TI lies in the assumption that sensory stimulation only activates patterns previously existing in the brain/mind system. Behrendt supports this assumption by studying the functional neuroanatomy of the thalamocortical system. One important feature is the distinction between specific and non-specific depolarizing inputs. The largest part of thalamic relay cells receives their input from corticothalamic projections, while only 10% of these cells transduce sensory afferent (input) information to the cortex. This quantitative evidence seems to support Behrendt's proposal.

Another important fact is that ascending brainstem cholinergic activation of attention mechanisms, in wakefulness, dreaming and hallucination, is not content-specific. Although acetylcholine is called a "transmitter", especially when binding to nicotinic receptors and generating action potentials, cholinergic signals apparently *do not transmit a sensory message* from thalamus to cortical target areas. They would only activate informational patterns already existing in a potential state in the system. Therefore, the role of ascending cholinergic excitatory transmission (in spite of the term "transmission") would be only to actualize the potential patterns.

An important probe for any neurocognitive model is the performance in the explanation of dreams and hallucinations. The naive Empiricist views of perception have been challenged to explain such phenomena, since René Descartes raised the possibility of the human mind generating illusory conscious content in the absence of a corresponding external stimulus. The

difficulty found in this explanation was frequently used in the past as an argument for Idealism.

Behrendt (2003) explains hallucinations by three main factors:

a) a dysfunction of the reticular thalamic nucleus, leading to a loss of sensory-specific inhibition and the consequent loss of signal-to-noise ratio, which is important for the processing of external information;

b) the increased spontaneous activity of thalamic relay cells, leading to a under constrained activation of thalamocortical circuits in the gamma frequency range;

c) the presence of psychological factors that determine the content and frequency of hallucinations.

According to a widely accepted hypothesis (Baars, 1995), cholinergic input released from the reticular activating system to thalamocortical circuits is related to the *state* of consciousness (i.e., to the function of supporting wakefulness and attention), but not to the definition of the *contents* of consciousness. In Behrendt's view, the content of hallucinations depends on psychological factors, but he does not explain the biological mechanisms responsible for them.

For TI, the encoding mechanism should be one that is not affected by afferent sensory patterns. For Empiricism, there should be a mechanism by which sensory patterns are "impressed" into the brain. Although Behrendt presents a large review of cholinergic and related GABAergic inhibitory mechanisms defining the state of consciousness and attentional control of incoming signals, he does not discuss glutamatergic projections from thalamus to cortex.

Glutamate (Glu) projections and their corresponding cortical post-synaptic mechanisms, besides being involved in selective *memory* formation

and unconscious perceptual *priming,* are also adequate to the role of giving a bottom-up contribution to conscious content, thus suggesting that the Empiricist position is neurobiologically possible. The Glu-activated post-synaptic machinery is suitable for the register, recording and processing of sensory patterns. These mechanisms have been mostly studied as the early stage of memory formation (an excellent review and discussion can be found in Bickle, 2003; a possible relation of CaMKII activity with consciousness was previoulsy proposed by Nunn, 2003). They involve biological molecular structures and functions, including the system of Glu receptors, and calcium-binding proteins as Calmodulin (CaM) and Calmodulin-Dependent Protein Kinase II (CamKII, a protein from the kinase family, having several receptor and effector active sites). Besides the hippocampus, where it is largely studied, this mechanism also operates in dendritic spines distributed over the whole neocortex.

Glu possibly has a central role in the composition of conscious content, in normal states, dreams and altered states. This role has been proved in experiments when the Glu NMDA receptor is transiently blocked by sub anesthetic doses of an antagonist (ketamine, PCP or MK-801), thus generating perceptual distortions and hallucinations (for a review, see Pereira and Johnson, 2003).

Dreams and hallucinations are arguably made of the recombination of patterns obtained from past experiences during wakefulness. While the organism is awake and interacting with the environment, properties of external stimuli are captured by brain mechanisms, brought to consciousness and eventually retained in memory. A mechanism in the brain that records patterns from the interaction with the body and environment, in our emotionally and

motivationally relevant experiences, could subsequently reactivate and recombine them, in dreams and hallucinated episodes.

In the case of hallucinating, incoming sensory information is perturbed by thalamic low signal-to-noise ratio, as proposed by Behrendt, but the brain can make use of patterns obtained from previous perceptual processes as building blocks to construct the dreamt and hallucinated episodes. In this case such episodes are not an exclusive creation of the brain, since they contain patterns from the external world that were previously registered.

