GENES, BRAIN AND MATERNAL BEHAVIOUR

Natalia López-Moratalla. Professor of Biochemistry and Molecular Biology. University of Navarra

> *The tender intimacy and selflessness of a mother's love for her infant occupies a unique and exalted position in human conduct... It provides one of the most powerful motivations for human action, and has been celebrated throughout the ages—in literature, art and music—as one of the most beautiful and inspiring manifestations of human behaviour (Zeki, 2004).*

NEURAL MECHANISMS UNDERLYING COMPLEX MATERNAL BEHAVIOUR

Mothers demonstrate a unique ability to recognize different sensory cues from their own infants, including visual and auditory cues. These stimuli, such as a smiling or sad face, are powerful motivators

for a mother to respond through care giving, physical touch, speech, or play.

Brain is organised to mediate the complex maternal behaviour. For that, gene expression is orchestrated by different hormonal and neurochemical factors.

Maternal care will be used here as a model of study to go in depth into the description of *brain/mind relationship* after exploring the circuits for cognitive–emotional integration. The complex emotional-cognitive maternal behaviour offers significant data, which will help us entering what is specifically human in brain/mind relationships.

This model is of special importance for several reasons:

- it allows the study of neural support in the *plastic construction of emotional life* and offers a response to the question about how social experiences influence the brain.

- it allows approaching the complex *cognitive–emotional behaviours* that have their basis in dynamic coalitions of networks of brain areas, none of which should be conceptualized as specifically affective or cognitive.

- and, it allosws a broadening in our knowledge of circuit cognitive–affective *control system* permitting possible activacions and simultaneous inhibitions of neural circuits.

Behaviour cannot be cleanly separated into cognitive or emotional categories

Behaviour is a product of the orchestration of many brain areas; the aggregate function of these brain areas leads to emotion and cognition. Often true integration of emotion and cognition takes place, strongly blurring the distinction between the two. Emotion and cognition are, in fact, only minimally decomposable.

The current view of brain organization supports the notion that there is a considerable degree of functional specialization and that many regions can be conceptualized as either 'affective' or 'cognitive': for example, the amygdala in the domain of emotion and the lateral prefrontal cortex in the case of cognition; however, none of them should be conceptualized as specifically affective or cognitive.

Recent studies[1] expose that complex cognitive–emotional behaviours have their basis in dynamic coalitions of networks of brain areas, due to the existence of neural networks integrating functions at cortical and subcortical levels.

Cognition refers to processes such as memory, attention and language, problem solving and planning. Many cognitive processes are thought to involve sophisticated functions that might be

[1] Pessoa, L. (2008) "On the relationship between emotion and cognition". *Nature Reviews Neuroscience* 9, 148–158.

uniquely human. Furthermore, they often involve so-called *controlled processes*. Cognitive processes appear to engage cortical regions.

From a neuropsychological point of view affectivity entails entirely the emotional life. Neural correlates of emotions are being difficult to be investigated due to the fact that emotions imply a diversity of factors, which should be tackled by a diversity of researchers[2]: some researchers incorporate concepts of drive and motivation; others involve emotions in the conscious (or unconscious) evaluation of events; and others link emotions to the body[3]. Brain structures linked to emotion are often subcortical, such as the amygdala, ventral striatum and hypothalamus. Each one of the 'core' and 'extended' affective regions form a complex area that is involved in numerous functions.

The emotional brain involves:

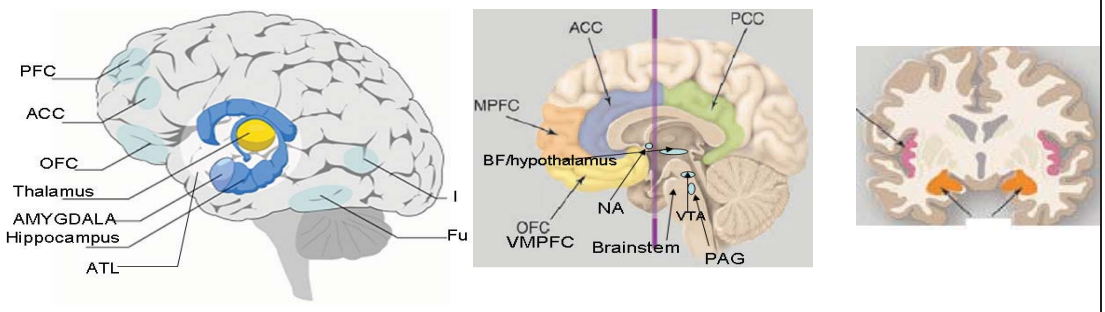
- The *core* emotional regions include sub-cortically, the amygdala (A), the nucleus accumbens (NA) and the hypothalamus. Cortically, the orbitofrontal cortex

[2] Rolls, E. T. *Emotion explained*. Oxford University Press, Oxford, 2005

[3] Damasio, A. R. The feeling of what happens: body and emotion in the making of consciousness (Harcourt Brace, New York, 1999). Damasio, A. R. Descartes' error: Emotion, reason, and the human brain (ed. Putnam, G. P. New York, 1994).

(OFC), the anterior cingulated cortex (ACC), and the ventromedial prefrontal cortex (VMPFC).

- *Extended* regions include, subcortically, the brain stem, the ventral tegmental area (VTA) and associated mesolimbic dopamine system, the hippocampus, the periaquaeductal grey (PAG), the septum and the basal forebrain (BF). Cortically, the anterior insula (I), the prefrontal cortex (PFC), the anterior temporal lobe (ATL), the posterior cingulate cortex (PCC), superior temporal sulcus (STS), and somatosensory cortex.



There are also subcortical sructures involved in cognition processes:thalamus, basal ganglia, aminergic cortical and subcortical projections from the brainstem.

Functional connectivity

Central to cognitive–emotional interactions are brain areas with a high degree of connectivity, called hubs, which are critical for regulating the flow and integration of information between regions.

Moreover, the three-dimensional topology of regions involved in behaviour is dynamic. Multiple neurotransmitter systems affect and implement these

dynamic specific regions. Some circuits can implement reverberating activity that can be sustained for several seconds. Such dynamics are not only extending the repertoire of computations but they are also likely to influence the precise form of functional connectivity with other regions. Thus local physiological properties impact both short- and long-range brain interactions.

Maternal behaviours might be reasonably well characterized in terms of cognitive–emotional interactions and amygdala function is their cognitive–emotional connector hub. Located at a strategic position in brain hemispheres, *grosso modo* we could say that limbic system integrates vegetative visceral impulses with cognitive behavior through emotions. The amygdala is not only highly connected, but that its connectivity topology might be consistent with that of a connector hub that links multiple provincial hubs, each of which links regions within separate functional clusters.

Limbic system structures operate fast and in an automatic fashion, so that certain trigger features are relatively unfiltered and always evoke responses that might be important for survival. Furthermore, the functioning of subcortical structures that mediate emotions is thought to be 'unaware', and an individual is not necessarily conscious of a stimulus that might have triggered brain responses in an affective brain region

In summary, functional circuits include both multiple regions and neuromodulatory systems (excitatory or

inhibitors, which might even act with a feedback). Network affiliations are context-dependent and dynamic. And, given the small-world topology of brain structural connectivity, hub regions, such as the amygdale have more important roles than regions that are not as highly connected.

MATERNAL BRAIN AND PREGNANCY

Pregnancy requires multiple adaptations of the mother's physiology to optimize foetal growth and development, to protect the foetus, and to ensure that adequate maternal care is provided after parturition. By contrast, adaptations in the mother's brain during lactation are maintained by external stimuli from the young.

Many of these adaptations are organized by the mother's brain, predominantly through changes in neuroendocrine systems, and these changes are primarily driven by the hormones of pregnancy[4]. Pregnancy stimulates the production of brain neurotransmitters in the mother: *oxytocin* (hormone of trust) and dopamine (regulator of movements and *prize and reward* systems). These molecules join their

[4] Brunton, P.J., Russell, J.A. (2008) "The expectant brain: adapting for motherhood". *Nature Reviews Neuroscience* 9, 11-25; Meaney, M.J., Szyf, M. (2005) "Maternal care as a model for experience-dependent chromatin plasticity?" *TRENDS in Neurosciences* 28, 456-463; Champagne, F.A., James, P (2005) "How social experiences influence the brain". *Curley Current Opinion in Neurobiology* 15, 704–709.

receptors in different regions of the brain and regulate their specific activity.

When mothers feel the movements of the foetus, around the fifth month of pregnancy, then secretion of *oxytocin* begins. This hormone is decisive for the functional plasticity, which generates the bond of attachment to the foetus in the maternal brain. *Oxytocin* has its own receptors in all the areas connected to the amigdaline complex, a key centre for cognitive-vegetative-emotional integration. Body contact of mother and son induces release of *oxytocin* accumulated in neurons during pregnancy, thus strengthening attachment of mother to son after delivery. And breast-feeding strongly stimulates *oxytocin* thus reinforing that attachment.

Pregnancy natural biological processes attenuate stress.

Complex adaptations of the maternal brain are likely to be a consequence of an increased activity of brain systems with inhibitory effects on the hypothalamus-pituitary-adrenal (HPA) axis and a reduced activity of excitatory pathways noradrenaline, norepinephrine, corticotrophin-releasing factor and opioids[5].

