Evolution of the nervous system: a critical evaluation of how genetic changes translate into morphological changes

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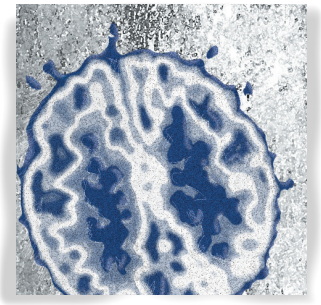

Living creatures evolve, and this evolution allows them to adapt to an ever-changing milieu. Two main adaptive strategies coexist. The first involves genetic mutations taking place at the species level. The second strategy occurs at the individual level, and primarily involves changes in chromatin organization and brain circuits. We shall illustrate how the two modes of adaptation are interdependent, and will show the difference in their respective importance depending on the species. It will be proposed that changes in developmental strategies, genetically selected, can lead to more or less epigenetic freedom, sometimes with dramatic consequences. In particular it will be shown, taking chimpanzees and humans as examples, how minor genetic modifications can translate into nonlinear changes in brain structure and cultural practices, placing the two types of primates at a much greater distance than had been anticipated.

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Context

Living creatures, from bacteria to humans, can only live in the context of the milieu to which they have to adapt. In this sense, intelligence could be defined as the capacity to adapt. One could therefore propose that all living creatures think, thought being defined by the evolving relationship between individuals and their biotope.

Indeed, the definition of what an individual is can vary between species. For example, in very simple organisms that replicate or reproduce rapidly, adaptation takes place primarily at the species level through the rapid selection of genetic variants with survival or reproductive advantages, in a given milieu. In these species all members of the community are very much alike, and there is little space for individual learning. However, this does not mean that there is no individualization at all.

Another mode of adaptation is at the individual level. We can call it learning or, more accurately, individualization, as it consists of epigenetic modifications of the individuals that take place at the genomic level, and also, in the case of animals, in the nervous system through the rewiring of neural circuits and/or long-term changes in synaptic strength.[1-5] When taking place at the genomic level, epigenetic modifications do not consist of mutations, but of chemical modifications of the DNA or of DNA-associated proteins, with important consequences

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on chromatin structure and gene expression. In both cases epigenetic changes can be implemented for very long periods of time—in many cases throughout the whole lifetime.

This does not mean that, in species where adaptation relies primarily on epigenetic changes (eg, in *Homo sapiens*), genetics is out of the game. It means that, in the course of evolution, developmental strategies have been genetically selected to allow an extreme use of adaptation processes taking place in individuals through the process of epigenetic individualization.

Not all animal species are equal when it comes to individualization. Since the nervous system (the brain in particular) is the most important—although not the only—interactive organ, its evolution is a key factor in the complexity and wealth of our interactions with the surrounding world. In short, if humans are individuals to an extreme, it is because they are social-extreme individuals.

Small causes with dramatic consequences

In the context of the general process of evolution, this short review is intended to summarize our present understanding of the enormous leap that we could call "humanization," permitted by the dramatic differences between *Homo sapiens* and his closest cousins, *Pan paniscus* and *Pan troglodytes*, from which he separated approximately 7 million years ago.

These differences are obvious from a morphological, cognitive, and cultural point of view. In terms of morphology, the first variable to consider is size. Among primates, the size of the brain is grossly proportional to that of the body. This rule is easily understandable if one realizes that the brain is primarily, and at its origin, an organ with sensory-motor functions; this is why plants do not need a nervous system. Applied to *Homo sapiens*, this rule would mean a brain weighing approximately 500 g for a body weighing 75 kg, meaning that we have an excess of 900 g of brain matter.

In addition to this size difference, say between chimpanzees and humans, there are also structural differences, since this increase is not proportional between all structures. A good example is the relative decrease in the size of areas devoted to vision or smell in humans and, conversely, the increase in the size of areas devoted to language (barely present in the chimpanzee) and, above all, to associative and cognitive tasks. This forces us to consider mechanisms that not only have allowed a size increase, but also have modified the positioning of boundaries between territories, ie, cortical areas.[6]

As for cognitive and cultural traits, this is not intended to imply, for instance, that chimpanzees (or other animals) have no culture, as many researchers have reported the existence of cultural and social practices in our "cousins,"[7,8] but it does not take long for the unbiased observer to become aware of the qualitative differences between the cultural activities of *Homo sapiens* and those of *Pan troglodytes*.