A Model of Glutamatergic Mechanisms Supporting Perceptual Learning

Glutamate is the main excitatory transmitter in the brain, being largely present in cortico-cortical networks (see e.g. Stahl, 1996, for a tutorial) and operating both on excitatory (as pyramidal cortical) and inhibitory neurons (as GABAergic interneurons). The Glu-induced excitation (i.e., membrane depolarization) of interneurons increases their inhibitory action (i.e., GABAergic transmission inducing the flow of chloride ions to hyperpolarize the membrane) on the excitatory ones. Glu transmission is a key component in the balance of excitation and inhibition that is a necessary condition for brain function (Marino et al., 2005).

Besides this role, Glu also operates as an information carrier in thalamo-cortical and cortico-cortical synapses, a role that is crucial for understanding of how perceptual learning is possible in the brain. According to Jones (2003), “within the brainstem, neurons of the reticular formation, which predominantly utilize glutamate as a neurotransmitter, stimulate cortical activation by exciting the widespread projecting neurons of the nonspecific thalamo-cortical projection system, which similarly utilize glutamate, and

neurons of the ventral extra-thalamic relay systems located in the posterior hypothalamus and basal forebrain, many of which also utilize glutamate". The basic thalamocortical Glu-GABA circuits that carry both the excitatory and informational roles of Glu are depicted in Fig. 1.

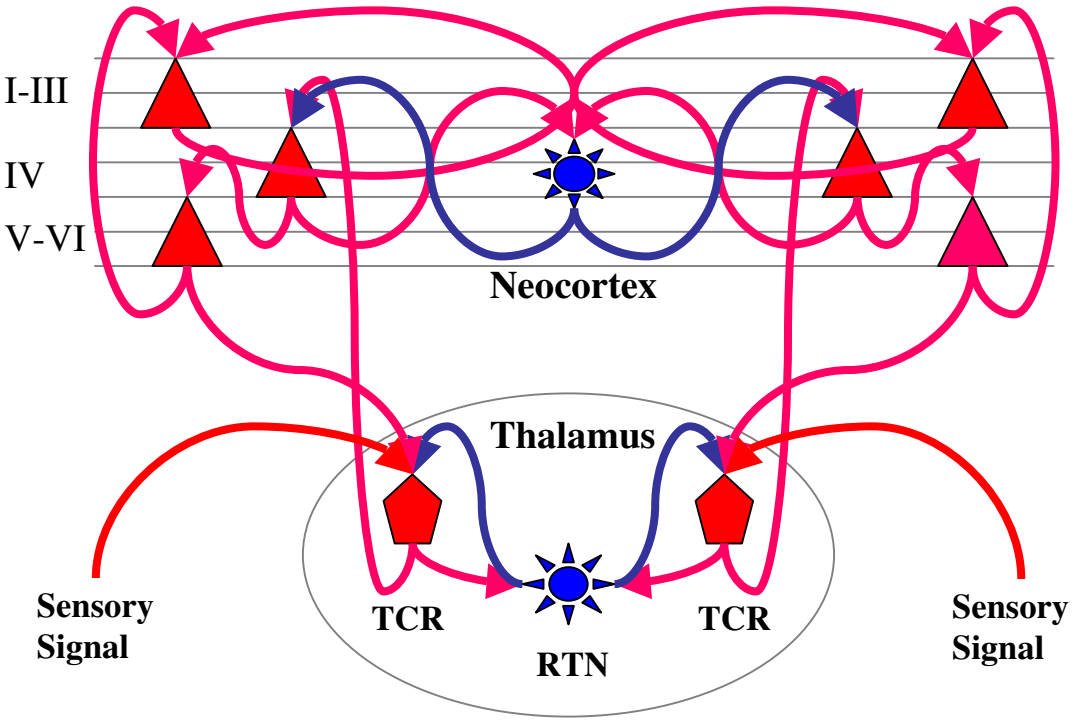

Figure 1 - *Thalamocortical Glutamatergic and GABAergic Circuits.* *Caption: Red: Excitatory; Blue: Inhibitory; TCR: Thalamocortical Relay Cell; RTN: Reticular Thalamic Nucleus Cell.*

In the sensory cortex, afferent patterns transmitted through thalamocortical glutamatergic projections are received and processed by post-synaptic mechanisms located in dendritic spines (see Sabatini et al., 2001; Sabatini et al., 2002; Holthoff et al., 2002).