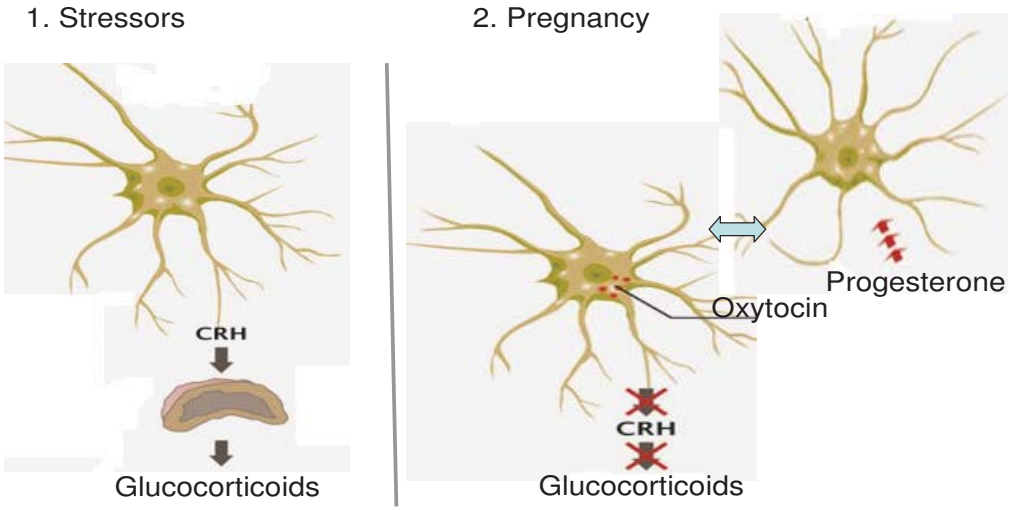
Emotional and physical stressors convey information to the HPA axis and activate neurosecretory corticotropin-releasing-hormone (CRH), and arginine-

[5] Slattery, D.A., Neumann I.D. (2008) "No stress please! Mechanisms of stress hyporesponsiveness of the maternal brain". *J Physiol* 586, 377–385

vasopressin (AVP) neurons, in the parvocellular region of the hypothalamic paraventricular nucleus (pPVN). CRH and AVP stimulate adrenocorticotropic (ACTH) release from anterior pituitary, which in turn stimulates the secretion of glucocorticoids, which inhibit their own release. Those hormones alert the brain to a state of stress and induce the corresponding emotional response to stress.

In late pregnancy, the hormonal response of the HPA axis to stressors is severely attenuated. CRH and oxytocin release are suppressed during pregnancy. Progesterone levels in the brain and the circulation are increased during pregnancy. Progesterone is converted into allopregnanolone and in brainstem neurons the levels of opioid peptides and μ-opioid receptor increase. Noradrenergic neurons project to the hypothalamus, to magnocellular oxytocin in the (PVN), and to oxytocin neurons in the supraoptic nuclei. However, in pregnancy, fails to evoke noradrenaline release. This is a result of increased opioid inhibition of noradrenaline release.

Emotional and physical stressors convey information to the HPA axis and activate neurosecretory corticotropin-releasing-hormone (CRH). CRH stimulates adrenocorticotropic (ACTH) release from anterior pituitary, which in turn stimulates the secretion of glucocorticoids. Those hormones induce the corresponding emotional response to stress.



In late pregnancy, the hormonal response of the HPA axis to stressors is severely attenuated because progesterone levels, in the brain and the circulation, are increased during pregnancy.

Thus, anxiety-related behaviour and emotional responsiveness to stressful stimuli are reduced with the result of general calmness. CRH mRNA levels are low and hence reduced ACTH and glucocorticoid secretion. Moreover, magnocellular oxytocin neurons are also subject to increased GABA (γ-aminobutyric

acid) inhibition during pregnancy. Allopregnanolone prolongs the opening time of GABA-receptor Cl– channels, enhancing the inhibitory GABA input. Oestrogen and oxytocin, acting together, increase the number of GABA synapses.

THE NEUROPEPTIDE OXYTOCIN APPEARS TO INCREASE TRUST AMONG HUMANS

Oxytocin is a nonapeptide released from the paraventricular nucleus of the hypothalamus through the posterior pituitary. The essential role for oxytocin is a biological basis of prosocial approach behaviour[6].

In nonhuman mammals oxytocin plays a central role in the ability to form social attachments and affiliations, including parental care, pair bonding, and social memory. Oxytocin promotes prosocial approach behaviour by inhibiting defensive behaviours. However, there is no evidence that oxytocin affects reciprocity in animals. Oxytocin seems to permit animals to overcome their natural avoidance of proximity and thereby facilitates approach behaviour. Both animal and human studies showing that oxytocin ameliorates the symptoms associated with social anxiety and stress.
Trust is indispensable in friendship, love, families and organizations to increasing the benefits from social interactions. It affects an individual's

[6] Kosfeld, M., Heinrichs, M., Zak, P.J. Fischbacher, U., Fehr, E. (2005) Oxytocin increases trust in humans *Nature*, 435, 673-678.

willingness to accept social risks arising through interpersonal interactions. And oxytocin's effect on trust in terms of betrayal aversion is known.

The behavioural function of oxytocin release depends on the regions containing a high density of receptors for this neuropeptide.

The amygdala and other brain regions express oxytocin receptors

The amygdala is a central component of the neurocircuitry of fear and social cognition that has been linked to trust and reduces anxiety and impacts on fear conditioning and extinction. Amygdala function is strongly modulated by oxytocin. *Oxytocin* activates the connections of the amigdaline complex with the brainstem, which regulates i*instincts and vegetative impulses*.

Amygdale receives and integrates sensory and prefrontal/ limbic inputs and excites, possibly indirectly, neurons in the central nucleus that evoke fear responses via their projections to brainstem regions including periaqueductal gray and reticular formation. The effect of oxytocin on anxiety in humans may be attributable to a combined effect on both amygdala activation and coupling to regions mediating *fear response*.
Functional magnetic resonance imaging has been used[7] to image amygdala activation by fear-inducing

[7] Kirsch P., Esslinger Ch., Chen Q., Mier D., Lis S., Siddhanti S., Gruppe H., Mattay V.S., Gallhofer B., Meyer-Lindenberg, A.

visual stimuli after double-blind crossover intranasal application of placebo or oxytocin. Compared with placebo, oxytocin potently reduced activation of the amygdala and reduced coupling of the amygdala to brainstem regions implicated in autonomic and behavioural manifestations of fear. The reduction in amygdala activation was more significant for socially relevant stimuli (faces) than for the socially less relevant scenes.

It is also involved in several functions that are closely linked to cognition, including attention and associative learning. Brain circuits implicated in *reward* contain a high density of receptors for oxytocin. Trust is bound to dopamine. Midbrain dopamine systems are crucially involved in *motivational processes* underlying the learning and execution of goal-directed behaviour. Dopamine neurons in monkeys are uniformly activated by unpredicted appetitive stimuli such as food and liquid rewards and conditioned reward-predicting stimuli[8]. Dopamine neurons preferentially report environmental stimuli with appetitive rather than aversive motivational value. This bain region plays a key role in learning reward stimuli and potentiating attention and memory. Neurons of ventral tegmental area (rich in oxitocina receptors) are projected to

(2005), "Oxytocin Modulates Neural Circuitry for Social Cognition and Fear in Humans". *The Journal of Neuroscience* 25, 11489 – 11493.

[8] Mirenowicz, J., Schultz, W. (1996) |"Preferential activation of midbrain dopamine neurons by appetitive rather than aversive stimuli". *Nature* 379, 449-451.

nucleus accumbens núcleo (NA) and there they release dopamine creating a motivational state.

Dopamine acts as drug of vitality exciting neurons controlling movement in motor centres.

Finally, Baumgartner[9] et al. have shown that subjects receiving intranasal administration of oxytocin undergo deactivation of brain areas. They show no change in their trusting behaviour after they learned that their trust had been breached several times while subjects receiving placebo decrease their trust. The *adaptation* is associated with a specific reduction in activation in the amygdala, the midbrain regions, and the dorsal striatum in subjects receiving oxytocin, suggesting that neural systems mediating fear processing (amygdala and midbrain regions) and behavioural adaptations to feedback information (dorsal striatum) modulate oxytocin's effect on trust.

Oxytocin could also act to potentiate classical transmitters

Oxytocin influence maternal behaviour through the regularon of functions of amygdala and other brain regions with appropriate receptors.

---

[9] Baumgartner, T., Heinrichs, M. Vonlanthen, A., Fischbacher, U., Fehr, E. (2008) "Oxytocin Shapes the Neural Circuitry of Trust and Trust Adaptation in Humans". *Neuron* 58, 639–650,

Oxytocin participates also in the regulation of neurotransmitter release just in a restricted number of brain regions. 1) Once oxytocin is released within the PVN it can promote activity of the oxytocinergic neurons to stimulate further oxytocin release in a short-loop feedback. 2) Oxytocin into the PVN inhibits glutamate and aspartate release. 3) Glutamate, GABA, noradrenaline, 5-HT, and dopamine concentrations all increase significantly in the PVN when oxytocin concentrations are also increased. 4) GABA release from local interneurons may also play modulatory role by oxytocinergic neurons and noradrenaline from the brainstem stimulates the activity of oxytocinergic neurons.

PLASTICITY

Social experiences throughout life seem to influence gene expression and behaviour: epigenetic DNA modification.

Adult behaviour is a product of the dynamic interplay between genes and social environment. These induced changes are, in part, mediated by sustained alterations in gene expression in selected brain regions and are associated with epigenetic modifications of the genome. In mammals, mother–infant interactions are the primary source of social stimulation and result in long-term changes in offspring phenotype. These changes reflect permanently altered gene expression, so-called ‘environmental programming’.

The term “plasticity”·refers to the ability to vary phenotype in response to environmental conditions. Brain plasticity is thus ready o fine tune the development of brain to enhance the match between phenotype and environmental demand.

Genes will influence what can broadly be termed bonding and social behaviour. These genes can be divided into two general classes[10]: a) mother–offspring interactions (suckling, attachment and maternal behaviours); these early experience permanently alters behavior and physiology; and b) adult social interactions, when there is an asymmetry of relatedness in social groups.

