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CONSEQUENCES OF ADVERSITY ON THE DEVELOPMENT OF ATTACHMENT-RELATED NEUROTRANSMITTER SYSTEMS: INTEGRATIVE REVIEW AND ANALYSIS OF BRAZILIAN FEDERAL POLICIES FOR EARLY CHILDHOOD

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ABSTRACT

Decades of research have shown that abuse and neglect in early childhood increase the probability of unhealthy and psychopathological outcomes in adulthood. However, mechanisms concerning mediator and moderator variables are not completely clear. Drawing from Bowlby's Attachment Theory and evolutionary-developmental models, this work aims to uncover the effects of gene-environment interactions in neurotransmitter systems related to attachment styles. It is hypothesized that early adversity affects the development of decision making, emotion regulation and social bonding behaviors in a lifelong perspective, due to phylogenetically and evolutionary causes. Using the integrative review method, literature on gene-environment interplay and attachment behavior is analysed, particularly experiments on genetic polymorphisms linked to dopamine, serotonin, oxytocin/vasopressin and opioid neurotransmitter systems. Results of experiments so far conducted are not straightforward, due mainly to design limitations and to the multilevel complexity between genetic polymorphisms and social behavior. However, research does provide good evidence on the importance and efficacy of early intervention. In an evidence-based policy perspective, it is claimed that Brazilian federal policies toward children have significantly advanced since 1988, but there is still much to be done. Neuroscientific, genetic and epigenetic studies may help to explain why changing early environments is so important and what are the most effective ways to do it, considering the existing political and institutional constraints and the dynamic reality of policy networks.

Keywords: Attachment, Early Adversity, Gene-Environment Interaction, Polymorphisms, Dopamine, Serotonin, Oxytocin, Opioids, Evidence-based policy

For Oyama,

βασίλεια των ὀνείρων μου

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Abbreviations and Acronyms

5-HT	5-Hydroxytriptamine (Serotonin)
5-HTT	Serotonin Transporter
5-HTTLPR	Serotonin-transporter-linked polymorphic region
AAI	Adult Attachment Interview
ACC	Anterior Cingulate Cortex
ADHD	Attention Deficit-Hyperactivity Disorder
AVPR	Arginine Vasopressin Receptor
BDNF	Brain-Derived Neurotrophic Factor
bp	Base pair (of nucleotides)
COMT	Catechol-O-methyltransferase
CONANDA	Conselho Nacional de Direitos da Criança e do Adolescente
CNV	Copy Number Variation
CSF	Cerebrospinal Fluid
DNA	Deoxyribonucleic acid
DRD4	Dopamine D4 Receptor
ECA	Estatuto da Criança e do Adolescente
fMRI	Functional Magnetic Ressonance Imaging
GWAS	Genome-Wide Association Studies
HPA	Hipothalamic-pituitary-adrenal (axis)
MAOA	Monoamine oxidase A

NAcc	Nucleus Accumbens
NPY	Neuropeptide Y
OFC	Orbitofrontal Cortex
OPRM	Mu-opioid receptor
OXTR	Oxytocin Receptor
PAG	Periaqueductal Gray
PCR	Polymerase Chain Reaction
PFC	Prefrontal Cortex
RNA	Ribonucleic acid
mRNA	Messenger RNA
SES	Socioeconomic Status
SNP	Single Nucleotide Polymorphism
SSP	Strange Situation Procedure
SUS	Sistema Único de Saúde
VNTR	Variable Number Tandem Repeat
VTA	Ventral Tegmental Area

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Acknowledgements

This thesis undoubtedly faced early adversity. Entering a Master's Program in a new and challenging area, moving to Brasilia, assuming a high-responsibility position in the very core of federal government, taking planes in a weekly basis to get to classes in Belo Horizonte on time, getting married, structuring a home with my wife – it all overlapped in an intense, rapid and often stressful manner in the last two years. Given these conditions, planning and writing this thesis, while working in an insane daily rhythm, seemed like having to accomplish a physical and mental marathon. Hopefully, in spite of this, the outcome could not be more rewarding, fruitful and encouraging.

This would not have been possible without the fundamental role played by many people: a highly supportive family, valuable lifelong friends, intelligent work fellows from Casa Civil and elsewhere in the federal government, as well as peers in discussion foruns *Grupo de Estudos Indisciplinares* and *Repensar a Esquerda*. I start by thanking them all. But I would also like to dedicate a few more words on some people that were especially important in these last two years.

First of all, I owe this project of bridging the gap of natural and social sciences through neuroscience to Vitor Haase. I still remember one afternoon when I met him in an Evolutionary Psychology course. His acute intelligence, unquiet mind, together with his unconfounding white beard and cackling immediately captivated me. A fruitful and stimulant intellectual relation emerged, and I have enjoyed it ever since. Vitor taught me how narrow social scientist's reasoning can be if it disconsiders the wonderful methods and findings of true science; the value of the word "bio" in the expression "biopsychosocial"; and to be skeptical of intellectuals who claim knowledge without embracing scientific rigor.

I also thank Angela Ribeiro for always having an open mind to those stubborn students who, like me, think interdisciplinarity is the key to the future in Neurosciences. Professor Angela, since the beginning of my Master course, helped me in this enriching task of learning what is the role of a true neuroscientist.

Studying neuroscience in an interdisciplinary approach was especially fun because I had by my side the company of Pedro Pinheiro-Chagas, a brilliant fellow who knows well how poetry, cooking, photographing and understanding the brain can all be merged together in amusing and insightful conversations. Living the human comedy would be pointless without good friends like him around.

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Finally, the research was possible due to one of the most important policies in science and technology from the Brazilian government in the last decades: the CAPES Portal of scientific journals. It may seem strange to thank those who implemented it, but, as Vitor once said, in Brazil, there is research before and research after the CAPES Portal. Knowledge should have no frontiers, barriers, or restrictions.

Hence, it is also essential to thank all those anonymous individuals or researchers who, around the World Wide Web, struggle daily for free culture and open

access to scientific books and texts that otherwise would not be available for research. I eager for a day in which copyright laws – that still follow an ancient logic that should have been washed away with obsolete kings and monarchs that once conceded royal publication monopolies – will be adapted to the Digital Age, and free culture will be our reality. Unfortunately, in Brazil this still seems a distant dream.

“The child shall enjoy special protection, and shall be given opportunities and facilities, by law and by other means, to enable him to develop physically, mentally, morally, spiritually and socially in a healthy and normal manner and in conditions of freedom and dignity. In the enactment of laws for this purpose, the best interests of the child shall be the paramount consideration. (…) The child, for the full and harmonious development of his personality, needs love and understanding. He shall, wherever possible, grow up in the care and under the responsibility of his parents, and, in any case, in an atmosphere of affection and of moral and material security”.

United Nations Declaration of the Rights of the Child (1959)

“It is usual for every creature that is born—and the human child as much as any— to utter at once a loud outcry; and, what is more, the child is the most liable of them all to be afflicted with tears as well as outcries. (…) When nurses are trying to discover what a baby wants, they judge by these very same signs in offering it things.(…) If it remains silent when the thing is offered, they conclude that it is the right thing, but the wrong thing if it weeps and cries out. Thus infants indicate what they like by means of weepings and outcries—truly no happy signals!—and this period of infancy lasts not less than three years, which is no small fraction of one's time to spend ill or well (…) Well then, suppose one should try to secure by every available means that our nursling should experience the least possible amount of grief or fear or pain of any kind, may we not believe that by this means the soul of the nursling would be rendered more bright and cheerful?”.

Plato, *Laws*, Book VII, 791e-792b.

"Is evolution a theory, a system, or a hypothesis?
It is much more: it is a general postulate to which all theories, all hypotheses, all systems much henceforward bow and which they must satisfy in order to be thinkable and true. Evolution is a light which illuminates all facts, a trajectory which all lines of though must follow – this is what evolution is”.

Pierre Teilhard de Chardin, quoted in: Dobzhansky, T (1973). Nothing in Biology Makes Sense Except in the Light of Evolution. *The American Biology Teacher*, 35:125-129.

1. General Introduction

This is an interdisciplinary work. As such, it employs methods and references from various disciplines in order to better understand a specific problem, going further than each individual research field could do only by itself. Moreover, we share the belief that the natural and social sciences should not be separated by an abyss, but should instead accept some common notions – namely, the reality of social constructs, social learning processes, mind-body monism, gene-culture coevolution, an evolutionary-developmental approach, the need for and usefulness of multimethodological convergence – to truly understand human social behavior and the decision making process in a consilient manner[1].

Simply put, the idea that guides this investigation is: environmental conditions interact with individual genomes, influencing gene expression; environmental stressors such as child abuse (physical, sexual, emotional), maltreatment and neglect are risk factors that bring different impacts to each person and interfere with the formation of attachment bonds between parents and offspring; altered gene expression in neurotransmitter systems may influence attachment patterns, which by their turn act as moderator variables that, in the course of the developmental process, can lead to unfavorable outcomes. It is also presupposed that evidence-based intervention in environments can change this reality and avoid these unfavorable outcomes.

Understanding the mechanisms underlying these processes can help governments formulate better policies toward infants. In a country like Brazil, with a significant population of children facing risky environments, this is even more relevant, since targeted government action can change the fate of millions of children. The aim of this work, therefore, is to elaborate a framework out of neurobiological and social science models, to advance in the comprehension of this phenomenon and inform policymakers.

[1] It is necessary to mention, as an inspiration for the present work, the pioneering interdisciplinary research in neurolaw by Fernandez & Fernandez (2008). We thank professor Atahualpa Fernandez for always being receptive to new students willing to follow his steps.

1.1. An interdisciplinary approach

According to neuroeconomist Paul Glimcher, a scientific approach to behavior consists in different levels of analysis. From physics to chemistry, and then to biology, and finally to psychology, light is shed upon many phenomena that ultimately cause human behavior. Some concepts can be reduced from one science to another, whereas others do not: some phenomena emerge only in a certain level of analysis.

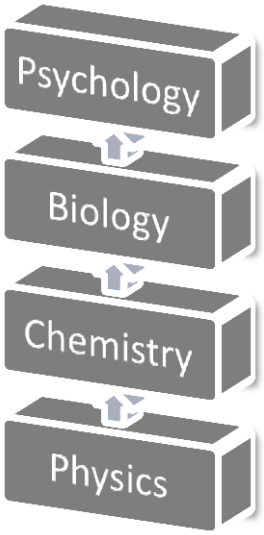

Figure 1.1. Levels of Analysis concerning human behavior

For instance, it is impossible to explain how the pancreas works counting solely on the description of the chemical molecules within it, the same way it is impossible to understand what an ecosystem is just by isolating its constituent parts – both are complex systems, with properties that emerge in higher levels of integration (a fact already pointed out by Mayr, 1961). Notwithstanding occasional failures of reduction, an attempt to synthesize findings from these sciences in an interdisciplinary basis should, in some cases, be tried (Glimcher, 2011).

That is precisely the case when it comes to the interplay between biological individual differences and distinct rearing environments: maybe we can obtain a better theoretical framework from this synthesis. The problem addressed in this research demands this kind of interdisciplinary approach.

We draw attachment theory from psychology. The neurobiological substrates of social bonds come from cognitive neuroscience. The mechanisms concerning gene and environment interaction are guided by molecular and behavioral genetics. Policy implications are examined in the light of policy analysis literature.

Attachment theory is not new. It has been proposed by psychologists from different perspectives, and decades of research have been made on attachment issues. John Bowlby's theory of attachment (Bowlby, 1969/1982), nonetheless, is the one that best integrates social and biological evidence. Bowlby posited that we could understand the bonds between infants and caregivers – which serve as references for social bonds throughout life – using an ethological approach. For Bowlby, the nature of child's ties to its mother, in humans and other animals alike, derive from a biological predisposition, resultant of natural selection, that constitutes a behavioral system responsible for balancing the need for, on one hand, a secure base for protection, and on the other hand, the drive to explore the outside world (Cassidy, 2008).

Crucially, Bowlby suggested that the patterns of attachment set in early childhood influenced internal mental representations of the self and of attachment figures. These mental representations were called Internal Working Models (IWM's), which guide emotion regulation throughout life and shape the way the individual manages relationships in adulthood (Coan, 2008).

Attachment theory, then, clearly provides a conceptual framework on early adversity's implications on the long run. Not surprisingly, much work has been done in searching for the neurobiology of attachment (Coan, 2008; Fox & Hane, 2008; Polan & Hofer, 2008).

Every behavior depends in some measure of its neural underpinnings, although mental representations and neural electric impulses obviously belong to different levels of analysis. Therefore, to understand behavior, one must turn to brain structure and function. The brain is a highly complex organ, consisting in networks of interconnected components organized in a hierarchical and modular manner, and its main function is information processing (Haase et al., 2008; Meunier et al., 2010).

Brain networks consist of neurons, which are cells specialized in signaling. Neurotransmitters are molecules that promote or block chemical communication between neurons in the synaptic cleft[2]. Neurotransmitter release, reuptake, synthesis or degradation interfere directly in the flow of signals and consequently in the dynamics of specific circuits (Baars & Gage, 2010). It can thus be hypothesized that changes in the expression of genes concerning neurotransmitters may somehow alter behavioral traits. That matter is addressed by chapter 2.

In chapter 3, the goal is to trace an overview of Brazilian federal policies turned to early childhood since 1988, when the Constitution brought new rules on child protection. Based on this, it shall be analyzed if what has been done ever since aligns with the scientific evidence concerning child developmental processes and attachment theory findings.

In putting these things together, the aim of the present work is to reduce the distance between natural and social sciences, theory and practice, university and government.

[2]Some basics of neurotransmission for social scientists: information passes within neurons because of *action potentials*, that is, ionic differences between the cell membrane and its surroundings. When the signal reaches the "end" of the neuron – that is, the axon – it causes the release of specific neurotransmitters. The neurotransmitters are proteins that play the role of chemically transmitting information from one neuron to the next, in a space among them known as the *synapse*. Once released, neurotransmitters may bind to receptors in the membrane of the following neuron, which will eventualy create a new action potential in this following neuron, exciting it, and making the signal pass on. After that, the neurotransmitter can be cleared from the synapse, being either degraded by some enzyme or reuptaken by *transporters*.

1.2. Problem and hypothesis

The aim of this work is to understand what are the mechanisms through which genes and environments interact in shaping neurotransmitter systems concerning attachment patterns.

The first working hypothesis[3] is that social environment interacts with individual genomes, leading to changes in specific neurotransmitter systems, which affectformation of attachment bonds,which, by their turn, will moderate[4] the association between early adversity and future physical, mental and behavioral outcomes (Figure 1.2).

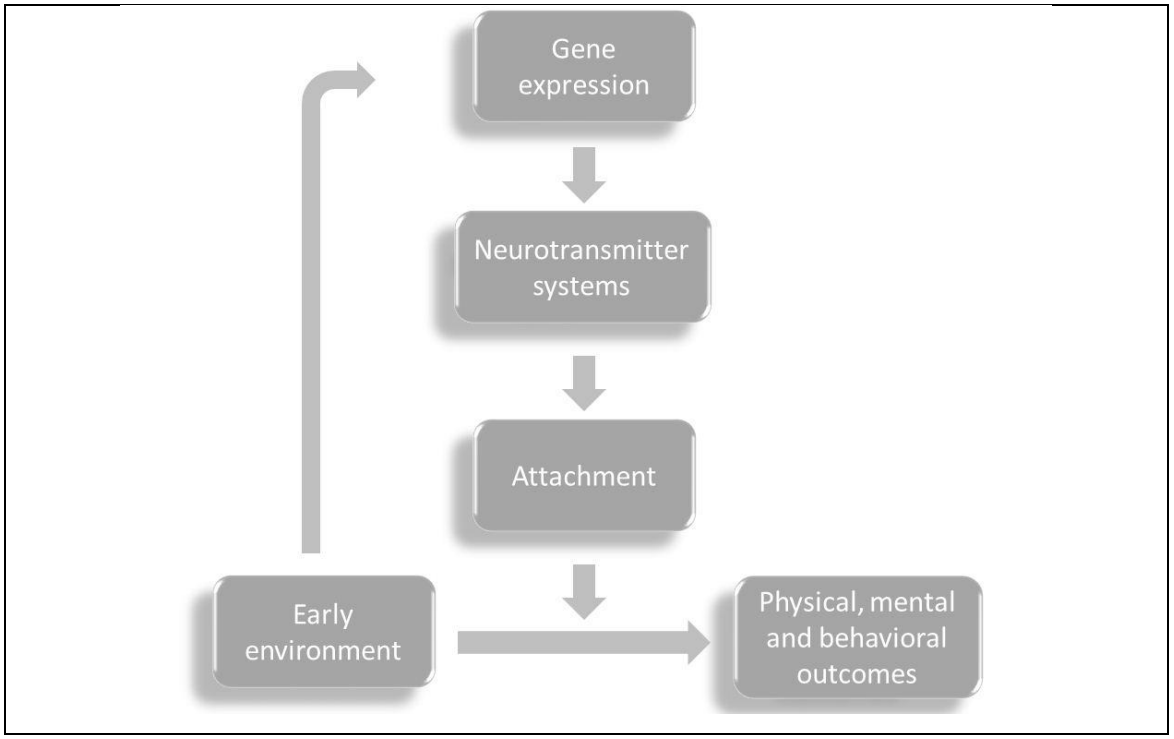

Figure 1.2. Initial hypothesis

[3]A good theory in developmental-behavioral pediatrics has the following features: "(1) a clarity of focus; (2) a developmental emphasis; (3) the ability to address limitations of previous research; (4) specifications of predictors (i.e., independent variables)and outcomes (i.e., dependent variables), with a clear rationale for each; (5) a clear articulation of links between predictors and outcomes (that sometimes involves specification of mediational and moderational effects) with accompanying testable hypotheses; and (6) clear implications for interventions" (Holmbeck et al., 2008:14).

[4] "A mediator is an explanatory link in the relationship between two other variables. Often a mediator variable is conceptualized as the mechanism through which one variable (i.e., the predictor) influences another variable (i.e., the criterion). (…) A *moderator*, unlike a mediator, is a variable that influences the *strength* or the *direction* of a relationship between a predictor variable and a criterion variable" (Holmbeck et al., 2008:16).

Based on this framework, we then try to understand how policy aimed at child protection could benefit from this scientifically inspired perspective to ameliorate environmental intervention. The present work also started with the presupposition that evidence-based policy formulation could result in more effective government action.

1.3. Considerations on the scope of the review

As an interdisciplinary work, the effort in putting together contributions of several fields brings in the need to clear notions and concepts that are presupposed in the integrative review of chapter 2. First, in section 1.4, we present basic notions on gene-environment interactions and attachment theory. Then, in section 1.5, we present review some models that are useful to interpret the results of original studies reviewed in chapter 2.

We thus recommend those already familiar to the fields of Genetics and Neuroscience, and also on the literature on attachment and evolutionary-developmental theories, to skip straight to chapter 2.

Importantly, since the formation of social bonds is a complex phenomenon, and its neurobiological substrates are many, it was necessary to concentrate on some neurotransmitter systems. Our choice was to concentrate on five neurotransmitter systems traditionally implied in attachment behavior: oxytocin, vasopressin, dopamine, serotonin, and opioids.

Hence, the literature linking early adversity to epigenetic and developmental consequences on the HPA axis was left aside from the review. There are already several good and comprehensive published reviews on this issue (to mention a few: McEwen, 2007; Gunnar & Quevedo, 2007; Kapoor et al., 2008; Dedovic et al., 2009; Loman & Gunnar, 2010; McEwen & Gianaros, 2010; McCrory et al., 2010; Harris & Seckl, 2011; McClelland et al., 2011). When relevant, these studies with humans and animal models, together with its conclusions, will be mentioned.

For a similar reason, other neurotransmitter or neuromodulator systems, which have been less studied, and only in the last years have received some attention, were not included. Such is the case of Neuropeptide Y (NPY). NPY is a neuropeptide which has four kinds of G protein-coupled receptors[5] (Y_1, Y_2, Y_4 and Y_5), some of which are

[5] Some more basics to social scientists: neurotransmitter receptors may be ionotropic or metabotropic. Ionotropic receptors, when activated, allow ions to pass through the neuron membrane. Conversely, metabotropic receptors are coupled to G proteins, and once activated, provoke a cascade of chemical

densely expressed in the cortex, hippocampus, and amygdala, areas associated with mood disorders, stress responses and memory processing. Research on humans and animals have pointed out to the role of NPY in reducing the anxiogenic effects of stress, what could suggest a clinical role in depression (for a review, see Morales-Medina et al., 2010). There are already studies linking genetic polymorphisms of the NPY gene, early adversity, and stress responses (for a recent example, see Witt et al., 2011). Nevertheless, more studies are clearly necessary to truly understand its role in affective behavior.

Another candidate that has been growingly implied in epigenetic process related to early adversity is the Brain-Derived Neurotrophic Factor (BDNF) gene. BDNF belongs to the group of neurotrophins, regulatory factors that mediate differentiation, proliferation and survival of neurons. BDNF is expressed throughout the brain, especially in the PFC and hippocampus. In the last years, several studies have linked BDNF to mechanisms related to plasticity and memory (Savitz et al., 2006; D'Souza & Craig, 2010; Moreira et al., 2011; Roth & Sweatt, 2011b). A recent review of animal model experiments pointed out that DNA methylation in the BDNF gene is a plausible mechanism for lifelong structural and functional changes in the brain due to early adversity. Interestingly, treating adult rats with zebularine, a demethylating agent, resulted in reversion of gene expression patterns incited by early-life adversity, what suggests that epigenetic markers could be modified into adulthood (Roth & Sweatt, 2011a). Future developmental models of epigenetic change will probably have to incorporate the role of BDNF (Curley et al., 2011a).

While all these aspects are essential to understand neurobiology of attachment and epigenetic transmission of attachment behavior, the goal of the present work is not to provide a definite and comprehensive account on attachment, but specifically to better understand some lines of evidence on gene-environment interaction mechanisms and attachment behavior.

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events inside the neuron. The action of metabotropic receptors is slower, but their effects are more lasting and diffuse.

1.4. Scientific background

Since this is an interdisciplinary work, it is important not to presuppose that people from different areas will be familiar with every concept and discussion. This section then tries to summarize recent findings and promising hypotheses.

In order to fully understand the "state of the art" in Developmental Cognitive Neuroscience, one must first turn to the last advances in Molecular and Behavioral Genetics, together with Epigenetics.

From Genetics to Epigenetics

Genetics as a science has conventionally begun in 1900, year in which works of three botanists – Hugo de Vries, Carl Correns, and Erich von Tschermak – on heredity in plants were published, confirming the breeding experiments the Czech monk Gregor Mendel had done forty years before. The name "Genetics" was coined by William Bateson in 1905, and term "gene" was first used by Wilhelm Johannsen in 1909. Its etymological root is the Greek word γένος, *génos* (origin). The definition of "gene", nonetheless, remained somewhat abstract, since its structure was unknown by that time. In the 1910's, T.H. Morgan began working with mutations in the fruitfly *Drosophila melanogaster* (Jablonka & Lamb, 2005; Gerstein et al., 2007).

Not until the 1940's, with the merging of Mendel's and Darwin's contributions in what was called by Julian Huxley "The Modern Synthesis", did it become clear that genes were the information-coding base that rendered natural selection possible. The "Modern Synthesis" theoretical framework derived of research from scientists such as Ernst Mayr, R.A. Fisher, J.B.S. Haldane and Theodosius Dobzhansky. This unified theory of biology stated that information is passed through generations by genetic inheritance. Genes influence the characteristics of an individual, and these individual differences conferred more or less fitness to certain organisms in their environment. Therefore, natural selection would increase the frequency of genes that contributed to

fitness, and decrease the frequency of those which diminished it (Bateson & Gluckman, 2011).

In 1953, Watson and Crick described the three-dimensional structure of DNA, allowing scientists to explore how DNA coded for enzymes and proteins (Gerstein et al., 2007; Danchin et al., 2011). In the 1960's and 1970's, a new generation of biologists, such as John Maynard Smith, George C. Williams, William D. Hamilton, Richard D. Alexander, E. O. Wilson and Richard Dawkins, known as "neo-Darwinists", advanced the Modern Synthesis framework, some suggesting the gene as the basic unit of natural selection (Jablonka & Lamb, 2005).

During the second half of the 20th century, the "central dogma" of genetics came to be widely accepted, according to which there was a unidirectional flow of information-carrying molecules: DNA-DNA replication; transcription from DNA to mRNA; and translation from mRNA to proteins. Together with this view, came the notion that one gene would code for one protein each; and that DNA was basically formed of coding material (Baars & Gage, 2010). But by the end of the century, this dogma had been severely challenged, especially after the conclusion of the Human Genome Project, in 2001.

We now know that there are immense portions of the genome that do not code for specific proteins, but in turn exhibit regulatory functions. Among many findings, it is now widely accepted that gene expression affects how transcription occurs; that many genes code for more than one protein; that genes interact with the environment, and can be activated or silenced according to the molecular environment; and that non-genetic information can be inherited from parents to offspring (Gerstein et al., 2007; Carvalho et al., 2009; Danchin et al., 2011; Charney, in press).

Table 1.1 conveys some of this complexity, concentrating some useful information relevant to the next chapter.

Table 1.1. Relevant notions in Genetics

DNA: DNA is organized in a double helix structure, with two nucleotide strands each side. The strand is formed by a sequence of different combinations of four different nucleotides (bases composed by a sugar-phosphate group and one of the following bases: adenine, guanine, thymine, and cytosine).

Gene: Unit of genetic inheritance. The concept is still evolving, but it can be said that a gene is a sequence of DNA that is transcribed into mRNA and then translated into proteins and RNA molecules. Genes vary in their size: some are a few thousand nucleotide bases in length, while others are over a million bases long. Gene regions may be introns or exons (see below).

Genome: The whole sequence of DNA for a particular organism. The human genome is composed of a double strand of 3 billion base pairs (bps) of DNA.

Chromosome: Each human cell has 46 chromosomes, divided into 23 pairs. DNA sequences lie within the chromosomes.

Locus *(pl. loci)*: Location of a specific gene within the chromosome.

Allele: Generally, each cell has two copies of a gene. These copies, which can have alternative forms, are called alleles. When both of the alleles for a given gene are identical, then one is *homozygous* for that gene; when the alleles differ, one is *heterozygous*.

Genotype: The alleles of an individual in a specific locus.

Phenotype: Expressed characteristics of an organism.

Endophenotype: In the psychiatric discussion of disease symptoms, it has been posited that it is possible to characterize a specific disease or trait in a level of analysis closer to genes. An endophenotype may be neurophysiological, biochemical, endocrinological, neuroanatomical, cognitive, or neuropsychological. They are measurable expressed characteristics, unseen by the unaided eye, that stand along the pathway between disease and distal genotype.

Exon: Sequence of the gene that is transcribed into mRNA and transported out of the nucleus for processing into protein.

Intron: Non coding region of the gene, not transcribed into mRNA. Introns often contain regulatory domains, which mean they can influence exon splicing.

Promoter: Region of DNA where proteins known as transcription factors bind, in order to initiate the process of gene transcription.

Regulatory region: Segment of DNA where transcription factors and other regulatory proteins preferentially bind.

Genetic polymorphisms: When two or more variations of an allele for a single gene occur in greater than 1% frequency of a given population, it is called a polymorphism. If it occurs in less than 1% of the population, it is known as a *mutation*.

Single Nucleotide Polymorphism (SNP): The most common kind of polymorphism, occurring usually every 500 bps, consisting in the change of a single nucleotide in the sequence.

Copy Number Variation (CNV): Variation in the copy number of DNA sequences. CNV are stretches of DNA at least a thousand bp (Kbp) long, containing bps that are either deleted or present in multiple copies, relative to a "normal" genome.

Variable Number Tandem Repeat (VNTR): Nucleotide sequences may be repeated within DNA. The repetition may be of two nucleotides (dinucleotide repeat), microsatellites (repeat units of 2–8 bp), minisatellites (more than 8 bp), or even a larger or unknown number of nucleotides, clustered and adjacent to each other (tandem repeats). Individuals usually have different VNTRs in a specific allele – for example, the dopamine D4 receptor gene may appear as a 4-repeat, or as a 7-repeat, 4 or 7 indicating the number of base pair sequence repetitions in that part of the chromosome.

***Sources*:** Carvalho et al., 2009; Charney, in press; Gottesman & Gould, 2003; Kempf & Weinberger, 2009.

The genetic dimension of inheritance, central to the Modern Synthesis, is currently considered only one of various dimensions. It has been proposed that transgenerational transmission of information depends not only on DNA sequences, but also on other non-genetic mechanisms, such as DNA patterns of activity (epigenetic inheritance), niche construction and modification (ecological inheritance), parental influences on offspring environment (parental effects), social information learning and transmission, and even symbolic information (cultural inheritance) (Jablonka & Lamb, 2005; Danchin et al., 2011).

The term "Epigenetics" was coined in 1957 by Conrad Waddington, whose idea was to put together developmental biology and genetics. Without the molecular understanding at that time, Waddington looked for an explanation on how inherited genotype could be influenced during the development of the organism, so as to produce phenotypes. In his metaphor of the "genetic landscape", a ball rolls down a hill, with many valleys in which it may fall. The more it rolls down, the less are the available possibilities to changing its fate. This increasing determination of the organism, which is constrained by is path, recalls how the phenotypic character is developmentally "canalized". Epigenetics would be the discipline aimed to explain this process (Holliday, 2006; Bateson & Gluckman, 2011).

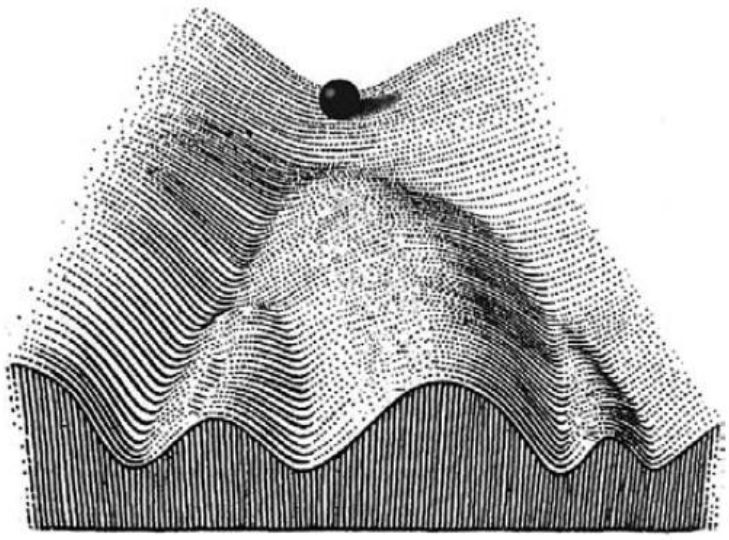

Figure 1.3. Waddington's Epigenetic Landscape metaphor (From Bateson & Gluckman, 2011).

Back in the 1970's, studies already suggested that DNA could undergo methylation processes. In the 1990's, studies showed that DNA methylation lead to gene expression silencing. Soon, animal studies indicated that these changes in gene expression could be inherited, and it was progressively accepted that epigenetic change could have transgenerational effects. Presently, Epigenetics is a bourgeoning scientific field, and gene expression, epistasis and gene-environment interactions form the basic vocabulary of whole areas of research (Holliday, 2006; McClung & Nestler, 2008; Champagne & Mashoodh, 2009; Francis, 2011).

Table 1.2 summarizes some important concepts regarding Epigenetics.