Activation of three kinds of Glu receptors (NMDA, AMPA and metabotropic), combined with voltage-dependent calcium channels (VDCCs),

converges to the dendritic spine (Fig. 2), where the calcium ions (Ca) entering through NMDA and VDCC control CaM/CaMKII computational mechanisms. Calcium cations are largely employed biological ions with a flexible electronic structure able to encode information (for a review, see Loewenstein, 1999). CaM and CamKII have several receptor and effector active sites, where the entering are trapped. The informational state of the Ca/CaM/CaMKII molecular complex is dependent on the interaction with the Ca population entering through NMDA and VDCC.

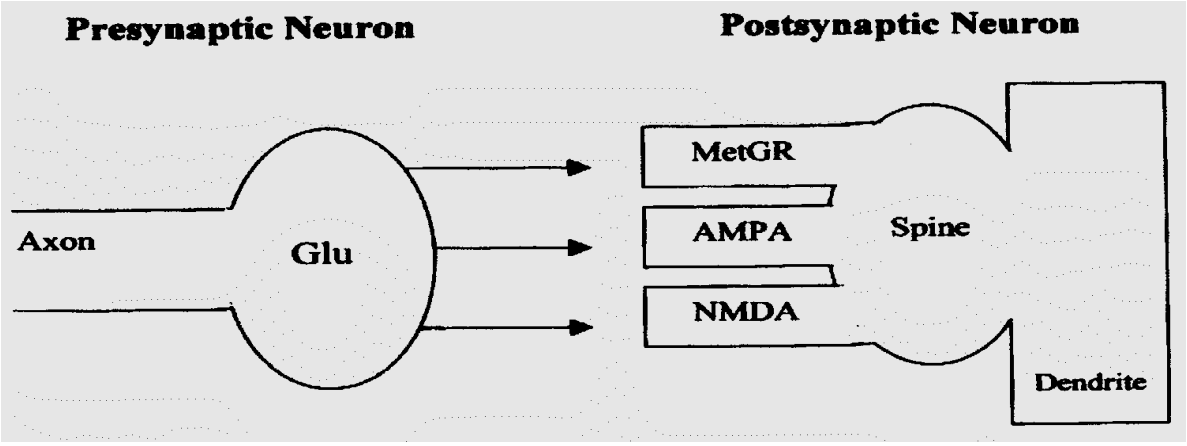

Figure 2 - The Glutamatergic Synapse. *Glu released from the pre-synaptic neuron's axon terminal is spread in synaptic space and bind to three different kinds of receptors (AMPA, NMDA and Metabotropic Glu Receptors – MetGR) located at the post-synaptic neuron membrane. The three kinds of receptors activate signal-transduction pathways that converge into the dendritic spine.*

The NMDA channel is considered to be a coincidence-detector for both bottom-up (sensory afferent) and top-down (previously learned) patterns (Rocha et al., 2001), since it opens to Ca entering only after two pulses reach the dendrite in a small time window. The first pulse is necessary to remove a

magnesium molecule that blocks the channel, and the other one creates the membrane potential that prompts the Ca movement. Because of this condition, the NMDA channel is possibly important to assure the reliability of percepts in regard to stimuli, since it is opened only if endogenous and exogenous (afferent) pulses reach the NMDA receptor.

When VDCCs (which are not coincidence detectors) assume the main role in glutamatergic transmission, perceptual distortions and hallucinations are likely to occur (See Table 1).

Table 1 - Three Different Modes of Functioning of the Glutamatergic Synapse *(adapted from Krystal el al., 1999)*

Presynaptic	**Postsynaptic**	**Ca++ Entry**	**Ca++ Channel**
Inactive	**Inactive**	**No**	**No transmission**
Active	**Inactive**	**Low**	**VDCC following AMPA activation**
Inactive	**Active**	**Low**	**VDCC following AMPA activation**
Active	**Active**	**High**	**VDCC and NMDA following AMPA**

The multimeric structure of CamKII, having binding sites for CaM and phosphatases that participate in the phosphorylation of other proteins, constitutes a *biological computing device* able to read information from the CaM conformational changes caused by the population of incoming Ca, to process this information, and to activate other proteins according to the results of the information processing (Fig. 3).