For example, the nature of maternal care that an infant receives can affect the child’s emotional and cognitive development, which is endured into adulthood. The mechanism of these environmental "programming" effects was examined with an animal model that studies the consequences of variations in mother-infant interactions on the development of individual differences in behavioral and endocrine responses to stress in adulthood[11].
Maternal behavior in the rat can alter the hippocampal glucocorticoid receptor (GR) expression in the offspring, which concomitantly alters the hypothalamic-pituitary-adrenal (HPA) axis and the

[10] Isles, A.R., Davies, W., Wilkinson, L.S. (2006) “Genomic imprinting and the social brain”. *Phil. Trans. R. Soc. B* 361, 2229–2237.
[11] Weaver, .C.G. (2007) “Epigenetic Programming by Maternal Behavior and Pharmacological Intervention. Nature Versus Nurture Let’s Call The Whole Thing Off” *Epigenetics* 21, 22-28.

stress responsiveness of these animals. Maternal behavior increases GR expression in the offspring via increased hippocampal serotonergic tone accompanied by increased histone acetylase transferase activity, histone acetylation and DNA demethylation mediated by the transcription factor NGFI-A. In the absence of increased NGFI-A expression, the promoter of GR remains methylated. The unmethylated promoter will maintain high affinity to NGFI throughout adulthood, resulting in greater activity of the GR, whereas the methylated GR promoter exhibits reduced afinity for NGFI resulting in low activity of the GR in adulthood (Figure 2).

DNA methylation alters GR expression through modifications of chromatin structure; thus the DNA can be established through environmental programming and given the inherent stability of this epigenomic marker, this dynamics is potentially reversible. Epigenetic state of GR gene can be established through early-in-life experience and is potentially reversible in adulthood.

In summary, GR gene is an anti-stressor gen. Glucocorticoid receptor links corticoid and dims the response. As Michael Meany[12] shows that stimuli related to body care activate the expression of antistress gene. Oxytocin release as a consequence of this tactile stimulus increases the cascade of signals

[12] Meaney, M.J., Szyf, M. (2005) "Maternal care as model for experience-dependent chromatin plasticity? "*TRENDS in Neurosciences*. 28, 456-463.

leading to the elimination of metil groups in the promoter of GR gene. The social brain specializedd in social interactions is affected and somehow reshaped by them[13].

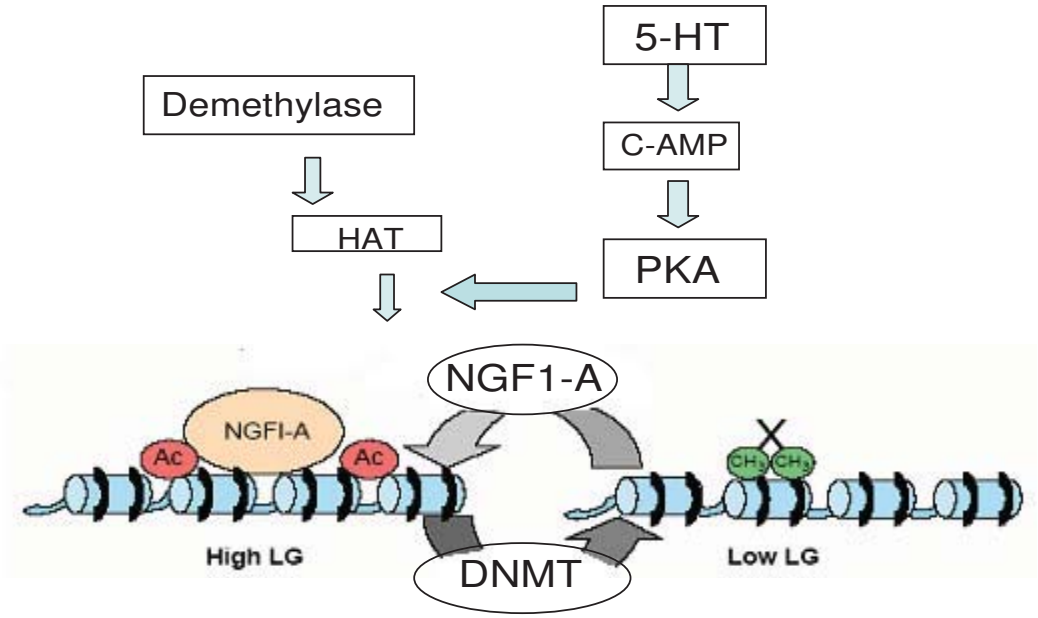
'Environmental programming': Chromatin structure and DNA methylation

Most DNA is tightly packaged into nucleosomes and wrapped around a core of histone proteins. The histone–DNA configuration is maintained by electrostatic bonds between histones and DNA, and regulates gene expression. These chromatin structures hinders transcription factor binding to DNA and therefore gene expression.

The acetylation of selected positively-charged amino acids modifies histone–DNA interactions, opening chromatin and facilitating transcription-factor binding to DNA. In general, histone modifications are transient and cannot directly explain enduring early environmental programming effects. However, modification of the genome itself is a stable, enduring 'epigenetic' mark. DNA is covalently modified by DNA methyltransferases (DNMT) that transfer the methyl to the carbon atom at the fifth position in the cytosine ring. Methylation is involved in gene imprinting and in early phases of cellular differentiation and DNA methylation promotes

[13] Champagne, F.A., Curley, J.P. (2005)"How social experiences influence the brain". *Current Opinion in Neurobiology* 15, 704–709.

gene silencing through effects on chromatin structure.



A silencing mechanism links DNA methylation to inactive chromatin structure. A region of methylated DNA attracts different members of a family of methylated DNA-binding proteins, which recruit chromatin-remodelling complex protein. This relationship between chromatin state and DNA methylation forms a molecular link through which environmental signals might alter DNA methylation in specific genes in neurons.

In the absence of increased NGFI-A expression, the promoter remains methylated. The unmethylated promoter will maintain high affinity to NGFI-A throughout adulthood, resulting in greater activity of the GR promoter, whereas the methylated GR promoter exhibits reduced affinity for NGFI-A, resulting in low activity of the GR in adult.

According to this model, environmental signals trigger cellular signalling pathways, which activate trans-acting factors that recruit histone acetyltranfesases (HAT) resulting in histone acetylation, chromatin opening and increased accessibility to DNA demethylating agents. This mechanism would enable reversal of the methylation mark.

4.2. Astrocyte-neuron reversible plasticity

Adult nervous system can undergo significant experience-related structural changes throughout life (structural plasticity). It has been recently known the notion that morphological plasticity affects not only neurons but glial cells as well[14]. Dynamic astrocyte-neuron interactions are part of the physiology of several adult neuronal systems; under physiological conditions as different as reproduction, sensory stimulation, and learning, they display a remarkable structural plasticity.

The magnocellular system of the hypothalamus constitutes a physiologically controlled system. Its morphological reorganization involves both its

[14] Theodosis, D.T., Poulain, D.A., Oliet, S.H.R. (2008) "Activity-Dependent Structural and Functional Plasticity of Astrocyte-Neuron Interactions". *Physiol Rev* 88, 983–1008; Oliet, S.H.R., Panatier, A., Piet, R., Mothet, J.P., Poulain, D.A., Theodosis, D.T. Neuron–glia interactions in the rat supraoptic nucleus. In *Progress in Brain Research*, Vol. 170, Chapter10, I.D. Neumann and R. Landgraf (Eds.).

neurons and glia during parturition and lactation. The adult hypothalamo-neurohypophysial system undergoes a striking activity-dependent morphological remodelling that modifies the glial wrapping of its magnocellular neurons. The repercussions of glial environment modifications on the physiology of magnocellular neurosecretory cells are at the synaptic level. Reduced astrocytic coverage of magnocellular neurons occurring on supraoptic nucleus affects various functions in which astrocytes play key roles.

These functions include uptake of neurotransmitters such as glutamate, restricting diffusion of neuroactive substances within the extracellular space and release of informative molecules known as gliotransmitters that act on neighbouring neurons to modulate synaptic transmission and excitability. The magnocellular system (oxytocin neurons) of the hypothalamus constitutes a physiologically controlled system. Its morphological reorganization involves both its neurons and glia during parturition and lactation. In the hypothalamus, OT neurons usually occur in tightly packed clusters, but under basal conditions of neurosecretion, they remain separated by fine astrocytic processes. In contrast, during parturition and lactation there is a significant reduction in the astrocytic coverage of all portions of OT neurons.These changes occur within a few hours and are completely reversible upon the cessation of the stimulation.

Astrocytic environment of neurons contributes to the regulation of synaptic and extrasynaptic transmisión.

Distal astrocytic processes contribute to transmission at the tripartite synapse.

NEURAL SUBSTRATES CONTROLLING MATERNAL BEHAVIOR

The newly developed ability to study the neural correlates of subjective mental states with brain imaging techniques has allowed neurobiologists to learn something about the neural bases of maternal love. Obviously brain imaging techniques are not indicative of a direct cause; activation, deactivation or absence of recording is not a manifestation *per se* of the cause of the phenomenon.

Functional neuroimage techniques show how certain brain areas are activated, while others become silent, when a mother sees her son or heasr his voice. This is the neural correlate of the emotion, which the presence o her son generates under diverse circumstances in the mother. This type of social and emotional behaviour is processed in the so called *social brain*, which integrates longitudinally sructures of both cerebral hemispheres, such as orbitofrontal cortex and amygdale complex. Routes potentiating the cerebral processing of relevant stimuli are thus created in interpersonal relations. All the areas of the activated cerebral cortex correspond to neural zones participating in cognitive-emotional processings. In these processes of integration, the limbic system combines synchronic activations and deactivations of its components.

Human attachment seems therefore to employ a push–pull mechanism that overcomes social distance by deactivating networks used for critical social assessment and negative emotions, and at the same time bonds individuals through the involvement of the reward circuitry.

Changes revealed when mothers viewed their own child versus an age and familiarity matched acquainted child.