Table 1.2. Relevant notions in Epigenetics

Gene-environment interaction (GxE): occurs when the effects of exposure to environment are conditional on a person's genotype. In other words, different individuals display different sensitivity to the impacts of environmental experiences.
Gene-environment correlation (rGxE): occurs when genetic factors interfere with the individual's exposure to particular environments. Distinct personality traits, for instance, lead to different relations and reactions to the surrounding environment. Because of this, certain individuals may even select certain environmental niches, reinforcing idiosyncratic tendencies.
Chromatin: DNA is tightly packed around octamers of the histone proteins. The assembling of DNA and proteins composes the chromatin. Histone proteins can be modified, allowing DNA to unwind and transcription factors to bind, leading to gene activation.
Histones: Proteins that tightly pack DNA in order to reduce its overall size. Histone proteins can be modifiedto allow the DNA to unwind and permit transcription factorbinding and gene activation. In turn, othermodifications to histone proteins can inhibit transcription factor binding.
Transcription factor: Protein that transiently binds to chromatin, allowing DNA information to be transcribed into mRNA. Dynamic interactions of transcription factors arephysiologically relevant regulatory mechanism in gene expression.
Methylation: Gene activation is linked to histone or DNA methylation. Histone methylation leads to condensed chromatin and transcriptional repression.DNA methylation occurs when a methyl group is added to cytosine residues in the 5-position of the pyrimidine ring, within a gene sequence. DNA methylation patterns that occur during early childhood result in long-lasting, but reversible, changes in gene expression that affect adult behavior. Methylation is catalyzed by DNA Methyltransferase (DNMT) enzyme.
Acetylation: The binding of an acetyl group into DNA. Acetylation decreases the affinity between protein tail and DNA, relaxing chromatin and promoting gene transcription. Thus, gene activation is linked to histone acetylation. Acetylation is catalyzed by a histone acetyltransferase (HAT) enzyme.
Epistasis: Interactions between genes, which may cause one to suppress the phenotypic effects of another. Epistasis play a prominent role in evolutionary processes such as divergence and speciation, and can affect fitnessandevolvability of organisms.

***Sources*:** Champagne & Mashoodh, 2009; Hager et al., 2009; Jaffee & Price, 2007; McClung & Nestler, 2008; Moffitt et al., 2005; de Visser et al, 2011.

The Epigenetic turn is relevant because it proved that it is not possible to understand inheritance without turning to a developmental approach. The "Modern Synthesis" view, according to which development was already "programmed" in genes, proved to be implausible: instead, genes, cells, and physical, biological and social environments are in constant interaction in the developmental process (Lickliter & Honeycutt, 2010). Many molecular events take place between the DNA template and the functional protein. In other words, phenotypes are not the result of genes only: instead, a network of genetic events somehow lead to phenotypes (Robertroux et al., 2010).

Compelling experiments made with rat pups suggest that maternal tactile stimulation dampens the stress response patterns in a lifelong and transgenerational manner because of epigenetic mechanisms. In the postnatal handling design, the experimenter manipulates rat pups, separating them from the mother for a few minutes, in a way that simulates normal periods of separation that occur in the natural environment. Longer periods of maternal separation may also be induced. Handling produced more mothers' licking and grooming in pups – another naturally occurring behavior, which reinforces mother-infant bonds – while long periods of separation reduced it. Moreover, rat pups of high licking and grooming mothers exhibited milder stress responses due to increased hippocampal glucocorticoid receptor gene expression[6] whereas pups of low licking and grooming mothers presented diminished glucocorticoid receptor gene expression (Meaney, 2001).

More interestingly though is the fact that if the rat pups were cross-fostered, and pups of low licking and grooming mothers came to be reared by high licking and grooming ones, the stress reactivity and gene expression patterns would be the same of highly licked and grooming pups. This evidence clearly indicates that the behavioral trait was not genetically inherited, but conversely, that gene expression could be affected by parenting. By its turn, the following generation – offspring of these foster-reared pups – displayed the same behavioral stress reactivity patterns as their parents, suggesting a transgenerational transmission of gene expression (Meaney, 2001).

[6] The hippocampus is a down-regulator of the HPA stress axis.

Recently, a distinction has been drawn upon *context-dependent* epigenetic change and *germline-dependent* epigenetic change. While the former refers to cases in which epigenetic change is maintained as long as factors that bring epigenetic change (e.g. contamination, maternal behavior) remain in the environment and originate it over and over; the latter would happen when epigenetic imprint is mediated through the germline, even though the original environmental stressor is already gone. Crucially, context-dependent would be a reversible process, whereas germline-dependent would not. According to this view, only germline-dependent would truly be a transgenerational phenomenon (Crews, 2011).

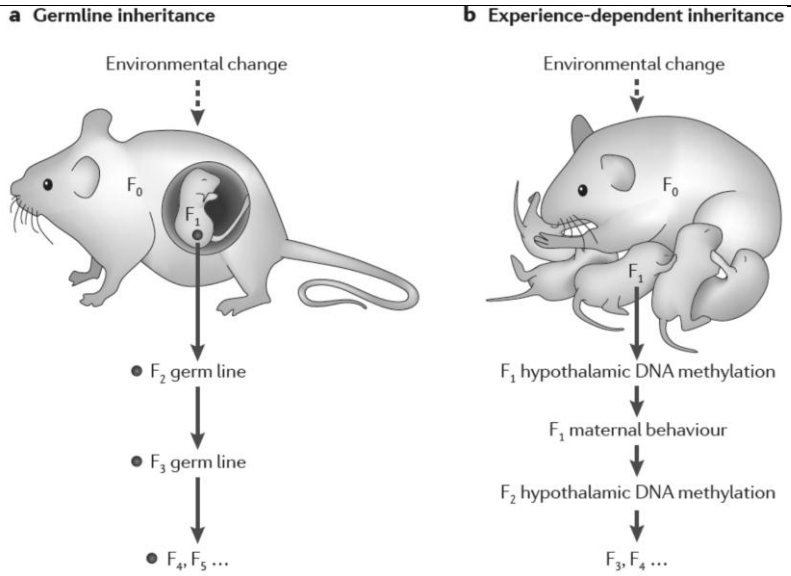

Figure 1.4. Germline inherintance and context/experience-dependent inheritance. From: Danchin et al., 2011.

Strikingly, studies have shown evidence that suggested that germline-dependent epigenetic change could be transmitted not only by mothers, but also from fathers (see Figure 1.5). In rats, factors prior to male mating, such as paternal exposure to drugs, toxins, and endocrine disruptions, as well as nutrition quality and age, may lead to offspring phenotypic change. Maternal investiment in offspring and behavioral interactions between pups and mothers are all affected by father's epigenetic effects (Curley et al., 2011b). These new speculations securely demonstrate how promising the field of Epigenetics is nowadays.

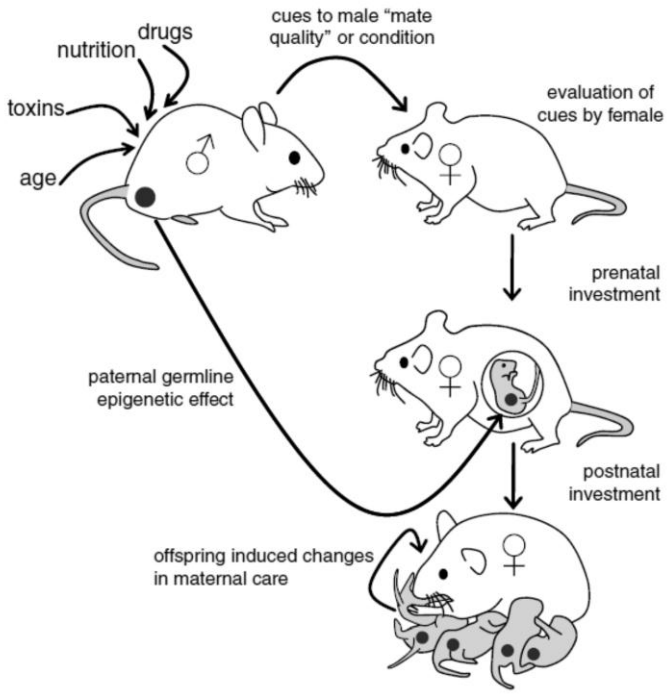

Figure 1.5. Father's behaviors may result in long-lasting epigenetic change in offspring. From: Curley et al., 2011b.

Genes, brain, and behavior

Social Cognitive Neuroscience's aim is to uncover the neural underpinnings of behaviors that had already been studied by social psychology since its inception. It begun by the end of 1990's, when several neuroscientists started investigating social behaviors and traits such as empathy, fairness, social pain, moral reasoning and theory of mind using neuroimaging techniques, particularly fMRI. The name of the field was first used in a scientific publication in year 2000 (for an historical account, see Lieberman, in press).The notion that what the brain does is information processing is one of central presuppositions of Social Cognitive Neuroscience (Haase et al., 2009).

In the last years, there have been calls on adjusting the approach in order to incorporate in it the ontogeny of behaviors. In other words, coupled with the inquiry on structural and functional brain aspects related to social behavior, the importance to consider sociocultural aspects of childhood environments, and its interplay with genes has been stressed. It has been suggested that "Developmental Social Cognitive Neuroscience" is a more appropriate term for this area (Zelazo et al, 2010).

Closely related to this research field, there is a tradition that identifies itself as "Affective Neuroscience". It congregates studies with animals and humans, and tries to identify neural circuits linked to socioemotional aspects (for an overview, see Dalgleish et al., 2009). Both interdisciplinary fields have consistently revealed how some brain structures are associated with social interaction. What is beginning to become clear is how specific genes code for proteins, enzymes, receptors and neurotransmitters within these structures, and how gene expression may affect their functioning.

Individual differences and gene-environment interactions

Before passing on to the next section, two more aspects must be treated. The first is the research design that is utilized in studies that will be reviewed in chapter 2. Finally, some important notions of attachment theory will be briefly exposed.

Behavior geneticists have long known that social behavior has strong genetic backgrounds. Before gene association studies became common, this knowledge came from quantitative genetic designs such as twin and adoption studies.

The principle underlying twin and adoption studies is that differences between individuals not attributed to genetic similarity arise from environmental influence. Identical, monozygotic twins (MZ) share the whole same genotype, whereas fraternal, dizygotic twins (DZ) share 50% of genes only; biological offspring share 50% of the genotype with each parent, while adopted children have no such genetic similarity. The variance of a certain trait attributed to genetics is called heritability. Variance attributed to environmental factors, by its turn, can be due to either shared environment, or non-shared environment (Plomin & Asbury, 2005).

Non-shared environment has puzzled scientists in the last decades. It has been found that part of non-shared environment estimates were in fact due to measurement error. Many studies have drawn attention on the caveat that siblings raised on the same family experience very different environments, since parenting, idiosyncratic experiences and occupied niches vary. Extrafamilal factors such as peer influences are other important sources of non-shared environments (Plomin et al.,

2001; Plomin & Asbury, 2005). As a result, it is now generally accepted that non-shared environmental factors operate through mechanisms that make offspring different rather than similar – in other words, siblings are no more alike than individuals selected at random from the population (Petronis, 2010).

Decades of research had pointed out that there is high heritability in mental illnesses such as schizophrenia and autism, personality traits, cognitive disabilities and abilities, behaviors like drug use and abuse, and even social behaviors such as altruism and empathy (Plomin & Asbury, 2005; Ebstein et al., 2010). However, in the last few years, another trend has emerged, and this division of variation in traits in three components – genes, common environment and non-shared environment – has been challenged for numerous reasons (Turkheimer, 2011).

First, this partition of variance turned out to be no more than a statistical finding, not an explanation for causation. Second, it was figured that the proportions of variance of a determined trait vary across population samples. In other words, in a certain environment, variance attributable to an environmental factor is not the same variance verifyied in another situation (Turkheimer, 2011). It has been suggested that the concept of non-shared environment variance in behavior should be replaced for the notion of epigenetic stochasticity. Hence, phenotypic differences in siblings who share the same genes would actually be a result of GxE processes in the course of development (Petronis, 2010).

These points have been remarkably stated as it follows:

> "Something, and presumably something that can be broadly characterized as environmental, makes siblings, even identical twins, different from each other. But whatever that something is, attempts to decompose it into an additive collection of systematic environmental causes that produce systematic differences in outcome almost always end in disappointment. Non-shared environment is a catch-all name for a catch-all variance component comprising all the uncountable and uncontrollable events that accumulate over a lifetime to make us different from each other (…) Developmental events are correlated within lives because they share a very general familial background, but plausible causation, in the form of non-shared environmental links among life events, is damnably hard to find.

> (…) Individual differences in complex human characteristics do not, in general, have causes, neither genetic nor environmental. Complex human behaviour emerges out of a hyper-complex developmental network into which individual genes and individual environmental events are inputs. The systematic causal effects of any of those inputs are lost in the developmental complexity of the network. Causal explanations of complex differences among humans are therefore not going to be found in individual genes or environments any more than explanations of plate tectonics can be found in the chemical composition of individual rocks. Some new paradigm, unglimpsed at present, will be required before meaningful progress can be made on the causal structure of either the family dynamics or genomics underlying the parent–child relationship." (Turkheimer, 2011:600)

In the current debate, therefore, the complex relationships between genes and environments invite some to elaborate better developmental models, whereas others feel it is time to embrace chance and randomness in the complexity of behaviors, giving up models of linear causation and recognizing a dead end for research (for a thrilling account on this "gloomy prospect", see Smith, 2011)[7].

But let us return to the road opened by Behavior Geneticists and heritability studies around thirty years ago. Polymorphism studies blossomed in the last decade, due mostly to the development of the field Molecular Genetics.

Importantly, although twin and sibling studies allowed an overall estimate of heritability, the number of genes and the effect size of each gene could not be fully determined. Since the number of genes involved and their effect sizes could not be determined, research indicated that the heuristic value of quantitative estimates of heritability was limited. Nevertheless, techniques and tools have arisen with Molecular Genetics, allowing scientists to discover the location of specific chromosomal loci linked to phenotypic traits.

[7] It is important, though, not to interpret these findings not as a dead end of research as a whole, but as the recognition that population studies tell us something in the group level of analysis, but are not so informative when it comes to a specific individual. That is to say genetic and environmental risk factors can be known and its dynamics can be explained, but the individual life trajectories and experiences are unique and cannot be foreseen. See Smith, 2011.

Traditional gene association studies compared individual traits and checked for specific “candidate genes”, based on previous hypotheses, in order to establish how allele variation could interfere with it. In the last years, Genome-Wide Association Studies (GWAS) permitted large-scale genotyping, sampling the entire genome, in a hypothesis-free manner. Many polymorphisms and *loci* linked to phenotypic variance have been discovered since then.

However, a noteworthy discovery was that multifactorial traits such as complex behaviors derive not from a specific or a few genes, but else from the combination of several genes, with small effect magnitudes each (Ebstein et al., 2010). In addition, the individual and cumulative effects of these polymorphisms are small and do not approach the size derived from heritability studies (Petronis, 2010). It should be noted that the identification of a SNP or another polymorphism and its relation to a certain phenotype does not say much about the pathway through which genetic variability can interfere in the individual’s developmental process.

In the past decade, experimental neuroscience, genetics and epidemiology have joined forces, trying to integrate accumulated knowledge on causes of psychopathology and gene-environment interplays. The starting point is the conclusion that mental disorders have environmental causes, but also that people respond heterogeneously to them. In addition, as mental functioning is related to neural substrate activity, then genes related to the disorder must in some fashion affect brain functioning. It is then possible to formulate hypotheses based on what is known on gene expression in the brain, brain areas linked to mental disorders, and specific environmental pathogens (Caspi & Moffitt, 2006).

The following step is to test these hypotheses, for which epidemiological research design, based on longitudinal prospective studies, are the most indicated. Brain activity measures can come from neuroimaging, behavioral tasks, substance assessing; environmental factors can be measured through self-reports, interviews and follow-ups. The chain of inferences derived from the findings may help elaborating a nomological network, that is, a set of theoretical relationships that subsidize a construct (Caspi & Moffitt, 2006). This tradition of studies has shown, among other

findings, that hostile environments impact differently individuals carrying specific genetic polymorphisms.

The pioneering study by Avshalom Caspi, Terrie Moffitt and coworkers, published in 2002 (Caspi et al., 2002), suggested that the influence of child maltreatment on adult antisocial behavior was moderated by a functional polymorphism coding Monoamine Oxidase A (MAOA), an enzyme linked to monoamine (e.g. serotonin, dopamine, adrenaline, noradrenaline) degradation in the synaptic cleft. The polymorphisms analyzed where two different VNTRs in the promoter gene of the MAOA gene, one characterized as “high activity”, and the other as “low activity”. The sample came from the Dunedin longitudinal study cohort, which had records with rigorous on measures of child maltreatment.

The effect of childhood maltreatment on adolescent antisocial behavior was found to be *conditional* on the MAOA polymorphism they carried. Males with a maltreatment history which had the low-MAOA activity genotype where more likely to develop conduct disorder, antisocial personality, disorder symptoms, and to be convicted for violence in adulthood; while in males with the high-MAOA activity allele, child maltreatment did not mean more risk of these antisocial outcomes, even if they were abused in childhood. The results suggested that child maltreatment alone did not account for the outcome, since there was a genetic moderation effect (Caspi et al. 2002).

This study provided an interesting response to a question long unanswered by social science models of behavior: why do some children that are maltreated in childhood become antisocial adults, whereas others who experienced similar hostile environments do not? Gene-environment interaction studies suggest that individual differences linked to genetic polymorphisms account for some of the divergence in these developmental pathways.

In another groundbreaking research, published the following year, using similar epidemiological methods, Caspi, Moffitt and coworkers demonstrated that there was a moderating effect of the 5-HTTLPR gene on the relationship between child maltreatment, stressful life events and the outcome of depression. Maltreated

individuals carrying one or two of the short alleles of the 5-HTTLPR gene displayed higher association to depressive symptoms, diagnosable depression and suicidality in relation to stressful events than maltreated individuals with the long allele of the same gene (Caspi et al., 2003). Several replications have been made since then, most with positive findings, although some failed to replicate it. Importantly, positive replications outnumber failures of replication (Caspi et al., 2011; Rutter, 2011).

These results were usually interpreted according to a *diathesis-stress* model (also known as *dual risk model*). According to this model, some individuals have a specific vulnerability (diathesis), which acts as a potential individual risk factor. This vulnerability may interplay with the environmental risk (stress), resulting in unfavorable outcomes. The dichotomy then emerges between *vulnerability* factors (carrying specific polymorphisms that predispose to psychopathological outcomes, if there is environmental risk) and *protective* factors (carrying genes that do not predispose to these outcomes, even if environment is hostile). This notion will be relevant on section 1.5, where we review the alternative model of differential susceptibility (Belsky et al., 2009).

Some caveats concerning this research design of gene-environment interaction must be stressed. Gene-environment interaction studies must follow some requirements, and face diverse challenges. We next turn to them, for a better understanding of studies presented in the next chapter.

Caspi, Moffitt and Rutter recommended 7 steps gene-environment studies should follow to guarantee methodological rigor. Heritability studies from Behavior Genetics, as twin studies discussed above, are the starting point. Next, it is necessary to identify the environmental pathogen, and based on sound biological evidence that it may be related to a certain biological system, considering that people may respond differently to it. It also necessary to rule out rGE, for which evidence from randomized samples, longitudinal studies and twin studies may be useful. Third, measuring environments rigorously is another important step. The fourth step is to identify candidate susceptibility polymorphic variants for which there is evidence of an association to disorder, and that could play a functional role between gene and

environmental pahtogen. Fifth, interaction must be tested using statistical methods. The most informative design for data collection and testing, as the authors emphasize, is epidemiological longitudinal cohorts. If the interaction is obtained, then it should be evaluated if it persists if one of the components of the triad gene-environmental pathogen-disorder is replaced by another. Finally, if the six previous steps have confirmed GxE, replications and meta-analysis should be done (Moffitt et al., 2005).

It should be noted that this "gold standard" of GxE research is not only expensive and time consuming, but faces significant challenges. Genetic and non-genetic factors interplay in various and confounding forms. Many risk or protective environmental factors derive from human behavior: e.g., marital conflict or breakup, social support, loss of jobs. Environments are not objective: individuals conceptualize and interpret them, and hence environmental effects may vary in their effects according to the perceiver. It has been noted that current environmental measures are far from the quality standards needed to postulate that a statistic association truly reflects environmentally mediated causation[8] (Rutter, 2011; Rutter & Dodge, 2011).

As we shall see in chapter 2, several lines of evidence point to GxE involving polymorphisms related to attachment systems. The elements discussed in this section will return when some remarks on methodological issues concerning them are made.

Attachment Theory

British psychiatrist and psychoanalyst John Bowlby proposed attachment theory drawing heavily from an ethological perspective. In his formulation, attachment is a biologically based desire for proximity between infant and caregiver, derived of a natural selection process, an instinct common to humans and other mammals. In an evolutionary perspective, genetic selection would have favored attachment behaviors

[8]When it comes to child maltreatment, the challenge is even harder. There are animal models of early maltreatment, but their generalizability to humans is not straightforward. Ethical concerns obviously forbid certain designs that mean intended harm for children. Disentangling negative effects from co-occurring risk factors, such as poverty, require controls that are not often available. Moreover, environmental measures are far from being simple: children experience and interpret maltreatment differently, so it is hard to compare "maltreatment" within samples. See Sanchez & Pollak, 2009.

because they increased the likelihood of child-infant proximity and thus enhanced the child's protection and chance of survival. Infant-caregiver bond provides the child with a "secure base" from which environment can be explored (Cassidy, 2008; Main et al., 2008; Polan & Hofer, 2008).

The innovation of Bowlby's theory cannot be downplayed, since when it was first suggested, psychoanalytical theories affirmed that the infant's relationship to the mother emerged only because she fed the child and then provided a pleasurable experience of no longer feeling hungry (Cassidy, 2008). This theory was falsified when another researcher, Harry Harlow, proved that rhesus monkey infants preferred staying in close contact to cloth mother surrogates rather than wire mother surrogates, notwithstanding the latter provided them with milk (Harlow, 1958).

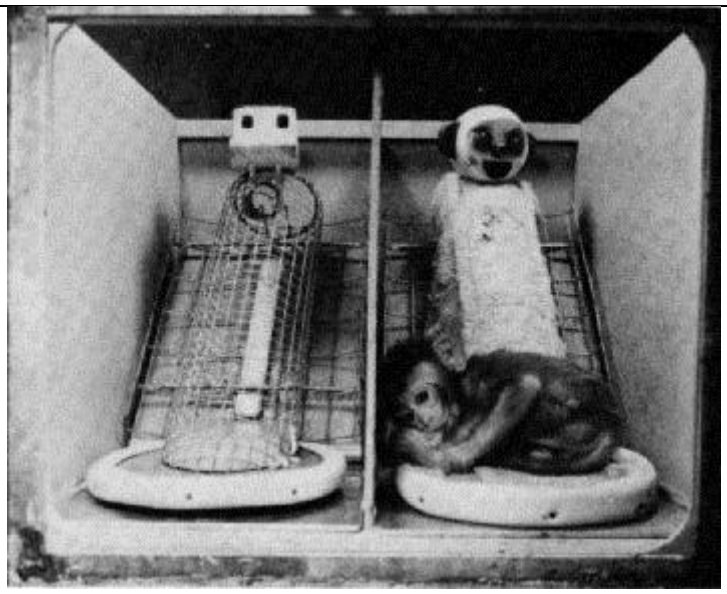

Figure 1.6. Rhesus monkey infants find comfort in cloth mother surrogates, as Harry Harlow noticed.
From: Harlow, 1958.

Attachment is also a theory of social-stress regulation (Chen et al., 2011b). When mother and infant are separated, the child experiences a stressful and painful experience, a feeling of loss, and this elicits a behavior of crying and calling the caregiver back. Being left alone or with a stranger are clearly a stressful and dangerous situations if analyzed in the evolutionary perspective of the "environment of

evolutionary adaptedness" (Belsky & Simpson, 2008), and thus it can be hypothesized that natural selection would have favored strategies to deal with it.

Mary Ainsworth's studies that led to the creation of the Strange Situation Procedure (SSP) targeted precisely this phenomenon. In this experimental design, the child enters a room in which he or she can play with toys next to his or her caregiver. Next, he or she lives a strange situation when a stranger walks in. Then, the caregiver walks away, inducing the stress of separation. Finally, the caregiver returns. While observing how infants would behave when exploring the environment, their reactions after being left in the room and when the caregiver returns, Ainsworth observed different patterns of attachment behavior (Cassidy, 2008; Main et al., 2008).

She characterized them as Secure Attachment, Insecure-Avoidant Attachment, and Insecure-Ambivalent Attachment. Securely attached children use their caregivers as secure bases of world exploration. When left alone, they experience distress, but when parent returns, they soon feel soothed and calm down. Insecure children do not seem to feel as if they had a secure base to explore the environment. Insecure-avoidant children exhibit minimal distress when left alone; when reunited to caregiver, show little or no interest, avoiding to look upon him, focusing on toys instead. Insecure-ambivalent infants similarly don't feel comforted by the parent's return, and may alternate the bid for contact with signs of angry rejection and of being upset (Solomon & George, 2008).

In 1990, Mary Main and Judith Solomon noted that many children did not fit into one of these three categories, and suggested a fourth one, Disorganized Attachment. Disorganized children show contradictory, frightening and apprehensive behaviors when next to their caretakers (Main et al., 2008; Solomon & George, 2008). The disorganized child's dilemma is that he cannot resolve the stress and anxiety he or she feels, in some cases because the parent is at the same time the source of fear and the only possible protective figure to turn to (van IJzendoorn & Bakermans-Kranenburg, 2006). Many studies ever since pointed out that Disorganized Attachment in childhood was strongly associated to psychopathological outcomes in adulthood (Main et al., 2008). Strikingly, the prevalence of attachment disorganization ranges

from 15% in normal, non-clinical samples, to 80% in clinical samples (Bakermans-Kranenburg & van IJzendoorn, 2007).

Traditionally, these differences have been attributed to maternal responsivity to the child's needs; as it shall be seen ahead, children's individual differences, originated in genotype variance, each day receive more attention through Molecular Genetic studies (Bakermans-Kranenburg & van IJzendoorn, 2007).

It is noteworthy that, although most attachment studies stressed the desirability of secure attachment as the "best" or "normal" pattern, a truly ethological approach should consider each attachment pattern a different behavioral strategy, which can be adaptive in one situation, but not in another. In this view, attachment behavior patterns respond to contextual conditions in a flexible manner (Belsky, 2008).

One of Bowlby's main ideas is that attachment relationships in early childhood somehow serve as references that shape adult social bonds. Infant-caregiver relationship provided the child with mental representations of himself or herself, as well as representations of the caregiver and of others. These representations were called Internal Working Models (IWM's), and influenced relationships later in life. Procedures for assessing adult attachment were developed; the most widely used being the Adult Attachment Interview (AAI), created by Carol George and Nancy Kaplan (Main et al., 2008). In the AAI, based on the adult's own experiences in childhood and how it shaped attachment representations, his or her IWM's are assessed, and classified as Secure-Autonomous, Dismising, Preoccupied or Unresolved-Disorganized (Hesse, 2008).

In the last decades, Attachment Theory was used in an uncountable number of studies, many of which with longitudinal cohort designs. Animal models for attachment theory have traditionally been rhesus monkeys, rats, voles, and sheep[9]

[9] The reason for studying sheep as attachment behavior models is quite interesting: "*First, sheep and other ungulates give birth to precocial young that are mature and mobile at birth, which contrasts with the altricial young born to most rodents and rabbits. Second, sheep are grazing/herding mammals with a synchronized breeding season, which results in the temporally restricted birth of numerous mobile and genetically unrelated lambs within the herd. Since it would not be advantageous, in terms of reproductive success, for a ewe to care for a lamb that is not her own, and since the particular context within which sheep maternal behavior occurs increases the likelihood that lamb confusions might occur, mechanisms have evolved in sheep that result in a heightened maternal*

(Ross & Young, 2009; Insel, 2010). Human attachment has been analyzed in a mental health perspective, together with constructs as antisocial behavior or temperament, either with adopted or institutionalized children, and also using different data collection methods. Some of the results of this long-lasting tradition can be found in (Grossman et al., 2008).

It is noteworthy that attachment patterns seem to be universal even in a cross-cultural perspective. Research in diverse cultural niches, from African hunter-gatherer societies to Israeli kibbutzim, from Chinese single children families to Muslim homes, indicate that the four styles of infant-caregiver relationship proposed by Attachment Theory are shared by all human beings. It is true that these studies suggest that there are idiosyncrasies and contextual influences, such as some variation in the relative frequency of specific attachment styles, as well as certain culture-specific behavioral markers. Nevertheless, around all cultures, most children tend to display a secure attachment pattern, and parents tend to prefer secure children. These findings indicate that Bowlby's construct is not restricted to middle-class Western societies, what underscores the validity of Attachment Theory (van IJzendoorn & Sagi-Schwartz, 2008).

Once it was accepted that the Attachment System plays an important evolutionary role, many studies with animals begun to search for the neurobiological basis for attachment behavior. Attachment is a complex phenomenon, and Bowlby had already noted that many behavioral systems are involved with it. Psychobiologists have traditionally implied, in attachment studies, the Hipothalamic-Pituitary-Adrenal (HPA) and Autonomic Nervous System (ANS) stress axis activation and down-regulation (by the hypothalamus and hippocampus, respectively), dopaminergic pathways of the brain reward circuitry, emotion regulation systems linked to the amygdala and prefrontal areas, and also oxytocinergic and opioid activity (Fox & Hane, 2008; Coan, 2008).

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responsiveness near the time of parturition, followed by the formation of a highly selective maternal bond between a mother and the particular offspring she interacted with at birth." (Numan & Insel, 2003:30).

From an evolutionary biology viewpoint, this data can be assembled together in different levels of analysis. Ethological science provides an interesting heuristic tool to do so.

Discussing the matter of cause and effect in biology in a classical conference paper, Ernst Mayr stated that causation in biology may bear different meanings. From a functional point of view, there is the question on "how" a certain phenomenon happens, related to the operation and interaction of structural elements. On the other hand, biologists may look for evolutionary causes, referred to "why" a determined phenomenon may have arisen in the course of history. In this perspective, an animal behavior may be explained both by its *ultimate* causes, shaped by natural selection, and by its *proximate* causes, linked to the physiological and environmental factors of that specific organism (Mayr, 1961).

In another classical paper, ethologist Nikolaas Tinbergen posited that the biological study of behavior faced four major problems – which later would be known as "Tibernegen's four questions". An animal behavior can be analyzed in four distinct perspectives: causation, ontogeny, survival value, and evolution – the former two being "proximate factors", and the latter two "distal factors" (Bateson, 2010).

Causation refers to the neurophysiological mechanisms underlying a behavior. Ontogeny deals with the explanation of the development of a specific behavior in a particular organism, in the course of its lifetime. In addition, a behavior can be seen from the fitness it may bring to the organism, that is, its survival value in the dynamics of natural selection. Finally, phylogeny issues are concerned with the dynamics that led to the evolution of the behavior (Tinbergen, 1963). All four questions represent important and distinct levels of enquiry about the behavioral phenomenon. Attachment system can be conceived in the light of these four questions.

Table 1.3. Tinbergen's four questions applied to the attachment system	
Levels of causality	**What is attachment behavior?**
Proximate questions	
Mechanism/causation	Behavioral systems linked to stress reactivity, emotion regulation, attention, reward, memory and social bonding.
Ontogenesis	Children develop different patterns of bonding to their primary caregiver, according to caregiver sensitivity to infant's cues. These patterns relate to the IWM that will be reference for future social relationships.
Distal/Ultimate questions	
Survival value/ adaptation	Babies that searched for close contact with mothers would have more chances of being protected from environmental risk.
Phylogenetics	Evolution has selected attachment behavior in social species, favoring the development of a hardwired parental and child brain in mammals.

Many theorists have conceived causal models that place the attachment system in an evolutionary and developmental perspective. In the next section, we present some of these models that provide important clues for interpreting the results of experimental research on attachment.

1.5. Evolutionary and developmental models: an overview

In the last decades, the biopsychosocial approach has appeared as an alternative to the biomedical model. This new paradigm tries to assume a richer notion of health, including not only illness-related aspects, but also the notion of wellbeing. Some biopsychosocial models integrate brain, organism, and physical and social environments, in an ecological perspective. Behavioral traits are multifactorial, and arise from complex and interwoven biological, psychological and social causes (Haase, 2009).

Several models concerning early environments and adult physical and mental health suggest mechanisms for the interaction between predictor and outcome variables, as well as the moderator or mediator variables. In this section some of the recently proposed models concerning the development of human attachment are briefly reviewed, while we refine the model of four questions sketched in the last section.

Mechanism: cognitive and emotional social information processing

In course of individual history, environmental input leads to differential development of cognitive and emotional systems important for social bonds.

Emotion regulation is crucial for social behavior. The balance between cognitive and affective domains determines how aversive or appetitive stimuli will be processed in brain areas. Emotions are "modes of functioning, shaped by natural selection, that coordinate physiological, cognitive, motivational, behavioral, and subjective responses in patterns that increase the ability to meet the adaptive challenges of situations that have recurred over evolutionary time" (Nesse & Ellsworth, 2009:129). Social emotions such as trust, guilt, rejection and lust are part of everyday life in which social exchange occurs (Nesse & Ellsworth, 2009).

