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Erasmus Lecture

Brain and mind

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We are beginning to understand how the brain is organized and works, how it evolved in the remote past and how it continually forms during the embryonic development of individual organisms. The study of the brain and its activity has recently advanced at an accelerating pace thanks to the convergence of a number of research strategies. At least three research lines occupy a particular position among these strategies: genetics and the molecular biology of neural cells and the central nervous system; cognitive science; and brain imaging. If the brain is the subject of biological studies at the cellular, intercellular and circuitry levels, the approach to the study of mind should be more subtle. Nonetheless, science has progressed a long way in this direction. Some recent advances in this field are briefly reviewed here, with particular emphasis on brain evolution and development, the role of sensory organs, coding and the processing of sensorial information, memory, rationality, meaning and consciousness.

It is particularly rewarding and appropriate to speak these days about the brain and the mind. A great deal has been learnt in this research field over the past few decades. This is primarily due to the convergence of at least three powerful and promising research lines: experimental psychology (nowadays often termed cognitive science), biology (especially molecular biology) and brain imaging methodologies. These latter techniques allow us, in particular, to visualise which part of the brain is actually at work when a particular mental task is performed. For the first time in our history we are able to look into the machinery of the brain of a live, healthy and active individual. Due to the confluence of these research lines, we are at present in a position to say a few clear words about the brain, and how it is formed and works. We may operationally define the mind as the whole body of higher cerebral functions.

Let us start with the brain. There is no doubt that the brain is a body organ, composed of cells. Nonetheless, it is clear that neural cells, or neurons, are very special cells. They have many specific features, among which is their large surface, or perhaps more precisely, their large surface-to-volume ratio. They may have a surface up to three orders of magnitude larger than other types of cells of comparable volume, and of comparable organic mass. A cell characterized by such a large surface is especially suited for communication. In fact, the larger the surface, the larger the number of possible exchanges of matter or energy per time unit. Neurons also possess a variety of extended structures, such as dendrites and, especially, axons, capable of reaching distant cells and exchanging information with them. It is rather difficult to imagine how higher organisms could achieve neural coordination and activity using cells of a different type. But the question remains open, as is the case for most biological 'why' questions. We only know of a single type of life, evolved in a certain way on this planet, through innumerable, more or less random, events over time.

Communication between neural cells takes place through specific local microstructures present at the end of axons and termed synapses. The number of synapses present in the central nervous system is impressive. In the human cerebral cortex, for example, there are not less than 10^{11} neural cells, each one possessing an average of 10^{4} synapses. This makes a grand total of approximately 10^{15} synapses. Common wisdom at present claims that the essence of our cerebral cortex unambiguously resides in the configuration of these 10^{15} synapses. They mediate and embody the set of cerebral functions, from memory to reasoning, thinking or artistic creation. They are necessary to be a human being and uniquely characterize every single individual, through their common features and individual differences.

A fundamental question is how all these synapses are formed. It is relatively well established that the biological instructions encoded in the genome of every individual are not sufficient to dictate and specify all of the synapses. A considerable portion of them, but by no means all, is in fact established through the implementation of our biological instructions. On the other hand, some of them are established on the basis of our personal experience, the collection of major or minor events we experience – especially in the early months and years of our lives. We must include essentially everything in the definition of experience: what we ate, what we did not eat, what we saw, what we listened to, which diseases we had, which diseases we did not have, what satisfaction and what frustration we experienced, how much we were cared for and by whom, and subsequently what we were taught and what we learned. It is widely believed that all this shapes the microscopic wiring of our cerebral circuits, especially by setting, erasing, confirming and reshuffling most of our synaptic connections.

