

Epigenetics and its implications for Psychology

Héctor González-Pardo and Marino Pérez Álvarez
Universidad de Oviedo

Abstract

Background: Epigenetics is changing the widely accepted linear conception of genome function by explaining how environmental and psychological factors regulate the activity of our genome without involving changes in the DNA sequence. Research has identified epigenetic mechanisms mediating between environmental and psychological factors that contribute to normal and abnormal behavioral development. **Method:** the emerging field of epigenetics as related to psychology is reviewed. **Results:** the relationship between genes and behavior is reconsidered in terms of epigenetic mechanisms acting after birth and not only prenatally, as traditionally held. Behavioral epigenetics shows that our behavior could have long-term effects on the regulation of the genome function. In addition, epigenetic mechanisms would be related to psychopathology, as in the case of schizophrenia. In the latter case, it would be especially relevant to consider epigenetic factors such as life adversities (trauma, disorganized attachment, etc.) as related to its clinical manifestations, rather than genetic factors. Moreover, epigenetics implies overcoming classical dualist dichotomies such as nature-nurture, genotype-phenotype or pathogenesis-pathoplasty. **Conclusions:** In general, it can be stated that behavior and environment will finally take on a leading role in human development through epigenetic mechanisms.

Keywords: epigenetics, gene, behavioral epigenetics, memory, schizophrenia.

Resumen

La epigenética y sus implicaciones para la Psicología. Antecedentes: la epigenética está cambiando la concepción lineal que se suele tener de la genética al mostrar cómo eventos ambientales y psicológicos regulan la actividad de nuestro genoma sin implicar modificación en la secuencia de ADN. La investigación ha identificado mecanismos epigenéticos que juegan un papel mediador entre eventos ambientales y psicológicos y el desarrollo normal y alterado. **Método:** el artículo revisa el campo emergente de la epigenética y sus implicaciones para la psicología. **Resultados:** entre sus implicaciones destacan la reconsideración de la relación entre genes y conducta en términos de procesos epigenéticos que acontecen a lo largo de la vida y no solo prenatalmente como se asumía. La epigenética conductual muestra que nuestra conducta puede tener efectos a largo plazo sobre la función genómica. Otra implicación concierne a la psicopatología, señaladamente a la esquizofrenia. Más que de causas genéticas, habría que hablar de mediadores epigenéticos entre las adversidades de la vida (trauma, apego desorganizado) y formas clínicas. Asimismo, la epigenética implica la superación de dicotomías dualistas como herencia-medio, genotipo-fenotipo y patogenia-patoplastia. **Conclusiones:** en general, se puede decir que la conducta y el ambiente asumirán finalmente un papel protagonista en el desarrollo humano mediante mecanismos epigenéticos.

Palabras clave: epigenética, gen, epigenética de la conducta, memoria, esquizofrenia.

The twentieth century was the century of genes (Barahona & Ayala, 2009; Keller, 2000). Indeed, it was precisely in 1900 that Gregor Mendel's experiments, performed more than thirty years earlier, were rediscovered. Mendelian factors were redubbed as genes by Wilhelm Johannsen in 1909, who also introduced, in 1911, the genotype-phenotype distinction. The combination of Mendelian genetics and the Darwinian theory of evolution led to the synthetic theory of evolution during the 1930s and 40s. In 1953, James Watson and Francis Crick discovered the "double-helix" molecular structure of DNA (deoxyribonucleic acid), described by them as "the secret of life". In 1958, Crick himself announced "the central dogma" of molecular biology, stating that the hereditary "biological information" flows in a single direction: from DNA transcribed to

RNA (ribonucleic acid), which is in turn translated into proteins. The central dogma assumed a unidirectional determinism of the *phenotype* (the set of observable characteristics of an organism, such as its morphology, physiology and behavior) by the *genotype* (the particular set of genes contained in the DNA of an organism). The 1970s saw the arrival of sociobiology, the proposal of the "selfish gene" theory (1976), and hence the development of a kind of "genetic fundamentalism" on human nature. Such beliefs are exemplified by a famous quote from Watson during the promotion of the Human Genome Project (HGP): "we used to think our fate was in our stars. Now we know that, in large measure, our fate is in our genes" (Jaroff, 1989). As an epilogue to the developments of the twentieth century, the HGP was launched in 1990 with a budget of US \$2,800 million. James Watson was appointed head of the project, aiming to determine the sequence of genes and their location in the DNA (genome), with the promise and hope of deciphering "the language of life" and the key to many diseases. The HGP was completed in 2003. What was found, and where are we now?

The most surprising result according to Francis Collins, actual director of the HGP, was that "human DNA only contains about

twenty thousand genes encoding proteins. We hoped to find many more genes. Even a humble earthworm has more than nineteen thousand genes!" (Collins, 2011, p. 31). As Collins himself acknowledges, "a decade after sequencing the human genome, the promises of this project remain unfulfilled" (p. 27). Another unexpected result was that only 1.5% of the DNA is directly related to protein synthesis (coding DNA). The remainder was earlier mostly considered as "junk DNA" or noncoding DNA because its function was largely unknown (Collins, 2011, p. 313). However, this notion has recently been discarded, following the results of the international ENCODE (Encyclopedia of DNA Elements) project consortium, which indicate that most of the noncoding DNA actually regulates the function of the coding DNA itself. This is a breakthrough discovery that challenges our present concept of protein-coding genes as fundamental units of the genome responsible for hereditary biological traits (Stamatoyannopoulos, 2012).