In Ernst and coworkers' triadic model, integration between distinct neural circuits is responsible for emotion regulation. There are different systems concerning approach (striatum), avoidance (amygdala) and behavioral regulation (prefrontal

cortex), and the balance between them affects motivated behavior. During the course of neural development, this equilibrium changes: for instance, in adolescence, while the prefrontal cortex is still immature, and unable to counteract a fully developed dopaminergic circuitry in the striatum. As a result, adolescents tend to exhibit more impulsive, risk-taking and present-oriented behavior (Ernst et al., 2009). Emotion regulation has obvious implications in attachment behavior, since it may provoke more or less intense approaching or aversive behavior.

Another important model is Kenneth Dodge's social information processing. Based on information processing theories, Dodge suggested that early adversity could interfere with processes of encoding, representing and retrieving information derived from social cues. During social interactions, individuals perceive stimuli, represent and interpret them, select an appropriate reaction, and finally exhibit behavioral responses in different manners. A same social stimulus can be perceived as hostile or neutral, and behavioral reactions may be evaluated as morally acceptable or not by the individual. In clinical cases of depression or aggressive behavior, a common feature is the presence of biases and deficits in some of these stages of processing (Dodge, 1993).

Aggressive children usually pay more attention to hostile environmental stimuli, attribute them a harmful bias more often, have a smaller repertoire of possible reactions – such as retaliatory or physically aggressive ones –, and therefore tend to show externalizing behavior more frequently. Depressive children, on the other hand, filter more environmental information related to loss, failure or negative self-reference, usually interpret their own performance as negative, and exhibit relatively few assertive responses to their difficulties, showing similar patterns of biased information processing (Dodge, 1993).

In this model, early adverse environments, abuse, neglect, and insecure attachment relationships make children experience situations that lead to internal representations of the world as a hostile place. These representations influence information processing, since children's views on relationships and behaviors will be coherent with the environment of their past negative experiences. In the developmental process, these deviant information processing patterns reinforce the

feeling of constant threat, especially in boys, or of low self-esteem, usually in girls. These cognitive biases are mediators between early adversity and psychopathological outcomes such as aggressive behavior and depression, respectively (Dodge, 1993).

In a further refinement of the model, biological predispositions and sociocultural contexts are added to the schema. Discussing the possible links between early adversity and antisocial conduct in adolescence, research on the roles of genetics and of social factors – cultural values, socioeconomic status, aggressive peers, disrupted family environment – as predictor variables is reviewed. The updated model suggests that the influence of genetic risk factors, as well as sociocultural contexts, is indirect. The common proximal mediator is still the child's acquired pattern of processing social information (Dodge & Pettit, 2003).

Across development, neural and psychophysiological functioning, life experiences and sociocultural context recursively iterate, leading children to develop idiosyncratic social knowledge about the world. In brief, upon the presentation of a social stimulus, children use this social knowledge to guide information processing, what in turn shapes future behavior. Children who experienced erratic and harsh discipline, low supervision and insecure attachment patterns tend to develop hipervigilance to negative cues, access rapid aggressive responses, and gradually shift to impulsive present-oriented reactions. Crucially, this selective and biased information processing shapes the children's behavioral pathway in the development process, which may lead to switchpoints of both realignment or worsening of conduct disorders. This model brings interesting implications for policy, since it enhances the importance of intervention in the initial stages of development of high-risk children. Early prevention is more likely to succeed before developmental trajectory has become already overdetermined (Dodge & Pettit, 2003).

Ontogenesis: Attachment as a reproductive strategy

A major turn on attachment theory research was caused by a groundbreaking theoretical work by Jay Belsky, Laurence Steinberg and Patricia Draper (Belsky et al.,

1991). These researchers applied the concept of reproductive strategy from behavioral ecology to attachment theory, employing an evolutionary and developmental approach. The heart of the theory is that early environment provides infants with clues on what will be the future conditions that he or she will face; and hence the child sets a reproductive strategy that will better suit these challenges. This is an unconscious process: evolution would have selected humans so as to learn, in the first 5-7 first years of life, the availability and predictability of resources, together with the existing interpersonal relationship patterns, in order to adjust behavior in the developmental process (Belsky et al., 1991).

In what comes to attachment behavior, children grown up in a stressful environment of marital discord, insensitive, harsh and unpredictable parenting, and scarce or unpredictable resources have clues that the world is a hostile place. These children develop insecure forms of attachment, tending to perceive others as untrustworthy, relationships as opportunistic and self-serving, and to see themselves as unlovable and untrustworthy, and establish behavior patterns that accelerate sexual maturity and focuses on ephemeral and promiscuous relationships. Conversely, children reared in environments where parenting is sensitive, resources are available and predictable, relationships are rewarding and trustworthy will develop more favorable internal working models concerning the others and themselves, and display secure attachment patterns, thus tending to delay their puberty onset and form long-term pair bonds. In sum, family ecology gives offspring clues to the programming of the best behavioral strategy for adolescence and adulthood. It is argued, in an evolutionary basis, that this plasticity would have enhanced reproductive success, and consequently, increased fitness (Belsky et al., 1991).

An important innovation from this theoretical model is that it proposes that insecure attachment patterns are not necessarily dysfunctional and disadvantageous, as it had been often suggested. Attachment patterns would only be possible reproductive strategies, well suited for each type of environment found by the individual (Belsky et al., 1991).

This model converges with Kenneth Dodge's model of social information processing: it suggests that abused/neglected and securely attached children focus on more negative or positive social cues, respectively. The advance is that it gives an evolutionary functional explanation for this. Absent from Belsky et al.'s original proposal, however, are a couple of features later underscored by attachment evolutionary-developmental theories. The environmental programming in pre-natal period (Pluess & Belsky, 2011) is not addressed[10], and although sex differences in internalizing or externalizing behaviors are mentioned, the mechanisms concerning gender-specific attachment strategies are not specified (Del Giudice, 2009). Nonetheless, genetic polymorphisms as moderators were already mentioned, as well as the notion of differential susceptibility to environmental experience (Belsky et al., 1991:650).

In a further update of the model, Marco Del Giudice adds sex differences and age-specific refinements. Inspired by sexual selection and parental investment theory, the author reminds that males and females face different trade-offs in the course of life history, what induces diverse attachment patterns. According to this model, in infancy and early childhood, attachment system has the function of eliciting care and protection to dependent children, and serves as a "socioassay" of current (and expected) local ecology. In this phase, no strong sex differences arise. In middle childhood, however, the system undergoes reorganization and attachment patterns become highly sex-biased, according to the needs of intrasexual competition. Insecure-avoidant attachment patterns, associated with aggression, self-reliance and inflated self-esteem, favor boys that face high-risk situations. Conversely, insecure-ambivalent pattern, with its anxious and care-eliciting behaviors may better fit high-risk female sex strategies (Del Giudice, 2009).

A relevant feature of Del Giudice's proposal is that attachment patterns not necessarily remain constant throughout lifetime. They play different roles in early childhood, when the focus is parental investment; in middle childhood, when

[10]Recent studies with glucocorticoid receptor genes have strongly suggested fetuses undergo prenatal programming of the stress axis in a GxE fashion. Since evidence of this phenomenon is present on various animal models, it has been suggested that it has been conserved during evolution for adaptive reasons. See Kapoor et al, 2008; Curley et al., 2011a; Harris & Seckl, 2011.

intrasexual competition emerges; and in adolescence, with puberty and the beginning of sexual activity. There is a major shift of attachment patterns in middle childhood, due to adrenarche, and not until adolescence does the attachment system reach its maturation. Finally, the model draws attention on the importance of hormones and stress regulation mechanisms: in the course of development, sexual hormones directly influence the children's attachment pattern and stress regulation system (Del Giudice, 2009). This neuroendocrine focus will be the basis for the later formulation of another evolutionary-developmental theory, aimed at individual differences in the functioning of the stress response system, called "Adaptive Calibration Model" (ACM) (Del Giudice et al., 2011).

In sum, then, early environments serve as proxies for unconsciously evaluating the reproductive strategies that are more fitness-maximizing. Whereas secure environments give cues that favor later reproduction, less intense delay discouting and more qualitative offspring investiment, harsh environments stimulate impulsive and risk-seeking behavior, early sexual maturation, and a quantitative reproductive strategy (Haase, 2009).

Adaptation: plasticity toward environmental cues

According to the dominant paradigm of diathesis-stress, gene-environment interaction happens in a "dual-risk" perspective: an environmental risk or stressor acts upon individuals with different genetic make-ups, some predisposing to vulnerability to, others to resilience against it. In this perspective, there are, in one hand, "vulnerability genes" or "risk alleles", and on the other, protective genotypes. In non-adverse or supportive environments, people would respond more or less similarly. Therefore, vulnerable or resilient individuals would behave differently only in a situation of environmental stress (Ellis et al., 2011).

Studying the function of stress systems, Thomas Boyce and Bruce Ellis suggested that biological reactivity to stressors prepared organisms for challenge or threat, but also to increase susceptibility to resources and support when available.

Biological Sensitivity to Context would be a neurobiological susceptibility for both cost-inflicting and benefit-conferring features of the environment, an endophenotypic property that would confer more or less reactivity to stressors. In addition, physiological mechanisms linked to autonomic, adrenocortical and immune reactivity to psychosocial stressors would moderate the effects of early environment on physical and mental health outcomes in this bivalent manner (Boyce & Ellis, 2005; Ellis et al., 2011).

In this model, children exposed to both enriched, high-supportive, and to threatening, stressful, low-supportive environments would show heightened biological sensitivity, whereas environments that are not extreme would downregulate biological sensitivity, buffering individuals against chronic stressors in a reality of neither highly threatening nor constant safety (Ellis et al., 2011).

There is a quite interesting metaphor for this model. A Swedish idiomatic expression, *maskrosbarn* (dandelion child), is used to describe those children that survive and even thrive in whatever situation they find, the same way dandelions seem to grow irrespective of soil, sun, drought, or rain. A neologism was adopted, *orkidebarn* (orchid child), for those children who are highly context-sensitive, whose survival and flourishing is closely tied, like that of the orchid, to the nurturing or neglectful character of the environment. Orchids do not survive in neglectful environments, but can flower with unusual delicacy and beauty in conditions of support and nurturance (Boyce & Ellis, 2005).

Also in disagreement with traditional diathesis-stress models is Differential Susceptibility Theory. It has been sketched and developed since the 1990's by Jay Belsky, and in the last five years it has served as a framework for Dutch researchers' Marinus van IJzendoorn and Marian Bakermans-Kranenburg work on Molecular Genetics of attachment (Bakermans-Kranenburg & van IJzendoorn, 2011).

It also suggests that gene and environments interact not only in negative contexts, but it also has a "bright side". Children that show heightened stress reactivity and sensitivity to social cues would be most harmed in stressful experiences, but they would also benefit more in highly supportive environments. They stand in contrast to

less susceptible children, which would be less harmed by risky environments, but would not benefit as much of enriched and protective contexts. In sum, some children would be more susceptible for both adverse and supportive rearing styles, that is, their plasticity would act in a "for better and for worse" manner (Belsky et al., 2007; Ellis et al., 2011).

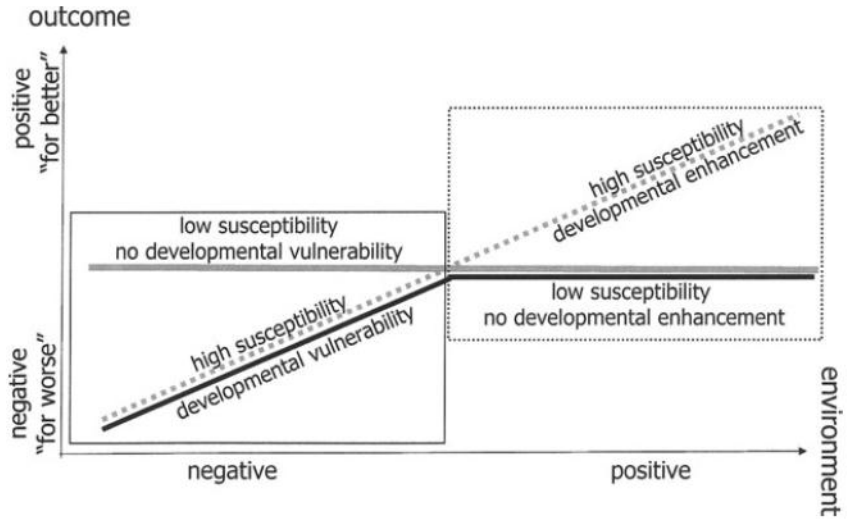

Figure 1.7. Diathesis–stress/dual risk model (solid black and solid gray lines) versus Differential Susceptibility model (solid gray and dotted gray lines).
From: Ellis et al., 2011.

Phylogenetics: the hardwired mammal brain

Another interesting evolutionary perspective on attachment behavior comes from the Polyvagal Theory, which focus on the mammalian autonomic nervous system. Social animals must first recognize facial and emotional cues, in order to recognize if the other represents threat or not, evaluate is the surroundings are safe, and communicate with their caregiver. The elicited reaction may be a fight or flight response if there is a perceived menace, or else, in case there is no apparent risk, an immobilization aimed to approximation and social bonding (Porges, 2003).

According to this model, a fundamental shift has occurred in the evolution from reptiles to mammals. The latter have a nervous system suited not only to engage in fight-flight reactions, but also to engage in social interactions (Porges & Furman, 2011). Only mammals have a myelinated vagus nerve, together with the unmyelinated vagus

common to all vertebrates, what suggests that the vagus circuit may play a role in more complex social skills (Porges, 2009).

In mammals, brainstem motor systems integrate cardiovascular functions, face, head and neck, what forms a “Social Engagement System”. These systems, located in the corticobulbar pathways (cranial nerves V, VII, IX, X and XI), regulate social gaze, voice listening, emotion expression, and also behaviors like swallowing, sucking, and ingestion, which are clearly related to social environment perception, expression of needs and feeding in newborns (Porges & Furman, 2011).

Risk assessment (in the model, *neuroception*) initiate in the temporal cortex such as the fusiform gyrus and the superior temporal sulcus, involved in movement, vocalization and face detection. These two areas have inhibitory projections to the central nucleus of the amygdala, and can thus inhibit the limbic defense systems if there is no danger, giving opportunity for social engagement. If the amygdala is otherwise activated, then limbic structures such as the PAG are activated, what results in autonomic responses of fight or flight or immobilization. In this model, then, the vagal nerve is a visceral pathway essential to attachment behavior (Porges, 2003).

In summary, the vagal circuit (in the brain, cranial nerve X) connects face and heart, behavioral and visceral features of social engagement. There is a “vagal break” which turns off defensive systems (fight-flight behaviors) and allows immobilization necessary for social interaction (Porges & Furman, 2011). Vertebrates have autonomic subsystems linked to *social communication* (facial expression, vocalization, listening), *mobilization* (fight-flight behaviors), and *immobilization* (feigning death, vasovagal syncope, behavioral and physiological shutdown). The mobilization system is dependent on the sympathetic nervous system, whereas the social communication system depends on the myelinated vagus, which inhibits sympathetic influences, dampens the HPA axis, and is related to neuropeptide (such as oxytocin) activity and inflammation reducing in the immune system. The most phylogenetically primitive is the immobilization system, which is active before the vagus nerve is myelinated, and therefore is already functional in newborns (Porges, 2003; Porges, 2009).

Risk evaluation and social bonding behavior in them could not a conscious and voluntary behavior, since neural regulation of spinal motor pathways is immature at birth. Hence, babies depend on autonomic nervous processing for recognizing when they are threatened or not. In the course of infant development, the vagal system is myelinated, self-regulatory skills develop and his behavioral and affective repertoire enriches (Porges, 2003).

The relevant feature of the Polyvagal Theory is that it draws attention to the autonomic nervous system, which is generally ignored in many contemporary developmental psychology theories (Porges & Furman, 2011).

Putting it all together

Seth Pollak indicated that the study of developmental psychopathology should follow two general principles: specify components of complex social processes and specify mechanisms underlying change. In other words, it is necessary to characterize the specific components that are intertwined in social behavior, as well as the causal chains that link input and output (Pollak, 2005). In our view, the models presented above give valuable clues in this direction, and help us answer Tinbergen's four questions concerning causality.

Both Biological Sensitivity and Differential Susceptibility models share common features. They suggest individuals with heightened susceptibility display enhanced sensitivity to both negative and positive environments due to neurobiological factors. In the course of lifetime development, susceptibility may vary, and more sensitive individuals will be more affected by environmental factors which will, by its turn, determine the course of this developmental process. The models are also based in the presupposition that this plasticity is highly adaptive in a context of constant change. The conclusion that can be drawn from them is that individuals that experience the exact same environment will react differently – contrary to diathesis-stress models, in which this would happen only in stressful environments (Ellis et al., 2011).

The models reviewed give us interesting elements concerning Tibergen's four questions. A neurodevelopmental-evolutionary perspective goes beyond traditional psychosocial models that concentrate in proximal causes, since it considers variables such as ecological strategies related to the distal levels (Haase, 2009). Hence, table 1.4 is a refinement of Table 1.3, including some of the mechanisms discussed above.

Table 1.4. Attachment systems: Causal levels in an evolutionary-developmental perspective

Levels of causality	What is attachment behavior?
Proximate questions	
Mechanism/causation	Neural circuitry linked to stress reactivity (HPA axis, glucocorticoid receptors, NPY), emotion regulation (serotoninergic networks; limbic structures), reward (dopaminergic networks), attention (cortical areas), memory (hippocampus, BDNF) and social bonding (hypothalamus, neuropeptide systems, opioids). Epigenetic programming occurs in the intrauterine environment. Environmental stimuli guide the development of social information processing toward a more positive or negative interpretation of social cues, if environment is secure or harsh, respectively. These patterns relate to the IWM that will be reference for social relationships, that is, for setting future reproductive strategies.
Ontogenesis	Children develop different patterns of bonding to their primary caregiver, according to caregiver sensitivity to infant's cues. Harsh environments favor quantitative strategies, whereas secure environments favor qualitative strategies.
Distal/Ultimate questions	
Survival value/ Adaptation	The plasticity infants show toward environment can be seen as a maximizing fitness scheme, since it allows survival in ever changing contexts. Sensitivity to environments allows the adoption of unconscious reproductive and social strategies more tuned to the challenges they will face as adults.
Phylogenetics	Evolution would have selected attachment behavior in social species, favoring the development of a hardwired mammal brain, both in parents and offspring. In infants, the autonomous nervous system (vagal circuit) is ready, since birth, to make possible unconscious movements of approaching the caregiver, as well as of recognition of threat and crying for help.

Based on this framework, we now refine the hypothesis concerning the relationship of variables previously suggested.

Attachment security is a major moderator variable between environment and physical, mental and behavioral outcomes; but it essentially depends on the genetic makeup both of the child and caregiver, which shape neural circuits related to attachment behavior. The mechanisms through which gene expression influences neural circuits are gradually being revealed. It should be noted nonetheless that it is clear that sensitivity genes interact with social environment: gene expression causes individual differences in attention, social skills, memory, emotion regulation and reward processing; this leads to different information perception and reactions; then, in a developmental lifelong perspective, the individual pathway is progressively shaped.

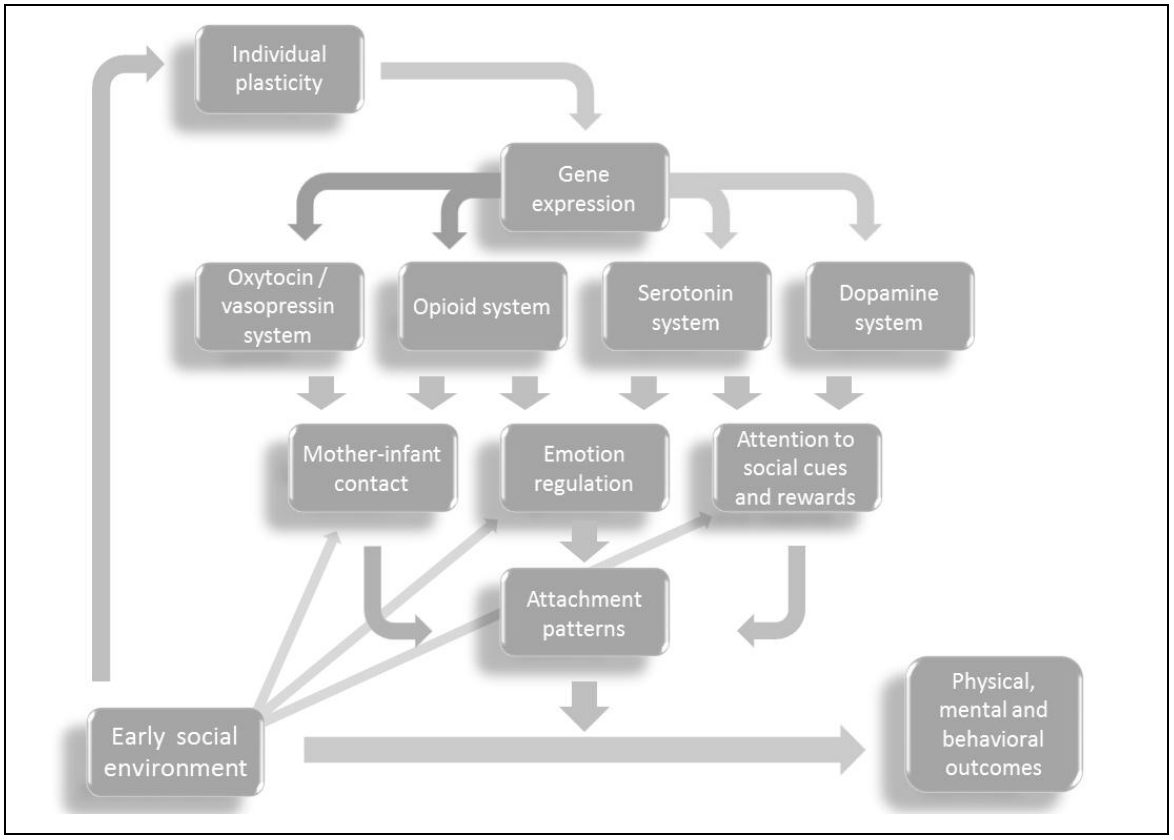

Figure 1.8. Hypothesis refining

2. Early adversity consequences on the development of attachment-related neurotransmitter systems: an integrative review

2.1. Introduction

Child maltreatment and neglect have long been associated with poor life history outcomes. A recent meta-analytic literature review on child abuse and medical outcomes in adulthood found that early adversity is strongly associated to neurological and musculoskeletal problems, cardiovascular and respiratory disease, and gastrointestinal and metabolic disorders in adult life (Wegman & Stetler, 2009). A review of 29 studies linking child maltreatment and neurobiological outcomes pointed out to structural brain consequences such as disruptive development of corpus callosum, hippocampus and amygdale, besides HPA axis reprogramming (Grassi-Oliveira et al., 2008). Experiments with animal models of early adversity have consistently related maltreatment and enhanced stress reactivity (Loman & Gunnar, 2010). A Review of seven Meta-Analyses on child sexual abuse and adult mental health indicated abuse as a risk factor that increases infant vulnerability for the development of various types of psychopathology with small to moderate effect sizes (Hillberg et al., 2011). Outcomes such as depression, anxiety, antisocial behavior, lower cerebrospinal fluid (CSF) levels of oxytocin and proinflammatory activity in the immune system have also been associated to child maltreatment (Sanchez & Pollak, 2009).

Child neglect occurs when there is a relevant omission by a parent or caregiver, that creates an imminent risk of serious physical or mental health to a child (De Bellis, 2005). Child abuse may be physical, psychological or sexual. Acts of physical abuse may vary from hitting that leaves bruising to severe harm such as broken bones and injury to internal tissues (Swenson & Saldana, 2010). Psychological refers to verbal, mental or emotional abuse, usually consisting in statements, teasing and threats that interfere with the psychological adjustment of the victim (Donohue et al., 2010). Sexual exploitation involving physical contact between a child and an abuser, in an unequal power balance, falls into the category of sexual abuse (Cohen, 2010). There are several

findings suggesting that the way stressful events affect individuals vary according to their genetic makeup (Blackwood & Knight, 2010).

Importantly, it has been suggested that attachment security plays pivotal role in moderating these effects. Sometimes, the children's caregiver is the perpetrator of abuse. In high-risk, low socioeconomic status environments, maltreated children are more likely to develop disorganized attachments if compared to non-maltreated children, as evidenced by another recent meta-analytic review (Cyr et al., 2010). Disorganized and insecure attachment patterns have also been related to externalizing behaviors, although mechanisms are still not completely clear (Fearon et al., 2010).

Since a pioneering experiment (Lakatos et al., 2000), several lines of evidence have suggested gene-environment interactions concerning attachment behavior and genetic polymorphisms. Even though an initial twin study revealed the heritability of attachment patterns to be negligible and accounted variation to environmental factors (Bokhorst et al., 2003), researchers quickly acknowledged the role of genetic variants, as demonstrated by numerous experiments (see Tables 2.3-2.7 for a sample). Consistently implied to attachment are dopamine, serotonin, oxytocin, vasopressin, and opioid neurotransmitter systems (Insel et al., 2010; Curley, 2011; Hrubý et al., 2011; Luijk et al., 2011; Saltzman & Maestripieri, 2011), which will be briefly presented below .

Two of the neurotransmitters linked to attachment behavior in the human brain are monoamines: dopamine and serotonin. Dopamine neurotransmission is related to motor control, endocrine function, reward and cognition. Disruptions in the dopamine system are involved in Parkinson's disease, addiction, schizophrenia and Huntington's chorea (Oak et al., 2000; Wong et al., 2000). Numerous human and animal studies have investigated the relationship between dopamine activity and cognition (Savitz et al., 2006).

Dopamine has traditionally been linked to processing of reward stimuli. The neuroanatomical substrates of reward processing are the cortico-basal ganglia pathways, involving structures such as VTA, NAcc, ventral pallidum, midbrain dopamine neurons, ACC, OFC and, as recently shown, the habenula (Haber, 2009).

However, a new wave of studies has demonstrated that dopaminergic pathways are also recruiting in aversive stimuli processing (Trainor, 2011), and numerous other possible interpretations of dopamine's role in reward processing and reinforcement learning have been proposed. Neuroeconomic theory has brought computational models as tools to understand how dopamine codes for subjective value of stimuli. Discussing them goes way beyond the scope of the present review (for comprehensive reviews on dopaminergic processing of environmental stimuli, see Berridge & Robinson, 1998; Schultz, 2006; Berridge, 2007; Balleine et al., 2009).

What should be retained for the moment is that dopaminergic pathways have been consistently linked to attachment behavior, due to the obvious rewarding pleasure related to mother-infant interactions and the neuroanatomical overlaps with the neuropeptidergic circuits (Skuse & Gallagher, 2009; Baskerville & Douglas, 2010; Strathearn, 2011).

Dopamine system has five G-protein coupled dopamine receptors, located in diverse brain areas and coded by different genes (Oak et al., 2000). The D1 family includes D1 and D5 receptors, which are excitatory in nature, whereas the D2 family is composed by D2, D3 and D4 receptors, inhibitory in nature (Ernst et al., 2009). D4 receptor has been a special target of attachment-related behaviors. It is expressed in the cerebral cortex, amygdala, hippocampus and pituitary, but also in the striatum (Oak et al., 2000).

The DRD4 gene has various polymorphic variants – in the third exon, there were identified 10 VNTRs of 48 base pair repeats, from 2-fold to 11-fold repeats. The two most frequent VNTRs are 4-repeat (64%) and 7-repeat (20%). These variants imply functional change in receptor efficacy: for instance, the 7-repeat DRD4 has a 2- to 3-fold lower potency for dopamine-mediated coupling to adenylyl cyclase as compared to 4-repeat and 2-repeat receptors (Oak et al., 2000; Wong et al., 2000). This functional feature has been linked to behavioral traits: there is consistent evidence of association between the 7-repeat allele and ADHD (Vaidya & Stollstorf, 2008), and many studies investigating its relation to novelty-seeking behavior (Wong et al., 2000).

Relevant for attachment behavior is also the catechol-O-methyltransferase (COMT) gene. COMT is an enzyme responsible for degrading cortical dopamine. A common SNP in the COMT gene is Val158Met (rs4680), in which occurs a substitution of a valine (Val) by methionine (Met) in position 158 of the peptide sequence. The Met allele has been associated to be less stable, resulting in diminished enzymatic activity of the gene. The high activity Val allele, by its turn, leads to more enzymatic activity and therefore extrasynaptic dopamine decrease. Numerous studies have shown that the COMT polymorphism affects prefrontally-mediated cognition, specifically memory, attention, fluid intelligence and executive functioning[11]; it has been associated to schizophrenia risk and anxiety (Chen et al., 2004; Savitz et al., 2006; for a review, see Dickison & Elvevag, 2009).

Serotonin is a key central and peripheral nervous system neurotransmitter and neuromodulator, associated with behavioral functions such as mood, sleep cycles, aggression, food intake, memory and learning, and its dysfunction plays a central role in anxiety and depressive disorders (D'Souza & Craig, 2010). It has been suggested that serotonin is involved in two functions, analogous but opposite to those of dopamine: aversive processing and behavioral inhibition (Cools et al., 2011).

The various serotonin transporter (5-HTT) subtypes are responsible for the reuptake of serotonin in the presynaptic neuron, thus terminating 5-HT action in the synaptic cleft and shutting neurotransmission down (Sugden, 2010). Numerous antidepressants such as selective serotonin reuptake inhibitors (SSRIs), fluoxetine, sertraline, and paroxetine act upon 5-HTT. For such reason, 5-HTT gene has long been one of the most widely studied neurotransmitter genes (Sugden, 2010). Since it was reported that a VNTR polymorphism in the promoter region of the gene – the short allele of 5-HTTLPR – was related to decreased 5-HTT expression and neuroticism personality trait (Lesch et al., 1996), it has become the most researched genetic variant in psychiatry, psychology, and neuroscience, particularly in gene-environment interaction studies (Caspi et al., 2011), as already mentioned in the first chapter. In the

[11]In Neuropsychology, "Executive Functions" refer to various cognitive skills related to planning, inhibitory control, defining courses of action for problem-solving and setting strategies for decision making. Its neurobiological substrates have been associated especially to prefrontal cortical areas, basal ganglia and cingulate cortex (see Malloy-Diniz et al., 2008).

past decade, dozens of studies have linked this polymorphism to attachment and social behavior, and also to plasticity toward the environment (Kiser et al., in press), some of which will be reviewed next.

Two neurohypophyseal peptides have prominent roles in sexual behavior and social bonding: oxytocin and vasopressin. Both belong to neuropeptide lineages that humans share with other vertebrates: the isotocin-mesotocin-oxytocin line, concerned with reproduction and female sexual behavior, and the vasotocin line concerned with water and electrolyte balance and male sexual behavior (Hoyle, 1999; Gimpl & Fahrenholz, 2001; Curley & Keverne, 2005).

Oxytocin is a nonapeptide hormone – it consists of a nine amino acid sequence. Its major endocrine function consists in uterotonic action at partutirion and milk ejection. Peripherally, oxytocin is synthesized in tissues such as in the uterus, placenta, amnion, corpus luteum, testis, and heart. It has traditionally been linked to maternal behavior in animal and human experiments (Insel & Young, 2001). Early inadequate caregiving has been associated to change in oxytocinergic system (Fries et al., 2005).

In the central nervous system, oxytocin has one receptor, OXTR. OXTR is a member of the G protein-coupled, seven-transmembrane domain receptor superfamily. The major site of OXTR gene expression is the magnocellular neurons of the hypothalamic paraventricular (PVN) and supraoptic nuclei (SON), where the peptide is synthesized before being stored in the posterior pituitary (Inoue et al., 1994; Gimpl & Fahrenholz, 2001; Saltzman & Maestripieri, 2011). Lately, two SNPs in the OXTR gene polymorphisms have been implicated in autism, maternal sensitivity, empathy and stress reactivity: rs53576 and rs2254298 (Rodrigues et al., 2009; Ebstein et al., 2010; Insel, 2010).

A well-known evidence of OXTR's role in pair bonding comes from studies with different vole species. The prairie vole (*Microtus ochrogaster*) exhibits monogamous behavior, engaging in lifelong relationships and biparental offspring care, whereas the montane (*Microtus montanus*) and meadow (*Microtus pennsylvanicus*) are non-monogamous and do not display biparental care. Monogamous prairie voles have found to have higher OXTR density in the NAcc than non-monogamous voles.