When a mother contemplates a photograph of her son a few months of age she enters a pleasant state, not produced when she she sees photographs of other children, even if they are known to her. Neuroimage techniques reflect the activation of the *social brain,* and areas of the cognitive-affective system of *reward* are activated, and others participating in negative judgmente are silenced[15] .

Activations with maternal love: Anterior cingulate cortex, ventral cingulate cortex; Caudate nucleus; Frontal eye fields; Fusiform cortex; Insula; Lateral prefrontal Cortex (ventral); Occipital cortex; Orbito-frontal cortex; Thalamus; Striatum (consisting of putamen, caudate nucleus, globus pallidus); Periaqueductal (central) gray; Substantia nigra.

Deactivations: Prefrontal cortex (Mes.sup. front gyrus; Lateral prefront; Ventro-lateral prefront).

[15] Zeki, S. (2007) "The neurobiology of love". *FEBS Letters* 581, 2575-2579; Bartels, A., Zeki, S. (2004), "The neural correlates of maternal and romantic love". *Neuroimage* 21, 1155-1166.

Parietal cortex (Lateral parietal; Parieto/occ. Junction). Temporal cortex (Medial temporal; Medial STS; Medial STG; Inferior temporal lobe; Temporal pole). Posterior cingulate cortex (Retrosplenium; Medial precuneus) Amygdaloid region.

Parental Status–Specific Response to Infant Crying and Laughing

Women but not men, independent of their parental status, showed neural deactivation in the anterior cingulate cortex, in response to both infant crying and laughing.

The response pattern changed fundamentally with parental experience: in the right amygdala and interconnected limbic regions, parents (independent of sex) showed stronger activation from crying, whereas nonparents showed stronger activation from laughing[16].

The same pattern (parents vs. nonparents) stimulus (crying vs. laughing) was present in the other brain areas shown: ventral prefrontal cortex; insole; temporoparietal junction; middle cingulated cortex, together with the amygdala.

Thus, the modulation of responses by experience seems to represent an adaptive mechanism. The

[16] Seifritz, E., Esposito, F., Neuhoff, J.G., Luthi, A., Mustovic, H., et al. (2003) "Differential Sex-Independent Amygdala Response to Infant Crying and Laughing in Parents versus Nonparents". *Biological Psychiatry* 54, 1367–1375.

influence of paternity on the brain facilitates care when when viewing the needs of the crying child.

Mother-infant attachment is not a unilateral process: the infant's behaviour has a powerful effect on the mother's emotions.

Maternal love, which may be the core of maternal behaviour, is essential for the mother-infant attachment relationship. Patterns of maternal brain activation in response to infant cues using video clips[17] show a highly elaborate neural mechanism mediating maternal love and diverse and complex maternal behaviours for vigilant protectiveness.

A limited number of the mother's brain areas were involved in recognition of the mother's own infant: orbitofrontal cortex (OFC), periaqueductal gray, anterior insula, and dorsal and ventrolateral parts of putamen.

And strong and specific mother's brain response for the mother's own infant's distress: caudate nucleus, right inferior frontal gyrus, dorsomedial prefrontal cortex, anterior cingulate, posterior cingulate, thalamus, substantia nigra, posterior superior temporal sulcus and prefrontal cortex.

[17] Noriuchi, M., Kikuchi, Y., Senoo, A. (2008) "The functional neuroanatomy of maternal love: mother's response to infant's attachment behaviors". *Biological Psychiatry* 63, 415–423.

Face stimuli activated brain regions along the ventral visual pathway from the primary visual cortex to the temporal lobe, including fusiform face area.

There was no significant difference in posterior visual pathway response between the own and unknown infant-face stimuli.

Mothers respond stronger to cry than smiling. The mother's emotional state was more complicated when viewing her own infant in a separation situation: positive emotions, such as love, coexisted with negative ones such as anxious feeling and worry in the mother herself. The emotional responses to her own infant might be appropriately regulated by monitoring her own emotional states and by inhibiting her excessive negative affects so as not to show negative expressions to her infant who is in distress.

The complexity of this reaction implies, among other processes, decodifying facial expression of emotions of her child and reducing her anguish. That requires high levels of alertness and protection, a reflection of integration of complex cognitive and emocional aspects.

With smiling faces specifically activating dopamine-associated reward processing regions

When first-time mothers see their own infant's face, an extensive brain network seems to be activated, wherein affective and cognitive information may be

integrated and directed toward motor/behavioral outputs[18]. Significant areas of activation were seen when the mothers were shown happy faces of their own infant compared with an unknown infant. In response to happy, but not sad, infant faces dopaminergic reward related brain regions are activated specifically: dopaminergic brain regions involved in cognitive, affective, and motor information processing.

The striatum is believed to be an important relay station between the limbic and motor systems, integrating affective information from limbic regions with cognitive information from the prefrontal cortex in shaping motor/ behavioral response. Each striatal region is integrally connected to a corresponding region the forebrain including those involved in emotion processing, cognition, and motor/behavioural outputs (primary motor area). And each striatal region is integrally connected to a corresponding region of the midbrain's VTA and substantia nigra via ascending and descending dopaminergic neurons.

Smiling, but not neutral or sad, faces specifically activate nigrostriatal brain regions interconnected by dopaminergic neurons.

Understanding how a mother responds uniquely to her own infant, when smiling or crying, may be the

[18] Strathearn, L., Li, J., Fonagy P., Montague P.R. (2008) "What's in a Smile? Maternal Brain Responses to Infant Facial Cues". *PEDIATRICS*, 122, 49-51.

first step in understanding the neural basis of mother–infant attachment.

According to data commented above, several regions of the nervous system could be implicated in the affective-emotional bond of maternity, and at the same time could also influence on cognitive processes supporting the stability of affective life of the woman. An imbalance of these processes could lead to mental alterations in some psychiatric ailments[19].

CIRCUITS FOR COGNITIVE–EMOTIONAL INTEGRATION OF MOTHER–INFANT ATTACHMENT: FUNCTIONAL AND STRUCTURAL CONNECTIVITY

Human attachment seems to employ a push–pull mechanism that overcomes social distance by deactivating networks used for critical social assessment and negative emotions, while it bonds individuals through the involvement of the reward circuitry. Cortical areas associated to limbic system in the processing of emotions become activated in the grain of the mother, when viewing her infant. However, the generation of appropriate behavioral responses involves selecting the most fitting response among competing possibilities and involve also while inhibiting those responses deemed inappropriate.

---

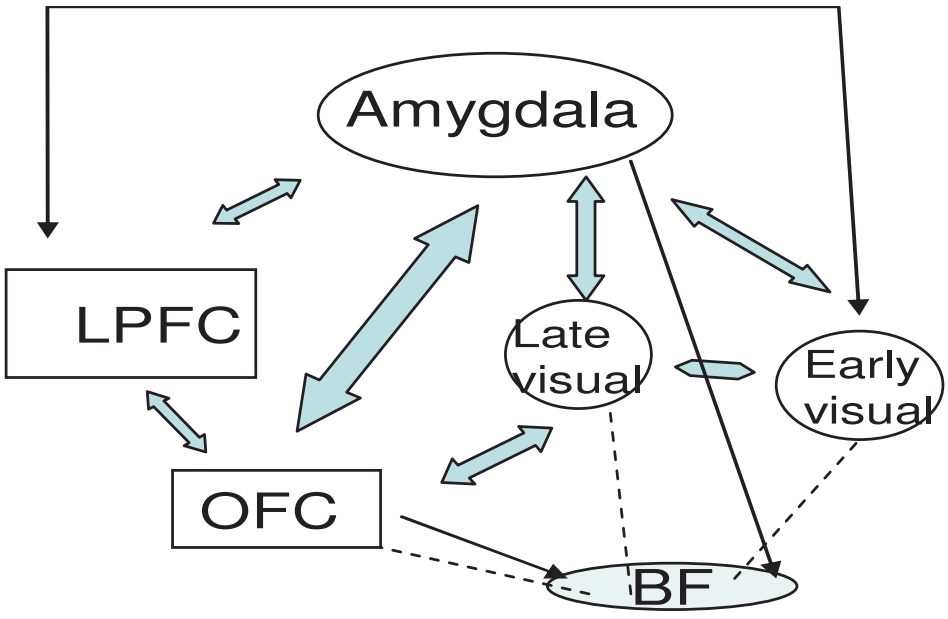
[19] Monkul, E.S., Onkul, J.P., Hatch, M.A., Spence, N.S., Brambilla, P., et al. (2007), "Fronto-limbic brain structures in suicidal and non-suicidal female patients with major depressive disorder". *Molecular Psychiatry* 12, 360-366.

The orbitofrontal cortex (OFC) and the amygdala in the evaluation of sensory information.

The orbitofrontal area is bound to functions related to information in the orgamism itself, old memories, affections, feelings, reward and so on. The OFC plays a determining role in neurobiological integration of reward systems, since it is connected with neurons producing dopamine, a substance crucial to value the nature of stimuli and how reward might be implied.

The affective component of a visual item is reflected at multiple processing stages, from early visual areas to prefrontal sites. The OFC and the amygdala have strong reciprocal connections with visual sensory areas and receive highly processed visual input from these late visual areas. Amygdala connects to areas of early visual cortex and the ventrolateral prefrontal cortex (PFC) and lateral (LPFC) receive projections from late visual areas. Stimulation is rapidly conveyed to multiple regions that collectively are capable of evaluating the input and determines the significance of the stimulus.

Circuit for the processing of visual information: OFC and Amyddala in the evaluation of sensorial information. The affective component of a visual item is reflected at multiple processing stages, from early visual areas to prefrontal sites. Visual cortical responses reflecting an item's significance is a result of simultaneous top-down modulation from frontoparietal attentional regions (LPFC) and emotional modulation from the amygdala. In this manner, behaviour is both cognitive and emotional.