This does not mean that we have not evolved from a common ancestor shared with the chimpanzees, but it underscores that, in spite of this close relationship, something happened that put us apart, and it would not seem unreasonable to propose that this is closely related to the "excess" 900 g sitting on our shoulders.

Considering these facts, we are confronted with the established, and widely known, 1.23% genetic difference between man and chimpanzee. How can such a small difference translate into such a huge phenotypic gap, to the point where some individuals, probably in good faith but beyond reason, do not hesitate to question the phenotypic differences mentioned above? It is thus important to explain, on the basis of a series of recent observations, why this 1.23% is a myth,[9] and this is what will now be attempted on the basis of a series of recent observations.

All genes are not equal, nor are mutations

The core of the argument is that, in the course of evolution, developmental strategies have been selected that favor adaptive processes that escape pure genetic determinism.[10] Adaptation involves an epigenetic part, each individual being modified—"individualized"—through his or her interactions with the environment. In humans, this epigenetic process is stretched to an extreme due to the very large (900 grams in excess) brain size, and the way the brain areas are distributed, and also of the extraordinary richness of our cultural environment which is itself due to the amazing structure of the human brain.[11]

Hence the extreme importance of mutations that modify the expression, or the structure, of developmental genes, on which adaptive strategies are based both at the genetic (evolution) and epigenetic (development and individualization) levels.

To go into some detail, the protein coding sequences, the 25 000 or so genes that we share (with some variations) with most animal species, account for less than 2% of our

genome. They are transcribed into messenger RNAs and translated into proteins that function as structural elements or have enzymatic activities participating in all aspects of cell physiology. The other 98% is primarily composed of sequences that regulate gene expression, including sequences encoding noncoding RNAs with regulatory functions (for example microRNAs). Mutations that affect these regulatory domains modify the levels, sites, and durations of expression of the downstream gene(s). In the case of a developmental gene, ie, a gene involved in morphogenesis, the effects can be massive, out of proportion with the physical modification of the genome. In most cases these effects are deleterious and the individuals are severely affected. At the level of evolution these mutations are normally not conserved, but in a few cases they can give rise to interesting new characteristics capable of passing the screening of natural selection.

This clearly explains why the distance between species cannot be measured only by sequence comparisons. Based on such calculations we can indeed conclude that we are closer to chimpanzees than to mice (we know this from other physical traits), but this does not mean that we are 98.77% chimpanzee and 80% mouse. An important message here is that what counts is not the number of mutations, but where they occur—where they hit the genome. Mutations in regulatory domains are not identical, in term of consequences, to mutations in coding sequences. Their effects will vary depending on the type of gene under their control; for example a developmental gene or a gene encoding a protein of little physiological importance, eg, eye color. Also in the case of coding sequences, some mutations can have important evolutionary consequences, as will be illustrated in the case of FoxP2, a transcription factor that may have played a role in the evolution of animal behavior and communication.[12] Finally, it must be underlined that, also for coding sequences, some mutations are silent and others possibly dramatic, depending on the similarities or differences between the normal amino acid and the new one resulting from the mutation. Technically speaking, some substitutions are synonymous and others nonsynonymous.

Point mutations accounting for the 1.23% difference are not the end of the story

If one considers the genetic diversity of our species, and its approximate date of appearance (200 000 years ago, more or less), it can be deduced that the founding population was composed of approximately 10 000 individuals. The fact that we have the same number of genes as the chimpanzees from whom we separated 7 million years ago leads to the conclusion that mutations in regulatory domains have been decisive. For example, a mutation in a gene regulating the division of neural stem cells in a given region of the brain neuroepithelium will specifically modify the size of this region.[10,13] The conclusion is evident: the famous 1.23% implies sequences of considerable qualitative importance, including regulatory elements of developmental genes, with potentially spectacular effects on the morphology and physiology of the organisms.