Surprisingly, OXTR antagonist infusion in female prairie voles blocks partner-preference formation, what suggests that monogamous behavior is due to reward learning in NAcc, where dopaminergic and oxytocinergic pathways converge (Young & Wang, 2004).

The past decade has also seen many studies on oxytocin administration and behavioral effects. The inception of intranasal neuropeptide sprays experiments, in 2002, has changed the figure, since this method allows these neurotransmitters to cross the blood-brain barrier and reach the central nervous system (Born et al., 2002). Several experiments have been set ever since, of which maybe the most well-known is the one pointing out that intranasal oxytocin provokes the increase in trusting behavior between human subjects in social interactions, as measured by a behavioral game design with real monetary stakes (Kosfeld et al., 2005). Similar studies have associated intranasal oxytocin administration and diverse other social behaviors, such as reduced amygdala fMRI activation after fear-inducing visual stimuli (Kirsch et al., 2005), increased response to hypnosis technique (Bryant et al., 2012), and, notably, in increased experience of attachment security in insecurely attached adults (Buchheim et al., 2009).

Vasopressin is also a nonapeptide, having significant structural similarity (80% homology) with oxytocin, although its peripheral functions are quite different, concerning water and electrolyte balance through antidiuretic effects (Hoyle, 1999). In an evolutionary perspective, male pair bonding is associated to vasopressin. In voles, vasopressin receptor distribution is related to monogamous or promiscuous sexual behavior, since it interacts with dopaminergic reward networks in an analogous way to oxytocin in females (Young & Wang, 2004; Curley & Keverne, 2005). Of the vasopressin receptors, the 1a (AVPR1a) has received attention on studies that associated two of its polymorphisms – microsatellites RS1 and RS3 – with emotional processing, interpersonal skills and autism (Ebstein et al., 2010; Insel, 2010).

Other relevant peptides are opioids, which have been artificially used for pain relief pain for millennia (Ribeiro et al., 2005). Humans have several different families of G-protein coupled opioid receptors– particularly μ, κ, and δ-receptors, encoded by the

OPRM1, OPRK1, and OPRD1 genes, respectively – that are widespread in the organism, but particularly abundant in the cingulate cortex, thalamus, PAG, ventral pallidum, caudate nucleus, NAcc, amygdala, insula and hippocampus (Drolet et al., 2001; Pasternak, 2004; Ribeiro et al., 2005). In a PET Scan study, subjects exposed to sustained pain showed higher activation of μ-opioid receptor system in relation to the control group in brain areas related to sensorial and affective components of pain, although there was significant interindividual variability (Zubieta et al., 2001). The release of endogenous opioids in face of painful stimuli suggest that this system's role is to attenuate excessive pain response and prevent the detrimental effects of such a prolonged reaction, thus contributing to the maintenance of homeostasis (Drolet et al., 2001; Ribeiro et al., 2005).

Opioids also play a role in emotion regulation and stress buffering (Weller & Feldman, 2003). The HPA axis is under inhibitory control of μ-opioid receptors, and when opioid antagonists such as naloxone are administered, HPA axis is activated (Drolet et al., 2001; Kroslak et al., 2007). Self-induced sadness conditions were associated to deactivation in μ-opioid neurotransmission in a PET Scan paradigm, suggesting self-allowed negative affect may reduce endogenous pain relief mechanisms (Zubieta et al., 2003). Placebo's analgesic effect is attributed to the release of endogenous opioids (Ribeiro et al., 2005; Panksepp, 2011). Recently, it has been shown that social pain activates networks – particularly ACC, thalamus and PAG – and neurotransmitter systems that overlap with those of physical pain (Eisenberger, 2011).

Research with humans and mammal models has long underscored the importance of opioids for infant-mother attachment. Social bonds, in this view, depend on an opioid addictive dynamics in the brain. Maternal tactile stimulation and skin-to-skin contact provide offspring with endogenous opioids, and therefore feelings of calmness and comfort, what reinforces attachment security (Weller & Feldman, 2003; for a recent account, see Panksepp, 2011).

The μ-opioid receptor gene (OPRM1) codes for the receptor which is the target of most clinically used opioid analgesics, since it is a major site of action for

endogenous opioids like beta-endorphin and exogenous opioids like morphine (Curley, 2011). One of the three most frequent polymorphisms in the OPRM1 gene is the functional SNP A118G, located in exon 1, consisting in the substitution of adenine for guanine in the 118th nucleotide position. It is focused in numerous opioid therapies. It has been suggested that the G allele leads to reduced receptor expression (Way & Taylor, 2011). Carriers of the G allele are less sensitive to exogenous opioids such as morphine (Lötsch & Geisslinger, 2006) and show enhanced pain tolerance (Curley, 2011).

Table 2.1 (see next page) summarizes some of this information on genetic polymorphisms related to attachment behavior.

Several reviews and meta-analysis have been published aimed at one or two of those neurotransmitter systems, usually dopamine and serotonin (see, for example, Gervai, 2009; Strathearn, 2011; Bakermans-Kranenburg & van IJzendoorn, 2011). However, to date no review has analyzed all those neurotransmitter systems as a whole. In order to fulfill this gap, we decided to interpret the results of all original studies with polymorphisms in an integrated manner.

The aims of this review are: (i) to reunite the literature on genetic polymorphisms related to attachment; (ii) to assess if there are evidence on the moderating role of genetic polymorphisms on attachment security; (iii) to compare results of human and animal studies in an evolutionary perspective; (iv) to examine if the data available on genetic polymorphisms is consistent with the differential susceptibility framework.

Table 2.1. Attachment-related candidate gene polymorphisms and its effects

Neurotransmitter	Gene	Chromosome	Polymorphisms	Function
Dopamine	Catechol-O-methyltransferase (COMT)	22q11	COMT SNP rs4680 Val and Met alleles	Met allele is associated to lower enzyme activity and less cortical dopamine degradation. Met allele carriers show better performance in prefrontally mediated cognition, but more negative emotional states.
	D4 receptor (DRD4)	11p15.5	DRD4 VNTRs Short and long alleles 7-repeat- long 4-repeat - short (2 to 11 repeats less frequent)	4-repeat and 2-repeat receptor variants are 2- to 3-fold more potent than the 7-repeat allele in dopamine-mediated coupling to adenylyl cyclase. Previous studies have implied 7-repeat polymorphism with novelty-seeking trait.
Serotonin	Serotonin Transporter (5-HTT)	17q11.2 (SLC6A4 gene)	5-HTTLPR VNTRs Short and long alleles 14 repeat – short 16 repeat – long	5-HTT removes 5-HT from the synaptic cleft and determines the magnitude and duration of postsynaptic receptor-mediated signaling. The short variant of the 5-HTTLPR polymorphism reduces the transcriptional efficiency of the 5-HTT gene promoter, resulting in decreased 5-HTT expression and diminished 5-HT uptake, what is linked to anxiety-related traits. Changes in 5-HT function are associated with anxiety and depressive spectrum disorders.
Opioids	μ-Opioid Receptor (OPRM1)	6q24-25	OPRM1 SNP 118 A and G alleles	Carriers of 118G alleles experience decreased clinical effects of opioid therapy and enhanced pain tolerance. Although it seems that the G allele decreases receptor activity, mechanisms are still not clear.
Oxytocin	Oxytocin Receptor (OXTR)	3p25-26	OXTR SNPs rs53576 rs2254298 A and G alleles	The rs53576 SNP has been associated with measures of parental sensitivity, altruism, stress reactivity, empathy, and theory of mind. The rs2254298 SNP has been associated with emotional deficits.
Vasopressin	Vasopressin Receptor 1a (AVPR1a)	12q13-15	AVPR1a microsatellites RS1 and RS3	The 5' flanking region microsatellites RS1 and RS3 have been associated with emotional arousal, altruism, sexual and social behavior.

Sources: Inoue et al., 1994; Lesch et al., 1996; Lesch and Mössner, 1998; Hoyle, 1999; Wong et al., 2000; Gimpl & Fahrenholz, 2001; Chen et al., 2004; Lötsch & Geisslinger, 2006; Ebstein et al., 2010; Insel, 2010; Sugden, 2010; Curley, 2011; Mayer-Lidenberg et al., 2011.

2.2. Methods

Since the focus was on distinct neurotransmitter systems, with variable clinical questions, studies with potential different experimental designs, and both human and animal samples, the review method chosen was integrative review. Integrative review is an approach that allows inclusion of diverse methodologies, without renouncing scientific rigor and strategies to overcome biases, what distinguishes it from ordinary narrative reviews (Whittemore & Knafl, 2005).

The search for articles was made in the Medline/Pubmed database. The aim was to select only original studies focusing on gene-environment interaction concerning the above mentioned neurotransmitter systems and employing the attachment construct. No date limits or language restrictions were previously set. The keywords were: “attachment” and “dopamin*” (or “oxytocin*”, “serotonin*”, “opioid*”, “vasopress*”) and “gene-environment interaction” (or “polymorphism” or “epigenet*”). Search returned 53 entries, all published since 2000.

Next, all abstracts were read. 3 articles were not available through CAPES scientific journal Portal, and were thus left out of the review. 7 articles brought reviews exclusively, without original experiments, and were rejected. The 43 remaining papers were then downloaded and fully read.

Studies with humans were excluded if no attachment measure was employed or if attachment was not among constructs measured (such as personality traits, substance abuse, sexual behavior, etc.). By this criterion, 13 more articles were discarded. In one study, neurotransmitter levels were assessed only peripherally, and no genotyping was involved, what led to its exclusion. The same was done with another study that was a theoretical comment on an experiment.

Finally, while reading and analyzing data of these 28 remaining studies, 10 others were identified by cross-referencing, found to meet the inclusion criteria, and subsequently added to the sample, resulting in 38 reviewed articles.

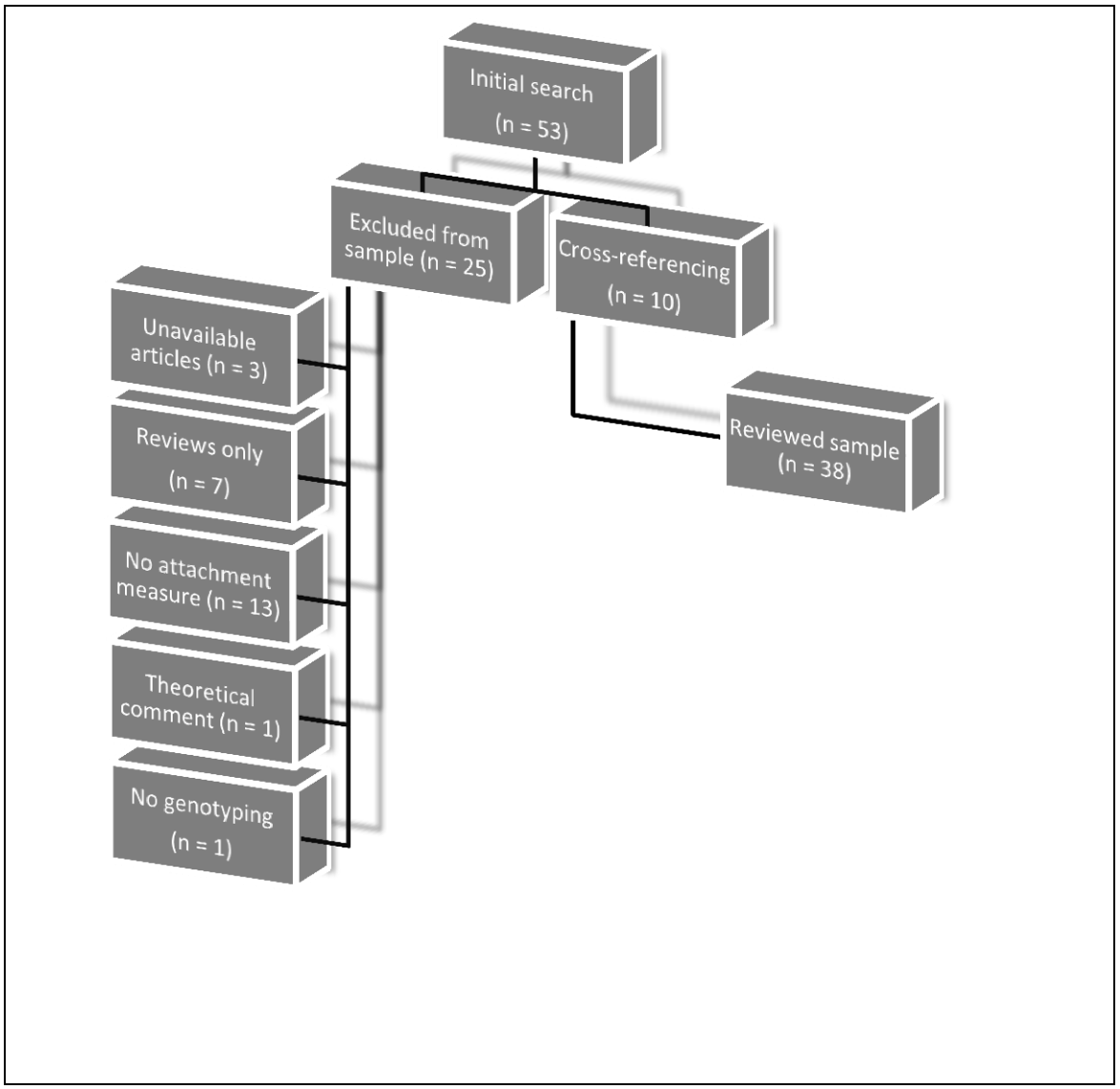

Figure 2.1. Inclusion criteria for review sample

2.3. Results

Research on gene-environment interactions on neurotransmitter-related polymorphisms and attachment begun with the pioneering study of Lakatos, Gervai and colleagues on DRD4 7-repeat and attachment disorganization (Lakatos et al, 2000). It is therefore a recent literature, and the numerous recently published works show that its pace is accelerating.

Many different cognitive, behavioral and attachment measures were employed in the studies within this tradition, as summarized in Table 2.2. The most common attachment measures were Ainsworth's Strange Situation Procedure and George and Kaplan's Adult Attachment Interview. Gene polymorphisms were obtained in virtually all studies with the Polymerase Chain Reaction (PCR) technique. Animal studies used mice, voles and rhesus monkeys. Human studies were done with both community and clinical samples, longitudinal cohort and transversal designs, adults and children, mother-infant dyads or offspring only. There were studies focused in children's disorganized attachment versus security, while others adopted insecure versus secure attachment patterns as variables. Some studies explicitly use data to test diathesis-stress and differential susceptibility models. Tables 2.3, 2.4, 2.5, 2.6 and 2.7 summarize experiments concerning, respectively, dopamine (DRD4 and COMT), serotonin (HTTLPR), oxytocin and vasopressin (OXTR and AVPR1a), opioid (OPRM) genes and studies that jointly considered various genes related to attachment behavior.

Table 2.2. Behavioral, cognitive, and attachment instruments frequently used in sample

Method	Abbreviation	Measure of
Adult Attachment Interview	AAI	Security of the adult's overall working model of attachment
Adult Attachment Questionnaire	AAQ	Adult attachment patterns
Attachment Story Completion Task	ASCT	Classification of infant's patterns of attachment
Attachment Style Questionnaire	ASQ	Adult romantic attachment patterns
Buss-Durkee Hostility Inventory	BDHI	Impulsive aggressiveness
Brief Symptom Instrument	BSI	Psychological health / mood disturbance
Child Behavior Checklist	CBCL	Child behavior problems
Childbearing Attitudes Questionnaire	CAQ	Mothers' feelings and attitudes about mothering and the infant
California Child-Q-sort	CCQ	Alternative method for adult attachment assessing
Childhood Trauma Questionnaire	CTQ	Physical, emotional and sexual abuse; emotional and physical neglect
Clinical Interview Schedule, Revised	CIS-R	Common psychiatric disorders
Early Childhood Behavior Questionnaire	ECBQ	Child's Temperament
Rothbart's Infant Behavior Questionnaire-Mother Report	IBQ	Child's Temperament
Infant Characteristics Questionnaire	ICQ	Child's Temperament
Life History Calendar	LHC	Life-event histories (e.g. employment, financial, health, and relationship stressors).
Parental Bonding Instrument	PBI	Quality of parenting experienced during the subjects' first 16 years of life.
Profile of Mood States	POMS	Current mood states
Relationship Questionnaire	RQ	Adult attachment patterns
Snaith-Hamilton Pleasure Scale	SHAPS	Capacity to experience pleasure in social situations
Strange Situation Procedure	SSP	Classification of infant's patterns of attachment
Laboratory Temperament Assessment Battery	LAB-TAB	Child's Temperament
Temperament and Character Inventory	TCI	Temperament / Personality
Trier Social Stress Test for Children	TSST-C	Physiological responses to psychosocial stressors

Table 2.3. Dopamine polymorphism studies

Article (year)	Sample	Methods	Main Results
Lakatos *et al.* (2000)	Human infants N=90 Age = 1 year old	SSP	The 7-repeat allele was represented with a significantly higher frequency in infants classified as disorganized compared to non-disorganized infants: 12 of 17 (71%) vs 21 of 73 (29%) had at least one 7-repeat allele. Increased risk for disorganized attachment was fourfold in children with 7-repeat.
Lakatos *et al.* (2002)	Human infants N = 95 (41f, 54m) From the Longitudinal Budapest Infant Parent Study (BIPS)	SSP	The association between disorganized attachment and the 7-repeat allele was enhanced in the presence of the − 521 T allele. In the presence of both risk alleles the odds ratio for disorganized attachment increased tenfold.
Bakermans-Kranenburg & van IJzendoorn (2004)	Human infants N = 132 76 same-sex twin pairs (27MZ, 49 DZ) from the Netherlands Twin Register	SSP	No association was found between risk of disorganized attachment and the presence of 7-repeat DRD4 allele, nor with the -521C/T genotype. The interaction was not significant either. In sum, the presence of the -521 T variant, the 7-repeat DRD4 allele did not increase the risk for attachment disorganization.
Gervai *et al.* (2005)	Human infants and parents N = 95 (41 girls, 54 boys Hungarian families with a firstborn infant) participating in the longitudinal Budapest Infant Parent Study (BIPS)	SSP, Parental genetic data in TDT	It was found a trend for preferential transmission of the seven-repeat allele to disorganized infants, and a significantly lower-than-expected rate of transmission of the same allele to securely attached infants. The overall allele-wise TDT of the -521 C/T was not significant for either the disorganized, or the secure group.
Bakermans-Kranenburg & van IJzendoorn (2006)	Human infants n = 47 infants (23m, 24f) Netherlands Twin Register	Ainsworth's 9-point rating scale; CBCL	Children with the 7-repeat DRD4 and insensitive mothers displayed significantly more externalizing behaviors than children with the 7-repeat with sensitive mothers and than children without the DRD4 7-repeat, irrespective of maternal sensitivity. In children with the 7-repeat allele exposed to insensitive care there was a sixfold increase in externalizing behaviors compared to children without this combination.
van IJzendoorn & Bakermans-Kranenburg (2006)	Human mother-infant dyads n = 63 Experienced loss of first-degree kin (n=21) and other loss (n=42)	AAI, SSP	Mother's unresolved loss/trauma was only associated with 18.8-fold increase in levels of infant disorganization if the children had 7-repeat allele. Children with the 7-repeat allele did not show higher scores for disorganized attachment when their mother was unresolved.

Table 2.3. Dopamine polymorphism studies			
Article (year)	**Sample**	**Methods**	**Main Results**
Sheese *et al.* (2007)	Human infants n = 45 (16f, 29m) Age = 18-21 months old	ECBQ, Video-taped free-play procedure	Presence of the 7 repeat is associated with a greater influence of parenting. Children with the 7-repeat allele were more influenced by parenting quality, with lower quality parenting associated with higher levels of sensation seeking; children without the 7-repeat allele were uninfluenced by parenting quality.
Gervai *et al.* (2007)	Human mother-infant dyads n = 138 96 from a Hungarian low-social-risk sample and 42 from a US high-social-risk sample	SSP, AMBIANCE coding scheme, genotyping	Among infants who carried the 7-repeat allele, infant disorganization was unrelated to the level of maternal disrupted communication. Infants with the 7-repeat allele were less sensitive to regulation by the caregiving relationship.
Bakermans-Kranenburg *et al.* (2008a)	Human infants n = 157 Age = 1-3 years old Families with children with scores above the 75th percentile on the CBCL Externalizing Problems scale behavior	RCT of VIPP-SD intervention	The intervention produced a decrease of oppositional behavior, but only in children with the 7-repeat allele of the DRD4 gene. VIPP-SD effects were largest in children with the DRD4 7-repeat allele whose parents showed the largest increase in the use of positive discipline.
Bakermans-Kranenburg *et al.* (2008b)	Human infants n = 130 Age = 1-3 years old Families with children with scores above the 75th percentile on the CBCL Externalizing Problems scale behavior	RCT of VIPP-SD intervention; ICQ; salivary cortisol measures	The VIPP-SD program was effective in decreasing daily cortisol production in children with the DRD4 7-repeat allele, but not in children without the DRD4 7-repeat allele.
van IJzendoorn & Bakermans-Kranenburg (2008)	Human mother-infant dyads n = 176 Mothers with 23-month old toddlers (56% m) with scores above the 75th percentile on the CBCL Externalizing Problems scale behavior	Scales for daily hassles and maternal sensitivity	In parents with the combination of DRD4 7-repeat allele and COMT Val allele, more daily hassles were associated with less sensitive parenting, and lower levels of daily hassles were associated with more sensitive parenting.

Table 2.3. Dopamine polymorphism studies			
Article (year)	**Sample**	**Methods**	**Main Results**
Bakermans-Kranenburg & van IJzendoorn (2011)	Human children n = 91(43m, 48f) Age = 7 years old	UNICEF donating task; ASCT	Attachment security was related to donating more money to UNICEF, but only in the presence of the DRD4 7-repeat allele.

Table 2.4. Serotonin polymorphism studies

Article (year)	Sample	Methods	Main Results
Olsson *et al.* (2005)	Human adolescents n = 752 (443m, 309f) Young Australians from the Victorian Adolescent Health Cohort Study	CIS-R, Worry and Anxiety subscales; alcohol measures (7-day diary); AAQ	Among insecurely attached young people only, the risk of persisting ruminative anxiety (worry) reduced in a dose-dependent manner with each additional copy of the S-allele (around 30% per allele). Among securely attached young people only, the risk of persisting high-dose alcohol consumption (bingeing) reduced in a dose-dependent manner with each additional copy of the S-allele (35% per allele).
Gerra *et al.* (2007)	Human adult cocaine users n = 96 Age = 19-25 years old With a history of cocaine use of 1-3 years Control group: healthy male volunteers n = 105 Age = 18-24 years old	Psychiatric Assessments, PBI, BDHI	Persons bearing the SS genotype have a risk of becoming cocaine user almost three times higher than those having the LL genotype. However, large part of the change in the risk associated to the SS genotype was actually due to the low perception of parental bonding of the individuals bearing such a genotype, rather than to the genotype itself.
Gilissen *et al.* (2008)	Human children n = 92 (43m, 49f) Age = 7 years old	ASCT; TSST-C; electrodermal reactivity measure	Children with a secure representation of their attachment relationship were less reactive to the stress of the TSST-C. Children with two long alleles and a secure representation of attachment showed the lowest levels of stress reactivity during the TSST-C.
Barry *et al.* (2008)	Human infants n = 88 (39m, 49f) Ages = 7, 15 and 52 months old (measures were taken in 3 phases)	Mother's responsiveness measures (7mo); SSP (15mo); (52mo)	For infants with a short allele (ss/sl), variation in mothers' responsiveness was significantly associated with attachment security. For those infants, low responsiveness predicted particularly high risk for insecure attachment, and high responsiveness offset that risk. For infants homozygous for the long allele (ll), there was no association between responsiveness and attachment organization. Children with ss/sl genotype who had responsive mothers were as secure– but not more secure – than children with the ll genotype who had responsive mothers.
Pauli-Pott *et al.* (2009)	Human infants n = 69 (35f, 34m)	Infant emotion scale' of the Mannheim assessment battery of mother–infant interaction; IBQ; LAB-TAB; SSP	Development of high negative emotionality in s/l and l/l carriers seems not to be systematically moderated by attachment insecurity. Insecurely attached s/s carrying infants decreased in positive emotionality from 4 to 8and 12 months while securely attached s/s carrying infants showed an increase in positive emotionality.

Table 2.4. Serotonin polymorphism studies

Article (year)	Sample	Methods	Main Results
Kochanska *et al.* (2009)	Human infants n = 88 (44m, 44f)	SSP; Multitask self-regulation batteries at 25, 38, and 52 mo	Among children who carried a short 5-HTTLPR allele (ss/sl), those who were insecurely attached developed poor regulatory capacities, but those who were securely attached developed as good regulatory capacities as children who were homozygotic for the long allele (ll).There was no effect of security for ll homozygotes.
Caspers *et al.* (2009)	Human adults n =86	AAI; Temperament Scales;	There was an association between the short allele and increased risk for unresolved attachment in adulthood. It was found a strong dominant effect of the short allele on unresolved loss.
Zimmerman *et al.* (2009)	Human adolescents n = 91 (45m, 46f) Age = 12 years old	CCQ; Measures of emotion expression; observed autonomy; Mother's observed intrusiveness; Late Childhood Attachment Interview	Carriers of the short version of the 5-HTTLPR showed more agreeable autonomy when they had a secure attachment behavior strategy but showed more hostile autonomy when they were insecurely attached.
van IJzendoorn *et al.* (2010)	Human adult adoptees n = 142 (71m, 71f) From the Iowa Adoption Studies	AAI; BSI	Higher levels of methylation of 5-HTTLPR was associated with increased risk of unresolved responses to loss or other trauma in carriers of the usually protective long variant. The short variant of 5-HTTLPR predicted more unresolved loss or trauma, but only in case of lower levels of methylation. Higher levels of methylation of the short variant were associated with less unresolved loss or other trauma.
Mileva-Seitz *et al.* (2011)	Human mothers n = 204 From the Maternal Adversity, Vulnerability and Neurodevelopment (MAVAN) cohort	Video-recorded mother–infant interactionat 6 months postpartum for maternal sensitivity measure; CAQ; LHC; PBI; CTQ	Mothers with an S allele were more sensitive than mothers who lacked the allele during a 30-min recorded mother–infant interaction such that mothers with no S alleles oriented away more frequently from their babies if they also reported more negative early care quality. Mothers with the S allele and with greater early care quality scored higher on ratings of their perceived attachment to their baby.

Table 2.5. Oxytocin-vasopressin polymorphism studies

Article (year)	Sample	Methods	Main Results
Hammock *et al.* (2005)	Animal – male prairie voles n = 20	Behavioral tests: elevated plus maze, open field test, paternal care, juvenile affiliation, partner preference and resident-intruder; brain V1aR autoradiography	There are a high number of correlations among individual differences in microsatellite length, brain V1aR binding density and behavior. V1aR levels in the main and accessory olfactory bulbs, the amygdala and thalamus were all positively correlated with genotype.
Costa *et al.* (2009)	Human psychiatric patients n = 185 Patients with major depression (50.3%) or bipolar I or II disorders (49.7%) Control group: healthy adults n = 192	ASQ; Adult Separation Anxiety Checklist	A positive association between the GG genotype of OXTRrs53576 and rs2254298 SNPs unipolar depression was demonstrated. GG individuals showed high scores on Attachment Style Questionnaire associated with depression.GG genotype was also associated with high levels of adult separation anxiety.
Chen *et al.* (2011)	Human infants n = 176 infants (98m, 78f; 77 Caucasian, 99 non-Caucasian)	SSP	Ethnic distinction: Caucasian vs. non-Caucasian. The association between the genotype at rs2254298 (presence vs.absence of the A allele) and the behavioral outcome (secure vs. insecure) appeared to differ as a function of ethnicity (Caucasians vs. non-Caucasian), with the opposite directions of association in the two groups. The A allele of OXTR rs2254298 was associated with attachment security in the non-Caucasianinfants. Non-Caucasian infants were almost four times more likely to develop a secure attachmentif they had the A allele at rs2254298 than if they did not.

Table 2.6. Opioid polymorphism studies

Article (year)	Sample	Methods	Main Results
Moles *et al.* (2004)	Animal – mouse knockout OPRM pups n = 5 Controls n = 6	UV measures in separation from mothers; and in presence of stressful physical (cold) and social (clean and novel male bedding compared to nest odor bedding) stimuli	Knockout OPRM pups emitted fewer distress calls than their wild-type controls in response to isolation at various developmental time points. However, pups of both genotypes showed a similar UV response when exposed to stressful stimuli such as cold or strange male odors.
Barr *et al.* (2008)	Animal – captive Rhesus monkeys infants n = 97	Maternal separation; behavioral observations;	Infants carrying the OPRM1 77G allele exhibited stronger attachment to their mothers in baseline conditions. The OPRM1 77G allele also affected social preference during reunion. C/G infants spent increasing amounts of time in social contact with their mothers as a function of repeated separation and were less likely to interact with other individuals in the social group, a pattern not observed among infants with the C/C genotype.
Way *et al.* (2009)	Human adults n=122 fMRI subsample n=31 (12m, 19 f)	Self-report Subsample: fMRI with Cyberball	The A118G polymorphism was associated with dispositional sensitivity to rejection in the entire sample and subsample. G allele carriers showed greater reactivity to social rejection in dACC and anterior insula.
Troisi *et al.* (2011a)	Human adults Psychiatric patients n = 84 (73%f) Control group: healthy n =130 (66% f)	RQ; ASQ; SHAPS; TCI; POMS	Compared to individuals expressing only the major allele (A) of the A118G polymorphism, subjects expressing the minor allele (G) had an increased tendency to become engaged in affectionate relationships, as indicated by lower scores on a self-report measure of avoidant attachment, and experienced more pleasure in social situations, as indicated by lower scores on a self-report measure of social anhedonia. The significant association between the A118Gpolymorphism and social hedonic capacity was independent of the participants' mental health status.
Troisi *et al.* (2011b)	Human psychiatric patients n = 112 (74% f)	PBI; RQ	Participants expressing the minor 118 G allele had similar and relatively high scores on fearful attachment regardless of the quality of maternal care. By contrast, early experience made a major difference for participants carrying the A/A genotype. Those who recalled higher levels of maternal care reported the lowest levels of fearful attachment whereas those who recalled lower levels of maternal care scored highest on fearful attachment. Data fit well with the differential susceptibility model.

Table 2.6. Opioid polymorphism studies			
Article (year)	**Sample**	**Methods**	**Main Results**
Higham *et al.* (2011)	Animals - Free-ranging female Rhesus monkeys n = 33	Observational Behavioral data; CSF OXT measure	Females possessing the G allele restrain their infants more (i.e., prevent infants from separating from them by pulling them back) than females homozygous for the C allele. Females possessing the G allele also show higher CSF OXT levels when lactating, and lower OXT levels when neither lactating nor pregnant, than females homozygous for the A allele.

Table 2.7. Various neurotransmitter polymorphism studies

Article (year)	Polymorphism	Sample	Methods	Main Results
Lakatos *et al.* (2003)	DRD4 7-repeat allele, 5-HTTLPR s/l alleles	Human infants N=90 Age = 1 year old Participating in the longitudinal Budapest Infant Parent Study (BIPS)	SSP, IBQ	Infants with at least one copy of both the 7-repeat DRD4 allele and the long variant of 5-HTTLPR responded with significantly less anxiety than infants with other genotypes. However, infants with the 7-repeat DRD4 allele and homozygous for the short allele of 5-HTTLPR showed more anxiety and resistance to the stranger's initiation of interaction.
Bakermans-Kranenburg & van IJzendoorn (2008)	5-HTTLPR, OXTR rs53576	Human mother-infant dyads Children - n =237 (57% m) Age = 1-3 years old with scores above the 75th percentile on the CBCL Externalizing Problems scale Mothers - n = 176	Egeland's parental sensitivity scale; subscale of Dutch Family Problems Questionnaire for marital discord; Young Adult Self-Report, short form	Both polymorphisms were associated with maternal sensitivity. Mothers with OXTR AA or AG genotypes were less sensitive than mothers with the GG genotype, and mothers with 5-HTT ss were less sensitive than mothers with 5-HTT sl or ll
Gillath *et al.* (2008)	DRD2 A1 allele HTR2A - T102C OXTR rs53576 G/A alleles	Human adults n = 147(40m, 107f) Age = 18-29 years old	ECR inventory; Big Five Inventory	Attachment anxiety was associated with the presence of two copies of the A1 allele of the DRD2dopamine receptor. The TT pattern of alleles on the serotonin HTR2A receptor gene was associated with avoidant attachment. Variants of the OXTR oxytocin receptor gene were not related to either attachment anxiety or avoidance.
Spangler *et al.* (2009)	DRD4 7-repeat allele, -521 C/T, 5-HTTLPR s/l alleles	Human infants n = 106 (53m, 53f) Age = 12 months old From the Regensburg Longitudinal Study IV	SSP	There were no significant associations between attachment security (secure vs. insecure) and any of the three gene markers. Significant associations were found between attachment disorganization and the short allele of 5-HTTLPR.