Today, the central dogma of molecular biology is untenable. Identical genotypes can lead to different phenotypes in most living organisms. In particular, monozygotic twins who supposedly share identical genes can have very different morphological and psychological traits, as well as different vulnerability to diseases that arise during their lifetime (Fraga, Ballestar, Paz, Ropero, Setien, Ballestar, ... & Esteller, 2005). Individual differences challenge the impact of genetics on the general population, since "the DNA sequences of two human beings randomly chosen is 99.6% identical and unrelated to the nationality of their ancestors" (Collins, 2011, p. 167). In fact, clonation cannot produce identical organisms because the genesis of an individual depends not only on his or her DNA sequence, but also on the cellular and tissue environments, the organism itself and the surrounding ecosystem in which it is developing. The term "development" may be misleading in suggesting that everything is "coiled" or folded in the DNA helix and ready to be "uncoiled" or unfolded at a particular stage of life. Moreover, the helpful metaphors commonly used to explain the function of the gene and the genome, such as "code", "program" or "information", should not be understood literally. This would be akin to "confusing the map with the territory". Indeed, most events that actually affect a living organism are above and beyond genetics, which is precisely what epigenetics actually means.

Epigenetics has major implications for psychology (Harper, 2005; Masterpasqua, 2009; Zhang & Meaney, 2010). First of all, the "heritability" percentages attributed to genes and environment, as in the case of the intelligence quotient or schizophrenia, are no longer valid, given not only the methodology used (Lewontin, 1974/2006; Vineis & Pearce, 2011) but also the "interactionist consensus", which may provide a solution to the nature versus nurture problem (Robert, 2004). This consensus acknowledges that both genotype and environment are necessary, but insufficient on their own, as causal influences on human development and behavior. It is frequently believed that genome and environment are separate entities that interact, rather than ongoing, dynamic "construction" and "deconstruction" processes between heterogeneous resources that assemble themselves in contingency cycles over the lifetime (Oyama, Griffiths, & Gray, 2001; Sánchez & Loredó, 2007). Paradoxically, and ironically, epigenetics is bringing back the leading role of organisms' environment and behavior, by including their effects on genome function. In addition, it opens up the possibility of memory being stored in the DNA or the "epigenome", so that our experiences may be embedded in our genome by epigenetic mechanisms.

What is epigenetics?

Epigenetics can be described as the study of the complex interactions (or 'constructions' and 'deconstructions') underlying the development of an organism over its lifetime. Modern epigenetics was introduced by Conrad Waddington in 1942, defined as "the branch of biology which studies the causal interactions between genes and their products which bring the phenotype into being" (Jablonka & Lamb, 2002). In particular, it deals with the study of reversible changes in gene function that are mitotically and/or meiotically heritable and that do not entail a change in the DNA sequence (Holliday, 2002).

Epigenetic processes, far from being rare, are ubiquitous in the development of organisms. The process of cell differentiation involving the transformation of a single cell or totipotent zygote (with the ability to be any cell type) into each of the more than 200 different specialized cells in the human body is largely epigenetic. Epigenetic processes mean that the morphology and function of each cell type are quite different (neurons, muscle cells, liver cells, white blood cells, rods and cones in the retina, etc.). The relevance of epigenetic processes in cell differentiation was highlighted by the award of the 2012 Nobel Prize for medicine to John Gurdon and Shinya Yamanaka, who discovered that differentiated or mature cells can be reverted to an earlier pluripotent or embryonic state by introducing a combination of "only" four genes. Epigenetic changes are also related to the development of various diseases, including cancers or genetically-inherited diseases – fragile X syndrome, Prader-Willi syndrome, Angelman syndrome, several mental disorders, and so on. Epigenetic mechanisms explain how it is possible that the environment can modify neural and behavioral functions. In summary, epigenetics involves the study of how the environment shapes our genes (Francis, 2011).

Epigenetic modifications of DNA invalidate the central dogma of molecular biology. It is now known that RNA can be converted back to DNA and even that RNA itself interferes with its own transcription (for example, through interfering RNA or iRNA)

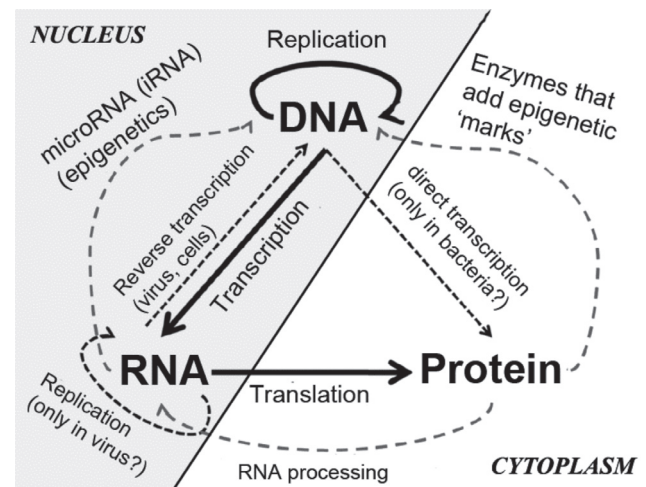


Figure 1. Schematic representation of the "central dogma of molecular biology" adapted from the original by Crick in 1958 and modified according to current knowledge. Black arrows show processes initially proposed by Crick, and broken lines represent processes discovered later, many of them not present together in all living organism. Note that epigenetic processes involve regulation of gene transcription from DNA without modifications in its sequence, and appear to be commonly found in animal cells

in animal cells. It is also well known that proteins continuously interact with both the DNA and RNA in the cell nucleus through epigenetic mechanisms throughout the entire cell cycle. Figure 1 shows a simplified schema of the central dogma of molecular biology modified in accordance with present knowledge.

It is known also that behavior and lifestyle are linked to epigenetic modifications. Hence, traditional linear causality gives way to reciprocal causality at both the developmental and evolutionary levels (Gottlieb, 2000; Laland, Sterelny, Odling-Smee, Hoppitt, & Uller, 2011).

What is the meaning of *gene* today?