Most importantly, the differences are not limited to the 1.23% of point mutations, as one must add all genomic deletions and insertions, plus the duplications that modify gene dosage. Given the size of the human genome, 1.23% translates into 30 million point mutations (a number not to be underestimated), to which one should add duplications, insertions, and deletions (between man and chimpanzee, gene copy numbers differ by more than 6%). Taken together, mutations, duplications, insertions, and deletions modify the global chromatin structure, and thus the regulation of gene expression.

Point mutations within coding sequences: the case of *FoxP2*

Even though they are probably less decisive than mutations in regulatory domains or deletions and duplications of large DNA fragments (sometimes an entire chromosome), point mutations in coding sequences can be of high evolutionary value. As mentioned above, this will be illustrated with the *FoxP2* case. Studies in individuals with hereditary linguistic deficits have led to the identification of a mutation in the coding sequence of *FoxP2*.[12,14,15] This gene is present in all vertebrates, not only in humans, and its coding sequence is highly conserved. Despite this conservation, the chimpanzee and human genes differ by two nonsynonymous substitutions that probably appeared less than 200 000 years ago. It was thus proposed that these mutations may have participated in the appearance of human language.[16]

The human version of the gene influences the development and the function of several brain regions associated with the learning and production of speech sequences. Also, and most importantly, in the control and fine tuning of the delicate motor tasks that accompany

articulate languages.[17] These point mutations may thus have contributed to the exceptional linguistic fluidity that characterizes our species. It is established that they reduced the separation between Neanderthals and modern humans, suggesting that our close cousins who disappeared 30 000 years ago had mastered some sort of articulate language.

Gene networks, gene copies, and energy in the brain

We will now leave aside point mutations in coding sequences, and develop a few examples of modifications in gene regulatory sequences. It is impossible to go into great detail here; the interested reader should consult the specialized literature on the genes and regulatory elements that have evolved separately in the chimpanzee and human lineages since they separated. Here, a few facts regarding the brain will be discussed.

First, there is the fact that individual genes matter less than gene networks, which vary synchronously in specific brain regions. These networks can be seen as homeostatic devices in the sense that any modification in the rate of expression of one gene in the network will be "buffered" by the others. Genetics is like physiology (is physiology!) as, at equilibrium, it only transiently allows extreme variations to take place. On this basis, several modules of coregulated genes can be defined in distinct brain regions, with some of them differing between the two species.[18,19] Investigators identified a module specifically present in the human, and thus of high interest from an evolutionary viewpoint. A rapid survey of the genes composing this "human module" shows that they encode proteins that regulate energy metabolism, the distribution and morphology of mitochondria, neuronal shape, and neurotransmitter secretion.

That neuronal shape and physiology should be important is not a surprise, but the importance of the energy component (metabolism and mitochondria) might be more surprising. In fact it should not be. As already mentioned, in most primates there is a strict proportionality between the size of the body and that of the brain, and if this proportionality rule was respected, the human brain volume would not exceed 500 cm^3 (compared with our 1500 cm^3). These 1500 cm^3 account for 2% of our body weight (averaged at 75 kg) but consume 20% of our daily energy, making it quite obvious that the price in energy to pay for this development is very high. Thus, this difference (not a 1.23% difference, but a 300% difference) presents an enormous evolutionary advantage; otherwise the price would be too high. In this context it is noteworthy that the promoter regions of nutrition-related genes have undergone positive selection in man.[20]

Let us now consider the number of gene copies (for specific genes). This number has been analyzed in ten primate species, some of them separated from our own lineage 60 million years ago.[21] Approximately 7000 genes show a change in copy number in at least one of the species. These changes are in the most dynamic regions of the genome, in chromosomal regions subject to reorganization and encoding specifically human traits, like cognition or physical endurance, in particular for long-distance running, a specific human trait strongly related to our exceptional energy metabolism (the mitochondria again). Interestingly, it is also in these regions that one can spot chromosomal abnormalities associated with human genetic diseases and genes encoding several proteins of the centrosome, a structure involved in cell division. This suggests a hypothetical link with the proliferation of neural stem cells, and thus with the enlargement of the human brain.