Table 2.7. Various neurotransmitter polymorphism studies

Article (year)	Polymorphism	Sample	Methods	Main Results
Frigerio *et al.* (2009)	DRD4 7-repeat allele, -521 C/T, 5-HTTLPR s/l alleles, GABRA6 & COMT val/met	Human infants n = 114 (63m) Age = 12-18months old	SSP; salivary cortisol and alpha amylase (AA) measures	Infants with avoidant attachment were more likely to have the T allele, whereas infants with resistant attachment were more likely to have the C allele. There was a significant effect of DRD4/-521 on basal AA; infants with the DRD4/-521 CC genotype had higher baseline AA levels than infants with CT and TT genotypes. No significant associations were found between attachment and 5-HTTLPR, COMT, GABRA6 or DRD4.
Reiner & Spangler (2010)	DRD4 7-repeat allele; 5-HTTLPR s/l allele	Human parents n = 167 (80m, 87f), Parents of children from the Regensburg Longitudinal Study IV	AAI	DRD4 7-repeat allele carriers were significantly more likely to be securely attached than those without 7-repeat but only for subjects with unloving caregiver recollections. No association between the 5-HTTLPR polymorphism and adult attachment was found.
Luijk *et al*. (2011)	DRD4 – 7-repeat allele COMT – Val/Met alleles 5-HTT – s/l alleles OXTR - rs53576 and rs2254298 alleles	Human parent-infant dyads n >1000* Two attachment cohorts: Generation R Study and NICHD Study of Early Care and Youth Development (SECCYD)	SSP; Maternal sensitivity measures; Continuous Attachment Security Scale; genotyping	In these two large cohort studies, no consistent evidence emerged for additive effects of candidate genes putatively involved in attachment security and disorganization. However, evidence for a codominant risk model for COMT Val158Met, consistent across both samples. Children with the Val/Met genotype showed higher disorganization scores.

* In this particular study, information on each polymorphism was not always available for all children in both cohorts. For this reason, sample of each polymorphism ranged from n=984 to n= 1069.

Twelve (n=12) human studies focused only in DRD4 receptor gene, particularly in the 7-repeat allele. Four (n=4) of them measured also SNP -521 C/T allele, and another one (n=1) addressed COMT Val/Met allele as well (see Table 2.3).

The first and pioneering study found a fourfould risk of disorganized attachment in children with the 7-repeat allele (Lakatos et al., 2000). Next, the same research group reported a combined effect of the 7-repeat and SNP -521 T allele: in presence of both, risk for disorganized attachment would be tenfold (Lakatos et al., 2002). The first attempt to replicate their findings, however, showed no similar results (Bakermans-Kranenburg & van IJzendoorn, 2004). Findings from the Hungarian sample followed when Transmission Disequilibrium Tests (TDT) assessed parent's and child's genotype and showed a trend of preferential transmission of the 7-repeat allele to disorganized infants, in relation to securely attached children; no such trend was found for -521 SNP (Gervai et al., 2005). Importantly, no studies belonging to this first wave measured environmental variables.

Following studies started focusing on environmental measures such as parental sensitivity. In a Dutch twin sample, children with the 7-repeat allele displayed a sixfold increase in externalizing behavior, if exposed to insensitive care. Children without the 7-repeat allele showed no such increase, even if there was parental insensitivity (Bakermans-Kranenburg & van IJzendoorn, 2006). The same authors investigated DRD4 gene alleles and mother's unresolved loss or trauma, in mother-infant dyads, using SSP with children and AAI with parents. A moderating role of 7-repeat allele was found: maternal unresolved loss or trauma was associated with infant disorganization, but only in the presence of the polymorphism. Strikingly, the increase in risk for disorganization in children with the 7-repeat allele, when exposed to maternal unresolved loss or trauma, was 18.8-fold, if compared to children without the 7-repeat (van IJzendoorn & Bakermans-Kranenburg, 2006). Another study with parenting measures associated presence of 7-repeat with influence of parenting: children with the 7-repeat and poor parenting showed higher levels of sensation-seeking, what did not happen in infants without the allele (Sheese et al., 2007). Such results indicated that differential susceptibility theory could be in the right track, but were also consistent with diathesis-stress models.

A new study on mother-infant dyads provided mixed findings. Measuring infant attachment patterns and maternal communication, researchers reported that the relation between maternal disrupted communication and infant disorganization was moderated by the infant's DRD4 7-repeat genotype. Surprisingly, in this case the 7-repeat allele appeared to dampen the infant's responsiveness to care, playing a protective role in the context of disrupted interactions, but providing less regulation in the high-quality care context (Gervai et al., 2007). These results were opposite to previous findings on the 7-repeat allele.

Randomized Control Trial design was adopted in two studies using the Video-feedback Intervention to promote Positive Parenting and Sensitive Discipline (VIPP-SD). Interestingly, children bearing the 7-repeat allele were more responsive to intervention than no carriers of the allele in both cases. In one study, intervention aimed at diminishing oppositional/externalizing behavior (Bakermans-Kranenburg et al., 2008a), whereas in the other focus was decreasing daily cortisol (Bakermans-Kranenburg et al., 2008b) through incentives for parents to use positive discipline.

In a further study, parent's genotype was associated to the occurrence of daily hassles – small stressful episodes. Parents that carried a combination of the least efficient dopaminergic system functioning alleles – DRD4 7-repeat and COMT Val alleles – were more negatively affected by daily hassles. DRD4 and COMT did not predict parental sensitivity separately, but only in interaction (van IJzendoorn & Bakermans-Kranenburg, 2008). Finally, in a recent experiment using UNICEF donating task, a measure of altruistic/prosocial behavior, attachment security was related to donating more money to charity for 7-repeat allele carriers (Bakermans-Kranenburg & van IJzendoorn, 2011).

Studies relating attachment to serotonin transporter gene only were ten (n = 10), all with human samples (see Table 2.4).

In a large sample of adolescents and measuring worry, anxiety and binge drinking, researchers found results suggesting a protective role for short allele of HTTLPR. In insecurely attached adolescents, each copy of the allele reduced in around 30% the risk of ruminative anxiety, whereas in securely attached adolescents, each s-

allele reduced in 35% risk of binge drinking (Olsson et al., 2005). Another study, with control group, found that association between cocaine use and presence of short allele was less significant than association between perception of parental bonding and cocaine use (Gerra et al., 2007).

Assessing stress measures through TSST in children, another study reported that children with two 5-HTTLPR long alleles appeared to be less stressed during the test, but only when they had a secure attachment representation (Gilissen et al., 2008). Studying attachment patterns and maternal responsivity, another team concluded that responsiveness was significantly associated with attachment security only in short allele carriers; no association existed for long allele carriers. However, short allele children with responsive mothers did not show more attachment security, contrary to differential susceptibility model would predict. Interestingly, in that sample all disorganized infants carried the short allele (Barry et al., 2008). Evaluating self-regulation, a further study associated short-allele with poor regulatory capacity when children were insecurely attached, but as good regulatory capacity as long-allele carriers when securely attached. These results were in line with diathesis-stress models, but not with differential susceptibility (Kochanska et al., 2009). Consistent with differential susceptibility, however, another study showed short-allele carriers developed negative emotionality when insecurely attached, but positive emotionality when experiencing attachment security. No such effect was found for long-allele carriers (Pauli-Pott et al., 2009).

A study with adults associated short allele and increased risk of unresolved attachment (Caspers et al., 2009). In a sample of short-allele adolescents, a secure attachment was associated to agreeable autonomy, whereas insecure attachment was associated to hostile autonomy. Carriers of the short allele were significantly more sensitive to restrictions of their autonomy by their parents, in line with the association between 5-HTTLPR short allele and heightened emotional reactivity (Zimmerman et al, 2009). Maternal sensitivity was highly gene-dependent in a further study that evaluated maternal sensitivity, behavior and attitudes: mothers with the short allele were more sensitive to their children (Mileva-Seitz et al, 2011).

A last study on 5-HTTLPR polymorphisms examined methylation patters. Short allele was linked to more unresolved loss and trauma in adults, but only in lower levels of methylation. Interestingly, long allele carriers also displayed heightened risk for unresolved loss or trauma if their methylation levels were high. Authors from this pioneering study posits that ignoring methylation patterns could lead to failures to replicate GxE effects on 5-HTTLPR (van IJzendoorn et al., 2010).

When it comes to peptides, human studies are coupled by experiments involving animals. Two (n= 2) human studies focus on OXTR only; another (n = 1) on prairie voles' AVPR1a only (see Table 2.5), and six (n = 6) on OPRM only, of which three (n = 3) with humans (see Table 2.6).

A positive association between GG genotype of OXTR rs53576 and rs2254298 SNPs and unipolar depression and higher levels of separation anxiety was found (Costa et al., 2009). A recent study that considered ethnicity as a variable reported rs2254298 polymorphism was associated fourfold to attachment security only in non-Caucasian infants. More interestingly though, in Caucasian children, the association appeared in the opposite direction. Authors emphasize the need to account for ethnic factors in research (Chen et al., 2011).

The one study focused only in AVPR1a reported correlations between the length of the polymorphism, brain receptor binding density and social behavior in 20 male prairie voles, coherent to previous findings (Hammock et al., 2005).

OPRM gene was tested in knockout mice, measuring ultrasonic vocalizations (UV), a distress call induced by maternal separation. Even though knockout mice showed fewer UV in response to isolation, they were still capable of emitting distress calls in stressful situations, ruling out the possibility that mutant animals would be unable to feel this kind of social pain (Moles et al., 2004). Two other studies were carried with Rhesus monkeys, with captive and free-ranging samples. In the first one, rhesus infants carrying the G allele of OPRM1 exhibited stronger attachment and social proximity behaviors than the ones with the C allele (Barr et al., 2008), a pattern replicated in the free-ranging sample of the study with rhesus mothers (Higham et al., 2011).

A human study combining genotyping with a fMRI task that simulates social rejection, the Cyberball game, found greater self-reports of rejection feelings, as well as dACC and anterior insula activation in G allele carriers (Way et al., 2009). Results are consistent with findings with G allele carriers in a study with psychiatric patients and a control group: having the allele was correlated to the experience of more pleasure in social situations, regardless of the participants' mental health status (Troisi et al, 2011a).These overall results showed that genetic makeup somehow influenced social sensitivity, although it was not clear how. In a following study with a clinical sample, it was suggested that the A allele would be the "plasticity allele" concerning social sensitivity, since quality of maternal care in childhood was not related to scores of fearful attachment in carriers of the G allele, but in participants carrying the A genotype (Troisi, 2011b).

Studies combining more than one polymorphism were seven (n = 7), all with human samples (see Table 2.7).

The first one focused on DRD4 and 5-HTTLPR found an interaction between the 7-repeat allele and short allele of 5-HTTLPR and anxiety in the SSP: infants with the 7-repeat and long allele of 5-HTTLPR showed less anxiety, but children with the 7-repeat allele and homozygous for the short 5-HTTLPR allele showed more anxiety (Lakatos et al., 2003). 5-HTTLPR was also studied together with OXTR SNP rs53576: the short allele of the former and the A allele of the latter were positively correlated to maternal sensitivity (Bakermans-Kranenburg & van IJzendoorn, 2008).

A third study focused on OXTR SNP rs53576, and also on dopamine receptor 2 (DRD2) and serotonin receptor 2a gene (HTR2A). There was a positive association between A1 alleles of DRD2 and attachment anxiety, T alleles of HTR2A and avoidant attachment. In this study, no association was found between variants of rs53576 and attachment anxiety or avoidance, a finding later replicated by Chen et al., 2011, an experiment we reviewed above. In addition, authors stressed that the genetic polymorphisms studied explained less than 20% of the variance in attachment anxiety and avoidance (Gillath et al., 2008). In line with it, another study found no significant associations between attachment security (secure vs. insecure) and DRD4 7-repeat

polymorphism, -521 SNP and 5-HTTLPR. There were, however, strong associations between short polymorphism of 5-HTTLPR and attachment disorganization, only when mothers exhibited low responsiveness, suggesting gene-environment interaction (Spangler et al., 2009).

Attachment pattern was related to DRD4 SNP -521 in a sample of 114 infants, T allele carriers more associated to avoidant attachment, whereas C allele carriers to resistant attachment. 5-HTTLPR, COMT and DRD4 were not related to attachment patterns. Levels of HPA axis activation, salivary cortisol and alpha amylase concentrations, were also associated to DRD4 SNP -521: C allele carriers showed higher levels of those biomarkers (Frigerio et al, 2009). In a sample of human parents, DRD4 7-repeat allele was associated to attachment security, but only for individuals with unloving caregiver recollections, whereas no 5-HTTLPR polymorphism effect was found (Reiner & Spangler, 2010).

The largest sample ever used, with two attachment cohorts, took over a thousand genotypes, of DRD4 7-repeat allele, COMT Val/Met, 5-HTTLPR and OXTR rs53576 and rs2254298 alleles. The study showed dopamine, serotonin, and oxytocin systems were not related to attachment quality. The only association reported was between COMT Val/Met genotype and attachment disorganization, suggesting higher susceptibility to environment (Luijk et al., 2011).

2.4. Discussion

Studies reviewed did not show a consistent and straightforward relationship between polymorphisms and attachment patterns. Other independent variables related to social behavior were assessed, but also with mixed results. Evidence pointing at a moderating effect of DRD4 7-repeat gene, COMT Met allele, 5-HTTLPR short allele, OPRM1 A allele, OXTR SNPs rs53576 and rs2254298 and AVPR1a microsatellites in early adversity have not been replicated in the largest samples, what points at the need for more studies.

Evidence supporting differential susceptibility theory emerged in some experiments (Sheese et al, 2007; Pauli-Pott et al., 2009; Troisi et al, 2011b), but not in others (Barry et al., 2008; Kochanska et al., 2009).

Initially, these results may seem frustrating, since the original hypotheses of the review could not be proven in a significant and unequivocal set of replications. Nonetheless, closely examining the designs employed and results obtained, it can be seen that this research tradition gradually overcame limitations and improved methods in a sort of learning process. In order to truly prove or falsify initial hypotheses, these issues must be addresses in future research.

First, reviewed studies showed numerous limitations, and methods were clearly improved from the first ones to more recent ones. Most sample sizes were too small – exceptions made to Olsson et al. (2005) and Luijk et al. (2011).

In the earlier studies, no environmental measure was made; in the following ones, in most cases, measures were limited to assessing quality of parent-infant relationship or attachment, not accounting for severe early conditions. GxE research has shown that inconsistencies and lack of robustness among studies may be due to methodological fails in rigorously characterizing environments, and also to ignored moderation by not-yet identified variables – as in case of GxExG and GxExE interactions (Rutter, 2011; Rutter & Dodge, 2011).

A very interesting result by Chen at al. (2011) called attention upon the need to account for ethniticy, since it influenced not just the strength, but the direction of OXTR gene allele effects. Most studies did not consider ethniticy, what could also have influenced results. In addition, as Bakermans-Kranenburg & van IJzendoorn (2010) pointed out, not controlling for methylation patterns may have confounded results, since the assessed genes in previous studies could have been silenced.

All these limitations indicate that polymorphism studies on attachment behavior have faced many challenges, but they could still reveal interesting results if their designs are improved. It should be noted, however, that the spread of GWAS in the last years has undoubtedly shown that complex traits such as human behavior is usually the result of multiple genes, each with small effect sizes (Marian, 2012).

Another important remark is that besides polymorphism studies, other methods have revealed interesting findings on neurotransmitter systems and brain architecture concerning human attachment. These results may help sketching a clear picture on the role of these elements, and reveal extensive interactions between neurotransmitter systems.

Dopamine and serotonin interact in numerous ways. The role of dopamine in reinforcement learning has already been mentioned. A new wave of studies has suggested that besides dopamine, serotonin also plays a relevant role on decision making, possibly acting in an opposing manner to dopamine in tasks such as reinforcement processing, intertemporal choice, risk seeking, attention shifting and action selection (for comprehensive recent reviews, see Rogers, 2011; Cools et al., 2011; Homberg, 2012).

Studies have also shown neurotransmitter interactions in what could be characterized as a “social bonding” system in the brain. A significant body of work has suggested Dopamine-Oxytocin interactions regulate socio-affiliative behavior: receptor binding sites of oxytocin and dopamine tend to coexist in several brain areas related to the reward system, such as the striatum, medial PFC and VTA (Skuse & Gallagher, 2009; Skuse & Gallagher, 2011). In animal studies, the hypothalamus has been identified as an area where oxytocin receptors and gonadal steroids converge

(Baskerville & Douglas, 2010; Mayer-Lindenberg et al., 2011). It has been posited that infant cues, such as suckling, vocalization and tactile stimulation stimulate oxytocin release in the hypothalamus, which is connected to the NAcc, therefore activating the dopamine reward pathway and leading to behavioral reinforcing in parents (Strathearn, 2011). Serotonin-oxytocin interactions have also been reported in the amygdala-cingulate cortex circuit (Mayer-Lindenberg et al., 2011).

Opioids also seem to function in an integrated fashion with the dopaminergic system. In the ventral basal ganglia, NAcc is connected to the ventral pallidum/substantia innominata through the dopamine-enkephalinergic striatopallidal pathway, a circuit of D2 receptors involved in processing of aversive stimuli. COMT gene activity has also been associated to dampening of μ-opioid receptor actvity (Ribeiro, 2005; Way & Taylor, 2011).

Neuroimaging studies also provide an interesting account on what happens in the brain when parents and infants form their bonds. The neural substrates of parenting have been addressed by various fMRI studies. It has been shown that parent-infant interaction[12] activates areas related to reward (dopaminergic pathways in the striatum, NAcc, VTA, orbitofrontal cortex, thalamus), oxytocinergic circuits (amygdala, bed nucleus of stria terminalis, PAG), regions linked to face processing (fusiform gyrus), emotion regulation (PFC, ACC, insula) and memory (hippocampus) (Bartels & Zeki, 2004; Swain et al., 2007; Swain et al., 2008; Noriuchi, 2008; Strathearn, 2008). This body of research provide a fairly overview of systems activated in the parental brain.

All these interactions of neurosystems and brain areas suggest attachment systems are extremely complex at the neurophysiological and neuroanatomical levels (for an elegant synthesis, see Barrett & Fleming, 2011). Much research lies ahead, until its full comprehension can be achieved. Therefore, our review suggest a further

[12] Research has also been done with romantic attachment, and many overlaps in brain activation with parental attachment were reported. In both forms of attachment, areas rich in dopamine, oxytocin and vasopressin receptors were activated, whereas activity in cortical regions associated with negative emotions, as 'mentalizing' and social judgment was supressed (Bartels & Zeki, 2004; Acevedo et al., 2011).

refinement of the initial hypothesis, as shown in Figure 2.2, that could be demonstrated or falsified as new – and better designed – research take place.

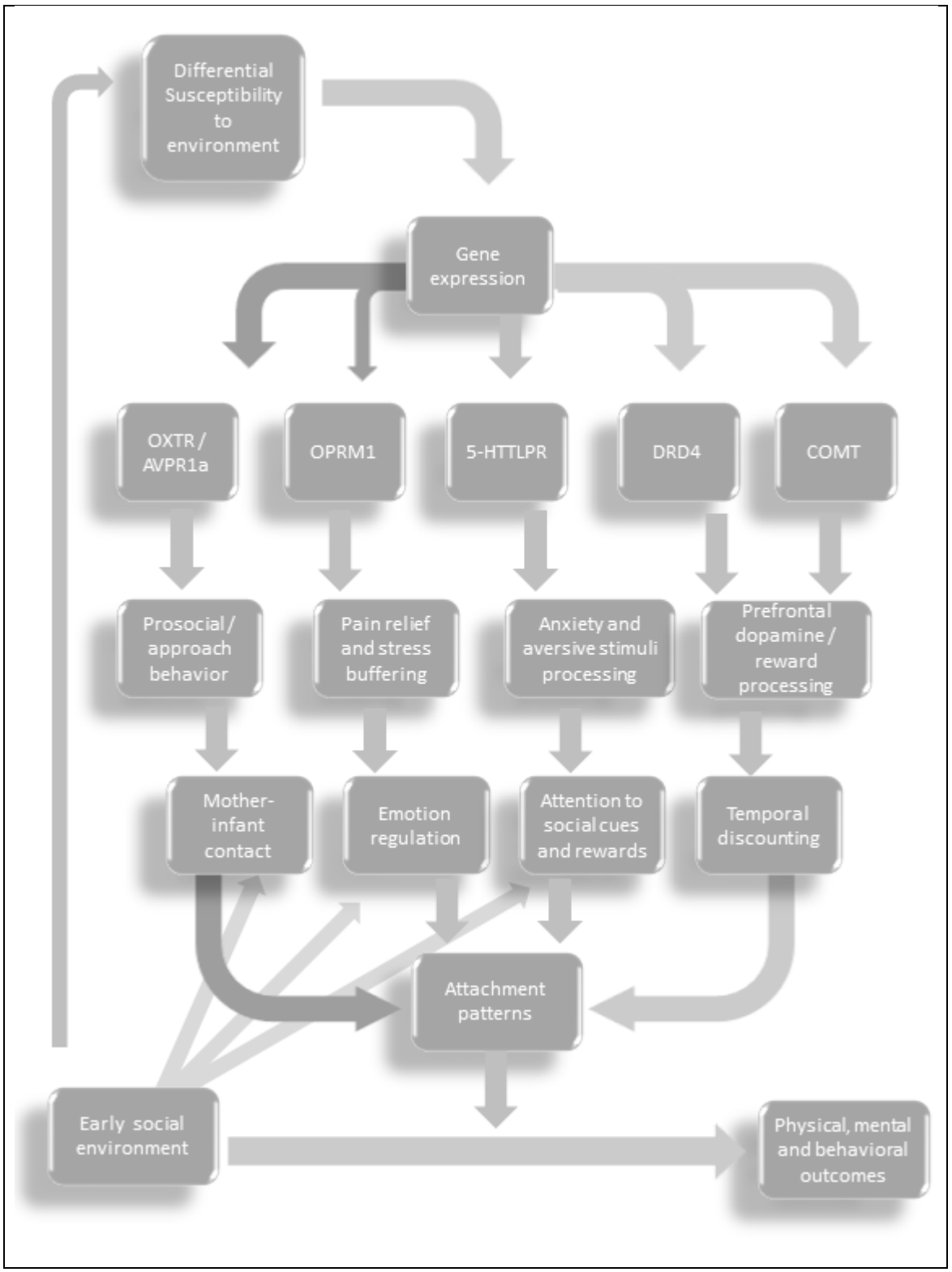

Figure 2.2. Gene expression and attachment-related neurotransmitter systems

2.5. Conclusions

Numerous neurotransmitter polymorphism studies in the GxE perspective have been made, both with humans and animals. Although several of them report GxE effects, replications have not been straightforward. Instead, ameliorations in research design seem to be necessary. Further studies may unravel how mechanisms underlying attachment behavior system, giving support to the differential susceptibility hypothesis and showing how specific genetic variations may predispose certain individuals to a higher permeability to environmental conditions.

Attachment interventions have a long history of use – and misuse (for a daunting account on the misuse of attachment theory in practice, see Allen 2011a, 2011b). However, Bowlby's theory played a major role in chaning how early care was viwed – residential nurseries and orphanages ceased to be be faced as fair solution for abandoned children, and the foster care and adoption started being preferred since it provided children with personalized care (Rutter, 2008). And in any case, attachment theory exerts a strong and widespread influence in the Neurosciences.

It has even been suggested that attachment goes well beyond the formation of social bonds among infants and caregivers, consisting in an integrated behavior system that, in an "extended" form, enabled humans to attach motivational significance to abstract ideas, cultural symbols and beliefs, playing a major role in altruism, cooperation and indirect reciprocity during evolution (Moll & Oliveira-Souza, 2009). Thus, attachment theory can be considered a good basis for formulating interventions aimed at first childhood.

In the following chapter, we turn to a more general approach on the use of evidence in early childhood policy, and discuss why policy formulation and implementation is far more complex than natural scientists may first figure.

3. Implications for policy: Brazilian federal policies addressed to early childhood since 1988

In the international debate, policies toward the first three to five years of life have received many names and distinct focuses. Terms such as Early Childhood Education (ECE), Early Childhood Care and Education (ECCE), Early Childhood Education and Care (ECEC), Early Childhood Care (ECC), Early Childhood Development (ECD) and Early Childhood Care and Development (ECCD) have all been employed, according to the emphasis given to educational, health or developmental intervention. Government Agencies or Ministries tend to act upon the specific aspect that concerns their legal attribution. This may result in policies tending not to consider child development as a whole and not actingupon the risk factors in an integrated manner (UNESCO, 2005).

This chapter aims both to assess the current situation and prospect of childhood policy in Brazil, and to bring some elements concerning the – in the accurate definition of Jack Shonkoff & Susan Bales – "messy process of policymaking", in which interest groups, scientific networks, politicians, bureaucrats and civil society engage in a "multidimensional process of debate, negotiation and compromise that results in a variety of explicit actions or implicit decisions not to act" (Shonkoff & Bales, 2011:28).

3.1. Theoretical framework: evidence-based policy

Recent calls have been widely made on the need to join together scientists, practitioners and policymakers in order to formulate and implement policies aimed to early childhood (for instance, Shonkoff, 2011). Similar opinions have been expressed in what comes to policies aimed at adolescents (Steinberg, 2009). Knowledge on the developing brain has growingly been employed as a tool for agenda-setting and drawing attention upon the need for early protection against stress and violence, environmental enrichment and educational improvements. This can be seen as some sort of *Zeitgeist*, considering the attention "Evidence-Based Policy" framework has received lately.

There are many theories in the social sciences aimed at describing structure and functioning of governmental organizations (Hill, 2009). Discussing which one is more accurate could be matter of a whole new thesis. Hence, we have chosen to adopt the description of government structure and action provided by network theory. In order not to interrupt the line of thought, we have summarized some essential features of network theory in Table 3.1.

Table 3.1. Government seen in a Network Perspective

Networks are non-hierarchical forms of collective action organization, in which transactions occur through networks of individuals engaged in reciprocal, spontaneous and mutually supportive actions. Information flows quickly, learning is more effective, and reciprocity norms may sustain cooperation in the long run. Network coordination can, but need not be formally instituted. In practical terms, policies do not emerge from governmental monoliths of highly organized and hierarchical departments, but are rather embedded in networks composed by numerous actors: public officials, politicians, interest and pressure groups, epistemic communities and policy entrepreneurs. In a highly complex world, given the vastness of existent Ministries and agencies, and the ever-growing need for coordination within the federal executive branch and with States and Municipalities, many policies are formulated and implemented in a network dynamic. A great challenge politicians and bureaucrats face is how to assemble, coordinate and work on conflict resolution within policy networks.

***Sources*:** Powell, 1990; Bonafont, 2004; Hill, 2009.

"Evidence-based policy" is a movement that gained momentum in the 1990's, especially in the United Kingdom. The idea was that government should spend resources in "what works", that is, in interventions that had proven efficacy. Social research and tools traditionally employed in health sciences, such as randomized control trials, systematic reviews and meta-analyses of experimental research studies could provide evidence that would inspire well-informed government decision making (Nutley et al., 2007).

To this end, databases on empirical research and its use in policy have been created. The Campbell Collaboration is perhaps the most well-known: the website gathers systematic reviews and meta-analyses of scientific research that can inform public policy in areas such as education, health and public security[13].

[13]Website: http://www.campbellcollaboration.org/.

A whole new field, often called “Neuroeducation”, has emerged as a result of neuroscientific findings that could be applied in the improvement of educational strategies (for an example, see Dias & Landeira-Fernandez, 2011).

The availability of research, however, does not say much about who produces it, and how it comes to be government action. The relationships between ideas and policies have been addressed by various models in policy literature (for a brief review, see Faria, 2003). The growing complexity of issues dealt by government officials, as well as the constant need for reliable information have broadened channels for scientists to influence decision making. In an insightful view, networks of actors that help articulate causal chains, formulate policies and reduce uncertainty surrounding a particular decision have been named Epistemic Communities (Haas, 1992).

An Epistemic Community is “a network of professionals with recognized expertise and competence in a particular domain and an authoritative claim to policy-relevant knowledge within that domain or issue-area” (Haas, 1992:3). Epistemic communities share normative and principled beliefs, causal beliefs on how to address certain problems, notions and criteria on what is valid knowledge, and also a common policy enterprise. That is to say scientists embedded in these communities not only agree on analytic and normative beliefs, but also share their commitment on a common agenda relative to policy issues. Since they congregate professionals that have expertise and reputation, epistemic communities have social power resources (Haas, 1992).

Epistemic Communities, however, need to translate their beliefs and prescriptions to politicians and government officials. This is no easy task: scientific publications are not always understandable by laymen; study results are often controversial; and not all of them are ready for translation into policy. Governments usually use various forms of knowledge, such as previous experience, common sense, political and ideological values. Policies have a greater chance of happening when they provide politicians with good electoral publicity. Budget cost is another significant limitation. Political leaders with a clear vision and leadership skills are not always

available for coordinating policy reform. Finally, organizations in general tend to resist change, and governments are no different (Bowen & Zwi, 2005).

Not surprisingly, “evidence-based policy” paradigm has faced many critiques. It has been pointed out that experimental research does not provide objective and definite answers; that it is naïve to conceive that governments will make decisions in a rational and scientific basis; and that science is just another factor influencing the decision making process. Ironically, research on evidence-inspired policies that were actually implemented has not shown so many benefits, and even indicated that in some cases they failed. Despite of this apparent early debacle, proposers of the evidence-based framework adjusted their expectations, adopted a more mature discourse and recognized that when it comes to policy, “evidence” is a label in which technical expertise and political power are entangled and dressed up in the guise of rationality (Nutley et al., 2007).

Remarks on its limitations made, “evidence-based policy” is the recognition that science has methods than can help understanding causal chains behind problems, solution finding and may also induce mentality shifts. More than just instrumental, research may have a conceptual use: it can aid the public, civil servants and politicians to have a better understanding of an issue; it may have a “consciousness-raising” role (Nutley et al., 2007).

An interesting example comes from a currently happening joint work by Harvard University and FrameWorks Intitute on bringing science and early childhood policy together. Their starting point was realizing that scientists are not always willing to engage in the policy debate – because research is not ready for translation, or because they do not want to mingle scholarship and advocacy, or even for fearing being accused of publicity-seeking. At the same time, they perceived that politicians and government officials tend to make their decisions according to common sense views that do not convey accurate descriptions of reality. On the contrary, as ordinary people, they tend to use simplistic metaphors that not only are uninformative about causal mechanisms, but can also result in misguided policy. Facing this diagnosis, these researchers decided to empirically asses what misconceptions are these; to

systematize available and uncontroversial scientific findings into a simple and easily understandable model; and to test if this model can actually be learned by laymen. In sum, they created a simple, but evidence-based narrative, in order to best inform the public debate on early child brain development – the result can be seen in Appendix II. Their aim is to influence society and government decision, without giving away scientific rigor (Shonkoff & Bales, 2011).

Last but not least, even if a good policy formulation emerges in an evidence-inspired basis, it not necessarily will be part of government's agenda: maybe it will never be implemented. Before we follow to the next section, we evoke a highly popular theory in policy literature to illustrate this point: Jon Kingdon's "Multiple Streams Model" (Kingdon, 1995).

Kingdon's intent was to overcome the distance between policy theory and practice. To this end, he made an empirical research with politicians, government officials and relevant actors in order to understand what actually happens in the policy process. He was inspired by the "garbage can" view of Government, according to which it is a fairly chaotic organization, where problems, decision makers and choice opportunities have independent and not necessarily coincident flows (Kingdon, 1995; Hill, 2009). The basis of his theory is that Government agenda setting depends on multiple streams.