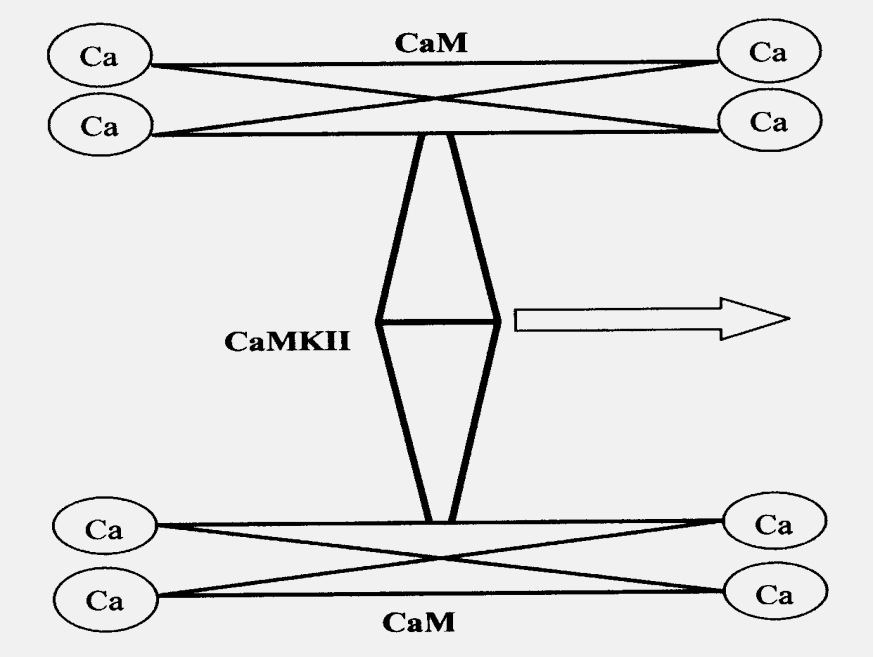

Figure 3 - Hypothetical Molecular Computer Based on the Multimeric Structure of CaMKII. *The input is composed by the flux of Ca entering the post-synaptic neuron and binding to CaM units and determining their conformational states. On a second step, the CaM units (only 2 in the picture, but a larger number in reality) bind to CaMKII, controlling its phosphorylation functions. The output of the computer is the action of CaMKII on other substrates (not depicted in the picture; for a review of neurobiological data supporting this model, see Squire et al., 1999).*

Such a computing device is in charge of performing distributed *perceptual imprinting* in large populations of cortical neurons. This process includes the following steps:

a) the afferent pattern is transmitted by means of spike trains, from the sensors to the thalamus (except for olfaction) and then to the cortex, reaching the cortical synapse, and then

b) the spikes cause the release of Glu, and then

c) Glu binds to AMPA and NMDA, leading to the opening of calcium channels, and then

d) the entering Ca population transfers afferent information to a population of CaM (more precisely, four or five calcium ions bind to each CaM; see Wilson and Brunger, 2000), and then

e) CaM undergoes a conformational change determined by the bound Ca population, and finally

f) the binding of a group of CaM group with one CaMKII creates a stable, self-organizing computing device that registers the information and makes it available for further processes.

The six steps describe a model of brain mechanisms supporting perceptual learning. Although the model is sketchy in the present formulation, it provides a theoretical basis for the formulation of new hypotheses and corresponding experimental designs, hopefully contributing to the advancement of knowledge in this area.

In the proposed model, each CaM binds with 4 or 5 calcium ions carrying a sensory message. Upon binding with Ca, each CaM undergoes a conformational transition, adopting one among hundreds of possible different states (see Gerstein and Krebs, 1998). The possibility of hundreds of different conformational transitions confer a high degree of plasticity to the Ca/CaM complex, possibly supporting different cognitive operations.

The binding of Ca/CaM with CaMKII forms a functional complex having this kinase as a powerful effector that auto-phosphorylates and phosphorylates other enzymes that control several intracellular signal-transduction pathways. The conformational state previously adopted by the Ca/CaM complex determines the intra-neuronal pathway triggered by this

kinase, and therefore determines the cognitive function that the Ca/CaM/CaMKII complex can perform.