Epigenetics profoundly alters our understanding of the traditional conception of the word “gene”. It has lost its original meaning, and there is in fact no universally accepted definition today. It was traditionally believed that a gene was “the smallest indivisible unit of transmission, recombination, mutation and gene function” (Portin, 2002). Genes cannot be compared to beads on a necklace or seeds within a shell. We have known since the 1970s that there are tandemly repeated genes, alternative gene splicing, mobile genes, genes with overlapping reading frames (the same gene encodes for different proteins according to the reading start point), pseudogenes (genes that lost their function), and distant regulatory promoters of gene activation/expression or silencing, among many other “abnormal” phenomena that complicate the traditional view of the gene as a discrete unit of heredity in DNA. Furthermore, a gene “may have no fixity at all; its existence is both transitory and contingent, depending critically on the functional dynamics of the entire organism” (Keller, 2000, p. 71). This is why there is currently no simple definition of the gene. “The gene has become many things —no longer a single entity but a word with great plasticity, defined only by the specific experimental context in which it is used” (Keller, 2000, p. 69).

Narrowly speaking, a gene can be defined from a biochemical point of view as a particular sequence of molecules known as “bases” or “nucleotides” (adenine, guanine, cytosine or thymine) that are linked to one another in a chain by chemical bonds constituting DNA, a type of nucleic acid. A gene can be transmitted from cell to cell or inherited over several generations of living beings. In order to be functional in cells, genes should be first “copied” or *transcribed* into a sequence of another type of nucleic acid containing similar (complementary) bases, and known as RNA. As opposed to DNA, RNA transcripts are fragments of nucleic acids that can move across living cell compartments out of the cell nucleus or the mitochondria (also containing small amounts of DNA). It should be mentioned that DNA is not a self-replicating macromolecule as commonly assumed, but it is another type of biomolecule like lipids or proteins interacting with one another to trigger biochemical reactions leading to DNA replication. In fact, even a virus, which is only DNA or RNA surrounded by a protective coat of protein, can only replicate inside living cells using their proteins and lipids.

A single gene is rarely responsible for the synthesis of an entire protein, but rather a shorter fragment called a peptide. Frequently, several genes are involved in the synthesis of a single protein, and likewise the same gene can lead to the synthesis of many proteins (an average of 5 to 6 proteins). To further complicate matters, both the RNA and related peptides “mature” or are further modified (“processed”) by enzymes present in the cell nucleus,

cytoplasm, and different organelles (endoplasmic reticulum, the Golgi apparatus, mitochondria, etc.) that cut and splice fragments of these biomolecules, making it difficult to determine whether a single gene will be responsible for a protein in a particular cell type. Moreover, most RNA transcribed from a gene is “non-coding”, meaning that it is not translated into peptides or proteins (examples being ribosomal RNA, transfer RNA, interfering RNA or microRNAs). In this regard, Richard J. Roberts, Nobel laureate and former director of the HGP, admitted after the publication of the genome data in 2001 that despite the sequencing of the entire human genome, it would actually be necessary to determine the RNA transcripts to demonstrate the function of a particular gene in every cell type, or even better, the “proteome” or set of all proteins synthesized in each cell type (Venter, Adams, Myers, Li, Mural, Sutton, ..., & Zhu, 2001). In fact, the results of the previously mentioned ENCODE project will require substantial rethinking of the gene concept as the basic unit of the genome instead of functional DNA products like RNA transcripts (Stamatoyannopoulos, 2012).

If the gene is a structural entity for molecular biologists, for developmental biologists it is a functional and temporary entity contingent upon a dynamic organism. On the other hand, evolutionary biologists and population geneticists consider the gene to represent a static unit of calculation, a construct rather than a structure (Griffiths & Neumann-Held, 1999; Portin, 2002). According to the developmental systems perspective, a gene is a developmental resource defined by its molecular sequence, which is itself undetermined as regards phenotype (Moss, 2001, p. 89). As for the evolutionary perspective, “an evolutionary gene is a theoretical entity with a role in a particular, atomistic approach to the selection of phenotypic and extended phenotypic traits. Evolutionary genes need not, and often do not, correspond to specific stretches of DNA” (Griffiths & Neumann-Held, 1999, p. 661). “Population geneticists can, on their part, treat the gene as a simple calculation unit segregating in the population” (Portin, 2002, p. 274).

In seeking an up-to-date definition of the gene we face a dilemma: between, on the one hand, rendering obsolete the traditional concept of gene as a discrete unit, and on the other, attempting a trade-off between the old and the new definitions (Gerstein, Bruce, Rozowsky, Zheng, Du, Korbel, ..., & Snyder, 2007). With the latter option, the definition could be along the following lines: “The gene is a union of genomic sequences encoding a coherent set of potentially overlapping functional products” (Gerstein et al., 2007, p. 677).

Another solution to this dilemma – based on current knowledge – would involve considering at least two different concepts of gene, as already mentioned (Griffiths & Neumann-Held, 1999; Keller, 2000; Moss, 2001). As the renowned physicist and molecular biologist Evelyn Fox Keller states: “the evidence accruing over recent decades obliges us to think of genes as (at least) two very different kinds of entities: one, a structural entity—maintained by the molecular machinery of the cell so that it can be faithfully transmitted from generation to generation; and the other, a functional entity that emerges only out of dynamic interaction between and among a great many players, only one of which is the structural gene from which the original protein sequences are derived. Or, to put it just a little differently, the function of a structural gene depends not only on its sequence but, as well, on its genetic context, on the chromosomal structure in which it is embedded (and which is itself subject to developmental regulation), and on

its developmentally specific cytoplasmic and nuclear context” (Keller, 2000, pp. 71-72). In fact, it may indeed be that the concept of gene itself represents an obstacle to our understanding of cell biology. According to the biologist Raphael Falk (1986) “the gene is [...] neither discrete [...] nor continuous [...], nor does it have a constant location [...], nor a clearcut function [...], nor even constant sequences [...] nor definite borderlines”.