And finally, the basal-forebrain system, which is interconnected with the amygdala and the OFC, provides diffuse neuromodulatory signals to both areas. The routes of reward bound to dopamine and with receptors to oxytocin and other hormones are located in the basal-forebrain system and play an important role in interpreting reward simuli in the process of learning. This arrangement is able to

enhance the processing of contextually significant information.

The amygdala might underlie a form of emotional modulation of information that in many ways parallels the attentional effects observed in the visual cortex. That is, increasing the affective significance of a stimulus turned strongly amygdale-dependent it has effects that are similar to those of increased attention.

Attention to a stimulus (a cognitive process) increases neuronal firing rates in sensory cortex and is believed to improve behavioural performance. Visual cortical responses reflecting an item's significance is a result of simultaneous top-down modulation from frontoparietal attentional regions (LPFC) and emotional modulation from the amygdale. In this manner, behaviour is both cognitive and emotional

Cognition and motivation are integrated in the lateral prefrontal cortex (LPFC).

Motivation is defined as what makes one work to obtain a reward or to avoid punishment. The lateral prefrontal cortex (LPFC) is activated with external visual, tactile and olfatory stimuli and is critical for the maintenance and manipulation of information. It is also believed to detect conflict and perform 'cognitive control' operations that regulate the flow of information during non-routine situations. This region not only holds information concerning an object, but is also modulated by reward magnitude.

Association of outer and inner information is important for taking decisions, inhbiting those irrelevan stimuli, which might disturb. The left PFC is involved in approach-related, appetitive goals, especially when multiple alternative responses are possible.

Circuit for executive control is of a cognitive–affective nature

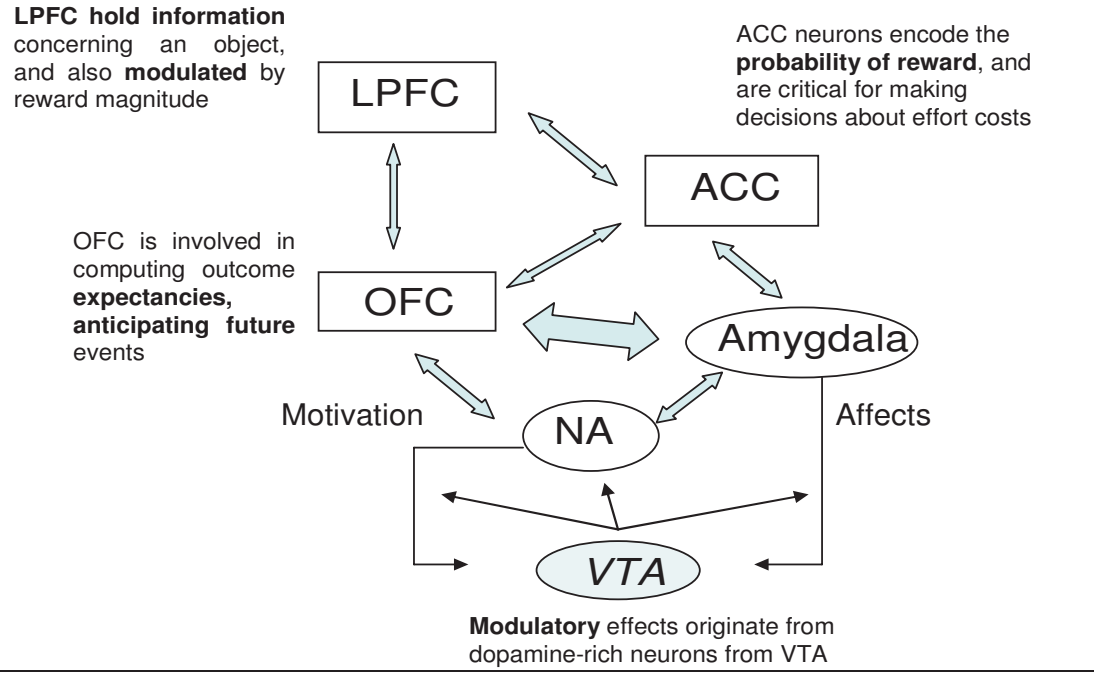
LPFC acts as a control hub. It can also integrate the content with both affective and motivational information. The convergence of both informations enables the LPFC to dynamically weigh multiple types of information in guiding action.

The participation of the amygdale, the OFC and the nucleus accumbens on the control circuit means that strategies for action dynamically incorporate value. Modulatory effects originate from dopamine-rich neurons from VTA.

The anterior region of the cingular cortex (ACC) becomes active in the evaluation of how should behave in the affective response when dealing with others. The function of the ACC includes conflict detection. ACC neurons encode the probability of reward and, at the same time, are critical for making decisions about effort costs. OFC is involved in computing outcome expectancies, anticipating future events extends to the amygdale. Therefore it discriminates among different types of response, allowing correct behavioural adaptations.

Other brain function that requires cognitive–emotional integration are the occipitotemporal cortex. The so-called fusiform cortex (Fu) contributes and facilitates understanding the child.

Circuit for executive control. The convergence of both cognitive and affective/motivational information enables the LPFC to dynamically weigh multiple types of information in guiding action. The participation of the A, the OFC and the NA in the on the control circuit means that strategies for action dynamically incorporate value.



In summary, amygdala is the most highly connected (structural connectivity) region of the brain. It makes very widespread projections, connecting with cortical areas the analysis. It occupies a position at the very geometric centre of the topological map. Overall, it appears that the amygdale, a core affective region, is

at least as well situated to integrate and distribute information. The region on the right hand side of amigadala processes negative emotions and it has also been called *the centre of fear*. This brain area alerting on danger in social interactons is silenced in the presence of the child; and other subcortical regions become also silent.

SOCIAL DECISION-MAKING

Human lives consist of a constant stream of decisions and choices, from the everyday to the highly consequential. Essentially, the study of decision-making attempts to understand our fundamental ability to process multiple alternatives, and to choose an optimal course of action.

As indicated above, seeing how a mother responds to her own infant when smiling or crying may be a model to understanding the neural basis of personal attachment. In social situations, the evaluation of emotional information conveyed by the facial expressions of other individuals becomes a central aspect of the decision-making process.

Neural systems involved in response inhibition in decision making

The ability to generate appropriate responses in social situations often requires the integration of emotional information conveyed through facial expressions, with ongoing cognitive processes; the response inhibition plays a key role.

Functional magnetic resonance imaging has been used[20] to investigate the emotionally guided response inhibition. Participants performed go/no-go tasks involving either letters or happy and sad faces. In these tests subjects were presented with happy or sad faces and were required to withhold responses for faces of a particular valence; standard go/no-go task involving letter sequences served as a comparison task for the emotional version. To determine the distinct neural circuitry engaged by happy and sad faces, as well as the neural regions responsible for inhibition during both emotions, the emotion task was divided into four distinct conditions. During a "happy-go condition" or a "sad-go condition" participants were instructed to respond to all faces. In a "sad no-go condition", or in a "happy no-go" condition presentations were divided evenly between happy and sad faces, and participants were instructed not to press for sad faces or to press for happy faces, respectively. This design allowed for direct comparison between each no-go condition with its respective go condition and direct comparison of emotional trials with standard (nonemotional) trials.

The fMRI results indicate that, independent of stimulus features and emotional salience, a core set of brain structures mediates response inhibition. However, the inclusion of emotional information leads

[20] Shafritz, K. M., Collins, S.H. , Blumberg, H.P. (2006) "The interaction of emotional and cognitive neural systems in emotionally guided response inhibition". *NeuroImage* 31, 468 – 475.

to the recruitment of paralimbic brain regions that process these signals and allow for appropriate decisions. Inhibition, within an emotional context, seems to recruit a distinct set of brain regions that includes areas beyond those normally activated by response inhibition tasks and that can be modulated by emotional valence.

1. Inhibiting responses to emotional faces activated *inferior frontal/insular cortex*, whereas response inhibition during the letter task did not strongly engage this region. Insular cortex is preferentially recruited for the emotional no-go conditions because of the specialized role of this region in the detection of emotional states. The anterior insula has also been implicated in more abstract emotional states, such as empathy. This region may serve to monitor the ongoing internal emotional state of the organism and integrate sensory information with motivational salience to guide behavioral responses.

Primary role of the insula was to guide the decision to respond or inhibit by analyzing the affective information conveyed by the happy and sad faces. The insula was most recruited when these offers were rejected and positive responses were withheld. Similarly, the association of insular cortex with negative emotional states, particularly disgust, supports the idea that this region would be most active during withdrawal behaviour, such as response inhibition. Therefore, when decision making includes a strong emotional or motivational component, the anterior insula may incorporate the

affective information into the decision-making process and determine whether it may be necessary to inhibit an ongoing behavioural response. In addition to its putative role in affective neural processing, the anterior insula has also been implicated in more global cognitive processes, such as attention and inhibition in non-emotional contexts.

2. In addition, distinct regions of *ventral anterior cingulated* cortex were preferentially activated for sad faces in the go and no-go conditions. Region in ventral ACC can be modulated by emotional valence. Activation within ACC can be modulated by emotional valence, as sad stimuli activated regions of ACC more than happy stimuli. Two distinct regions of ventral ACC were activated depending on the specific requirements of the emotional task. One (a region of pregenual ACC located at the intersection of dorsal and ventral cingulated), was activated when the task required participants to withhold responding for sad faces occurring among happy faces. Two (the more ventral subgenual ACC), was recruited when the task required responding.

The conditional recruitment of specific regions within ACC in the current study is interesting in light of the proposed role of this structure as a critical interface between emotion and cognition. Consistent with the notion that the ACC serves as an interface between emotion and cognition, authors suggest that the pregenual ACC activation found during the sad inhibition condition represents a unique region of

ACC that integrates emotional and cognitive neural signals. Thus, the emotional inhibition task additionally recruits the ACC at the intersection of its cognitive and emotional subdivisions, a region to integrate emotional and cognitive information. These findings suggest that emotionally guided response inhibition may require not only the cooperative effort of cognitive and emotional brain regions but also distinct regions that are specifically recruited to process cognitively demanding information in an emotional context in how these two neural processes interact to guide behavior in a socially relevant context.