The multiple streams are in fact three: problems, policy and political. The stream of *problems* concerns the matters that are considered as such by the public opinion: people's attention usually shift toward a particular issue if media coverage is intense, if there is a crisis or disaster, or if indicators that assess a given situation (e.g. educational indicators) are too bad. Problems may be defined in many different ways – and may even not be perceived as such. The second is the *policy* stream: the whole of proposed solutions and alternatives to deal with certain issues. There is a competition between policy communities to show that their solution fit best: it may be technically feasible or not; it can run against ideological values; if too expensive, budget constraints can render its implementation unlikely. The last one, the *political* stream, changes according to the national mood, electoral cycles and the dynamics of conflicts

in Congress and Personnel turnover. Presidential and parliamentary terms end, politicians may be pushed by pressure groups, political forces and bureaucrats backing or opposing an agenda may lose or gain power (Kingdon, 1995).

Interestingly, as the streams are independent: it may happen that there are policy alternatives available, but the matter it addresses is not perceived as a problem; there may be problems without possible or viable solutions; good policies for real problems may be proposed, but political forces can act in a way not to let it happen (Kingdon, 1995).

“Policy windows” emerge in very specific moments in which all three streams converge in a favorable way; these are the most appropriate moments for change. Kingdon reminds, however, that windows do not remain open for a long time (Kingdon, 1995). Therefore, scientists integrating epistemic communities should have in mind that inserting policy in the agenda is a matter of numerous streams, which may or may not converge depending on its timing.

3.2. Brazilian legislation and policy on child protection since 1988

The legal treatment directed to children in Brazil has traditionally been linked to criminal issues. Previous laws aimed at children and adolescents followed the "irregular situation doctrine", and were concerned about those in "irregular situations", as to say, those who committed some sort of crime, or that came from disrupted homes, wandered in the streets and could represent danger to public order[14] (Frota, 2008). At best, their aim was to prohibit child labor[15]. Not until the end of the 20th century did legislation start to consider children and adolescents as citizens and bearers of rights (Faleiros, 2005). Only in 1992 was the formal distinction between legitimate and illegitimate children – in other words, between those born within a legal marriage and, in the literal sense, "bastards" – abandoned[16].

This slow evolution was due to cultural change both in global and local perspectives. In 1959, United Nations Resolution 1386 adopted the Declaration of the Rights of the Child, which guaranteed social rights and protection against harm and discrimination. It was followed by the 1989 Convention on the Rights of the Child, promulgated in Brazil by Decreto nº 99.710, de 21 de novembro de 1990, also containing norms on child protection and assistance, education, health and protection against all forms of violence.

During the redemocratization process, several groups of civil society gathered and struggled for a better child protection framework. As a result, the 1988 Constitution innovated and displayed, in article 227, a conception of children and adolescents as bearers of civil and social rights, which should be guaranteed by the State and family alike. Two years later, Congress passed another revolutionary bill: *Estatuto da Criança e do Adolescente* (ECA). Its first article states: "this law is about full

[14] For a good notion of this narrow view, we recommend reading Lei nº 6.697, de 10 de outubro de 1979, the law predecessor to ECA. See also Frota, 2008.

[15] As in Decreto nº 1.313, de 17 de janeiro de 1891, that first prohibited child labor under age of 12. However, this bill allowed eight-year-old children to work as apprentices. But it gets worse: this norm was circumscribed to industrial plants and was applied only to Rio de Janeiro, nation's capital then.

[16] Lei 3.071, de 1º de janeiro de 1916, the previous Brazilian Civil Code, stated that "O parentesco é legitimo, ou ilegítimo, segundo procede, ou não de casamento", that is, parenthood is legitimate if it originates from legal marriage, otherwise it is illegitimate (article 332, revoked by Lei nº 8.650, de 29 de dezembro de 1992).

protection of child and adolescent". Social scientists have long called attention upon the Full Protection Doctrine, according to which children and adolescents are entitled with fundamental rights of physical and mental integrity, socioemotional and cognitive development, protection against every form of harm or violence, and that government should consider them as whole citizens (Bezerra, 2004; Frota, 2008).

Following ECA, a government protection system emerged. The law obliged members of Brazilian federation to create deliberative and administrative councils – Municipal, State and National rights councils and tutelage councils – as well as funds that would direct resources to child protection policies. The national rights council – *Conselho Nacional de Direitos da Criança e do Adolescente* (CONANDA) – was created by Lei nº 8.242, de 12 de outubro de 1991, and in the following years, states and cities gradually instituted their own councils. Other institutions, such as police –*delegacies especializadas* –, judicial – *varas da infância, promotorias da infância, defensorias* –, and administrative – *conselhos tutelares* – rapidly adapted to law requirements and specialized in child protection[17].

In 1995, Brazilian federal government addressed child protection from two lines of action: *Política de Promoção e Proteção Integral da Infância e da Adolescência* and *Comunidade Solidária*[18]. The first one was focused on child labor, drug abuse and criminal issues, whereas the second was aimed in social action to reverse poverty and vulnerability situations. By the same time, in 1994, a highly successful policy was conceived: *Programa Saúde da Família*, which provided high-risk communities with basic health assistance by teams of multidisciplinary professionals. Importantly, these policies were all focused on a more vulnerable public, not intending to be universal (Mendonça, 2002).In contrast, universality was attempted in child education. In the 1990's, school attendance grew in a fast pace – in 2002, 97% of children between 7 and 14 years went to school, even though this rate dropped to 36,5% when it came to children below 6 years old (Faleiros, 2005).

[17] In 2009, according to IBGE's Munic - Pesquisa de Informações Básicas Municipais, a research on Brazilian municipalities, out of 5.565 cities, 98,3% hadConselhos Tutelares,and 91,4%had Conselhos de direitos da criança e do adolescente.

[18] Importantly, other attempts to launch federal policies on child protection have been done earlier, such as *Projeto Minha Gente* (1992) and *Programa Nacional de Atenção Integral à Criança e ao Adolescente – Pronaica* (1993). It could not be stated, though, that they had much of a success.

Table 3.2. Relevant laws on child protection since 1988

Year	Name	Main subjects
1988	Constitution of Federative Republic of Brazil	Enunciates civil and social rights of children and adolescents, as well as State, society and family duties toward them; fixates criminal responsibility at age 18; prohibits labor below age 16. Determines a 4-month maternal license.
1990	Child and Adolescent Statue – ECA (Lei nº 8.069)	Enunciates civil and social rights of children and adolescents; guarantees family and community coexistence; establishes rules for child institutionalization, adoption and custody; it also brings criminal issues and creates government institutions aimed to child protection such as *Conselhos Tutelares*.
1990	UN Convention on the Rights of the Child (Decreto nº 99.710)	Enunciates basic rights of children, and obliges governments to protect them.
1992	Parental testing (Lei 8.650)	Regulates the use of DNA proof of paternity in court.
2002	New Civil Code (Lei nº 10.406)	Updates civil legislation concerning family, custody and adoption issues, according to the principles of the 1988 Constitution.
2006	Early education (Emenda Constitucional nº 53)	Guarantees basic free education to all children and adolescents from 4 to 17 years. Reduces school entrance age from 6 to 5 year old children.
2008	Joint Custody Law (Lei nº 11.698)	Creates the possibility of joint custody in case of parent separation or divorce.
2008	Expansion of Maternal License (Lei 11.770)	Provides stimuli for maternal license expansion to 6 months in private companies. But it is not mandatory.
2008	Law on Child Support during pregnancy (Lei nº 11.804)	Obliges fathers to provide child support during pregnancy (*alimentos gravídicos*).
2009	New Law of Adoption (Lei nº 12.010)	Limits child institutionalization to a maximum of 2 years, unless exceptional circumstances; prevents siblings from being adopted separately; creates a National Adoption Register.
2010	Parental Alienation Law (Lei nº 12.318)	Establishes means of child protection in case of parental alienantion.
2011	National Register System on Pregnant Women and Mortality Prevention (Medida Provisória nº 557)	Creates a universal National Register of all pregnant women; gives cash transfers to poor women to make pregnancy health exams.

Notes: This is an author selection, and is not an exhaustive list. All laws mentioned above can be found at http://www4.planalto.gov.br/legislacao.

Table 3.2 gathers some legislation relevant to child protection enacted in the last two decades.

In the year 2000, 189 countries, including Brazil, committed themselves with the Millennium Development Goals, which were turned to the areas of poverty and child mortality reduction, education, child and maternal health, HIV/AIDS combat, environment and development, until the year 2015 (see Appendix II). As most of these goals were clearly aimed at child well-being, a UN Report set a specific strategy for

government action toward them (Nações Unidas, 2002). Statistics have shown that Brazil has advanced more rapidly in reducing child mortality and undernourishment than necessary to fulfill Millennium Goals (Brasil, 2011b).

A great impact on early adversity was achieved through *Programa Bolsa Família*, a conditioned cash transfer policy that has received widespread attention of international agencies and foreign governments. Recent studies on health statistics reveal that indicators such as child mortality and undernourishment steadily declined in the last two decades, because of better health assistance, spreading of vaccination and breastfeeding, improvement of sewer systems, and also due to the better income of more vulnerable families. It is noteworthy that this amelioration of social indicators has contributed to the decline of inequality, since poorer family groups were more strongly benefitted in this process (for a good overview, see Paes de Barros et al., 2010). Researchers point out, nonetheless, that this undeniable progress is positive, but that Brazilian reality is still very far away from developed countries (Victora et al., 2011).

Numerous programs have been launched in the last years, focusing on specific aspects of child protection. *Programa de Erradicação do Trabalho Infantil* (PETI), launched in 1996, addressed child labor. *Programa de Ações Integradas e Referenciais de enfrentamento à violência sexual contra crianças e adolescentes no território brasileiro* – PAIR, created in 2003, aimed at sexual exploitation of children. In 2007, two educational policies directed to children followed: *Mais Educação*, an expansion of full time public schools; and *Programa Nacional de reestruturação e aquisição de equipamentos para a rede escolar pública de Educação Infantil* – Proinfância, intended to help States and Municipalities to build and improve public Kindergartens. For vulnerable families and their children, Social Assistance has been reinforced through the dissemination of *Centros de Referência de Assistência Social* (CRAS) and *Centros de Referência Especializados de Assistência Social* (CREAS)[19], where *Programa de Atenção*

[19] According to the Ministry responsible for Social Assistance, *Ministério do Desenvolvimento Social e Combate à Fome* (MDS), in 2011 there were 7.638 CRAS and 2.102 CREAS in Brazil (data from Censo SUAS 2011, available at http://aplicacoes.mds.gov.br/sagi/censo2011/auth/index.php). CRAS offer basic social assistance services, whereas CREAS are focused on more specialized and complex services, usually in the context of violence and violation of rights. See Lei nº 12.435/2011.

Integral à Família – PAIF and *Serviço de Proteção e Atendimento Especializado a Famílias e Indivíduos* – PAEFI take place. As for 2011, *Rede Cegonha* was created, a health program turned to pregnant women and infants.

Integrated government action has been planned. A National Plan aimed at the right for familiar and communitary coexistence was elaborated by the participative councils, emphasizing social assistance: *Plano Nacional de Promoção, Proteção e Defesa do Direito de Crianças e Adolescentes à Convivência Familiar e Comunitária*. One of its principles is that families should be supported and have their autonomous decisions respected, children should leave problematic homes only in a temporary basis, and that institutionalization and adoption should always be extreme measures, since they take the children out of their original sociocultural environment (Brasil, 2006). CONANDA has recently approved a document that serves as a guideline for child and adolescent human rights, prescribing strategic goals concerning the strengthening of government institutions aimed at their protection: *Plano Decenal dos Direitos Humanos de Crianças e Adolescentes* (Brasil, 2011a).

It is thus easy to realize that much has been done by the federal government in the last two decades. Importantly, though, all these programs focus on one specific social area – health, education, social assistance, protection against violence – and involve one or some federal Ministries. No official federal policy has since been conceived uniting all aspects of child protection and Ministries of the social area, and attempts of intersectorial coordination still seem feeble (UNESCO, 2005).

The problems with implementing different policies focusing on the same public by different Ministries are well-known in the policy literature. The excessive administrative divisions (departmentalization) tend to create "tunnel visions" – bureaucrats tend to export their problems away and defend themselves –, redundancies – two or more different units may perform the same actions –, lacunae – when no one is responsible for some significant activity – and incoherence – policies directed to the same public exhibit conflicting goals or different requirements (Hood, 2005). This seems to be precisely the case when it comes to policies for early childhood.

The current debate within federal government glimpses a change in this situation, considering the unification of policies toward early childhood. Jon Kingdon would call that a “window of opportunity”.

3.3. Political and institutional constraints on a unified federal program focused on early childhood

Every discussion on what is the best way to implement social policy in Brazil must consider a fundamental institutional reality that constrains possibilities of government action. In this section, we present natural scientists to the confusing and problematic world of government issues, and then bring elements concerning the current status of this debate.

Brazil is a Federation, composed by the Federal Union, 26 States and a Federal District, and finally 5.565 Municipalities. All of them are autonomous – each with legislative and policy attributions that are either specific or common to all. Political science has pointed out that Federations tend to show more *veto players*, that is, more actors that can successfully oppose reform attempts (Arretche, 2009).

Particularly in the Brazilian system, the Union often legislates over several subjects concerning State and Municipal action. In other words, in practical terms the Union has the power and authority to rule over courses of actions and policy implementation that are responsibilities of States and Municipalities (Arretche, 2009). Since 1996, numerous changes in tax legislation resulted in centralization of revenues in the Union, while States and Municipalities have grown more dependent on the federal budget (Riani, 2009). As a result, even though the Constitution guarantees their autonomy, State and Municipality action tend to be heavily influenced by federal legislation, policy and money. In addition, the Constitution brought few incentives on cooperation and action coordination between members of the Federation (Gaetani & Abrucio, 2006).

It can be said that in social policy, agenda setting and formulation usually start within the federal government, but its success essentially depends on States and Municipalities, which are responsible for implementation and execution (Arretche, 2006). A good example of Cooperative Federalism comes from the already mentioned *Programa Bolsa Família*: the Union has the budget for the conditioned cash transfers,

but the implementation of the policy relies heavily upon States' and especially Municipalities' management (Sposati, 2009).

This conception draws on the successful experience of *Sistema Único de Saúde* – SUS. Since the 1970's, civil society self-organized in a variety of forms and because of a myriad of themes. Brazilian health professionals formed networks that started struggling for a free and universal health system, in which assistance was a right and a government obligation toward citizens. Their action during the redemocratization process led to the achievement of having a Health Section in the Constitutional text, as well as a fundamental law – Lei nº 8.080, de 19 de setembro de 1990 – that institutionalized a public unified system in which Union, States and Municipalities were all responsible for guaranteeing the right for health. Financing and management of this system is made by all members of the Federation, each having specific obligations: the Union sets general regulations, whereas States and Municipalities are closer to the reality and needs of citizens. Other relevant principles of SUS are decentralized management and popular participation, which help dealing with regional idiosyncrasies, as well as specific problems that emerge in the daily relationships with the public (for a good review on history and structure of SUS, see Paim et al., 2011). Even though numerous problems and challenges persist (Menicucci, 2009), SUS has served as a model for numerous other attempts to establish nationwide systems of cooperative federalism[20].

On the other hand, Federalism may bring interesting elements. It has been suggested that subnational entities may play the role of policy innovation laboratories: state-level and municipal-level policymakers could attempt new policy designs, which, if well-succeeded, could be expanded nationwide by Federal government (Olsen & Peters, 1996). That seems to be the case in early childhood policy, in which numerous examples arise[21].

[20] Two of the most recent examples are *Sistema Único de Assistência Social* (SUAS), instituted by Lei nº 12.435, de 6 de julho de 2011, and *Sistema Nacional de Atendimento Socioeducativo* (Sinase), created by Lei nº 12.594, de 18 de janeiro de 2012.

[21] To name a few examples of State-level programs: "*Primeira Infância Melhor*", in Rio Grande do Sul; "*Asinhas da Florestania*", in Acre; and "*Mãe Coruja*", in Pernambuco. As for Municipal-level policies: "*Nova Semente*", in Petrolina/PE; "*Mãe Curitibana*", in Curitiba/PR; "*Trevo de Quatro Folhas*", in Sobral/CE; "*Brasileirinh@s de Floripa*", in Florianopolis/SC; "*Naves-Mãe*" in Campinas/SP; "*Mãe*

Another fundamental constraint to policy implementation comes from Brazilian political system. The combination of a presidential multiparty system, with legislative elections held with the proportional electoral method, established in 1988 Constitution, results in an institutional arrangement that came to be known as Coalition Presidentialism. In short, popular voting for the Legislative is dispersed among many parties; as no party can successfully win both elections to the Executive Office and to the majority of chairs in Congress, Presidents depend on a handful of parties to form majority and pass bills. Then coalitions have to be structured, often giving in Ministries of the Executive branch to allied parties, what influences government dynamics. Several studies have focused on how Presidents have powers such as constitutional prerogatives and control over public budget that guarantee a highly disciplined and compliant Congress (Inácio, 2006).

Brazilian Presidents have many power resources, but they are still limited by the Judicial branch, political leaders from States, as well as the need to find room for coalition parties in the Ministries of the Executive (Amorim Neto, 2007). Coalition Presidentialism has been characterized as an ordinary functional political arrangement (Limongi, 2006), but also criticized for inefficient decision making, a tendency to analysis paralysis and even for facilitating political corruption (Rennó, 2006; Amorim Neto, 2009).

What is relevant is to consider that no nationwide policy can be formulated and implemented easily by the Executive, since it usually depends on Legislative bills that need approval of several parties and political forces. Besides these political costs, control institutions, such as *Tribunal de Contas* and *Ministério Público* often take action to question decisions from the Executive that are considered misguided or illegal. As a reflex of the constant increase in political conflicts that end up in court, a literature on "Judicialization of Politics" has emerged (for an example, Vianna et al. 2007). Even if the Legislative and Judicial branches were not important *veto points*, there would still be constraints within the Executive branch itself. The challenge of government coordination is far from being trivial. Three Ministries, *Casa Civil*, *Ministério da*

Paulistana" in São Paulo/SP; "*Cegonha Carioca*" and "*Primeira Infância Completa*", in Rio de Janeiro/RJ. See Brasil, 2011.

*Fazend*a and *Ministério do Planejamento, Orçamento e Gestão* form a "triangle" through which every major policy formulation must first pass. However, the volume and complexity of demands overflow their possibilities of coordination (Gaetani, 2009).

Not to say that good policy formulation not always results in decent policy implementation. Policy theorists and practitioners are well acquainted with Michael Lipsky's "street-level bureaucrats": government workers that are directly in the front line of policy execution, who turn out to follow methods and routines to deal with daily problems and uncertainties that ultimately shape how policy will be (Hill, 2009). In other words, high-level Brasília bureaucrats are far from having control over what State and Municipality public servants in direct contact with citizens do.

Despite of this grim prospect, early childhood is clearly in a convergence of streams that favors its entrance in the political agenda. There is a widespread conviction that investing in early childhood is a highly necessary and efficient policy. This chapter has already shown that the current scenario is composed of a sum of variables that favor policy transfer, that is, the enrichment of policy arena with new ideas and programs: the emergence of an international consensus, the support from numerous internal and external agencies and non-governmental organizations, the action of policy entrepreneurs, subnational laboratories of policy experiences (Dolowitz & Marsh, 1999). What needs government decision is setting basic strategies of action, as well as addressing some unresolved issues. Evidence-based policy may help disentangling the complexity involved in these delicate steps.

When it comes to attachment theory-based interventions, decades of research have inspired diffent therapies. Interventions usually focus on supporting attachment security in parent-infant dyads. The methods usually aim at providing parents with better skills to deal with their infants, stimulating more sensitive and responsive parental behaviors, and also on altering parental internal working models of attachment. The targets are foster parents, high-risk multiproblem families, maltreated children, or juveniles on criminal justice programs. Results are encouraging,

especially due to long-term positive effects (for a review of methods and attachment programs, see Berlin et al., 2008).

A meta-analysis on 70 studies of attachment interventions (n=1.503) revealed interesting findings: early intervention on parental sensitivity and on infant attachment security proved to be effective in a wide range of populations; type and timing made a difference: the most effective interventions did not consist of a large number of sessions. Actually, brief interventions were more effective than long-term ones (Bakermans-Kranenburg et al., 2003).

Reasons for this have been hypothesized: longer treatments take time and energy away from the goal; more brief intervention has a clear focus and well-defined, modest aims; simpler designs are easier to be implemented by the intervener; and finally, adherence is easier to accomplish (Bakermans-Kranenburg et al., 2008b).

These are good news for policymakers, since policies that have simpler designs may be less susceptible to implementation problems. To date, however, no federal policy has focused specifically on attachment intervention.

This does not mean that attachment bonds between children and parents could not benefit from the federal policies already in course. If the framework outlined in chapters 1 and 2 is correct, government programs aimed at improving child feeding, health and nurturance quality, as well as diminishing domestic violence, all contribute to turn hostile early environments into better ones. In this manner, specific behavioral or neural systems are indirectly targeted, generating conditions that lead to secure attachment patterns, and consequently lead children to develop positive social information processing, future-oriented and less impulsive behaviors, and reproductive strategies that favor quality over quantity. In this perspective, Attachment Theory can provide extra knowledge on how policies aimed at low-socioeconomic status and risky environments can bring lifelong-lasting benefits to children.

Attachment research can also provide important insights into the challenges faced by institutionalized children. Studies have long shown that institutionalized

children tend to show deficits in motor development and experience delays in cognitive functioning and language development, in addition to atypical social behavior and disrupted attachment patterns (Loman et al., 2009; Reeb et al., 2009). It has been found that adopted children or children in foster care can form attachment relationships to new caregivers (Dozier & Rutter, 2008). However, post-institutionalized children that have experienced severe maltreatment often carry persistent change in neuroendocrine systems and brain functioning (Fries et al., 2008; Reeb et al., 2009).

A recent meta-analysis of foster and adopted children studies has confirmed Bowlby's suggestion that adopted children can overcome early adversity and form bonds with new caregivers. Adopted children display considerably less disorganized attachment than institutionalized children, and, importantly, children who were adopted after their first birthday are less capable of developing secure attachments (van den Fries et al., 2009). Adoption can thus be seen an effective intervention, as long as it occurs early.

In Brazil, data on institutionalized children indicate that orphans are a minority. A national survey in 2003 with nearly 20 thousand institutionalized children pointed that around 80% of them do have families. However, their profile revealed a situation of social vulnerability: 63% of them were black, of which 68,2% came from homes with a monthly income of less than ¼ minimum wage. The most common causes of institutionalization were poverty (24,1%), abandonment (18,8%) and domestic violence (11,6%). Half of them had been institutionalized for more than 2 years (Silva, 2004).

In this reality, then, most children are out of their original homes because of deprivation and lack of a stable relationship between parents. Hence, policies toward early childhood must focus on high-risk families, so as to avoid institutionalization. If institutionalization happen, however, the priority must be avoiding it will endure for a long period. Federal government already follows these principles, but there is still much to be done. The creation of a national register is a good policy in this sense.

There is a proposal of new approach to early childhood policy currently in debate (Brasil, 2011). Based on the work of IPEA economist Ricardo Paes de Barros, the idea is explicitly evidence-inspired, and aims to establish a single, nationwide policy.

In a nutshell, the plan is focused on infants up to three years old. A unified system, such as SUS, would be created, so as to register and identify vulnerable families. There would be reference centers for families, aimed not only at health and social assistance, but also child development. Customized service would be available for each parent and child, in this center, but also through home visits made by a multiprofessional team. Each child would have a unified file, containing data on physical, cognitive, and socioemotional development that would render progress evaluation possible. The emphasis would be in prevention and protection, but also in development and incentives. Finally, Kindergartens would be evaluated according to established parameters (Brasil, 2011).

This program proposal seems fairly coherent with what research has pointed as potential targets of government action. It is highly uncertain, nevertheless, that such an ambitious plan could prevail without a clear strategic-level decision to treat it as a government priority. In addition, unified systems are not simple arrangements to implement in a Federation like Brazil. Political and institutional constraints should not be underestimated by its proponents.

4. Conclusions: genes, brain, environment and policy – Brazil and child protection in the post-genomic era

Since the full sequencing of the human genome, in 2001, much has changed. It can be said that we are currently in a Post-Genomic Era (Carvalho et al., 2009; Charney, in press).

The available body of research on genetics, due to new technologies and growing data reveal an increasing complexity of models and explanations on how the information contained in strains of DNA turn out to compose and regulate living organisms. We now know, for instance, that simply mapping the human genome does not account for the causes that originate complex traits. A new flood of GWAS in the last years has shown that associations among genetic variations and behaviors explain only a small proportion of the phenotypic variance. In addition, a single genetic change may affect more than one phenotype, what is known as *Pleiotropy*. There are many causal chains linking the genome, internal phenotypes, external phenotypes, and environment, and for this reason, phenotypes are in constant change. Beholding this situation, some scientists now claim that we should map the Human Phenome, the same way which was done in the 1990's concerning the human genome (Houle et al., 2010).

However, this search for better models of causation, linking distinct levels of analysis, from molecules within cells to traits such as behaviors, depends not only on mapping the internal and external phenotypes, but also on understanding the mechanisms between each level. Gene expression leads to the RNA transcripts that form the Transcriptome, and the field of Epigenetics has still much to discover on how this works. Research advances are also needed in exploring how the Proteome and the Metabolome come out to be according to post-transcriptional and regulatory phenomena (Houle et al., 2010; Carvalho et al., 2009; Hunter & Borg, 2003). And there are still further challenges: it is necessary to uncover where exactly in the brain, or in the rest of the body, that certain proteins are found, considering a spatio-temporal dynamics. Cell, tissue and organ structure and function form the Physiome, which is essential for the comprehension of the biological organization. Several projects have

been launched to address each of these explanatory levels (Hunter & Borg, 2003; for the brain's transcriptome, see, for example, Kang et al., 2011).

This emerging picture of complexity involving interactions in multiple levels of analysis linking genes to behavior demand a holistic approach (Bateson, 2010). Causal mechanisms underlying human behavior belong to several different orders of complexity, and cannot be understood simply neither in socioeconomic or cultural terms only, neither ignoring genes, brain and mental representations (for a courageous synthesis, see Elster, 2009). And hence the consequences of early hostile environments must be searched not only in genes, but in contextual factors as well.

Recent empirical research in sociology has shown that there are strong cultural differences between the poor and low middle-class and high and high-middle class in Brazil. According to its results, there is a different social reproduction of values – such as the importance of discipline, self-control, social abilities, prospective thought, to avoid violent solutions for conflicts and premature sexual behaviors – within families of low and upper classes, that is, different access to symbolic values and cultural capital. Upper class families teach their children how to behave in social and professional environments, and also that they are important as persons – they learn to have self-esteem. On the other hand, lower class families generally do not have means, for instance, to teach their children the importance of education, of reading books (since the parents themselves never had these opportunities or habits). Early sexual initiation is also a feature often culturally stimulated in lower classes. Uneven familial inheritance of these values mean, in the long run, that good jobs and higher social positions are unequally distributed in Brazilian society, which reinforces a historical chasm between privileged and marginalized social classes (Souza, 2009).

These findings converge with extensive neurobiological research on socioeconomic status (SES)[22] and brain consequences. Low income homes usually congregate risk factors such as familial conflict, low quality parental care, harsh and inconsistent discipline, stress and unhealthy nutrition. Studies have shown that

[22] SES is a complex construct, and its measurements are still somewhat controversial. For a review of the discussion on research methods linking brain structure and function to SES, and also challenges and trends, see Hackman & Farah, 2008.

growing up in families with low SES has consistently been associated with worse physical and mental well-being, higher rates of depression, anxiety and externalizing behaviors, as well as poor cognitive development and low IQ and academic achievement. Living in poverty in childhood impairs language skills and executive functioning. Importantly, the earlier the experience of poverty, the stronger are the impacts. Neurobiological mechanisms behind this cause-effect chain are gradually being unraveled (Mustard, 2010; for a review, see Hackman et al., 2010).

The current challenge is to formulate and implement a policy that could intervene in early adverse environments. Contrary to what some "biophobical"[23] social scientists think, biological research provides evidence that reinforces the need for environmental intervention. Since neurobiological research shows that early adversity has effects upon language, cognitive and socioemotional development, stress and immune system function, gene expression, physical and mental health (Mustard, 2009), it serves as an extra argument for the importance of social and cultural environment, not the opposite.

Another important consequence is that scientific evidence may help people understand better mechanisms underlying the developmental process. Gene-environment interactions are good examples of biological research calling attention on the need of environmental change. This point has been precisely exposed by Caspi and coworkers:

> "**Public Understanding of Genetic Science**
> One of G × E research's important contributions is often overlooked by scientists: teaching the falsehood of genetic (and environmental) determinism (Moffitt, Caspi, & Rutter, 2006). For over a century the public has been fed a diet of determinism, beginning with early 20th-centuryeugenics policies to correct all human flaws by culling the breeding stock. Midcentury opinions swung back toward naive environmental determinism, exemplified by B. F. Skinner's 1948 Walden Two. In the late 20th century, public opinion was compelled toward

[23] In Brazilian Academia, "biophobia" (a term popularized by anthropologist Walter Neves; see Neves, 2007) is a curious and widespread phenomenon, especially in the social sciences' fields such as sociology, psychoanalysis, social psychology, law and anthropology. According to this prejudicial view, every attempt to associate behavior to genetics has to do with eugenic ideas spread in nazi Germany (Correa & Rocha, 2008). Usually, biophobical social scientists see the biological sciences as extremely deterministic, due mainly to their ignorance on the current discussions on natural sciences. At the same time, though, they often accept social deterministic models.

> genetic determinism again when high heritability estimates were taken to imply that nongenetic factors have little importance for mental health and behavior. Discoveries of single mutations causing rare disorders strengthened the public's belief that knowing one's genetic makeup is tantamount to knowing one's future. Deterministic beliefs, environmental or genetic, are dangerous. Determinism encourages policies that violate human rights (at worst) and waste resources on ill-conceived mental health improvement programs (at best). Media coverage of this century's new findings of G × E interaction (and environmental effects on gene expression) is persuading the public to embrace a more realistic, nuanced understanding of the causes of behavior, in which some genes' effects depend on lifestyle choices that are often under human control."(Caspi et al., 2011:46)

Another fundamental issue that has raised some debate is how research design can serve translation of science into policy. Besides the political and institutional conundrum related to evidence-based policy formulation briefly described in chapter 3, the way science is done may need some adjustment too. Experimentation in laboratory settings may seem a good and rigorous way of isolating variables – but that is precisely the point. When human subjects are taken out of their community contexts, many factors influencing their behavior are also wiped out. Behavioral phenomena are embedded in contextual circumstances, and the former change as the latter does. Therefore, generalizability of laboratory experiments may be compromised. For this reason, Kenneth Dodge has suggested a paradigm shift, arguing entire-community studies should be pursued due to higher ecological validity of findings (Dodge, 2011).

Truly interdisciplinary research on early environment, that is, joining social and natural scientists alike, is still a rare, if not inexistent, venture. Clear definitions of child maltreatment, rigorous environmental measures, a taxonomy of stressful life events, a multilevel causal model of early adversity and adult outcomes are all still absent. Social scientists resist collecting DNA samples, whereas natural scientists do not have adequate tools for sociocultural realities that shape human behavior. Based on this still foggy scenario, it may be too soon to suggest large intervention proposals, or worse, some sort of social or environmental engineering (Dodge & Rutter, 2011). We can

conclude the same scientists usually do after discussing their experiments: more studies on gene-environment interaction related to early adversity are needed.

As conclusion for this interdisciplinary venture, we synthesize below five principles that, in our view, should inform evidence-based policy debate in Brazil concerning early childhood.

- Epigenetic enquiries have shown that environmental and genetic factors are intertwined. There is no reasonable motive for maintaining an abyss between social and natural scientists when it comes to human behavior. Research should be conducted by interdisciplinary teams able to consider genetic and neurophysiological methods and theories, but also social and cultural factors.
- Environments matter. Therefore, a better understanding on how individuals experience their effects is fundamental for scientific models of human behavior. Since governmental action or inaction influences citizen's environments in various ways, publicly funded research in GxE effects and dynamics should be stimulated. Longitudinal and cross-cultural designs in large community samples, with rigorous and accurate environmental measures, should be undertaken.
- Translating evidence into policy is not an easy process, and depends on many actors within the political system and in civil society. Researchers should not be naïve and assume that a proposed solution to a problem will necessarily enter government agenda, be implemented and succeed.
- These caveats notwithstanding, there is enough evidence of long-term and transgenerational effects of early adversity. Unfavorable outcomes include changes in cognitive, language skills, and socioemotional development; earlier initiation of sexual activity; disruptions in the neuroimmunoendocrine system; enhanced HPA stress axis activity; physical and mental disease. It is also known that the earlier the intervention, the more effective it is. This overall evidence-informed picture only reinforces the urgency and usefulness of policy.
- If Differential Susceptibility hypothesis is proved to be true, this means that the children that benefit the most from environmental intervention are exactly those who suffer more from early hostile conditions.