Epigenetic mechanisms

Our genome contained in the strands of nucleic acids making up the famous double-helix is not alone or merely encapsulated (like seeds in a shell, waiting to be opened), but rather attached to a wide variety of organic compounds. These chemical attachments are fundamental to gene transcription, a process involving the copying of DNA sequences into RNA that may (or may not) be translated into peptides. RNA is a biomolecule very similar to DNA but much shorter, more fragile and mobile, which can interact with complex macromolecules called ribosomes (which themselves contain another type of RNA combined with proteins). Ribosomes are directly involved in the biosynthesis of peptides or short-sequence amino acids (20 different types) enchain by peptide bonds, based on a fragment of “messenger RNA” or mRNA that acts as a sort of template in a process known as “translation”. However, most of the RNA found in a cell is related to the regulation of DNA transcription, acting as an ‘on-off’ switch for particular genes that would be ‘expressed’ or ‘silenced’ by epigenetic mechanisms. In fact, a protein is composed of one or many folded polypeptides (each one containing more than 50 amino acids) with a three-

dimensional molecular structure and with many possible functions in cells (structural or physiological).

Each human cell contains approximately 2 meters of DNA if were stretched end-to-end; yet the nucleus of a human cell, where DNA is ‘supercoiled’ or tightly packed, is only about 6 micrometers (millionths of a meter) in diameter. In particular, DNA is packed with many proteins in a macromolecule known as ‘chromatin’ that makes up the ‘chromosomes’. Chromatin contains highly condensed DNA wrapped around alkaline or basic proteins called ‘histones’ in the cell nucleus. Figure 2 shows a schematic representation of chromatin structure, as well as the main epigenetic mechanisms involved in chromatin remodeling.

Chromatin strengthens the fragile DNA and prevents against possible damage (mutations) or breakage, even by repairing it (Bhaumik, Smith, & Shilaifard, 2007). Since DNA is tightly condensed in chromatin, it is only made accessible by particular enzymatic complexes during the transcription process to form RNA. The latter process occurs globally during cell division in the nucleus (mitosis or meiosis), but it also takes place continuously in non-dividing cells such as neurons. On the other hand, condensed DNA in chromatin wraps around repeating groups of eight histones called ‘nucleosomes’, which are organized like “beads on a string”. In turn, nucleosomes are coiled together with another type of histone to produce a condensed chromatin fiber that can be further condensed (Figure 2). Therefore, DNA function can be regulated (temporarily or permanently) by chromatin remodeling or modification that determines gene expression or silencing depending on the accessibility of DNA for transcription into RNA.

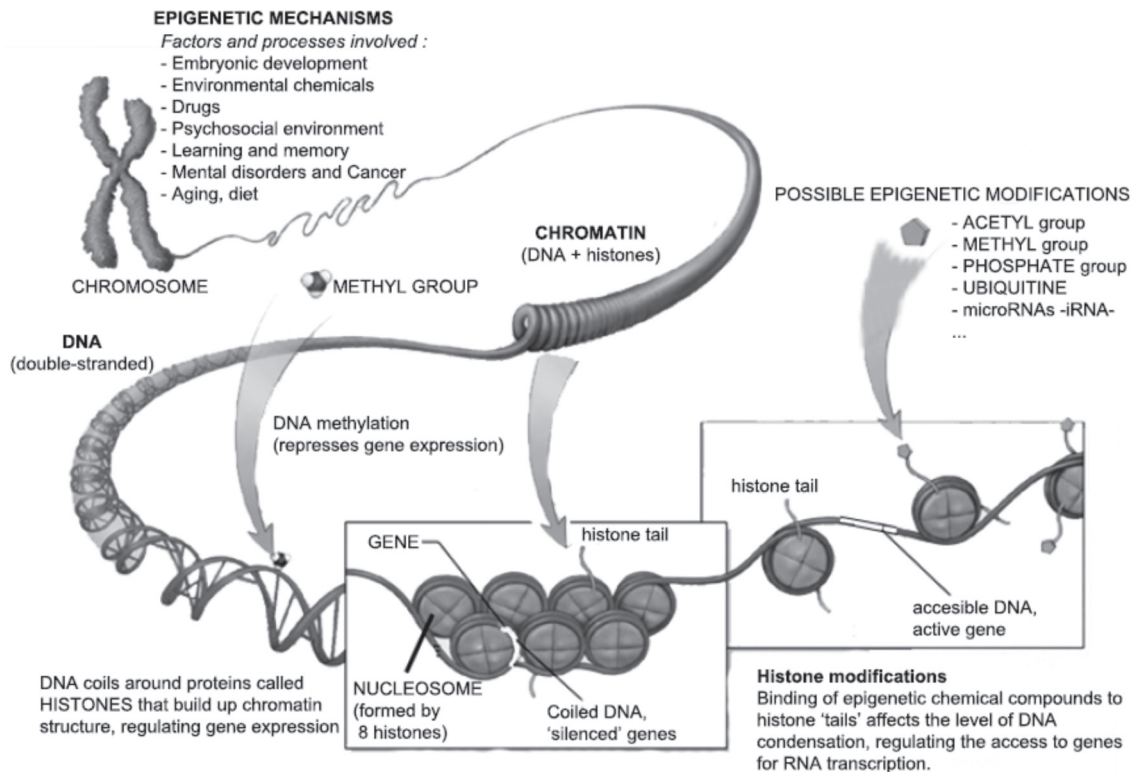


Figure 2. Simplified schematic drawing of chromatin structure showing the possible mechanisms of action of epigenetic factors on both DNA and histone “tails” present in chromatin. For example, acetylation activates or promotes gene transcription whereas histone methylation could have opposing effects on gene transcription according to the histone type and exact methylation point at histone “tails”

There are many proteins found in the cell nucleus that regulate DNA transcription, and which are known as “transcription factors”. Additional factors affecting RNA translation into peptides and proteins have also been described. Moreover, several additional proteins may even alter both messenger RNA and peptides/proteins after transcription or translation processes. All of these regulating proteins are also “coded” in gene sequences contained in DNA. However, epigenetic regulation of gene expression or silencing related to these factors depends on the particular experiences and environmental conditions during the life of an organism, and is not therefore directly ‘coded’ in DNA itself. Epigenetic processes may be heritable or at least relative stable in the cells of a particular organism. These processes indeed represent an interface between genes and environment. Several epigenetic mechanisms have been described and are still being investigated.