Results indicate that certain brain regions are recruited during this decision-making process that may give meaning to emotional facial expressions and allow for the most appropriate behavioural responses in a given situation. The emotional appraisal occurring in the anterior insula is then integrated with other signals in ventral ACC, and it is this integrative process that allows for the most appropriate behavioral decisions in social contexts.The neural systems specifically engaged during the no-go blocks could include brain regions responsible for decision making under high cognitive demands; and the most salient cognitive process during the no-go blocks is response inhibition.

The last cognitive control system

This type of highly processed information would also be able to support the more abstract processing that

is required for cognition. To perform that, a broader cognitive–affective control circuit should exist.

The emotive and cognitive processed response may be personally accepted or rejected. This important dimension of cognition involves behavioural inhibition. Response inhibition (the processes required to cancel an intended action) is believed to involve control regions in the prefrontal cortex.

The prefrontal cortex has as its main function that of inhibiting to avoid the confusion, which might be generated with the high number of stimuli the brain migh receive. Without that function of "liberation of functions", usually inhibited might take place. Perhaps where this phenomenon might be better observed is in the órbitofrontal cortex with its capaciy to innibit instincts and the límbico system in general.

Frontopolar cortex (FPC), the most rostral portion of the human prefrontal cortex (Brodman's area 10) activated in multitasking behavior, in which subjects postponed the execution of a task to perform another first. Sequencing of tasks to be endeavoured, establishing a schedule, that breaks the automatism of neural processes. Human capacity to postpone instinctive satisfaction and probably other satisfactions as well might be supported by the prefrontal cortex. It is known that any human being, a mother in this case, may offer her entire life without the hope of a reward she is uncertain to receive. This presupposes a considerable capacity of thinking in addvance, a function also bound to that part of the brain, as it will be commented later.

Etienne Koechlin and Alexandre Hyafil[21] have proposed a neurocomputational model of human frontopolar cortex function. According to these authors three types of neurons interact among them in an excitatory and inhibitory way and located in the lateral prefrontal cortex (Lpc); medial/orbital frontal cortex (Ofc) and neuronal populations in the lateral prefrontal cortex (Lpc); medial/orbital frontal cortex (Ofc) and frontopolar cortex (Fpc).

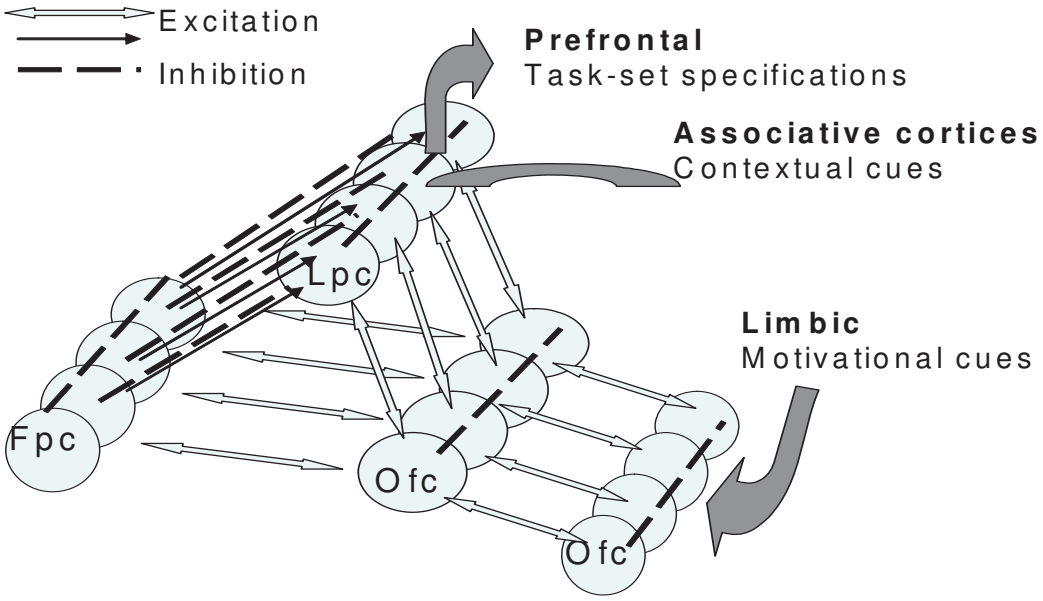
Brain areas commonly activated in social decision-making. A computational model of human frontopolar cortex function (FPC).

FPC the most rostral portion of the human prefrontal cortex activated in multitasking behavior, in which subjects postponed the execution of a task to perform another first.

1. Strong lateral inhibition within Lpc and Fpc enforces task-set selection; strong self-excitation facilitating task-set maintenance in the absence of any external inputs.

2. Weak lateral inhibition and self- excitation within Ofc enables Ofc neurons to maintain reward expectations related to multiple task sets, but only those corresponding to the task sets maintained in Lpc and Fpc.

[21] Koechlin, E., Hyafil, A.(2007) "Anterior Prefrontal Function and the Limits of Human Decision Making". *Science* 318, 594-598.



3. Ofc includes an input layer storing and updating expected reward values associated with task sets with respect to input signals (external or internal contextual cues): A) Lpc and Ofc neurons are reciprocally connected and receive input signals from other brain regions (posterior associative and paralimbic cortices) cueing activity toward specific task sets and updating expected future rewards; B) According to reward expectations, Fpc units form a possible back-up buffer for storing a previously selected task set in Lpc, while Lpc units are representing another. The Fpc buffer enables to possibly reinstantiate in Lpc the pending task set and consequently to reinstantiate its specifications in lower brain regions for execution, even in the absence of any external inputs.

Lpc and Fpc neurons are activated during the pending period. This situation perpetuates until one expected reward value drops below threshold: the

active task set is discarded and the pending task set becomes the active one for guiding subsequent behavior.

The second most rewarding task is placed in a pending state in the FPC, while lateral prefrontal regions are controlling the execution of the most rewarding task, provided that the future rewards expected from the two task sets are large enough. Thus, cognitive branching occurs and FPC is recruited with no supervisory optimization and control, because it would have been too costly to discard the second most rewarding task as suggested by empirical results.

It is of interest to emphasize that braking the flow of information is the key to understand that the response or decision is not strictly determined in the dynamics of the neural process. It is possible to reinstantiate again in Lpc. What in taking decisions is underlying is the liberation of automatism in the dynamics of cognitive and emotional flow precisely due to the inhibition capacity..

LPFC might therefore act as a control hub in which multiple types of information converge and are integrated. Critically, the convergence of both cognitive and affective/motivational information enables the LPFC to dynamically weigh multiple types of information in guiding action.

In summary, decision taking affecting other people requires the activation of brain areas.

1. The LPFC, the ACC and the parietal cortex guides behaviour while maintaining and manipulating goal-related information. LPFC circuits are especially adept at maintaining information for brief temporal intervals and manipulating information. The parietal cortex, in conjunction with the PFC, has an important role in the *control of attention*.

2. Since it is neessary taking into account the costs and benefits of such goals and actions, the participation of the amygdale, the OFC and the nucleus accumbens in the on the control circuit means that *strategies for action dynamically incorporate value.* In particular, the OFC and medial PFC are involved in computing outcome expectancies; the OFC's role in anticipating future events extends to the amygdale. Finally, dopamine neurons located in the ventral tegmental area and the substantia nigra (pars compacta) project not only to the nucleus accumbens, but also to the frontal cortex, including the LPFC.

3. The *prediction and expectation of future rewards*, including reward prediction errors, which might be an important function of the dopamine system, should feature prominently in the temporal unfolding of control. First, the ACC appears to be involved in computing the benefits and costs of acting. Second, the LPFC has a role in maintaining and manipulating

information, but can also integrate this content with both affective and motivational information.

4. It is also important to consider the role of ascending systems. The basal forebrain receives both cortical and amygdala inputs. It seems that a group of specific topographically organized prefrontal–basal forebrain–prefrontal loops exist. Such loops provide a direct substrate for cognitive–emotional integration.

5. Additionally, hypoactivation in the left PFC is linked to depression. By contrast, the right PFC is proposed to be involved in situations that require behavioural inhibition and withdrawal, again, especially when alternative approach options are possible.

PEOPLE ARE NOT "OBLIGATE ALTRUISTS": NEITHER ARE MOTHERS

Humans are able to live in large groups and to cooperate with unrelated individuals. They help others. Humans must be more than self-regarding rational decision-makers; they must also, at least to some degree, have concern for outcomes and behaviors affecting others, as well as a general concern for norms of fairness. Other regarding preferences and aversion to inequitable outcomes, which play key roles in human social organization, distinguish us from our closest living relatives.

People may be altruist, but people are not obligate altruists. People may be generous but do not tolerate abuse of their generosity. They punish who exploit them even if they themselves do not benefit from correcting the behavior of norm violators.

Neuroeconomic approach to the study of social decision-making has the potential to extend our knowledge of brain mechanisms involved in social decisions and to advance how we make decisions in a rich, interactive environment. Social exchange can act directly on the brain's reward system, and affective factors play an important role in bargaining and competitive games, and how the ability to assess another's intentions is related to strategic play. Although relatively understudied, these social situations offer a useful window into more complex forms of decisions, which may better approximate many of our real-life choices.[22]

Changes in he brain of mothers are mediated by different hormonal and neurochemical factors and generate a strongly altruist maternal behaviour. Mothers help their children at a great personal cost.
Positive sensory cues from infants, such as a smiling facial expression, may stimulate dopamine release in the striatum and promote responsive maternal care. A smiling infant's face usually leads to positive affective arousal in a mother, associations with other rewarding experiences, and contingent behavioral responses such as smiling, caressing, or playing.