At birth, human new-borns are particularly immature and unable to cope with the challenges of the external world. A general trend in vertebrate and mammalian evolution actually implies that animals are born increasingly immature, and this progression reaches its peak in our species. This phenomenon is mainly due to the immaturity of the brain. At birth, in fact, most of the cerebral cells are in place, but some gross connections and a remarkable number of synapses are yet to be established. They will largely be established in the first months and years of life under the influence of one's sensations and perceptions. Our brain completes its own development with eyes and ears wide open and all our senses already in contact with the external world. Many events leave a permanent trace in our cerebral circuitry and microwiring, so that part of these traces becomes an integral portion of our brain. Through the use of a metaphor drawn from the world of computers, we may say that part of the hardware of our brain derives from the internalization of the software we run on it early in our life. In other words, part of our cerebral hardware is printed and manufactured on the basis of the software we ran on it in our early days and months.

Nevertheless, detailed inspection of cerebral circuits in both lower and higher organisms has revealed that all this is still not sufficient to determine all of the synaptic connections, and sometimes also it is insufficient to establish brain circuitry. Actually, we are forced to admit the input of a significant stochastic component. Since it is necessary that some connections, both major and minor, are established within some fixed time-windows, if the input of experience is insufficient to reach this goal, then chance, and only chance, will achieve that. Although we do not know exactly what percentage of all synaptic connections are set up by chance, we expect this fraction not to be negligible. Micro-anatomical features have been reported to often be different even in the nervous system of simple kin crustaceans. This is even more the case in mammals and humans. It is also to be emphasized that we tend to attribute more importance to what differentiates one individual from another, than to what is common to all of us. Hence, even if the individual portion of synaptic connections, mostly of environmental and chance origin, is only a small part of the whole set, it is this that predominantly attracts our attention.

In conclusion, there are three sources of instructions for the cerebral microwiring: genome, life experience and chance. The combination of these three actions ensures that virtually no brain is identical to any other. This is important in connection with at least two currently hot issues: human cloning and consciousness. First, even if somebody would, in the future, embark on the insane project of cloning human beings, it is essentially impossible that two brains, not to speak of two minds, would be identical, even in closely related individuals. Secondly, if consciousness is at least, in part, a product of the brain, the irreducible individuality of every brain should be reflected in the uniqueness of individual consciousness and in the ensuing difficulty of grasping it, let alone understanding it. Science primarily deals with reproducible events and is in a particularly difficult position in coping with the problem of individual consciousness.

A particularly interesting research field is the evolutionary origin of brain. A sort of brain is present in essentially all higher animals, but the cerebral cortex is unique to mammals. This cerebral structure increases in size and complexity during mammalian evolution and shows dramatic changes in higher primates and in the transition from apes to man. In the past two decades, molecular biology has contributed much to improving our understanding of evolutionary events in general, and of those related to the brain in particular. It is certainly not possible to summarize all this here, so I will confine myself to a few issues.

First of all, conservation. Even if we are inclined to underline biological diversity, it is increasingly clear that an incredible number of features are conserved throughout the natural kingdoms. The genetic code, the structure of the cell and cell membrane, the machinery required for protein synthesis, most metabolic pathways and many other processes are notably conserved in evolution. In the past 15 years, we also learned that most relevant regulatory genes are exactly the same in all animals.

Developmental events are genetically controlled by a number of genes. Among them, some high level regulatory genes – often termed master control genes – stand out. They take decisions of high generality and hierarchical level, such as establishing the position of the head, the thorax and abdomen; the upper and lower limbs; where the eyes and nose are; whether limbs must be legs or wings and how many vertebrae have to be present in a given body region. These genes take rather general decisions, shape the body plan and control its regionalization. In addition, there are batteries of downstream genes controlled by master control genes and deputed to the implementation of their decisions. The master control genes are essentially the same throughout higher animals, if not throughout all animals. In particular, genes establishing the head versus trunk, the subdivision of the trunk and the shaping of the brain are the same in all Bilateria (animals exhibiting bilateral body symmetry).