At least three main epigenetic mechanisms have been described: a) direct DNA methylation; b) histone modifications through chemical reactions such as methylation, phosphorylation or acetylation; and c) the synthesis of small RNA fragments that interfere with DNA transcription (Fig. 2). Epigenetic modifications involve changes in gene transcription or ‘expression’ without alteration of the underlying DNA sequence.

Indeed, DNA itself can be methylated at particular sites on cytosine-guanine nucleotide pairs for example during embryonic development, leading to cell differentiation through the “silencing” of several genes involved in cell differentiation and replication. However, DNA methylation continues during postnatal development and aging in all cell types, and is also highly dependent on many environmental factors. Abnormal patterns of DNA methylation have been the focus of extensive research for decades, since they are associated with several types of cancer.

Overall, the most extensively studied epigenetic modifications are histone modifications such as methylation or acetylation of histone tails. In neither case does the chemical reaction always involve gene ‘silencing’ through the promotion of chromatin condensation. Conversely, histone acetylation promotes gene ‘expression’ by loosening up the DNA wrapped around histones and therefore opening it up for transcription (forming what is known as “euchromatin” instead of condensed “heterochromatin”). Histones are particularly accessible to enzymes because some have “tails” or unfolded ends of the protein that extend beyond the DNA wrapped around them. Histone tails are necessary for physical interaction between each other in a nucleosome, but they can be used as binding sites for proteins involved in DNA transcription. Many possible chemical modifications of the terminal amino acids that constitute these tails and related enzymes have been discovered, including the reactions mentioned above.

A third mechanism of epigenetic regulation was recently discovered in mammals by the detection of three classes of small fragments of non-coding RNAs (not transcribed into proteins) known as microRNAs that are important for gene expression and silencing (Berezikov, Cuppen, & Plasterk, 2006). For example, a class of small RNA fragment known as siRNA (small interfering RNA) can bind to complementary sequences of the messenger RNA suppressing its translation into peptides or proteins. MicroRNAs act together with DNA methylation and chromatin remodeling for the regulation of gene expression (Saetrom, Snøve, & Rossi, 2007).

Traditionally, epigenetic modifications were thought to be both irreversible and heritable, but this view has recently been challenged by different studies suggesting a more dynamic conception of

reversible epigenetic regulation underlying the complex interactions between genes and environment (Molfese, 2011).

Behavioral epigenetics: how the environment ‘gets into the mind’

For some years now, the relationship between genes and behavior has been studied in terms of epigenetic processes occurring during one’s lifetime rather than just prenatally, as was previously held. The first international scientific meeting on “behavioral epigenetics” was held in 2010 in Boston (USA) and organized by the New York Academy of Sciences at the University of Massachusetts. Several topics were featured, including basic biochemical and cellular mechanisms of epigenetic modulation during normal and pathological development, epigenetic mechanisms of psychopathology, and learning processes. “Behavioral epigenetics” was defined as the application of the principles of epigenetics to the study of physiological, genetic, environmental and developmental mechanisms of behavior in human and nonhuman animals (Lester, Tronic, Nestler, Abel, Kosofsky, ..., & Wood, 2011). Epigenetics is therefore an interdisciplinary approach including psychology, psychiatry, genetics, biochemistry and several branches of the neurosciences.

Epigenetic processes have been directly implicated in several rare genetic neurodevelopmental disorders (e.g., fragile X syndrome, Rett syndrome, Angelman syndrome, Prader-Willi syndrome), and many types of cancers are linked to abnormal chromatin and DNA methylation, since these are related to cell proliferation. In this regard, it should be noted here that most neurons (but not glial cells) are the only type of cells that lose their capacity for division after birth. However, epigenetic regulation (including DNA methylation or histone modification) is possible in post-mitotic or differentiated neurons, and is therefore a principal mechanism underlying steady changes in gene expression involved in both normal brain function (for example, learning and memory) and mental disorders (drug addiction, depression, anxiety, eating disorders, schizophrenia, and so on). Most epigenetic mechanisms have lasting effects on behavior, but seem not to be necessarily irreversible or even heritable, though this aspect is currently a matter of debate.

Epigenetic mechanisms would explain the changes in neuronal plasticity associated with memory consolidation, drug addiction or severe mental disorders like schizophrenia. Therefore, epigenetic “marks” could be involved in a kind of “cellular memory” of particular environmental events, as in the case of learning and memory processes. It is thus possible that the psycho-social environment or our life experiences (traumatic or pleasant), also classically known as “nurture”, have a strong impact on our brain through relatively enduring epigenetic modifications at a cellular level. It may also be that epigenetic mechanisms modulate “molecular memory” processes related, for example, to emotional memory in fear conditioning (Day & Sweatt, 2010) and drug-seeking behavior or its extinction (Robison & Nestler, 2011). In summary, behavioral epigenetics really studies how the environment, including of course the social environment, “gets into the mind” (Toyokawa, Uddin, Koenen, & Galea, 2012), or how early life experiences become embodied in the genome (Szyp & Bick, 2012).