- Growing evidence indicates that improving feeding, parenting and health conditions in early childhood may indirectly result in more secure attachment patterns, which, by their turn, favor less risk-taking and impulsive future behaviors, and lead to quality-oriented reproductive strategies. As a result, adolescent and adult antisocial and psychopathological behavior incidence would be smaller, benefitting society as a whole.

- Attachment interventions focused on enhancing parental sensitivity to infants are effective. Since the most effective ones have simple designs and are brief, they could be tried by the federal government in a nationwide policy for early childhood.

- In Brazil, institutional constraints and coordination problems will arise in every attempt to establish a nationwide intersectorial policy. This does not mean this should not be tried. The attempt to create and execute a unified full-protection program aimed at early childhood should no longer be delayed.

References

Acevedo BP, Aron A, Fisher HE, Brown LL. (2011) Neural correlates of long-term intense romantic love. *Soc Cogn Affect Neurosci*. Jan 5. [Epub ahead of print]

Allen B (2011a). The use and abuse of Attachment Theory in clinical practice with maltreated children, Part I: Diagnosis and Assessment. *Trauma, Violence & Abuse*. 12(1):3-12.

Allen B (2011b). The use and abuse of Attachment Theory in clinical practice with maltreated children, Part II: Treatment. *Trauma, Violence & Abuse*. 12(1):13-22.

Amorim Neto O (2007). O Poder Executivo, centro de gravidade do Sistema Político Brasileiro. In: Avelar L & Cintra AO. *Sistema Político Brasileiro: Uma Introdução*. Rio de Janeiro: Konrad Adenauer-Stiftung / São Paulo: Unesp.

Amorim Neto O (2009). O Brasil, Lijphart e o Modelo Consensual de Democracia. In: Inácio M & Rennó L. *Legislativo Brasileiro em Perspectiva Comparada*. Belo Horizonte: Editora UFMG.

Arretche M (2006). Método de Constituição de Instâncias Decisórias – Federalismo. In: Avritzer L & Anastasia F (orgs.) *Reforma Política no Brasil*. Belo Horizonte: Editora UFMG.

Arretche M (2009). Continuidades e descontinuidades da Federação brasileira: de como 1988 facilitou 1995. *DADOS – Revista de Ciências Sociais*. 52(2):377-423.

Baars BJ & Gage NM (2010). *Cognition, Brain and Consciousness – Introduction to Cognitive Neuroscience*. 2nd ed. New York: Elsevier.

Bakermans-Kranenburg MJ & van IJzendoorn MH.(2004) No association of the dopamine D4 receptor (DRD4) and -521 C/T promoter polymorphisms with infant attachment disorganization. *Attach Hum Dev*. Sep; 6(3):211-8; discussion 219-22.

Bakermans-Kranenburg, MJ & van IJzendoorn, MH (2006) Gene-Environment interaction of the Dopamine D4 Receptor (DRD4) and observed maternal

insensitivity predicting externalizing behavior in preschoolers. *Developmental Psychobiology*. 48, 406–409.

Bakermans-Kranenburg MJ & van IJzendoorn MH. (2007) Research Review: genetic vulnerability or differential susceptibility in child development: the case of attachment. *J Child Psychol Psychiatry*. Dec; 48(12):1160-73.

Bakermans-Kranenburg, MJ & van IJzendoorn, MH (2008) Oxytocin receptor (OXTR) and serotonin transporter (5-HTT) genes associated with observed parenting. *Soc Cogn Affect Neurosci*. 3,128–134.

Bakermans-Kranenburg MJ & van IJzendoorn MH. (2011) Differential susceptibility to rearing environment depending on dopamine-related genes: new evidence and a meta-analysis. *Dev Psychopathol*. Feb; 23(1):39-52.

Bakermans-Kranenburg M J, van IJzendoorn MH, Juffer F (2003). Less is more: Meta-analyses of sensitivity and attachment interventions in early childhood. *Psychological Bulletin*. 129:195–215.

Bakermans-Kranenburg MJ, van IJzendoorn MH, Piljman FTA, Mesman J, Juffer F. (2008a). Experimental Evidence for Differential Susceptibility: Dopamine D4 Receptor Polymorphism (DRD4 VNTR) moderates intervention effects on toddlers' externalizing behavior in a randomized controlled trial. *Developmental Psychology*. 44(1):293-300.

Bakermans-Kranenburg MJ, van IJzendoorn MH, Mesman J, Alink LR, Juffer F. (2008b) Effects of an attachment-based intervention on daily cortisol moderated by dopamine receptor D4: a randomized control trial on 1- to 3-year-olds screened for externalizing behavior. *Dev Psychopathol*. Summer; 20(3):805-20.

Balleine BW, Daw ND, O'Doherty JP (2009). Multiple forms of value learning and the function of dopamine. In: Glimcher PW, Camerer CF, Fehr E, Poldrack RA. *Neuroeconomics – Decision Making and the Brain*. London: Academic Press.

Barr CS, Schwandt ML, Lindell SG, Higley JD, Maestripieri D, Goldman D, Suomi SJ, Heilig M. (2008) Variation at the mu-opioid receptor gene (OPRM1) influences

attachment behavior in infant primates. *Proc Natl Acad Sci USA*. Apr 1; 105(13):5277-81. Epub Mar 31.

Barrett J & Fleming AS.(2011) Annual Research Review: All mothers are not created equal: neural and psychobiological perspectives on mothering and the importance of individual differences. *Journal of Child Psychology and Psychiatry.* 52(4):368-397.

Barry RA, Kochanska G, Philibert RA. (2008) GxE interaction in the organization of attachment: mothers' responsiveness as a moderator of children's genotypes. *J Child Psychol Psychiatry*. Dec; 49(12):1313-20.

Bartels A, Zeki S. (2004) The neural correlates of maternal and romantic love. *Neuroimage*. Mar; 21(3):1155-66.

Baskerville TA & Douglas AJ. (2010) Dopamine and oxytocin interactions underlying behaviors: potential contributions to behavioral disorders. *CNS Neuroscience & Therapeutics.* 16:e92-e123.

Bateson P (2010). The value of truly comparative and holistic approaches in the Neurosciences. In: Blumberg MS, Freeman JH, Robinson SR (eds.). *Oxford Handbook of Developmental Behavioral Neuroscience*. Oxford, UK: Oxford University Press.

Bateson P & Gluckman P (2011) *Plasticity, Robustness, Development, and Evolution*. New York: Cambridge University Press.

Belsky J (2008). Pesquisa e teoria do apego sob uma perspectiva ecológica – introspecções do Pennsylvania Infant and Family Development Project e do National Institute of Child Health and Infant Development Study of Early Child Care. In: Grossman KE, Grossman K, Waters E (2008). *Apego – da infância à idade adulta: os principais estudos longitudinais*. São Paulo: Roca.

Belsky J, Steinberg L, Draper P. (1991) Childhood experience, interpersonal development, and reproductive strategy: An Evolutionary Theory of Socialization. *Child Development*. 62:647-670.

Belsky J, Bakermans-Kranenburg MJ, van IJzendoorn MH (2007). For better and for worse: Differential Susceptibility to environmental influences. *Current Directions in Psychological Science*. 16(6):300-304.

Belsky J, Jonassaint C, Pluess M, Stanton M, Brummett B, Williams R. (2009) Vulnerability genes or plasticity genes? *Molecular Psychiatry.*14:746-754.

Belsky J & de Haan M. (2011). Annual Research Review: Parenting and children's brain development: the end of the beginning. *Journal of Child Psychology and Psychiatry*. 52(4):409-428.

Berlin LJ, Zeanah CH & Lieberman AF (2008). Prevention and intervention Programs for supporting early attachment security. In: Cassidy J & Shaver PR (eds.) *Handbook of Attachment – theory, research, and clinical applications*. 2nded. New York: The Guilford Press.

Berridge KC & Robinson TE (1998). What is the role of dopamine in reward: hedonic impact, reward learning, or incentive salience? *Brain Research Reviews*. 28:309-369.

Berridge KC (2007). The debate over dopamine's role in reward the case for incentive salience. *Psychopharmacology*. 191:391-431.

Berton O, McClung CA, DiLeone RJ, Krishnan V, Renthal W, Russo SJ, Graham D, Tsankova NM, Bolanos CA, Rios M, Monteggia LM, Self DW, Nestler EJ (2006). Essential role of BDNF in the mesolimbic dopamine pathway in Social Defeat Stress. *Science*. 311: 864-868.

Bezerra SC (2004). Estatuto da Criança e do Adolescente: Marco da Proteção Integral. In: Lima CA (Coord.). *Violência faz mal à saúde*. Brasília: Ministério da Saúde.

Blackwood D & Knight H (2010). Genetic predispositions to stressful conditions. In: Fink G (ed). *Stress Consequences: mental, neuropsychological and socioeconomic*. Oxford, UK: Academic Press.

Bockhorst CL, Bakermans-Kranenburg MJ, Pasco Fearon RM, van IJzendoorn MH, Fonagy P, Schuengel C (2003). The importance of shared environment in mother-

infant attachment security: A Behavioral Genetic Study. *Child Development*. November/December. 74(6):1769-1782.

Bonafont LC (2004). *Redes de Políticas Públicas*. Madrid: Centro de Investigaciones Sociológicas.

Born J, Lange T, Kern W, McGregor GP, Bickel U, Fehm HL (2002). Sniffing neuropeptides: a transnasal approach to the human brain. *Nature Neuroscience*. 5(6) 514-516.

Bowen S & Zwi AB (2005). Pathways to "Evidence-Informed" Policy and practice: a framework for action. *PLoS Medicine*. July. 2(7)e166:600-605.

Boyce WT & Ellis BJ (2005). Biological sensitivity to context: I. An evolutionary-developmental theory of the origins and functions of stress reactivity. *Development and Psychopathology*. 17:271-301.

Bowlby, J. (1969/1982). *Attachment and loss: Vol. 1. Attachment*. New York: Basic Books.

Brasil (2006). *Plano Nacional de Promoção, Proteção e Defesa do Direito de Crianças e Adolescentes à Convivência Familiar e Comunitária*. Presidência da República. Secretaria Especial dos Direitos Humanos. Conselho Nacional dos Direitos da Criança e do Adolescente. Brasília: Conanda.

Brasil (2011a). *Plano Decenal dos Direitos Humanos de Crianças e Adolescentes*. Approved in 19/april/2011. Brasília: CONANDA.

Brasil (2011b). *Construindo um Programa Único de Atenção Integral à Primeira Infância*. SAE – Secretaria de Assuntos Estratégicos da Presidência da República. Presented at "Seminário Cidadão do Futuro – Políticas para desenvolvimento na primeira infância". Brasília, 26/october/2011.

Bryant RA, Hung L, Guastella AJ, Mitchell PB (2012). Oxytocin as a moderator of hypnotizability. *Psychoneuroendocrinology*. 37:162-166.

Buchheim A, Heinrichs M, George C, Pokorny D, Koops E, Henningsen P, O'Connor MF, Gündel H (2009). Oxytocin enhances the experience of attachment security. *Psychoneuroendocrinology*. 34:1417-1422.

Carvalho MRS, Santos LL, Peixoto MGCD, Haase, VG (2009). Para melhor compreensão da base genética das doenças. In: *Aspectos Biopsicossociais da Saúde na Infância e na Adolescência*. Belo Horizonte: Coopmed.

Caspers KM, Paradiso S, Yucuis R, Troutman B, Arndt S, Philibert R. (2009) Association between the serotonin transporter promoter polymorphism (5-HTTLPR) and adult unresolved attachment. *Dev Psychol*. Jan;45(1):64-76.

Caspi A & Moffitt TE (2006). Gene-environment interactions in psychiatry: joining forces with neuroscience. *Nature Rev. Neurosci*. July.7:583-590.

Caspi A, McClay J, Moffitt TE, Mill J, MartinJ, Craig IW, Taylor A, Poulton R (2002). Role of genotype in the cycle of violence in maltreated children. *Science*. August 2. 297:851-854,

Caspi A, Sugden K, Moffitt TE, Taylor A, Craig IW, Harrington H, McClay J, Mill J, Martin J, Braitwhite A, Poulton R (2003). Influence of life stress on depression: Moderation by a polymorphism in the 5-HTT gene. *Science*. 301, 386–389.

Caspi A, Hariri AR, Holmes A, Uher R, Moffitt TE (2011). Genetic Sensitivity to the Environment: the case of the serotonin transporter gene and its implications for studying complex diseases and traits. In: Dodge KA & Rutter M (eds.). *Gene-Environment Interactions in Developmental Psychopathology*. New York: The Guilford Press.

Cassidy J (2008). The Nature of Child's Ties. In: Cassidy J & Shaver PR (eds.) *Handbook of Attachment – theory, research, and clinical applications*. 2nd ed. New York: The Guilford Press.

Charney E (in press). Behavior genetics and post genomics. To be published in *Behavioral and Brain Sciences*.

Chen J, Lipska BK, Halim N, Ma QD, Matsumoto M, Melhem S, Kolachana BS, Hyde TM, Herman MM, Apud J, Egan MF, Kleinman JE, Weinberger DR (2004). Functional analysis of genetic variation in Catechol-O-Methyltransferase (COMT): Effects on mRNA, protein, and enzyme activity in postmortem human brain. *Am. J. Hum. Genet*. 75:807-821.

Chen, FS; Barth, ME; Johnson, SL; Gotlib, IH and Johnson, SC. (2011) Oxytocin receptor (OXTR) polymorphisms and attachment in human infants. *Frontiers in Psychology*, vol 2, article 200.

Coan JA (2008). Toward a Neuroscience of Attachment. In: Cassidy J & Shaver PR (eds.) *Handbook of Attachment – theory, research, and clinical applications*. 2nd ed. New York: The Guilford Press.

Coates JM, Gurnell M, Sarnyai Z. (2010) From molecule to market: steroid hormones and financial risk-taking. *Phil. Trans. R. Soc. B.* 365:331-343.

Cohen JA (2010). Child sexual abuse. In: Fink G (ed). *Stress Consequences: mental, neuropsychological and socioeconomic*. Oxford, UK: Academic Press.

Cohen S, Janicki-Deverts D, Chen E, Matthews KA (2010). Childhood socioeconomic status and adult health. *Ann. N.Y. Acad. Sci.* 1186:37-55.

Cools R, Nakamura K, Daw ND. (2011) Serotonin and dopamine: unifying affective, activational, and decision functions. *Neuropsychopharmacology Reviews*. 36:98-113.

Correa H & Rocha FF (2008). Genética, comportamento e cognição. In: Malloy-Diniz L, Camargo CHP, Cosenza RM. *Neuropsicologia – Teoria e Prática.* Porto Alegre: Artmed.

Costa B, Pini S, Gabelloni P, Abelli M, Lari L, Cardini A, Muti M, Gesi C, Landi S, Galderisi S, Mucci A, Lucacchini A, Cassano GB, Martini C. (2009) Oxytocin receptor polymorphisms and adult attachment style in patients with depression. *Psychoneuroendocrinology*. Nov; 34(10):1506-14. Epub 2009 Jun9.

Crews D. (2011) Epigenetic modifications of brain and behavior: Theory and practice. *Hormones and Behavior.* 59:393-398.

Curley JP. (2011) The mu-opioid receptor and the evolution of mother-infant attachment: theoretical comment on Higham et al. (2011). *Behav Neurosci*. Apr; 125(2):273-8.

Curley JP & Keverne EB.(2005) Genes, brains and mammalian social bonds. *Trends in Ecology and Evolution*. 20(10):561-567.

Curley JP. Jensen CL, Mashoodh R, Champagne FA. (2011a) Social influences on neurobiology and behavior: Epigenetic effects during development. *Psychoneuroendocrinology.* 36:352-371.

Curley JP, Mashoodh R, Champagne FA (2011b). Epigenetics and the origins of paternal effects. *Hormones and Behavior*. 59:306-314.

Cyr C, Euser EM, Bakermans-Kranenburg MJ, van IJzendoorn MH (2010). Attachment security and disorganization in maltreating and high-risk families: A series of meta-analyses. *Development and Psychopathology*. 22:87-108.

Dalgleish T, Dunn BD, Mobbs D (2009). Affective Neuroscience: Past, Present, and Future. *Emotion Review*. October. 1(4):355–368.

de Bellis MD. (2005) The Psychobiology of Neglect. *Child Maltreatment*. May. 10(2):150-172.

Dedovic K, Duchesne A, Andrews J, Engert V, Pruessner JC. (2009). The brain and the stress axis: The neural correlates of cortisol regulation in response to stress. *NeuroImage*. 47:864-871.

Del Giudice M. (2009). Sex, attachment, and the development of reproductive strategies. *Behavioral and Brain Sciences.* 32:1-67.

Del Giudice M, Ellis BJ, Shirtcliff EA (2011). The Adaptive Calibration Model of stress responsivity. *Neuroscience and Biobehavioral Reviews*. 35:1562–1592.

Dias LBT & Landeira-Fernandez J (2011). Neuropsicologia do desenvolvimento da memória: da pré-escola ao período escolar. *Revista Neuropsicologia Latinoamericana*. 3(1):19-26.

Dickinson D & Elvevag B (2009). Genes, cognition and brain through a COMT lens. *Neuroscience*. 164:72-87.

Dodge KA (1993). Social-cognitive mechanisms in the development of conduct disorder and depression. *Annu. Rev. Psychol.* 44:559-584.

Dodge KA (2011). Context matters in Child and Family Policy. *Child Development*. January/February. 82(1):433-442.

Dodge KA & Pettit GS (2003). A biopsychosocial model of the development of chronic conduct problems in adolescence. *Developmental Psychology.* 39(2):349-371.

Dodge KA & Rutter M (2011). Genes, environments, and public policy. In: Dodge KA & Rutter M (eds.). *Gene-Environment Interactions in Developmental Psychopathology*. New York: The Guilford Press.

Dolowitz DP & Marsh D (1999). Policy Transfer: a framework for comparative analysis. In: Mongue M, Polidano C, Hulme D. *Beyond the New Public Management – Changing ideas and practices in governance*. Cheltenham, UK: Edward Elgar.

Donohue B, Hill H, Maier-Paarlberg T (2010). Domestic Violence. In: Fink G (ed). *Stress Consequences: mental, neuropsychological and socioeconomic*. Oxford, UK: Academic Press.

Dozier M & Rutter M (2008). Challenges to the development of attachment relationships faced by young children in foster and adoptive care. In: Cassidy J & Shaver PR (eds.) *Handbook of Attachment – theory, research, and clinical applications*. 2nd ed. New York: The Guilford Press.

Drolet G, Dumont EC, Gosselin I, Kinkead R, LaForest S, Trottier JF (2001). Role of endogenous opioid system in the regulation of the stress response. *Prog Neuro-Psychopharmacol & Biol Psychiat*. 25:729-741.

D'Souza UM & Craig IW (2010). Genetic organization of the serotonergic system. In: Muller CP & Jacobs B. *Handbook of the Behavioral Neurobiology of Serotonin*. London: Academic Press.

Ebstein RP, Israel S, Chew SH, Zhong S, Knafo A (2010). Genetics of Human Social Behavior. *Neuron*. March 25. 65:831-844,

Eisenberger N (2011). The neural basis of social pain: findings and implications. In: MacDonald G & Jensen-Campbell LA (eds.). *Social Pain: neuropsychological and health implications of loss and exclusion*. Washington, DC: American Psychological Association.

Ellis BJ, Boyce WT, Belsky J, Bakermans-Kranenburg MJ, van IJzendoorn MH. (2011) Differential susceptibility to the environment: An evolutionary-neurodevelopmental theory. *Development and Psychopathology.* 23:7-28.

Elster J (2009). *Explaining Social Behavior – More nuts and bolts for the social sciences*. Cambridge, Massachusetts: Cambridge University Press.

Ernst M, Romeo RD, Andersen SL (2009). Neurobiology of the development of motivated behaviors in adolescence: A window into a neural systems model. *Pharmacology, Biochemistry and Behavior*. 93:199-211.

Faleiros VP (2005). Políticas para a infância e adolescência e desenvolvimento. *Políticas Sociais – acompanhamento e análise (IPEA)*. 11:171-177.

Faria CAP (2003). Idéias, conhecimento e políticas públicas – um inventário das principais vertentes analíticas recentes. *Revista Brasileira de Ciências Sociais*. 18(51):21-29.

Fearon RP, Lapsley AM, Bakermans-Kranenburg MJ, van IJzendoorn MH, Roisman GI (2010). The significance of insecure attachment and disorganization in the development of children's externalizing behavior: A Meta-Analytic Study. *Child Development*. March/April, 81(2):435-456.

Feder A, Nestler EJ, Charney DS (2009). Psychobiology and molecular genetics of resilience. *Nature Reviews Neuroscience*. Jun., 10:446-457.

Fernandez A & Fernandez M. (2008). *Neuroética, Direito e Neurociência – Conduta Humana, Liberdade e Racionalidade Jurídica*. Curitiba: Juruá.

Fox NA & Hane AA (2008). Studying the biology of human attachment. In: Cassidy J & Shaver PR (eds.) *Handbook of Attachment – theory, research, and clinical applications*. 2nd ed. New York: The Guilford Press.

Francis, RC (2011). *Epigenetics – the ultimate mystery of inheritance*. New York: W.W. Norton & Company.

Fries ABW, Ziegler TE, Kurian JR, Jacoris S, Pollak SD (2005). Early experience in humans is associated with changes in neuropeptides critical for regulating social behavior. *Proc Natl Acad Sci USA*. November 22. 102(47):17237-17240.

Fries ABW, Schirtcliff EA, Pollak SD (2008). Neuroendocrine dysregulation following early social deprivation in children. *Dev Psychobiol*. 50: 588-599.

Frigerio A, Ceppi E, Rusconi M, Giorda R, Raggi ME, Fearon P. (2009) The role played by the interaction between genetic factors and attachment in the stress response in infancy. *J Child Psychol Psychiatry*. Dec; 50(12): 1513-22. Epub 2009 Jul 22.

Frota MGC (2008). A cidadania da infância e da adolescência: da situação irregular à proteção integral. In: Carvalho A, Salles F, Guimarães M, Ude W. *Políticas Públicas – coleção infância e adolescência*. Belo Horizonte: Editora UFMG.

Gaetani F (2009). Debate sobre políticas de gestión pública em el contexto de la OCDE: notas desde una perspectiva brasileña. *Revista del CLAD Reforma y Democracia*. Junio. 44:57-84.

Gaetani F & Abrucio FL (2006). Avanços e perspectivas da gestão pública nos estados: agenda, aprendizado e coalizão. In: *Avanços e Perspectivas da Gestão Pública nos Estados*. Brasília: CONSAD.

Gerra G, Zaimovic A, Garofano L, Ciusa F, Moi G, Avanzini P, Talarico E, Gardini F, Brambilla F, Manfredini M, Donnini C. (2007) Perceived parenting behavior in the childhood of cocaine users: relationship with genotype and personality traits.*Am J Med Genet B Neuropsychiatr Genet*. Jan 5;144B(1):52-7.

Gerstein MB, Bruce C, Rozowsky JS, Zheng D, Du J, Korbel JO, Emanuelsson O, Zhang ZD, Weissman S, Snyder M (2007). What is a gene, post-ENCODE? History and updated definition. *Genome Res*. 17: 669-681.

Gervai J. (2009) Environmental and genetic influences on early attachment. *Child and Adolescent Psychiatry and Mental Health.* September 4. 3(25):1-12.

Gervai J, Nemoda Z, Lakatos K, Ronai Z, Toth I, Ney K, Sasvari-Szekely M (2005). Transmission disequilibrium tests confirm the link between DRD4 gene polymorphism and infant attachment. *Am J Med Genet B Neuropsychiatr Genet*. Jan 5;132B(1):126-30.

Gervai J, Novak A, Lakatos K, Toth I, Danis I, Ronai Z, Nemoda Z, Sasvari-Szekely M, Bureau JF, Bronfman E, Lyons-Ruth K (2007). Infant genotype may moderate sensitivity to maternal affective communications: attachment disorganization, quality of care, and the DRD4 polymorphism. *Soc Neurosci*. 2(3-4):307-19.

Gilissen R, Bakermans-Kranenburg MJ, van Ijzendoorn MH, Linting M. (2008) Electrodermal reactivity during the Trier Social Stress Test for children: interaction between the serotonin transporter polymorphism and children's attachment representation. *Dev Psychobiol*. Sep; 50(6):615-25.

Gillath O, Shaver PR, Baek JM, Chun DS. (2008) Genetic correlates of adult attachment style. *Pers Soc Psychol Bull*. Oct; 34(10):1396-405. Epub 2008 Aug 7.

Giménez-Amaya JM. (2009) Neurobiología del "vínculo de apego" y embarazo. *Cuad Bioet*. 2009 Sep-Dec;20(70):333-8.

Gimpl G & Fahrenholz F (2001). The oxytocin receptor system: structure, function, and regulation. *Physiological Reviews*. 81(2):629-683.

Glimcher PW (2011). *Foundations of Neuroeconomic Analysis*. New York: Oxford University Press.

Gottesman II & Gould TD (2003).The Endophenotype Concept in Psychiatry: Etymology and Strategic Intentions. *Am J Psychiatry*. April; 160(4): 636-645.

Grassi-Oliveira R, Ashy M, Stein LM (2008). Psychobiology of childhood maltreatment: effects of allostatic load? *Rev Bras Psiquiatr.* 30(1):60-8.

Grossman KE, Grossman K, Waters E (2008). *Apego – da infância à idade adulta: os principais estudos longitudinais*. São Paulo: Roca.

Gunnar M & Quevedo K (2007). The Neurobiology of Stress and Development. *Annu. Rev. Psychol*. 58:145–73.

Haas PM (1992). Introduction: epistemic communities and international policy coordination. *International Organization*. 46(1):1-35.

Haase VG (2009) O enfoque biopsicossocial na saúde da criança e do adolescente. In: *Aspectos Biopsicossociais da Saúde na Infância e na Adolescência*. Belo Horizonte: Coopmed.

Haase VG, Pinheiro-Chagas P, Gonzaga DM, Mata FG, Silva JBL, Géo LA (2008). Um sistema nervoso conceitual para o diagnóstico neuropsicológico. julho-dezembro. *Contextos Clínicos*. 1(2):125-138.

Haase VG, Pinheiro-Chagas P, Arantes EA (2009). Um Convite à Neurociência Cognitiva Social. *Gerais: Revista Interinstitucional de Psicologia*, 2(1): 43-49.

Haber SN (2009). Anatomy and connectivity of the reward circuit. In: Dreher JC & Trémblay L. *Handbook of Reward and Decision Making*. New York: Academic Press.

Hackman DA & Farah MJ (2008) Socioeconomic status and the developing brain. *Trends in Cognitive Sciences*. 13(2):65-73.

Hackman DA, Farah MJ, Meaney MJ (2010) Socioeconomic status and the brain: mechanistic insights from human and animal research. *Nature Reviews Neuroscience*. Sept. 11:651-659.

Hager GL, McNally JG, Misteli T (2009) Transcription dynamics. *Mol Cell*. 35:741–753.

Hammock EA, Lim MM, Nair HP, Young LJ (2005). Association of vasopressin 1a receptor levels with a regulatory microsatellite and behavior. *Genes Brain Behav*. Jul;4(5):289-301.

Harlow H (1958).The Nature of Love. *American Psychologist*. 13:673-685.

Harris A & Seckl J (2011). Glucocorticoids, prenatal stress and the programming of disease. *Hormones and Behavior*. 59:279-289.

Hesse E (2008). The Adult Attachment Interview protocol, method of analysis, and empirical studies. In: Cassidy J & Shaver PR (eds.) *Handbook of Attachment – theory, research, and clinical applications*. 2nd ed. New York: The Guilford Press.

Higham JP, Barr CS, Hoffman CL, Mandalaywala TM, Parker KJ, Maestripieri D. (2011) Mu-opioid receptor (OPRM1) variation, oxytocin levels and maternal attachment in free-ranging rhesus macaques *Macaca mulatta*. *Behav Neurosci*. Apr;125(2):131-6.

Hill M (2009). *The Public Policy Process*. 5th ed. Harlow, UK: Pearson Longman.

Hillberg T, Hamilton-Giachritsis C, Dixon L. (2011) Review of meta-analyses on the association between child sexual abuse and adult mental health difficulties: a systematic approach. *Trauma, Violence & Abuse.* 12(1):38-49.

Holliday, R (2006). Epigenetics – a historical overview. *Epigenetics*. April/May/June. 1(2):76-80.

Holmbeck GN, Jandasek B, Sparks C, Zukerman J, Zurenda L (2008). Theoretical foundations of developmental-behavioral pediatrics. In: Wolraich ML (ed.) *Developmental-Behavioral Pediatrics: Evidence and Practice*. Philadelphia: Mosby Elsevier.

Homberg JR (2012). Serotonin and decision making process. *Neuroscience and Biobehavioral Reviews*. 36:218-236.

Hood C (2005). The Idea of Joined-Up Government: A Historical Perspective. In: Bogdanor V (Ed.). *Joined-Up Government*. Oxford, UK: Oxford University Press.

Houle D, Govindaraju DR, Omholt S (2010). Phenomics: the next challenge. *Nature Rev Genet*. Dec; 11:855-866.

Hoyle CHV (1999). Neuropeptide families and their receptors: evolutionary perspectives. *Brain Research*. 848:1–25.

Hrubý R, Hašto J, Minárik P. (2011) Attachment in integrative neuroscientific perspective. *Act Nerv Super Rediviva.*53(2):49-58.

Hunter PJ & Borg, TK (2003). Integration from proteins to organs: the Physiome Project. *Nature Rev*. *Moll. Cell Biol.* 4: 237-243.

Inácio M (2006). Poderes de Agenda do Presidente. In: Avritzer L & Anastasia F (orgs.) *Reforma Política no Brasil*. Belo Horizonte: Editora UFMG.

Inoue T, Kimura T, Azuma C, Inazawas J, Takemura M, Kikuchi T, Kubota Y, Ogita K, Saji F (1994). Structural organization of the human oxytocin receptor gene. *The Journal of Biological Chemistry*. 269(51):32451-32456.

Insel TR (2010). The challenge of translation in social neuroscience: a review of oxytocin, vasopressin, and affiliative behavior. *Neuron*. 65:768-779.

Insel TR & Young LJ (2001). The neurobiology of attachment. *Nature Reviews Neuroscience*. Feb. 2:129-136.

Jablonka, E & Lamb, MJ (2005). *Evolution in Four Dimensions - Genetic, epigenetic, behavioral, and symbolic variation in the history of life*. Cambridge, Massachusetts: MIT Press.

Jaffee SR & Price TS (2007). Gene-environment correlations: a review of the evidence and implications for prevention of mental illness. *Mol Psychiatry*. 12:432-442.

Jezierski G, Braun K, Gruss M (2006). Epigenetic modulation of the developing serotonergic neurotransmission in the semi-precocial rodent *Octodon degus*. *Neurochem Int*. Apr;48(5):350-7. Epub 2006 Jan 19.

Kang HJ, Kawasawa YI, Cheng F, Zhu Y, Xu X, Li M, Sousa AMM, Pletikos M, Meyer KA, Sedmak G, Guennel T, Shin Y, Johnson MB, Krsnik Z,Mayer S, Fertuzinhos S,

Umlauf S, Lisgo SN, Vortmeyer A, Weinberger DR, Mane S, Hyde TM, Huttner A, Reimers M , Kleinman JE, Sestan N. (2011) Spatio-temporal transcriptome of the human brain. *Nature*. Oct 27; 478: 483-489.

Kapoor A, Petropoulos S, Matthews SG. (2008) Fetal programming of hypothalamic-pituitary-adrenal (HPA) axis function and behavior by synthetic glucocorticoids. *Brain Research Reviews*. 57: 586-595.

Kempf L & Weinberger DR (2009). Molecular Genetics and Bioinformatics: An outline for Neuropsychological Genetics. In: Goldberg TE & Weinberger DR. *The Genetics of Cognitive Neuroscience*. Cambridge, Mass.: MIT Press.