A second major issue in evolution is discontinuity. Although we are accustomed to think of evolution as a continuous process, implying a number of small changes, the most important events in evolution actually occurred suddenly and altogether, as a result of genetic rearrangements and/or major events in the external world. If we follow the evolution of an individual animal species living today, e.g. the horse, we observe the accumulation of a variety of small changes. But the appearance of this and most other species and taxonomic subdivisions is a sudden, discontinuous event. Discontinuous events are at the basis of true evolutionary innovation and often imply several types of different anatomical and functional changes at a time. There are evolutionary periods where a clustering of major changes is observed. One of these ebullient periods was, for example, that of the so-called Cambrian explosion. In a period of some 20 million years, around 600 million years ago, all existing animal phyla, from Chordates to Arthropods, suddenly appeared – we can hardly imagine what really took place in those years.

Evolution is also a largely random and opportunistic process. In our current view, evolution results from two main driving forces. One is the random, non-directional and aimless appearance of genetic mutations. Most of which are neutral or deleterious. From time to time, individuals bearing new forms of some genes survive and out-compete individuals bearing the old and established forms of the same genes. In the long run, a new equilibrium is reached and the genetic composition of a given population changes. There is selection of some types of individuals of a given population at the expense of others. It is the environment in its entirety that selects some individuals rather than others. A change in the local environment usually changes the criteria met in the selective process. Natural selection is in a position to choose among given individuals bearing various forms of some genes, but cannot create or mould new gene forms.

Such an opportunistic selection behaviour is only bound by the demand of survival of at least some individuals and by their ability to reproduce. Living organisms have genomes that result from the accumulation and stratification of many different genetic changes. There is little room for adjustments and rearrangements of previous assets *en route* and no *de novo* design. This is particularly true for the brain of primates, since this organ evolved fairly rapidly.

The concept and discovery of master control genes powerfully contributed to helping to explain discontinuity and innovation in evolution. In fact, it is clear that a single mutation in some genes may create large changes, because it involves changes in the action of many downstream genes. It is not even necessary to have a structural mutation in these genes. It may be sufficient that the new mutation changes the timing and/or the place of action of some one of the master control genes. The two phenomena are termed *heterochrony* and *ectopic* expression, respectively. Heterochrony, in particular, may explain a variety of evolutionary phenomena. Let us suppose that a regulatory gene acts for some time during development and promotes the growth of a specific body structure. A delay in the time at which the gene is switched off may cause an abnormal growth of this organ, transforming a nose into a proboscis or a thin cerebral cortex into a thick one. Furthermore, many regulatory genes and most master control genes regulate a number of different body structures. A change in their expression causes variation in many anatomical structures at the same time. For example, at one time we studied a regulatory gene, namely OTX1, which controls among other things the thickness of the cerebral cortex and the form of the larynx and kidneys. A contemporary change in brain and larynx might explain exciting evolutionary innovations in the evolution of primates. These may, in turn, be brought about by the utility of changing some features of kidney physiology.

The function of the brain essentially consists of processing information. The information must first be acquired and this happens through our sensory organs. The single most relevant aspect of the action of sense organs is that they do not observe passively the world around us, but rather pose to it specific, stereotyped, genetically encoded questions. The answers to these questions belong to a discrete set of possibilities: is there a vertical bar or not? Is the visual scene bright or dark? How salty and how bitter is this particular piece of food?

Both in peripheral sensors and in intermediate nervous centres deputed to the elaboration of sensations, the rule is uniformly that of assigning sensory response to a preformed array of possibilities. The keywords in this context are discreteness and coding. All this aims at maximizing signal-to-noise ratio and belongs to a general strategy in living beings for reducing loss of information.

This is most important for the very persistence of living cells or organisms. In physical sciences, one usually deals with sets of billions and billions of molecules, and even if they are individually subjected to random fluctuations, their statistical properties are relatively stable and predictable. In biology, we are often faced with a very reduced number of molecules of a given species present in every single cell and they turn out to behave in a predictable quasi-determined way. This is particularly relevant considering that some protein molecules may be present in a few hundreds of copies, and DNA itself in only one or two copies per cell. Life appears to escape most problems derived from random molecular fluctuations essentially by means of an extensive use of coding; that is, storing and processing information in the form of a set of discrete choices.