More than sixty years ago, the renowned American psychologist Karl Lashley tried unsuccessfully to find the “engrams” or memory traces in the rat brain. However, he even suggested that immediate

memory could be maintained by some sort of after-discharge of the originally excited neurons, and he speculated about possible structural changes in the cell body and dendrites of neurons associated with more permanent memories (Lashley, 1950). It has been known for several decades that protein synthesis is essential for forming long-term memories linked to the strengthening of synaptic contacts (Agranoff, Davis, & Brink, 1965; Davis & Squire, 1984). In this regard, epigenetic mechanisms have been critically involved in the regulation of the synaptic plasticity required for long-term memory formation (Dulac, 2010; Bird, 2007; Levenson & Sweatt, 2005). In particular, chromatin or DNA methylation would act as “epigenetic marks or tags” at the cellular level during the process of long-term memory consolidation, as a sort of “cellular memory”. Moreover, it has been found that chromatin or DNA methylation in neurons of the cerebral cortex could even be reversible, depending on individual experiences throughout the lifespan (Miller, Gavin, White, Parrish, Honasoge, Yancey, ..., & Sweatt, 2010).

Several experiments in rodents have demonstrated that the formation and recall of contextual fear memories can be either improved or impaired by drugs that act on enzymes involved in the methylation or acetylation of histones (Levenson & Sweatt, 2005). In addition, it has been reported that both DNA and chromatin methylation in neurons as related to synaptic plasticity are essential for memory consolidation (Day & Sweatt, 2010; Levenson & Sweatt, 2005). Furthermore, transgenic mice lacking enzymes involved in histone methylation show impaired memory particularly in contextual fear tests (Gupta, Kim, Artis, Molfese, Schumacher, ..., & Lubin, 2010). Epigenetic “marks” would be especially associated with the process of long-term memory consolidation in neurons of the cerebral cortex, as several authors suggest (Lèsburgueres, Gobbo, Alaux-Catin, Hambucken, Trifilieff, & Bontempi, 2011). Recently, the epigenetic regulation of the genome by microRNAs (which are, as previously mentioned, small non-coding RNA fragments that regulate the translation of mRNA into proteins) has also been proposed as an important factor for neural plasticity and memory in the adult brain (Bredy, Lin, Wei, Baker-Andersen, & Mattick, 2011). Therefore, the search initiated by Lashley for the elusive “memory traces” may gradually be reaching its culmination thanks to the discovery of epigenetic mechanisms in brain cells.

The influence of social environment on the epigenome

A breakthrough discovery in behavioral epigenetics was reported some years ago in the prestigious journal *Nature Neuroscience* (Weaver, Cervoni, Champagne, D’Alessio, Sharma, ..., & Meaney, 2004). The leading research group headed by Meaney studying the effects of maternal care on offspring behavior and brain development, found that, after birth, rat mothers frequently lick and groom their offspring, and this kind of nurturing or maternal behavior has a deep impact on their pups’ brain development and neuroendocrine stress response. Although the effect of the amount of maternal care on physiological stress response has been well known for decades, Meaney discovered that the amount of maternal care also seems to literally shape the offspring’s brain and behavior through epigenetic modification of their neurons (Weaver et al., 2004). In particular, the neglected newborns that received less maternal care were more sensitive to the endocrine and behavioral effects of stressful events as adults. For example,

their corticosterone plasma levels were higher than newborns that had been frequently licked by their mothers. Corticosterone is a hormone homologous to human cortisol, released during the physiological stress response. Moreover, the brains of the neglected newborns also showed low density of glucocorticoid receptors (for corticosterone and related hormones), which would explain their abnormal stress response (Liu, Diorio, Tannenbaum, Caldji, Francis, Freedman, ..., & Meaney, 1997).

The most relevant finding of the studies by Meaney is the demonstration of a link between the level of DNA methylation on genes involved in the generation of glucocorticoid receptors and their density in neurons. They also proved that methylation levels could be reversed by short-term intracerebral administration of certain drugs, a result suggesting that methylation of genes causes enduring changes in their expression, but is not an irreversible process, as traditionally believed (Weaver et al., 2004). This was the first evidence that the psychosocial environment during infant development could have a profound impact on physiological and behavioral response to stress in adulthood. Additional studies showed that even the amount of maternal care in female rats could be heritable through similar epigenetic mechanisms (Gudsnuk & Champagne, 2011). Since early adverse experiences such as abuse, neglect and other traumatic events during childhood have been implicated in the etiology of several mental disorders including schizophrenia, the study of epigenetic factors in psychopathology is an emerging research field.

Epigenetics of psychopathology: The case of schizophrenia

Recent studies on the epigenetic links between social factors and clinical manifestations have provided insights about susceptibility to and protection against mental disorders (Dudley, Li, Kobar, Kippin, & Bredy, 2011; Hochberg, Feil, Constancia, Fraga, Junien, Carel, ..., & Waterland, 2011; Murgatroyd & Spengler, 2011; Rutten & Mill, 2009). It is no longer a matter of an *ex post facto* or retrospective estimation of genetic vulnerability, but rather one of addressing the question of how social-environmental aspects would be translated into psychopathological consequences (Toyokawa et al., 2012). The aforementioned studies reporting how maternal care experiences influence the development of adult behavior are paradigmatic examples highlighting the already-known social origin of mental disorders. In the words of Murgatroyd and Splange: “understanding how early life experiences can give rise to lasting epigenetic memories conferring increased risk for mental disorders is emerging at the epicenter of modern psychiatry” (Murgatroyd & Spengler, 2011, p. 11).