Three important implications follow from this theoretical modeling. First, it is necessary for each Ca entering the neuron to have at least three different states, in order to determine the conformational change of CaM (5 calcium ions determine one among 243 CaM states). Such different states consist of vibrational patterns related to the electronic structure of the atom, as revealed by experimentation with trapped Ca quantum computing (see Hughes et al., 1998). Therefore, the consideration of quantum information may be relevant to the neurobiology of learning, memory and consciousness.

Second, the informational variety found in this molecular complex suggests that it is able to support perceptual learning patterns. These patterns, formed at the sensory and associative areas of the neocortex, are reinforced by the hippocampal system during memory consolidation, and then reactivated during conscious recall of the original perceptual experience (of course, only in the case that such a recall effectively occurs).

Third, the model allows the prediction of brain dysfunction based on a quantitative calculus of Ca binding with CaM in dendritic spines. The normal proportion is 4 ions for each protein; both a smaller and larger number of ions for each available protein are predicted to correlate with perturbations or loss of consciousness. Correspondingly, available data indicate that altered perception and loss of consciousness in several conditions (anesthesia, epileptic seizures) correlate with low or high Ca entry, and the resulting abnormal function of the Ca/CaM/CaMKII complex. The function of the complex at the sensory cortex can be assessed by means of a review of molecular changes that follow such an abnormal functioning (for instance, see Yamagata et al., 2006).

Does the Model *Explain* Perceptual Learning?

The distinction of *Description* and *Explanation* is central to the Philosophy of Science. In the previous section, I described some micro and macrostructures discovered by empirical research. As complex biological structures usually have more than one function, these structures may be not an exception. Do they have the kind of function that I assign them? If they do, the model can be a neurobiological *explanation* of how stimuli patterns are registered and eventually recorded in the brain, a result that would probably count in favor of Empiricism.

Another important question refers to the relation of this function and perceptual processes. It is not impossible that such a register of stimuli patterns could have nothing to do with the phenomenology of perception. Is there any guarantee that the described processes support the experience of perceiving the world? Do these processes refer to conscious or unconscious perception, or to both kinds of perception?

An answer to the first question has to cover both theoretical and empirical grounds. Theoretically, learning functions have been addressed in artificial neural networks - according to Hebb's Law - as the stimulus-driven change of *synaptic weights* in the network. Originally Hebb made reference to *a change in metabolism*, which is a better way to describe the neurobiological correlate of learning. The neurobiological correlate of "change in synaptic weight" is not a single process. It involves changes in the quantity of neurotransmitters, modulators and ions available at the synaptic cleft; in the quantity and functionality of receptors available at the post-synaptic neuron membrane; and changes in cellular metabolism causing phenomena that occur

in a larger time scale, as dendritic growth (induced by molecules released by means of a previous genetic regulation).

Among the above possibilities, the cellular control of membrane receptor functionality is one of the most powerful and specific changes that can occur in a time interval compatible with perceptual processes. The increase in the quantity of a modulator, as dopamine, is powerful but not specific, i.e., it is not correlated with the *pattern* of the stimulus being learned. In the above descriptive model, perceptual learning is related to the activity of membrane receptors, leading to specific activations of the Ca-CaM-CaMKII molecular system. This system is able to encode the stimulus pattern and to exert feedback control on membrane receptors (AMPA), thus fulfilling the theoretical requirement.

Empirical evidence for the cognitive role of the Ca-CaM-CaMKII signaling system comes from a series of studies with genetically modified mice (see Tang et al., 1999; Wang et al., 2003). Genetically modified animals that express CaMKII at a higher rate were experimentally evaluated as "smart mice" for their increased learning capabilities, while mice that express CaMKII at a lower rate displayed diminished learning capacity. This effect of CaMKII is produced by means of the control of the AMPA population at the post-synaptic density, one of the main mechanisms by which learning leads to the formation of memory.

In current neurobiology, the molecular complex formed by Ca entering post-synaptic neurons and binding with CaM and CaMKII has been largely studied at the hippocampus. The activation of this complex is considered to be an early step in memory consolidation, which leads to the activation of transcriptional factors and gene expression. According to the model I presented here, the same molecular complex is related to a complementary

function at the neocortex: to support conscious perceptual learning and conscious recall of the learned patterns.