This is the case at many levels of organization. Consider first the genetic instructions. They are guarded in the innermost part of every cell and are organized as an encoded message. Its material support is DNA (or sometimes RNA), a long macromolecule consisting of a string of elementary constituents termed *nucleotides*. This message is used for the regulated synthesis of all the proteins necessary for life. A *message* is a sequence of symbols. In abstract terms, *symbols* are alternative entities selected from a closed inventory or alphabet. The existence of symbols implies, in turn, the existence of a code as a correspondence, which is generally unambiguous, between members of two inventories. This correspondence is fixed even if usually arbitrary. A short sequence of DNA, representing a gene or a portion of it, consists of a chain of nucleotides. What matters in this sequence is not only the actual identity of the various nucleotides – there are only four choices: A or G or C or T – but, more importantly, their order.

It is well known that this message is read in triplets; a group of three nucleotides encodes a specific amino acid. The sequence of the various triplets present in a gene unambiguously specifies the sequence of amino acids constituting the corresponding protein. For example, the triplet CCA encodes a proline residue. The C nucleotide present in the middle of this triplet may change as a consequence of a biological error, but it may only change into three possible directions: it may become a G or an A or a T. It cannot become anything else and, most importantly, it may never be something like 2/3 of C and 1/3 of G or 2.546 C. The choice is among discrete alternatives. This prevents a large portion of mistakes deriving from random fluctuations. Notably, it is not the intrinsic, biochemical, nature of single nucleotides that prevents the effects of random fluctuations but their status as coding entities, read and interpreted within the framework of a restricted array of possible occurrences.

This phenomenon is not confined to DNA sequences and their coding capacity. Even a gene can be either active or inactive and every cellular state is determined by the on/off state of some of its genes. Even considering only a set of a few genes, they may be either all on, or some of them on and others off. There are a high number of possible combinations, but this inventory is discrete and countable. Every cell may be in one of these states characterized by the combination of genes that are on and genes that are off, in a conceptual scheme frequently called *combinatorial*. This is also true at the level of tissues and even body regions. For example, an early embryonic epidermis may turn into a mature epidermis or into neuroepithelium, but not into anything else. A given embryonic body segment of a developing insect may turn into one of the 15 or so body segments, but very rarely turns into something intermediate between two body segments.

Another example is the firing of neurons. As is well known, neurones either fire or they do not. Many different signals converge on a single neuron that integrates them according to some, largely unknown, rules, but the eventual output is of the all-or-none type. Finally, modern neuroscience and cognitive science tell us that even at the highest level of mentation there are predetermined schemes – perceptive, representational or behavioural – and that we learn, evaluate and make decisions on the basis of these schemes. In every instance, life implies choice among a discrete set of alternative possibilities, most of them dictated by the generative project encoded in the genetic complement present in every cell.

The identity of some of the alternative possibilities or internal biological states just mentioned appears to be tightly controlled. For example, the exact pathway of a given nerve fibre or the shape of a spot present on the wing of a butterfly is often controlled by more than one process, to be traced back in turn to the action of more than one gene. Accidental silencing of one of these genes may not result in an alteration of these structures. These phenomena are usually ascribed to a sort of redundancy of the genetic information. In fact, it is often stated that biological information is redundant. Even if this cannot be completely excluded, there are good evolutionary arguments against the maintenance of genetic redundancy per se. The point is, to me, that most biological events are overdetermined. Overdetermination of biological internal states should be seen in terms of intersecting regulatory networks.

Let us now consider experience in abstract terms. Biological processes are obviously influenced by the environment and, in general, by external events. We may call this interaction *experience*, in a broad sense. Following this definition, experience may apply to elementary biological entities such as genes or cells, up to learning and behaviour in everyday life. In the light of what we have detailed so far, modern biology and neuroscience suggest that we may envisage experience as an influence of external inputs on the actual selection among alternative biological internal states belonging to a closed inventory. According to this view, experience is selection among pre-existing possible states representing discrete alternatives. As a consequence of this process, the repertoire of internal states available to a cell, an organ or a system is momentarily restricted, possibly to a single choice. The very concept of experience has broad implications as it bears on the general theme of innate versus acquired knowledge. In particular, it bears on the epistemological problem, because acquisition of knowledge is a particular, although most relevant, form of experience.