The case of schizophrenia is particularly significant because it is traditionally assumed that it has a strong genetic basis. In spite of intensive research over decades, no single *gene* or *genes* have been identified that *cause* schizophrenia (Hamilton, 2008). In addition, the assumed heritability of schizophrenia remains unexplained, and neither candidate gene approaches attempting to associate single genes with the disorder, nor recent genome-wide association studies have been successful (Gebicke-Haerter, 2012). In fact, what have been identified are social causes of schizophrenia (Fisher & Craig, 2008; Liotti & Gumley, 2008; Morgan & Hutchinson, 2010; Varese, Smeets, Drukker, Lieverse, Lataster, Viechtbauer, ..., & Bentall, 2012), probably mediated by epigenetic mechanisms (Labonté, Suderman, Maussion, Navaro, Yerko, Mahar, ..., & Turecki, 2012; Read, Bentall, & Rose, 2009; Rutten & Mill, 2009).

In this regard, it is known, for example, that the frontal cortex of suicide victims diagnosed with major psychosis has abnormal methylated DNA (Mill, Tang, Kaminsky, Khare, Yazdanpanah, Bouchard, ..., & Petronis, 2008), and differences have also been reported in the epigenetic regulation of glucocorticoid receptors in the hippocampus of individuals with a history of severe abuse during childhood (Labonté et al., 2012; McGowan, Sasaki, D'Alessio, Dymov, Labonté, Szyf, ..., & Meaney, 2009). Epigenetics, together with the known etiological role of life adversities, restore schizophrenia in a developmental perspective without assuming a predetermined genetic origin, but perhaps acknowledging epigenetic “marks” related to life experiences.

On the other hand, the epigenetic “marks” found should not be considered (genetic) causal factors of schizophrenia (Roth, Lubin, Sodhi, & Kleinman, 2009; Toyokawa et al., 2012). Given the mediating role of epigenetic mechanisms between social factors and clinical manifestations, the etiological load of schizophrenia would tilt the balance towards social factors (life adversities, etc.). Accordingly, a socio-evolutionary model of schizophrenia has been proposed as an alternative to the current neuroevolutionary or neurodevelopmental model (Fisher & Craig, 2008; Morgan & Hutchinson, 2010).

Schizophrenia, like any other human condition, should be understood within a particular social and cultural context. The most readily recognizable of such contexts is that linked to urban lifestyles (“urbanicity”), which can give rise to a kind of schizoid personality typically associated with modern society, and exacerbated by life adversities such as trauma, disorganized attachment or migration (Pérez-Álvarez, 2012). The path between life adversities and schizophrenia would be marked by “footprints” including epigenetic changes (DNA methylation, histone modifications, regulation of glucocorticoid receptors, dopaminergic, GABAergic or glutamatergic dysfunctions, etc.) and abnormal psychological processes (paranoid delusions, dissociative experiences, depersonalization, etc.). Figure 3 shows the possible epigenetic link between life adversities and schizophrenia.

Although many epigenetic studies suggest the possibility of using drug-centered therapy to reverse the effects of epigenetic “marks”, there is also support for the validity of therapies based

on social conditions, perhaps with better knowledge of the facts. Since social conditions induce epigenetic changes, they might also counteract such changes by generating alternative social conditions that will promote protection against mental disorders instead of vulnerability to them. The viability of psychological therapies even without medication is in line with the socio-evolutionary model (Pérez-Álvarez & García-Montes, 2012). According to Read, Bentall and Rose (2009), it is time to abandon the bio-bio-bio model of psychosis hidden behind the bio-psycho-social label.

Conceptual implications

The “epigenetic turn” implies reconsidering the long-held dichotomies of classical genetics, such as nature-nurture, genotype-phenotype, stress-vulnerability and pathogenesis-pathoplasty, which could be seen as redoubts of Cartesian dualism (Newman, 1988; Nicolosi & Ruivenkamp, 2012). The modern dualist version in biology is mainly based on the genotype-phenotype distinction, revolving around words such “code”, “information”, “program” or “instructions” – all of them metaphors taken from information theory, whose initial development coincided with that of molecular biology (Kay, 2000; Weigmann, 2004). Genes were attributed with the property of having a plan or encoded *form* of life that potentially materializes into a *substance* called an organism. Hence, genes represent a modern version of the traditional *form-substance* dualism and preformationism.

The challenge for epigenetics is to overcome this modern dualism based on genetics and preformationism. As previously mentioned, epigenetics as introduced by Waddington has its roots in Aristotle, who argued that development was progressive, despite the established view in his time that organisms were already preformed in the embryo. Although genetics does not support the existence of a miniature version of an organism, it does indeed support it as encoded by a series of instructions or by information.

In order to avoid the old dualisms, in the light of modern epigenetics it should be made clear that a gene does not itself code for information and instructions, but it could be better understood as a series of processes and events involved in the union of a particular DNA fragment and other non-DNA entities (biomolecules such as proteins, RNA or polysaccharides) leading to the synthesis of particular polypeptides or RNA fragments with different functions in an organism. This is a contextual and relational concept of gene, which always takes into account its interdependence and co-determination within the cellular environment of an organism (Meaney, 2001; Neumann-Held, 2001; Newman, 2002; Newman & Bhat, 2008). As pointed out by Richard Lewontin, DNA is not, strictly speaking, a self-replicating molecule. However, it is true that the strands of the double helix constituting DNA are separated to form new complementary nucleotide strands during cell division. Only complete living cells have the required machinery for “self”-replication of DNA. If DNA is available for proteins, it may provide a template for the modification of the serial order of amino acids that are required to be strung together for protein synthesis, but this string of amino acids is not yet a protein. Proteins in cells are synthesized by other proteins, and without protein machinery DNA would not do anything (Lewontin, 2001, p. 132). An organism cannot develop without its specific DNA, but DNA cannot develop without protein machinery.