Regulatory RNAs and jumping elements

Another point of interest is the comparison, for 6300 genes, of the rate of evolution in the human lineage of regulatory protein binding domains present in noncoding sequences. This analysis demonstrates a very rapid evolution of the regulation of genes involved in the formation of neural networks. A similar line of thought has led to the search for small genetic domains both highly conserved among vertebrates and showing an accelerated evolution rate in the human. Of the 49 "human accelerated regions" (HARs) identified so far, 96% are present in noncoding parts of the genome, and 25% in regions that regulate the expression of genes involved in the development of the nervous system.[22] The champion *HAR1* (18 changes out of 118 nucleotides since we separated from the chimpanzees) encodes an ARN transcript that has regulatory functions[23] and is expressed in the brain where it might participate in the regulation of neural migration (of glial cells and neurons) during brain development.[24]

Another important point is that RNAs are not only messenger RNAs (encoding proteins) and that many of them have pure regulatory functions both at the level of transcription (from DNA to RNA) and at that of splic-

ing, translation (from mRNA to protein), or even epigenetic regulation.[25,26] The currently much-studied family of noncoding RNAs is the microRNA family. MicroRNAs exert their function through direct binding to mRNA nontranslated regions. This indeed adds an important novel site of post-transcriptional regulation that can lead to important phenotypic changes provoked by discrete mutations in the genome.[23,27]

Finally, one should mention the "jumping gene" domain, consisting of short or less short repeated sequences that are transcribed into RNA and then retrotranscribed into DNA fragments that are inserted into the genome.[28] Such reinsertions provoke mutations that can have considerable consequences when they take place, as is often the case, in gene expression regulatory domains. Many of these sequences no longer jump, (although some still do[29,30]) but they are extremely numerous in primates, and particularly so in humans.

Conclusions: social consequences

This brief technical survey should convince the reader that the figure of 1.23% for the difference (in point mutations) between the chimpanzee and the human genomes is in fact meaningless. The consequences of this distance between us and the other primates bears consequences not only in term of brain morphologies but also for the proper understanding of what makes *Homo sapiens* unique among primates, in particular when comparing social behaviors. One of the most important consequences of the unique character of the human brain is that part of our social behavior is epigenetic, and thus geographically and historically contingent. This includes the laws that rule behavior between humans, but also our relationships with the nonhuman world, including the other living creatures with which, from bacteria to chimpanzees, we share common ancestors. ❑

La evolución del sistema nervioso: una evaluación crítica de cómo los cambios genéticos se traducen en cambios morfológicos

Los seres vivientes evolucionan y esta evolución permite que ellos se adapten a un medio siempre cambiante. Hay coexistencia de dos estrategias principales de adaptación. La primera involucra mutaciones genéticas, las cuales ocurren a nivel de las especies. La segunda estrategia se produce a nivel del individuo y comprende cambios primariamente en la organización de la cromatina y los circuitos cerebrales. Se ilustrará cómo las dos formas de adaptación son interdependientes y se mostrará la diferencia en su respectiva importancia dependiendo de las especies. Se propondrá que los cambios en las estrategias de desarrollo, genéticamente seleccionados, pueden llevar a más o menos libertad epigenética, algunas veces con consecuencias dramáticas. Tomando como ejemplos chimpancés y humanos, se mostrará en forma especial cómo pequeñas modificaciones genéticas pueden traducirse en cambios no lineales en la estructura cerebral y en las prácticas culturales, situando a los dos tipos de primates a una distancia mucho mayor de la esperada.

Évolution du système nerveux : une évaluation critique de la traduction des changements génétiques en changements morphologiques

Les êtres vivants évoluent et cette évolution leur permet de s'adapter à un milieu en perpétuel changement. Deux stratégies principales d'adaptation coexistent : la première implique des mutations génétiques s'installant au niveau des espèces, la seconde apparaît au niveau individuel et implique surtout des modifications de l'organisation de la chromatine et des circuits cérébraux. Nous illustrons l'interdépendance des deux modes d'adaptation et montrons la différence de leur importance respective selon les espèces. Les changements dans les stratégies développementales, génétiquement sélectionnés, pourraient entraîner plus ou moins d'autonomie épigénétique, parfois avec des conséquences importantes. Nous montrerons en particulier, en prenant comme exemple les chimpanzés et les humains, comment des modifications génétiques mineures peuvent se traduire en changements non linéaires de la structure cérébrale et des pratiques culturelles, éloignant beaucoup plus les deux types de primates que prévu antérieurement.

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