Kingdon JW (1995). *Agendas, Alternatives and Public Policies*. New York: Longman.

Kirsch P, Esslinge C, Chen Q, Mier D, Lis S, Siddhanti S, Gruppe H, Mattay VS,Gallhofer B, Meyer-Lindenberg A (2005). Oxytocin modulates neural circuitry for social cognition and fear in humans. *The Journal of Neuroscience*. 25(49):11489-11493.

Kiser D, Steemers B, Branchi I, Homberg JR (in press). The reciprocal interaction between serotonin and social behavior. *Neuroscience and Biobehavioral Reviews*.

Kochanska G, Philibert RA, Barry RA. (2009) Interplay of genes and early mother-child relationship in the development of self-regulation from toddler to preschool age. *J Child Psychol Psychiatry*. Nov;50(11):1331-8. Epub Jan 12.

Kosfeld M, Heinrichs M, Zak PJ, Fischbacher U, Fehr E (2005). Oxytocin increases trust in humans. *Nature*. June 2. 435:673-676.

Kroslak T, LaForge KS, Gianotti RJ, Ho A, Nielsen DA, Kreek MJ (2007). The single nucleotide polymorphism A118G alters functional properties of the human mu-opioid receptor. *Journal of Neurochemistry*. 103:77–87.

Lakatos K, Toth I, Nemoda Z, Ney K, Sasvari-Szekely M, Gervai J (2000). Dopamine D4 receptor (DRD4) gene polymorphism is associated with attachment disorganization in infants. *Mol Psychiatry*. Nov; 5(6):633-7.

Lakatos K, Nemoda Z, Toth I, Ronai Z, Ney K, Sasvari- Szekely M, Gervai J (2002). Further evidence for the role of the dopamine D4 receptor (DRD4) gene in attachment disorganization: interaction of the exon III 48-bp repeat and the -521 C/T promoter polymorphisms. *Mol Psychiatry*.7(1):27-31.

Lakatos K, Nemoda Z, Birkas E, Ronai Z, Kovacs E, Ney K, Toth I, Sasvari-Szekely M, Gervai J (2003). Association of D4 dopamine receptor gene and serotonin transporter promoter polymorphisms with infants' response to novelty. *Mol Psychiatry*. Jan; 8(1):90-7.

Lesch KP, Bengel D, Heils A, Sabol SZ,Greenberg BD, Petri S, Benjamin J,Muller CR, Hamer DH, Murphy DL (1996). Association of anxiety-related traits with a polymorphism in the serotonin transporter gene regulatory region. *Science*. 274:1527-1531.

Lesch KP & Mössner R (1998).Genetically driven variation in serotonin uptake: is there a link to affective spectrum, neurodevelopmental, and neurodegenerative disorders? *Biol Psychiatry*. 44: 179-182.

Lickliter R & Honeycutt H (2010). Rethinking Epigenesis and evolution in the light of developmental science. In: Blumberg MS, Freeman JH, Robinson SR (eds.). *Oxford Handbook of Developmental Behavioral Neuroscience*. Oxford, UK: Oxford University Press.

Lieberman, MD (in press). A geographical history of Social Cognitive Neuroscience. To be published in *NeuroImage*.

Limongi F (2006). Presidencialismo e Governo de Coalizão. In: Avritzer L & Anastasia F (orgs.) *Reforma Política no Brasil*. Belo Horizonte: Editora UFMG.

Loman MM & Gunnar MR (2010). Early experience and the development of stress reactivity and regulation in children. *Neuroscience and Biobehavioral Reviews*. 34: 867-876.

Loman MM, Wiik KL, Frenn KA, Pollak SD, Gunnar M (2009). Postinstitutionalized children's development: growth, cognitive, and language outcomes. *Journal of Developmental & Behavioral Pediatrics*. 30:426-434.

Lötsch J & Geisslinger G (2006). Relevance of frequent μ-opioid receptor polymorphisms for opioid activity in healthy volunteers. *The Pharmacogenomics Journal*. 6:200-210.

Luijk MPCM, Roisman GI, Haltigan JD, Tiemeier H, Booth-LaForce C, van IJzendoorn MH, Belsky J, Uitterlinden AG, Jaddoe VWV, Hofman A, Verhulst FC, Tharner A, Bakermans-Kranenburg MJ (2011). Dopaminergic, serotonergic, and oxytonergic candidate genes associated with infant attachment security and disorganization? In search of main and interaction effects. *Journal of Child Psychology and Psychiatry*. 52(12):1295-1307.

Main M, Hesse E, Kaplan N (2008). Previsibilidade do comportamento de apego e processos representacionais com 1, 6 e 19 anos de idade – Berkeley Longitudinal Study. In: Grossman KE, Grossman K, Waters E. *Apego – da infância à idade adulta: os principais estudos longitudinais*. São Paulo: Roca.

Malloy-Diniz L, Sedo M, Fuentes D, Leite WB (2008). Neuropsicologia das Funções Executivas. In: Malloy-Diniz L, Camargo CHP, Cosenza RM. *Neuropsicologia – Teoria e Prática.* Porto Alegre: Artmed.

Marian AJ (2012). Molecular genetic studies of complex phenotypes. *Translational Research*. 159(2):64-79.

Mayer-Lindenberg A, Domes G, Kirsch P, Heinrichs M. (2011) Oxytocin and vasopressin in the human brain: social neuropeptides for translational medicine. *Nature Reviews Neuroscience.* Sept. 12:524-538.

Mayr E (1961). Cause and effect in biology – kinds of causes, predictability, and teleology are viewed by a practicing biologist. *Science*. 10 november. 134:1501-1506.

McClelland S, Korosi A, Cope J, Ivy A, Baram TZ (2011). Emerging roles of epigenetic mechanisms in the enduring effects of early-life stress and experience on learning and memory. *Neurobiology of Learning and Memory*. 96:79–88.

McClung CA & Nestler EJ (2008). Neuroplasticity mediated by altered gene expression. *Neuropsychopharmacology Reviews*. 33:3-17.

McCrory E, De Brito SA, Viding E. (2010) Research Review: The neurobiology and genetics of maltreatment and adversity. *Journal of Child Psychology and Psychiatry*. 51(10):1079-1095.

McEwen BS & Gianaros PJ (2010). Central role of the brain in stress and adaptation: Links to socioeconomic status, health, and disease. *Ann. N.Y. Acad. Sci.* 1186: 190-222.

McEwen, BS (2007). Physiology and neurobiology of stress and adaptation: central role of the brain. *Physiol Rev*. 87: 873–904.

Meaney MJ (2001). Maternal care, gene expression, and the transmission of individual differences in stress reactivity across generations. *Annu. Rev. Neurosci*. 24:1161-192

Mendonça MHM (2002). O desafio da política de atendimento à infância e à adolescência na construção de políticas públicas equitativas. *Cad. Saúde Pública, Rio de Janeiro*. 18(Suplemento):113-120.

Menicucci TMG (2009). O Sistema Único de Saúde, 20 anos: balanço e perspectivas. *Cad. Saúde Pública, Rio de Janeiro*. Jul. 25(7):1620-1625.

Meunier D, Lambiotte R, Bullmore ET (2010). Modular and hierarchically modular organization of brain networks. *Frontiers in Neuroscience*, vol 4, article 200.

Mileva-Seitz V, Kennedy J, Atkinson L, Steiner M, Levitan R, Matthews SG, Meaney MJ, Sokolowski MB, Fleming AS. (2011) Serotonin transporter allelic variation in mothers predicts maternal sensitivity, behavior and attitudes toward 6-month-old infants. *Genes Brain Behav*. Apr;10(3):325-33.

Moffitt TE, Caspi A, Rutter M (2005). Strategy for investigating interactions between measured genes and measured environments. *Arch Gen Psychiatry*. 62:473-481.

Moles A, Kieffer BL, D'Amato FR (2004). Deficit in attachment behavior in mice lacking the mu-opioid receptor gene. *Science*. Jun 25; 304(5679):1983-6.

Moll, J & Oliveira-Souza, R (2009). "Extended attachment" and the Human Brain: internalized cultural values and evolutionary implications. In: Verplaetse J, De Schrijver J, Vanneste S, Braeckman J (eds.). *The Moral Brain – Essays on the Evolutionary and Neuroscientific Aspects of Morality*. New York: Springer.

Morales-Medina JC, Dumont Y, Quirion R. (2010). A possible role of neuropeptide Y in depression and stress. *Brain Research*, 1314:194-205.

Moreira L, Neves FS, Romano-Silva MA, Malloy-Diniz LF, Corrêa H (2011). BDNF e memória episódica em pacientes com transtorno afetivo bipolar. *Revista Brasileira de Psiquiatria*. 33:96-97.

Mustard JF (2009). Early Human Development – Equity from the Start – Latin America. *Revista Latinoamericana de Ciencias Sociales, Niñez y Juventud*. Dicembre. 7 (2):639-680.

Mustard JF (2010). Early brain development and human development. In: Tremblay RE, Barr RG, Peters RDeV, Boivin M, eds. *Encyclopedia on Early Childhood Development* [online]. Montreal, Quebec: Centre of Excellence for Early Childhood Development. 1-5. Available at: http://www.child-encyclopedia.com/documents/MustardANGxp.pdf. Retrieved in 08/nov/2011.

Nações Unidas (2002). *Um Mundo para as Crianças*. Relatório do Comitê Ad Hoc Pleno da vigésima sétima sessão especial da Assembléia Geral. Nova York.

Nesse RM & Ellsworth PC (2009). Evolution, Emotions, and Emotional Disorders. *American Psychologist*. February-March. 64(2):129-139.

Neves W (2007). Evolução Darwiniana e Ciências Sociais. São Paulo: USP / Instituto de Estudos Avançados. Available at: http://www.iea.usp.br/iea/ textos/nevesevolucaodarwiniana.pdf. Retrieved in 22/dez/2011.

Numan M & Insel TR (2003). The Neurobiology of Parental Behavior. New York: Springer.

Noriuchi M; Kikuchi Y; Senoo A (2008). The Functional Neuroanatomy of Maternal Love: Mother's Response to Infant's Attachment Behaviors. *Biol Psychiatry*. 63:415-423.

Nutley SM, Walter I, Davies HTO (2007). *Using Evidence: How Research can Inform Public Services*. Bristol, UK: The Policy Press.

Oak JN, Oldenhof J, van Tol HHM (2000). The dopamine D4 receptor: one decade of research. *European Journal of Pharmacology*. 405:303-327.

Olsen JP & Peters G (1996). Learning from experience? In: Olsen JP & Peters G. *Lessons from Experience – Experiential Learning in Administrative Reforms in Eight Democracies*. Oslo: Scandinavian University Press.

Olsson CA, Byrnes GB, Lotfi-Miri M, Collins V, Williamson R, Patton C, Anney RJ. (2005) Association between 5-HTTLPR genotypes and persisting patterns of anxiety and alcohol use: results from a 10-year longitudinal study of adolescent mental health. *Mol Psychiatry*. Sep;10(9):868-76.

Paes de Barros R, Biron L, Carvalho M, Fandinho M, Franco S, Mendonça R, Rosalém A, Scofano A, Tomas R (2010). Determinantes do desenvolvimento na Primeira Infância no Brasil. *IPEA: Texto para Discussão nº 1478*. Brasília: IPEA.

Paim J, Travassos C, Almeida C, Bahia L, Macinko J (2011). O sistema de saúde brasileiro: história, avanços e desafios. *The Lancet*. *Special issue: Saúde no Brasil*. Maio:11-31.

Panksepp J (2006). Emotional endophenotypes in evolutionary psychiatry. *Progress in Neuro-Psychopharmacology & Biological Psychiatry*. 30:774-784.

Panksepp J (2011). The Neurobiology of Social Loss in animals: some keys to the puzzle of psychic pain in humans. In: MacDonald G & Jensen-Campbell LA (eds.). *Social Pain: neuropsychological and health implications of loss and exclusion*. Washington, DC: American Psychological Association.

Pasternak GW (2004). Multiple opiate receptors: déjà vu all over again. *Neuropharmacology*. 47:312-323.

Pauli-Pott U, Friedel S, Hinney A, Hebebrand J. (2009) Serotonin transporter gene polymorphism (5-HTTLPR), environmental conditions, and developing negative emotionality and fear in early childhood. *J Neural Transm*. Apr; 116(4):503-12. Epub 2009 Jan 10.

Petronis A (2010). Epigenetics as a unifying principle in the aetiology of complex traits and diseases. *Nature*. June. 465:721-727.

Plomin R & Asbury K (2005). Nature and nurture: genetic and environmental influences on behavior. *Annals of the American Academy of Political and Social Science*. 600:86-98.

Plomin R, Asbury K, Dunn J (2001). Why are children in the same family so different? Nonshared environment a decade later. *Canadian Journal of Psychiatry*. 46:225-233.

Pluess M & Belsky J. (2011) Prenatal programming of postnatal plasticity? *Development and Psychopathology*. 23:29-38.

Pollak SD. (2005) Early adversity and mechanisms ofplasticity: Integrating Affective Neuroscience with developmental approaches to psychopathology. *Development and Psychopathology.*17:735-752.

Polan HJ & Hofer MA (2008).Psychobiological origins of infant attachment and its role in development. In: Cassidy J & Shaver PR (eds.) *Handbook of Attachment – theory, research, and clinical applications*. 2nd ed. New York: The Guilford Press.

Porges SW (2003). Social engagement and attachment – A Phylogenetic perspective. *Ann. N.Y. Acad. Sci.*1008:31-47.

Porges SW (2009). The polyvagal theory: New insights into adaptive reactions of the autonomic nervous system. *Cleveland Clinic Journal of Medicine*. 76(2):S86-S90.

Porges SW & Furman SA. (2011) The early development of the autonomic nervous system provides a neural platform for social behaviour: A Polyvagal Perspective. *Inf. Child. Dev.* 20:106-118.

Powell WW (1990). Neither Market nor Hierarchy: Network forms of organization. *Research in Organizational Behavior*. 12:295-336.

Reeb BC, Fox NA, Nelson CA, Zeanah CH (2009). The effects of early institutionalization on social behavior and underlying neural correlates. In: de Haan M & Gunnar MR (eds.). *Handbook of Developmental Social Neuroscience*. New York: The Guilford Press.

Reiner I & Spangler G (2010). Adult attachment and gene polymorphisms of the dopamine D4 receptor and serotonin transporter (5-HTT). *Attach Hum Dev*. May; 12(3):209-29.

Rennó LR (2006). Críticas ao Presidencialismo de Coalizão no Brasil – processos institucionalmente constritos ou individualmente dirigidos? In: Avritzer L & Anastasia F (orgs.) *Reforma Política no Brasil*. Belo Horizonte: Editora UFMG.

Riani F (2009). *Economia do Setor Público – uma abordagem introdutória*. 5ª ed. Rio de Janeiro: LTC.

Ribeiro SC, Kennedy SE, Smith YR, Stohler CS, Zubieta JK. (2005) Interface of physical and emotional stress regulation through the endogenous opioid system and μ-opioid receptors. *Progress in Neuro-Psychopharmacology & Biological Psychiatry*. 29:1264-1280.

Roubertoux PL, Jamon M, Carlier M (2010). Brain development: genes, epigenetic events, and maternal environments. In: Blumberg MS, Freeman JH, Robinson SR (eds.). *Oxford Handbook of Developmental Behavioral Neuroscience*. Oxford, UK: Oxford University Press.

Rodrigues SM, Saslow LR, Garcia N, John OP, Keltner D (2009). Oxytocin receptor genetic variation relates to empathy and stress reactivity in humans. *Proc Natl Acad Sci USA*. 106(50):21437-21441. Dec 15.

Rogers RD (2011). The roles of dopamine and serotonin in decision making: evidence from pharmacological experiments in humans. *Neuropsychopharmacology Reviews*. 36:114-132.

Ross HE & Young LJ (2009). Oxytocin and the neural mechanisms regulating social cognition and affiliative behavior. *Frontiers in Neuroendocrinology*. 30:534-547.

Roth TL & Sweatt JD (2011a). Epigenetic marking of the gene by early-life adverse experiences. *Hormones and Behavior*. 59:315–320.

Roth TL & Sweatt JD. (2011b) Annual Research Review: Epigenetic mechanisms and environmental shaping of the brain during sensitive periods of development. *Journal of Child Psychology and Psychiatry*.52(4):398-408.

Rutter M (2008). Implications of attachment theory and research for child care policies. In: Cassidy J & Shaver PR (eds.) *Handbook of Attachment – theory, research, and clinical applications*. 2nd ed. New York: The Guilford Press.

Rutter M (2011). Gene-environment interplay: scientific issues and challenges. In: Dodge KA & Rutter M (eds.). *Gene-Environment Interactions in Developmental Psychopathology*. New York: The Guilford Press.

Rutter M & Dodge KA (2011) Gene-environment interactions – state of the science. In: Dodge KA & Rutter M (eds.). *Gene-Environment Interactions in Developmental Psychopathology*. New York: The Guilford Press.

Sanchez MM & Pollak SD (2009). Socioemotional development following early abuse and neglect: challenges and insights from translational research. In: de Haan M & Gunnar MR (eds.). *Handbook of Developmental Social Neuroscience*. New York: The Guilford Press.

Saltzman W & Maestripieri D. (2011) The neuroendocrinology of primate maternal behavior. *Progress in Neuro-Psychopharmacology & Biological Psychiatry*. 35:1192-1204.

Savitz J, Solms M, Ramesar R (2006). The molecular genetics of cognition: dopamine, COMT and BDNF. *Genes, Brain and Behavior*.5: 311-328.

Shonkoff JP (2011). Protecting brains, not simply stimulating minds. *Science*. 19 august. 333:982-983.

Shonkoff JP & Bales SN (2011). Science does not speak for itself: Translating child development research for the public and its policymakers. *Child Development*. January/February. 82(1):17-32.

Schultz, W (2006). Behavioral theories and the neurophysiology of reward. *Annu. Rev. Psychol*. 57:87-115.

Seeman T, Epel E, Gruenewald T, Karlamangla A, McEwen BS. (2010) Socio-economic differentials in peripheral biology: Cumulative allostatic load. *Ann. N.Y. Acad. Sci.* 1186:223-239.

Sheese, B. E., Voelker, P. M., Rothbart, M. K., & Posner, M. I. (2007) Parenting quality interacts with genetic variation in dopamine receptor D4 to influence temperament in early childhood. *Development and Psychopathology*. 19, 1039–1046.

Silva ERA (2004). O perfil da criança e do adolescente nos abrigos pesquisados. In: Silva ERA (Org.). *O direito à convivência familiar e comunitária: os abrigos para crianças e adolescentes no Brasil*. Brasília: IPEA/CONANDA.

Simpson JA & Belsky J (2008). Attachment theory within a modern evolutionary framework. In: Cassidy J & Shaver PR (eds.) *Handbook of Attachment – theory, research, and clinical applications*. 2nd ed. New York: The Guilford Press.

Skuse DH & Gallagher L. (2009) Dopaminergic-neuropeptide interactions in the social brain. *Trends in Cognitive Sciences.* 13(1):27-35.

Skuse DH & Gallagher L. (2011) Genetic influences on social cognition. *Pediatric Research.* 69(5):85R-91R.

Smith GD (2011). Epidemiology, epigenetics and the 'Gloomy Prospect': embracing randomness in population health research and practice. *International Journal of Epidemiology*. 40:537-562.

Solomon J & George C (2008).The measurement of Attachment Security and related constructs in infancy and early childhood. In: Cassidy J & Shaver PR (eds.) *Handbook of Attachment – theory, research, and clinical applications*. 2nd ed. New York: The Guilford Press.

Souza, J (2009). *A ralé brasileira: quem é e como vive*. Belo Horizonte: Editora UFMG.

Spangler G, Johann M, Ronai Z, Zimmermann P. (2009) Genetic and environmental influence on attachment disorganization. *J Child Psychol Psychiatry*. Aug; 50(8):952-61.

Sposati A (2009). Modelo brasileiro de proteção social não contributiva: concepções fundantes. In: *Concepção e Gestão da Proteção Social não contributiva no Brasil*. Brasília: MDS/UNESCO.

Steinberg L (2009). Should the science of adolescent brain development inform Public Policy? *American Psychologist*. November. 739-750.

Strathearn L, Li J, Fonagy P, Montague PR. (2008) What's in a smile? Maternal brain responses to infant facial cues. *Pediatrics*. Jul;122(1):40-51.

Strathearn L. (2011) Maternal neglect: oxytocin, dopamine and the neurobiology of attachment. *J Neuroendocrinol*. Nov; 23(11):1054-65.

Sugden K (2010). Serotonin Transporter genetic modifications. In: Fink G (ed). *Stress Consequences: mental, neuropsychological and socioeconomic*. Oxford, UK: Academic Press.

Suomi SJ. (2011) Risk, resilience, and gene-environment interplay in primates. *J Can Acad Child Adolesc Psychiatry*. Nov;20(4):289-97.

Swain JE. (2008) Baby stimuli and the parent brain: functional neuroimaging of the neural substrates of parent-infant attachment. *Psychiatry (Edgemont).* 5(8):28-36.

Swain JE, Lorberbaum JP, Kose S, Strathearn L. (2007) Brain basis of early parent-infant interactions: psychology, physiology, and in vivo functional neuroimaging studies. *J Child Psychol Psychiatry*.Mar-Apr; 48(3-4):262-87.

Swenson CC & Saldana L (2010). Child abuse. In: Fink G (ed). *Stress Consequences: mental, neuropsychological and socioeconomic*. Oxford, UK: Academic Press.

Tinbergen N(1963). On aims and methods of ethology. *Zeitschrift für Tierpsychologie*. 20:410-433.

Trainor BC. (2011) Stress responses and the mesolimbic dopamine system: Social contexts and sex differences. *Hormones and Behavior*. 60:457-469.

Troisi A, Frazzetto G, Carola V, Di Lorenzo G, Coviello M, D'Amato FR, Moles A, Siracusano A, Gross C. (2011a) Social hedonic capacity is associated with the A118G polymorphism of the mu-opioid receptor gene (OPRM1) in adult healthy volunteers and psychiatric patients. *Soc Neurosci*. Feb;6(1):88-97. Epub 2010 May 17.

Troisi A, Frazzetto G, Carola V, Di Lorenzo G, Coviello M, Siracusano A, Gross C. (2011b) Variation in the {micro}-opioid receptor gene (OPRM1) moderates the influence of early maternal care on fearful attachment. *Soc Cogn Affect Neurosci*. Jul 8. [Epub ahead of print]

Turkheimer E (2011). Commentary: Variation and causation in the environment and genome. *International Journal of Epidemiology*. 40:598-601.

UNESCO (2005). Políticas para a Primeira Infância: notas sobre experiências internacionais. Brasília.

Vaidya CJ & Stollstorf M (2008). Cognitive Neuroscience of Attention Deficit Hyperactivity Disorder: current status and working hypotheses. *Developmental Disabilities Research Reviews*. 14:261-267.

van den Fries L, Juffer F, van IJzendoorn MH, Bakermans-Kranenburg MJ (2009). Fostering security? A meta-analysis of attachment in adopted children. *Children and Youth Services Review*. 31:410-421.

van IJzendoorn MH & Bakermans-Kranenburg MJ. (2006) DRD4 7-repeat polymorphism moderates the association between maternal unresolved loss or trauma and infant disorganization. *Attach Hum Dev*. Dec;8(4):291-307.

van IJzendoorn MH & Sagi-Schwartz A (2008). Cross-cultural patterns of attachment: universal and contextual dimensions. In: Cassidy J & Shaver PR (eds.) *Handbook of Attachment – theory, research, and clinical applications*. 2nd ed. New York: The Guilford Press.

van IJzendoorn MH, Bakermans-Kranenburg MJ, Mesman J. (2008) Dopamine system genes associated with parenting in the context of daily hassles. *Genes Brain Behav*. Jun;7(4):403-10. Epub 2007 Oct 31.

van IJzendoorn MH, Caspers K, Bakermans-Kranenburg MJ, Beach SR, Philibert R (2010). Methylation matters: interaction between methylation density and serotonin transporter genotype predicts unresolved loss or trauma.*Biol Psychiatry*. Sep 1; 68(5):405-7. Epub 2010 Jun 29.

Vianna LW, Burgos MB, Salles PM (2007). Dezessete anos de judicialização da política. *Tempo Social*. Nov. 19(2):39-85.

Victora CG, Aquino EML, Leal MC, Monteiro CA, Barros FC, Szwarcwald CL (2011). Saúde de mães e crianças no Brasil: progressos e desafios. *The Lancet*. *Special issue: Saúde no Brasil*. Maio:32-46.

de Visser JAGM, Cooper TF, Elena SF (2011) The causes of epistasis. *Proc. R. Soc. B*. [Epub ahead of print]

Way BM, Taylor SE, Eisenberger NI. (2009) Variation in the mu-opioid receptor gene (OPRM1) is associated with dispositional and neural sensitivity to social rejection. *Proc Natl Acad Sci USA*. Sep 1;106(35):15079-84. Epub Aug 14.

Way BM & Taylor SE (2011). Genetic factors in social pain. In: MacDonald G & Jensen-Campbell LA (eds.). *Social Pain: neuropsychological and health implications of loss and exclusion*. Washington, DC: American Psychological Association.

Wegman HL & Stetler C. (2009) A Meta-Analytic review of the effects of childhood abuse on medical outcomes in adulthood. *Psychosomatic Medicine*. 71:805-812. Epub.

Weller A & Feldman R. (2003) Emotion regulation and touch in infants: the role of cholecystokinin and opioids. *Peptides*. 24:779-788.

Whittemore & Knafl (2005). The integrative review: updated methodology. *Journal of Advanced Nursing.*52(5): 546–553.

Witt SH, Buchmann AF, Blomeyer D, Nieratschker V, Treutlein J, Esser G, Schmidt MH, Bidlingmaier M, Wiedemann K, Rietschel M, Laucht M, Wüst S, Zimmermann US (2011). An interaction between a neuropeptide Y gene polymorphism and early adversity modulates endocrine stress responses. *Psychoneuroendocrinology*, 36:1010-1020.

Wong AHC, Buckle CE, van Tol HHM (2000). Polymorphisms in dopamine receptors: what do they tell us? *European Journal of Pharmacology*. 410:183–203.

Young LJ & Wang Z (2004). The neurobiology of pair bonding. *Nature Neurosci.* 7(10):1048-1054.

Zelazo PD, Chandler M, Crone EA (2010). The birth and early development of a new discipline: Developmental Social Cognitive Neuroscience. In: Zelazo PD, Chandler M, Crone EA (eds.) *Developmental Social Cognitive Neuroscience*. New York: Psychology Press.

Zimmermann P, Mohr C, Spangler G. (2009) Genetic and attachment influences on adolescents' regulation of autonomy and aggressiveness. *J Child Psychol Psychiatry*. Nov;50(11):1339-47. Epub 2009 Sep 21.

Zubieta JK, Smith YR, Bueller JA, Xu Y, Kilbourn MR,Jewett DM, Meyer CR, Koeppe RA, Stohler CS (2001). Regional Mu-opioid receptor regulation of sensory and affective dimensions of pain.*Science*. July 13. 293:311-315.

Zubieta JK, Ketter TA, Bueller JA, Xu Y, Kilbourn MR, Young EA, Koeppe RA (2003). Regulation of human affective responses by anterior cingulate and limbic μ-opioid neurotransmission. *Arch Gen Psychiatry*.60:1145-1153.

Appendix I: A Simplified Tale of Child Development for Policymakers

The Core Story

1. Child development is a foundation for community development and economic development, as capable children become the foundation of a prosperous and sustainable society.

2. Brain architecture is constructed through an ongoing process that begins before birth and continues into adulthood. As it emerges, the quality of that architecture establishes either sturdy or a fragile foundation for all the capabilities and behavior that follow.

3. Skill begets skill as brains are built in a hierarchical fashion, from the bottom up. Increasingly complex circuits and skills build on simpler circuits and skills over time.

4. The interaction of genes and experience shapes the circuitry of the developing brain. Young children serve up frequent invitations to engage with adults, who are either responsive or unresponsive to their needs. This “serve and return’’ process (what developmental researchers call contingent reciprocity) is fundamental to the wiring of the brain, especially in the early years.

5. Cognitive, emotional, and social capacities are inextricably intertwined and learning, behavior, and both physical and mental health are highly interrelated over the life course. You cannot address one domain without affecting the others.

6. Although manageable levels of stress are normative and growth promoting, toxic stress in the early years (e.g., from severe poverty, serious parental mental health impairment such as maternal depression, child maltreatment, and⁄or family violence)can damage developing brain architecture and lead to problems in learning and behavior, as well as increased susceptibility to physical and mental illness.

7. Brain plasticity and the ability to change behavior decrease over time. Consequently, getting it right early leads to better outcomes and is less costly, to society and to individuals, than trying to fix it later. We can pay now or we will pay more later for society's failure to promote healthy development in the earliest years of life.

8. Effectiveness factors make the difference between early childhood intervention programs that work and those that do not work to support children's healthy development. These factors can be measured and can inform wise investments in effective policies and programs.

Simplifying Models

Simplifying model #1: Brain architecture.

The early years of life matter because early experiences affect the architecture of the maturing brain. As it emerges, the quality of that architecture establishes either a sturdy or a fragile foundation for all the development and behavior that follow—and getting things right the first time is easier and more effective than trying to fix them later. When interpersonal experiences are disruptive, neglectful, abusive, unstable, or otherwise stressful, they increase the probability of poor outcomes. When a young child experiences excessive adversity, chemicals are released in the brain that can damage its developing architecture

Simplifying model #2: Serve and return.

Scientists now know that the interactive influences of genes and experience literally shape the architecture of the developing brain. The active ingredient in what we refer to as experience is the ''serve and return'' nature of the relationships that children have with their parents and other caregivers in their family or community. Like the process of serve and return in games such as tennis and volleyball, very young children naturally reach out for interaction through vocalizing, facial expressions, and gestures. If adults do not respond by getting in sync and engaging in responsive, complementary behaviors, the child's learning process is disrupted and there can be negative implications for later development.

Simplifying model #3: Types of stress.

Scientists talk about distinguishing among three kinds of stress experience, characterized by differing intensity and duration of elevations in heart rate, blood pressure, and a range of stress hormones (such as cortisol) that can damage organ systems when they are activated for prolonged periods of time. Positive stress, such as a physiological response to the first day in a new preschool setting, is normative and short-lived. Tolerable stress, which is associated with potentially serious threats such as significant family illness or a natural disaster, could be damaging to young children but they are buffered from longterm, adverse effects by the presence of supportive relationships, like a strong family when a loved one dies. In contrast, toxic stress lasts longer, lacks consistent supportive relationships, and can cause damage to the developing brain and other organ systems that leads to lifelong problems in learning, behavior, and both physical and mental health. Toxic stress in early childhood can be precipitated by extreme poverty, physical abuse, chronic neglect, or severe maternal depression or parental substance abuse, among other risk factors.

Source: Shonkoff & Bales, 2011.

Appendix II: United Nations Millennium Development Goals

Poverty Targets by 2015:

- Reduce by half the proportion of people living on less than a dollar a day.
- Reduce by half the proportion of people who suffer from hunger.

Education Target by 2015:

- Ensure that all boys and girls complete a full course of primary schooling.

Gender Equality Target by 2015:

- Eliminate gender disparity at all levels of education and empower women.

Child Mortality Target by 2015:

- To reduce child mortality by two-thirds, from 93 children of every 1,000 dying before age five in 1990 to 31 of every 1,000 in 2015.

Maternal Health Target by 2015:

- Reduce the maternal mortality ratio by three quarters.

Disease Targets by 2015:

- Halt and begin to reverse the spread of HIV/AIDS.
- Halt and begin to reverse the incidence of malaria and other major diseases.

Environment Target by 2015:

- Reduce by half the proportion of people without access to safe drinking water and basic sanitation.

Development Targets by 2015:

- Develop further an open trading and financial system that includes a commitment to good governance, development and poverty reduction — nationally and internationally.

- Address the least developed countries' special needs, and the special needs of landlocked and small island developing states.
- Deal comprehensively with developing countries' debt problems.
- Develop decent and productive work for youth.
- In cooperation with pharmaceutical companies, provide access to affordable essential drugs in developing countries.
- In cooperation with the private sector, make available the benefits of new technologies — especially information and communications technologies.

Source: Nações Unidas, 2002.