The epigenetic turn conceived in terms of developmental systems or biocultural co-construction (Li, 2009; Oyama, Griffiths,

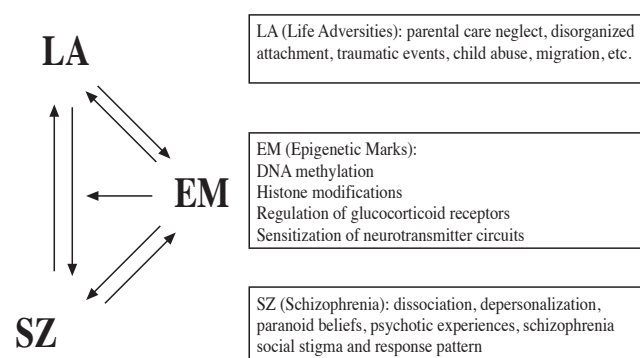


Figure 3. Epigenetic link between life adversities and schizophrenia. Life adversities (LA) may cause psychopathological alterations such as schizophrenia (SZ) through epigenetic mechanisms (EM). Schizophrenia would in turn contribute to life adversities (as social stigma) and to epigenetic changes as an ongoing response pattern (it would also be possible that the phenotype itself changes its own epigenome). Life adversities, epigenetic marks and clinical conditions may interact together through a feedback loop, constituting a kind of “psychiatric niche”

& Gray 2001), then, challenges the aforementioned dichotomies. It means that both the environment and the organism's behavior would recover their acknowledged leading role in "the nature of things" involved in human development.

The nature versus nurture debate is no longer tenable in terms of different interacting entities, since the human brain and the genome are known to be shaped by intertwined culture during development (Kitayama & Uskul, 2010; Laland, Odling-Smee, & Myles, 2010; Li, 2009; Meaney, 2001; Toyokawa et al., 2012). According to Michael Meaney, "everything we have learned about molecular biology has shown that gene activity is regulated by the intracellular environment. The intracellular environment is a function of the genetic makeup of the cell and the extracellular environment like hormones released by endocrine organs, cytokines from the immune system, neurotransmitters from neurons, nutrients derived from food. Signals from the extracellular environment, including hormones and neurotransmitters, can all serve to regulate gene expression. The extracellular environment is, of course, also influenced by the environment of the individual. Neurotransmitter and hormonal activity is profoundly influenced, for example, by social interactions, which lead to effects on gene activity, or expression. At no point in life is the operation of the genome independent of the context in which it functions" (Meaney, 2001, p. 52).

The genotype-phenotype distinction is also untenable, and for the same reason. In this regard, the role known to be played by the phenotype (like behavior in this case) in shaping our genotype contradicts the "dogmatically" assumed unidirectional genotype-phenotype relationship. As Massimo Pigliucci notes, "Phenotypic plasticity [the capacity of a single genotype to exhibit variable phenotypes in different environments] is now the paradigmatic way of thinking about gene-environment interactions, and it is one of the best studied biological phenomena in evolutionist literature, with ongoing knowledge about its molecular and genetic basis and its role in development and evolution" (Pigliucci, 2010).

The stress-vulnerability distinction should also be discarded, since it is based on a linear nature-nurture model, while the concept of interaction should itself be revised. The genome is not merely equipment *inside* an organism *interacting* with it, but is intertwined in causes and effects (Laland, Sterelny, Odling-Smee, Hoppitt, & Uller, 2011). In turn, the organism is not merely present in a particular environment, interacting *with* it and simply "self-unfolding" or developing, but constitutes a complete system of co-determinations and continuous readjustments (Kendal, Tehrani, & Odling-Smee, 2011; Laland et al., 2011; Sánchez & Loredó, 2007).

According to this perspective, vulnerability could be better understood as a developmental condition *dependent upon* biographical events, instead of a predetermined genetic condition *independent* of any past event (as in a kind of genetic lottery). Vulnerability may also play a causal role in psychopathology,

but without assuming a genetic origin, despite an association with epigenetic "marks". In this regard, vulnerability could be understood within cycles of contingency. For instance, life adversities such as disorganized attachment and early trauma may promote vulnerability expressed as increased sensitivity of the hypothalamic-pituitary-adrenal axis, together with an altered dopaminergic system that would likely cause abnormal psychological responses including paranoia and dissociation leading to a psychotic episode or even schizophrenia.

The terms pathogenesis and pathoplasty, introduced by the psychiatrist Karl Birnbaum, sought to distinguish between universal biological factors (pathogenesis) and cultural or personal aspects (pathoplasty). Pathoplasty would add *content*, color and contrast to "diseases" whose pathogenesis and basic *form* would be already biologically grounded. In general, this distinction was used to report culture-specific or culture-bound mental disorders in non-Western countries. However, what this perspective did not consider was that Western culture itself has its own peculiarities and peculiar disorders, being probably schizophrenia one of them (Pérez-Álvarez, 2012). The fact is that culture, including Western culture, may be pathogenic itself, involving epigenetic and associated neuronal processes (Kitayama & Uskul, 2010; Toyokawa et al., 2012).

To summarize, epigenetics is revolutionizing our understanding of genetics and heredity, and showing how nurture combines with nature to give rise to the infinite variety of life (Carey, 2012). Furthermore, it has shown that mapping the genetic code of an organism is not enough to determine how it develops or acts, and what strengths and weaknesses will emerge. It was traditionally believed that epigenetic changes were irreversible and took place only before birth. However, data from a number of recent studies suggest that epigenetic modifications are dynamic and potentially reversible processes occurring throughout the lifetime. The research results reviewed here support the hypothesis that epigenetic mechanisms would explain how the environment, and life adversities in particular, is linked to the development of mental disorders. Moreover, epigenetic modifications are involved in basic aspects of brain function, such as long-term memory consolidation. Recent studies on epigenetics have also revolutionized our understanding about the impact of behavior and environment on brain function. Nevertheless, a relevant question that remains for future research is whether there are increased susceptibility periods at particular stages of the lifespan, related to environmental influences on durable epigenetic modifications that in turn influence our behavior.

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