[22] Alan G. Sanfey Social Decision-Making: Insights from Game Theory and Neuroscience. Science, 2007, 318. 259-262.

However, a distressed infant usually evokes an empathic emotional response from a mother, as well as cognitive processes to determine, on the basis of past experience and knowledge, possible causes and remedies for her infant's distress.

The stimuli from their own infants are powerful motivators for a mother to respond to their demands. In responding to infant social cues, whether positive or negative, mothers need to integrate both affective and cognitive information about their infant, and evaluate competing demands, before choosing the most appropriate behavioral response.

The strength of natural maternal attachment does not give to maternal love the automatism of neurological processes of animals. Not all the mothers are generous in the same way: their responses are personal (unequal and different). A mother might not respond to the demands of her child, when she thinks that something else might be better.

Pregnancy prepares the mother to recognize the demands of the infant and respond to them with care and love. Mothers not only care their children, they educate them. The development of affective-emotional attachments is the result of a neurobiological framework specifically human.

On he contrary the closest living relatives to humans, chimpanzee (Pantroglodytes) engage in cooperative behavior such as group hunting, coalitionary aggression, and territorial patrols, but chimpanzees,

however, simply attend to their own expectations with no regard for what others receive. Test for examining sensitivity to fairness and other-regarding preferences is the "ultimatum game"[23]. In an ultimatum game, chimpanzees are self-interested rational maximizers and are not sensitive to fairness.

"Experiencing the future".

All animals can predict the hedonic consequences of events they've experienced before. With practice animals learn to associate pleasures and pains with their antecedents which enables them to steer toward pleasure and away from pain before they actually experience either. Humans have this ability too; but they can also predict the hedonic consequences of events they have never experienced.

This ability, as reviewed by Daniel T. Gilbert1 and Timothy D. Wilson[24], presupposes simulating those events in their minds. Thus, humans can have retrospection (refer to our past, reexperience the past) and prospection, which refers to our ability to "pre-experience" the future. The mental representation of a past event is a *memory*, the mental representation of a present event is a *perception*, and the mental representation of a future event is a *simulation*.

[23] Jensen, K., Call, J., Tomasello, M. (2007) "Chimpanzees Are Rational Maximizers in an Ultimatum Game". *Science*, 318 107-109.

[24] Gilbert, D. T., Wilson T.D. (2007) Prospection: Experiencing the Future. *Science* 317, 1351- 1354.

Mental simulation is the means by which the brain discovers what it already knows.

The brain combines incoming information with stored information to build "mental representations," or internal models, of the external world. When faced with decisions about future events, the *cortex generates simulations*, briefly tricking subcortical systems into believing that those events are unfolding in the present and then taking note of the feelings these systems produce. The cortex is interested in feelings because they encode the wisdom that our species has acquired over millennia about the adaptive significance of the events we perceive.

People mentally simulate future events and use those simulations to predict the event's hedonic consequences. For that, people use their immediate hedonic reactions. These simulating actually allow people to "preview" events and to "prefeel" the pleasures and pains those events will produce.

1. The brain frontal cortex appears to play a critical role in simulations process. Patients with damage to the prefrontal cortex are described as being "bound to present stimuli". Neuroimaging studies reveal that the prefrontal cortex and the medial temporal lobes are strongly activated by prospection. Animals, in spite of having evolved strategies to solve problems involving future events such as impending food shortages, they do not achieve these solutions by simulating future events. Indeed, the ability to simulate and pre-experience the future does not appear in human children until the appropriate

region is developed, when they are 3 or 4 years of age.

2. Prefeeling depends critically on the ventromedial prefrontal cortex. It appears that the activity of midbrain dopamine neurons encodes information about the magnitude of pleasure that a future event is likely to produce. Simulation of pleasurable future events activates subcortical structures such as the nucleus accumbens and the anterior regions of the ventral striatum. However, simulation of painful future events activates the amygdale and/or the posterior ventral striatum.

Cortex cannot generate simulations that have all the richness and reality of genuine sensory perceptions. In fact, our hedonic experiences are influenced both by our mental representation of the event and by contextual factors. Usually the prospection processes are based on simulations that are unrepresentative; they are based on a small number of memories because remembering our last one may be sufficient. Simulations are naturally abbreviated and represent just a few select moments of a future event. And they are decontextualized.

Although prospection allows us to navigate time in a way that no other animal can, we still see more than we foresaw. The richness of emotional life of the mother permits that the frontal cortex simulates future events trying to find out what subcortical structures know. And her predictions become more accurate if she is specifically encouraged to consider the contextual factors, because she has habits of reflexion.

TOWARDS A DESCRIPTION OF BRAIN/MIND RELATIONSHIP

The complex emotional-cognitive maternal behaviour offers significant data, which help us entering what is specifically human in brain/mind relationships.

"Correlates" between psychic and neural phenomena have been insistently searched, the term "correlate" being understood as a relationship between what is neural causing what is psychic. The paradigm installed in life sciences regarding the dynamism of temporal processes of living beings allows us to approach the concepts of vegetative, sensitive and intellect life as a unity, human life including the inferior levels of animal and plant life. Feeling is an act of a living organism and not of its brain, in the same way that thinking is proper of a living person.

Any form of life has as its key feature the fact that it posseses information for its construction and development. The dynamism of the living being is *regulative epigenetic:* the signals of the environment, which are generated by the process, modulate, expand and act as a feedback of the starting information in a unitary way in space and time and ordered to living. The dynamism of the brain flow of information is also of epigenetic nature.
The growth of the organism (the differential development of the organs) does not break the unity of the individual.

The material support of the genetic information, the chromosomes, is the same for all the cells of the

organism. However, along each line of cellular differentiation, only certain genes are specifically expressed and other genes are suppressed. Genetic information (the sequence of DNA nucleotides) is expressed or updated every time in the adequate place of the organism in development. Different organs evolve from different cells, all of them having the complete genetic information, but updating only part of it. To coordinate the whole unit a fine regulation of gene expression in each cell is required. That way liver and all the organs in the body are constructed and begin to work at the right place and in the right moment.

Genetic information, nucleotide order in DNA, is inmaterial and it is the formal cause of the construction of the different components of he organism. It is a first level of information. This information is controlled by the expression of genes. Coordination is a second level of information emerging from the process itself. The process itself permits to reach a higher level of information (second level), thus allowing matter to acquire its complete form. This information is not genetic (it is not a consequence of nucleotide sequence); it is what in biology is referred to as *epigenetics.*

Each stage of cell differentiation leaves a mark in the material support (changes in the structure of DNA, or chemicals changes in its bases) thus regulating gene expression. This new information leads and controls as a unit the differential expression of genes. Genetic information is brought up date in each cell and subjected to the entire organism as a unit. That

information would be potentiating the form, thus being the formal cause of growth as a unit.

The growth of the organism has a limit of space and time, which is intrinsic to the living being. Biological life, being a continuous renewing of potentialities, follows a route with a precise beginning and end established by the complete unit. Genetic information does not change, and epigenetic information has a feedback linked and limited by growth.

Activity of neurones initiates a new type of growth

Any organ, tissue or system of an organism, with the exception of nervous system, reaches an end in the prenatal period. Their structures are complete and carry out their specific functions. However, we might say that the nervous system reaches the terminal phase of its organic growth. The nervous system is arranged as a unit with a plurality of functions; and a he same time its aim would not be its own display.

The individuals of each animal species have genetic information to construct the cells of the nervous system and the molecules allowing and regulating the connexion among neurones. Similarly to those two formal levels (genetic and epigenetic information) of organic growth, the construction and maturing of nervous system, and especially the brain, depends also on two levels of information.

The first level of information depends each moment on neurones and circuits of transfer of information,

which are functionally active. They are not only anatomical, but also functional. Neurones occupy their corresponding anatomical place, but they may be connected through a spatial network; these connexions are functional and the whole network synchronized. On a neurone different synapsis may converge at a given momento. Each one leaves its message, and the neurone integrates them and sends to other neurones divergent messages transmitting impulses. Differentiated cells of the nervous system are active and living; the first level is the activity of the neurone.

The functional dynamics of the brain requires a second level controlling and integrating the diverse functions of the activity of the neurones: unity is to be preserved in the middle of changing connexions. This function should be harmonizing changes, interruptions and beginning of transmissions of information. And it should be integrating in the right way diverse functions. As it has been indicated above, functional circuits include both multiple regions and neuromodulatory systems; and the brain has areas with a high degree of connectivity, called hubs, critical for regulating the flow and integration of information between regions; and the brain has also regions that are not as highly connected.
Nervous system acts dematerializing, leaving matter away. It does not depend so much from cells, as from transmission functions (first level). At the same time, neurones or circuits, functionally active in a precise moment, have to be integrated through the unifying connexion function (second level). Integration presumes that whatever is already in act, the activity,

has to be with a potency of giving a "plus". Nervous system is not only formed by cells; it integrates all that, which is part of it. Therefore, the connexion function, or cognoscitive faculty bound to an organ, is the source of sensitive cognoscitive operations.

This potentiation of neurones is in agreement with the neurological concept of inhibition. At the interneuronal level we find excitatory and inhibitory functions. Potentiating the information (form) is eliminating from it whatever is efficient material cause of the stimulus. The stimulus generates various types of circuits, related among them, if the product of the activity of them is a triggering cue to another circuit[25]. The brain receives the stimulus, reaching it due to the efficiency of an excitation.

In order to potentiate the informative content of the stimulus, it is necessary to inhibit or lower the excitation. Inhibition consists of an attenuation of efficiency and a lowering of the material component in the physical-organic. That way it becomes integrated in the functional unit of the organ. Living neurones somehow "become dematerialized"; and because they are alive they are inhibitory, and they may be inhibited. They do not exert an inhibitory action (through a substance), but they are inhibited in act, and being inhibited, their form is being delimited.