The cognitive role of Ca entering post-synaptic neurons has been related to associative learning (see Alkon et al., 1998) and memory formation (Bliss and Collingridge, 1993) in hippocampal networks. There is also an understanding that the ion participates in the process of formation of declarative memory, a kind of memory that requires conscious recall. However, learning and memory formation processes are not restricted to the hippocampal system. Available evidence indicates that mnemonic patterns are recorded at the neocortex (Eichenbaum, 1997). Neuroimaging of conscious recall show an activation of neocortical areas that support the original conscious experience (Goldberg et al., 2006).

A complete separation of mechanisms of learning/memory and consciousness conflicts with a successful methodology used in the scientific study of consciousness. Consciousness is scientifically studied, in human subjects, on the basis of verbal reports (see Frith et al., 1999). This methodology implies that the earliest step of declarative memory formation (the register of the experience) is necessary for the generation of the report; more precisely, if the reported memory is not false, the motor systems that trigger the reporting behavior should gather the content of the report from the register that occurred in the brain areas that supported the original conscious experience. Therefore, the very early mechanisms of neocortical memory formation (Ca entry at post-synaptic neurons and binding to CaM), operating in the millisecond range, have to function properly for the conscious content to be registered and then consolidated - by means of inter-activation of the above cortical areas, entorhinal cortex and hippocampus - and finally reported - by means of conscious recall and activation of the speech motor circuits.

In cases of false memories, there may occur a mistake in the recall process, but the existence of some other conscious experience that is mistakenly gathered remains as a necessary requisite. As a consequence, both cognitive processes - declarative memory formation and consciousness - must share common mechanisms. More precisely, *episodic* declarative memory formation would require some conscious *perceptual experience*.

The answer to the second question derives from the abovementioned studies of psychological effects of NMDA channel antagonists (ketamine, MK-801 and PCP) on human subjects. In several scientifically controlled studies, an adequate dose of one of these drugs was ministered to the subjects. Their reports about subjective experiences revealed that the drugs induce perceptual distortions and/or hallucinations. Such results demonstrate that the blockage of the NMDA receptor channel to Ca entry perturbs conscious perceptual processing (the conscious effect being registered by means of the verbal reports of the subjects).

The existence of such effects on conscious perception is sufficient to reinforce the Empiricist claim that stimulus-derived impressions participate in the generation of vivid consciousness. The question that remains is about the role of Ca entry in the post-synaptic neuron: how does the blockage of Ca entry in a neuronal population generate perceptual distortions and hallucinations? As long as information about the stimulus pattern is carried by a Ca population entering NMDA channels, the blockage of Ca entry perturbs transmission of this information to the Ca-CaM-CaMKII system, where it is registered and made available to consciousness. This explanation is consistent with the fact that a lower dose of ketamine only generates distortions of the perceptual content, while a stronger dose generates hallucinations (in this

situation, the stimulus pattern is absent from the experienced conscious process).

Concluding Remarks

The proposed theoretical model of conscious perceptual learning leads to some neuroepistemological conclusions. The variety of Externalism that better expresses the position derived from the above discussion is *Interactionism*, i.e. the claim for an interaction of endogenous and exogenous factors in the generation of conscious percepts. For the Interactionist view, there is a complementarity of exogenous patterns reaching the brain and endogenous self-organizing processes that combine and recombine such patterns into conscious events and episodes.

This view is well depicted in S. Grossberg's neural network model (Grossberg, 1999). Previously learned endogenous patterns are transduced to one layer of a neural network, while sensory (input) patterns are impressed into another one. The matching - or not - of the patterns, generating a resonance or a correction signal between both layers, defines the information processed by the network.

Perceptual imprinting was proposed to be a biophysical process that follows a causal and informational chain of events, beginning with the presentation of a stimulus and the focusing of attention on it. Cholinergic mechanisms are surely necessary to control the attention function, but not sufficient to determine the perceptual content. They role is possibly to provide top-down control of perceptual operations. Once the brain attends to the stimulus, glutamatergic mechanisms are in charge of imprinting the afferent patterns in the cortical neurons having the corresponding receptive fields.

Therefore, glutamatergic mechanisms would support a bottom-up process that provides the building-blocks for the brain to construct conscious episodes.

The consideration of such brain mechanisms and their conjoint possibilities makes possible the construction of a neuroepistemological transdisciplinary paradigm, allowing the reformulation of classical problems of Theory of Knowledge in the light of current neurobiological findings.

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