[25] Damasio, Antonio. *El error de Descartes*. Ed. Crítica. S.L. Third Edition, Drakontos Bolsillo. 2007, p.295

This de-materializing, elevating what is formal at the expense of reducing what is material and efficient in the stimulus, permits to jump from what is organic to what is intencional. And besides it is juxtaposing in time what is synchronizable. Inhibition is not reducing the potency; it is simply a brake to the excitation of the neural circuit.

What is psychic or mental is the result of the integrating mechanism of the neural function, and it is not identified with it. It does emerge from the development of the nervous system following the epigenetic laws proper to the individual as belonging to an animal species. The dualism between what is intentional and real is not a parallelism; they are simply juxtaposed. Feeling and perceiving, for instance, are a single act in two dimensions, physiological and mental; they are not at all two related acts.

Sensitive life of the living animal

Nervous system fulfills functions involving our knowledge, trends, motion, etc. It does organize in a living unit the different sensitive cognoscitive operations, tendencies, motions, and so *animal behaviour* emerges. The sensitive animal life is immanent, i.e. it performs a dynamic integration permitting the indiviual react as a whole. The response of the animal to a stimulus (food, for instance) is not a simple physical mechanism produced only by interactions of molecules and cells; it is physiological, i.e. integrated in the living unit. The sitimulus is not the cause of the response; it is

only the occasion so that the animal reacts as a unit. Animal behaviour is intentional; the tendency or instinct to eat in order to satisfy hunger depends on the function ruling the need to secure food and preserve life in the environment proper to the individuals of that species. The response of the anmal to the stimulus is an automatism directed from inside to secure survival of the individual and the species. The animal knows and responds as a function to perform that.

In spite of the fact that the animal is even capable of knowing intersubjectively other animals, this knowledge is always in the state of *"on"*, in the "present time", while the object is present. The knowledge of the animal is included in the automatism of the response, and it is always acting to secure biological survival. It might be said that animals are self-interested rational maximizers. They are locked inside their automatism, inside their neurophysiology: events they have experienced before cannot help them to predict the hedonic consequences. Animals live always in the present time and never come out of their closed biology. Animals do not know objects as objects.

Knowledge of the animal is therefore integrated in the circuit stimulus-response. Sensitive knowledge in the animal requires very little potentiation of neurones, very little inhibition; in fact, knowing for them is only a phase of he response to the stimulus. Some animals with a knowledge considered "curious" or "strange" and not completely automatic might be considered as an exception. We might state that the

function of connexion is poor and limited. Sensitive life does not require that automatism should be broken. This is the limit of sensitive knowledge, which is not integrated at a higher level.

In humans psyche is open, and released from the automatism of the "animal mind"

Knowledge entering through senses does not go from what is physical to something else being also physical. It goes to what is intentional, due to the braking of neuronal excitation (inhibition). And the response to the stimulus allows again entering into the physical world. Human sensitivity is much richer than that of the animal, because human neuronal basis is highly plastic and capable of establishing thousands of synaptic connections. And similarly to what happens in animals, humans possess a function of brain connection[26] integrating the connective act to a much richer sensitivity.

[26] It is interesting to consider that the difference between genomes and chimpanzeesof human bengs and chimpancés consists mainly in a higher expression in man of genes directing connexions bewteen neurones while brain is developing (cfr, rewiev, Pennisi, E. (2006) "Mining the Molecules That Made Our Mind". *Science* 313, 1908-1911; López-Moratalla, N. (2007) *La dinámica de evolución humana. Más con menos*. Eunsa). It should be added the fact that incrporation of stem cells in the reserve to brain circuits takes place mainly in the brain cortex; that would be equivalent to say that neurogénesis in adult life means a selective contribution to specific dognitive functions (Zhang, Ch-Li, Zou, Y., He, W., Gage, F.H., Evans, R.M. (2008) A role for adult TLX-positive neural stem cells in learning and behaviour. *Nature*. doi:10.1038/nature06562)

As it has already been pointed out, human behaviour differs from that of the animal. Each human being has an objective knowledge of reality, as reality itself and not as a mere convenience to solve biological needs. That detachment of "the other" to take careo f something is accompanied by a voluntary acceptance and attachment, or detachment, of affection or disaffection to that "other"; all this being proper to human conduct.

Man is capable of drawing experience from an intellegible and essential abstract structure independently of biological needs. And this operation might be "*off*" and not only *"on"*. They may be "*on*" and "*off*" simultaneously. Man takes decisions; past is brought to the present and projected to the future. Man may *experience futurity*: he can predict the hedonic consequences of events he has never experienced. That human capacity of having simultaneously as present past, present and future forces thinking to be accompanied by an act of consciente: a reflexibility inseparable of cognoscitive intention. When viewing relity with conscience of being himself and at the same time different from reality, human conduct does not only tend to something; human conduct directs itself to aims of the subject itself.
Only human pyche possesses the function of conscience; that function allowing man detaching himself from the world outside himself and becoming conscious of himself. Which function is taking care of establishing the boundaries between functioning of the brain aand what is consciously known? It is indeed a regulatory function of dynamic integration of

multiple brain faculties, cognitive and emocional, carried out by the very summit of the hierarchy of nervous system.

Brain cortex, and specially the frontal lobe, is the most flexible region, and prone to be braked; this area keeps control of other archaic areas. In general, with regard to the flow of information to the cortex and their connexions (from the physical to the intencional) inhibition predominates, as already pointed out; however in the flow startng in the cortex excitation predominates. Terminal inhibition of neuronas in the cortex is not required for other functions of the nervous system not required to knowledge.

Braking of neuronal processes, exerted by inhibition, is not extrinsic. A regulation (second level) of functional dynamics is involved liberating psychic structures (first level) from biological auomatism. That way mental phenomena are released and controlled by the person, allowing him to direct activities not directly linked to what is strictly organic: intellectual knowledge and free decisions. This control is indeed intrinsic and decisive, integrating cognitive, emotional and vegetative elements, and acting on psychic structures.
Faculties exerting that control (intelligence, ability of exerting love) are not organic. A clear sign of this is that they grow by habit and are open in an undefined way, i.e. not limited by organic structures. They do reside in what commonly called freedom or spirit. Obviously, human thought cannot be neurologically localizad; but it always operates on psychic

phenomena, which do have a physiological component. For example, when we refer to “dryness”, we think of “something” or “somebody” and that “something” or “somebody” has been previously in other faculties and in a different way. And exactly the same happens, if something is desired. That is precisely what the traditional sentence states: nothing in the intellect, if not prior in senses.

As a summary it may be stated that the response to stimuli and the decisions to be taken demand a regulation of the functional dynamics with a hierarchical structure liberating psychic structures subjected to brain functioning. Braking through inhibition forces a synchronization of circuits to be integrated; and at the same time it allows their partial activity and their integration as a unit, which is the response and decision.

Are responses and decisions determined and established in man?

And a last question to be considered. Are we free to follow the response to stimuli and the decisions taken by the final hierarchical control? Human beings are very unpredictables when choosing a response; and apparently their decisions might be different under seemingly identical situations. The biological basis of this lack of determination turning man unpredictable –free- may be understood from the perspective of the *caotic* functioning of each individual brain.

In fact, the processing of information from neuronal circuits is complex. The flow of information

(membrane potentials, chemical signals, etc.) is permanently active and with a dynamism characteristic of caotic systems[27]. The brain operates in an undetermined and unpredictable way, and is highly sensitive to a change in inicial conditions. The expression "stop and think a little bit" is highly consistent: thinking really permits the inhibition of automatic circuits. Even more, that braking, when voluntary, introduces *personally* a change in the initial conditions of neural information.

It may be stated that that the response, once it has been decided, is not subject to regulation: it has the automatismo of the excitation. But breaking the automatism in the preparation of the response (i.e. making it unpredictable, not bound to a blind determinism) is the minimal change of the conditions in the hierarchical integration.

[27] The intrinsecal irregularity of the temporal and spatial dynamics of complex Systems is the irregular side on Nature; discontinuities and unpredictable behaviours are neither imperfections nor exceptions. It means not only an increase in he degree of freedom of a phenomenon, but a guideline arising from what is formless. Indetermination in the direction of a process is not random. An oscillation of the moment changing the fluctuation, an uncoupled frequency or an intermittence may lead to an undetermined aperiodic behaviour of a system in the absence of noise or any type of internal or external fluctuations. It may be asserted without any doubt that brain is the most caotic organ. Functioning of the brain does not respond to a lineal mecanicist simplification. (F. Montero y F. Morán *BIOFÍSICA. Procesos de autoorganización en Biología*. Ed EUDEMA; J. Gleick. *Caos, la creación de una ciencia*. Ed. Seix Barral, Barcelona, 1988).

As a conclusion, we may state that pregnancy prepares the brain of the woman in such a way that her mind is capable of recognizing her child and each one of his or her demands. Mothers are ready to fulfill at any rate any demand of the infant. Routes potentiating brain processing of relevant stimuli in interpersonal relations are built. All the areas of the brain cortex, which are activated, correspond to neural zones carrying out cognitive-emotional processings. In these processes of integration, the límbic system unites and coordinates synchronic activations and deactivations of its components. That way an authentic bond of attachment, natural and stable is generated through the integration of circuits activated or silenced by visual or auditory stimuli coming from the infant. However, the behaviour of the mother is not closed, as it happens with animal mothers. The response of the human mother might be altruist or not: she can break the automatism of the response. She does not feel herself to be "forced" to act as an altruist. And this care for her child is not performed in an automatic way. Maternal love is a personal dimension.

Acknowledgments: Special thanks to Professor José Manuel Giménez Amaya and Professor Esteban Santiago for their invaluable counsel in the preparation of the manuscript.