Information about the external world gained through senses must subsequently be processed in a variety of different ways and may end up eliciting an action – a response to a stimulus. In unicellular and lower multicellular organisms, a response almost invariably follows a stimulus. This response is often very quick and selected from a very limited inventory of possible responses. In moving from lower to higher organisms and humans, the time duration from the stimulus to the corresponding response increases progressively and may become remarkably long. In humans, many stimuli do not appear to generate a response and many of our actions do not appear to be responses to any stimulus. Elaboration of information on the status of the external world may require minutes, hours or days and takes many different forms. Operationally, we may call all this *thinking*, i.e. what happens in our brain between the reception of a stimulus and the enacting of the corresponding response. All animals have some degree of information processing, which is thinking, but humans certainly have more possibilities of elaboration and, eventual response. In this light, we may define freedom as the relatively large extension of our own inventory of possible responses to the same stimulus. We are free because we can react in many different ways to a given stimulus or series of stimuli and, for instance, are more free than a dog, since many more different responses are available to us than to a dog.

Memory is another issue on which we have recently learned a lot, even if we would certainly like to know much more. We now know, for example, that we have at least two types of memories, belonging to separate short term or long term memory compartments. We store for fractions of a second or for a few seconds many issues, such as the digits of a telephone number we are dialling, figures of mathematical operations, words of a sentence we are currently hearing or reading and so on. After some time, none of these memories is present in our minds, unless some of them are transferred to the long term memory compartment. This is both useful and unavoidable. It is hard to imagine what our lives might be like if we had to remember every single issue we memorized at one moment or another of our existence. The importance of forgetting is clear, even if it would be better to speak of a selective forgetting. Some memories are, in fact, transferred to the long term compartment where they last for months and years. We do not know yet where memories are stored and in which physical form, but we know that for the passage of notions from the short term to the long term compartment, the integrity of the hippocampus, a structure lying deep in our brain, is required. There is also preliminary evidence that a wide short term (sometimes termed working) memory is a component of high intelligence.

We also do not know what is the basis of the decision determining which short memories are to be erased and which promoted to long term memories. There is no doubt, however, that this process is heavily influenced by the emotional aspects of individual issues and their relationship with the interests and the attentional focus of the single individual. We may say that the decision is taken on the basis of the relevance of the various issues for the individual.

Relevance may, in turn, be considered as the higher mental correlate of selectivity, an intrinsic property of living matter present in every step of life. We may envisage a progression of abstract features throughout the world of life: discretization → coding → selection → relevance → meaning. Meaning, that is making sense of something, may be seen as the symbolic correlate of relevance and of all that lies behind it. This brings me to the issue of comparison between our minds and computer activity.

The comparison of the modes of action of computers and brains has been terribly helpful in understanding how the mind works, as well as how the mind does not work. We could mention many issues in this connection, but I will confine myself to one. Computers are able to process, one by one, chains of several logical steps. The length of the chain is only limited by the capacity of their memory and the rate of processing and by the quality of the central processing unit. For a computer, there is no significant difference between step 11 and step 26 of any running program. A mind is different. We have some difficulty in processing a chain of many logical steps, and from time to time we need to stop reasoning and try to summarize what happened up to that point. In doing that we attach, more or less consciously, tags of interpretation and meaning to the various steps. We need to interpret, according to any one of many possible interpretation schemes, and make sense of practically every step in a reasoning chain. This necessity has many consequences, both on the operational level and for our own attitude toward life and its interpretation. We tend, for example, to interpret and over-interpret everything, arriving at a number of basic universal questions that are intrinsically impossible to answer, such as the use and meaning of our very existence.

Another unique feature of our mind is its limited rationality. We are perfectly aware of the limited role played by reason and rationality in our everyday life, but we tend to assume that, whenever we make an effort to use our mind in a rational way, we may achieve a perfect rationality. It has recently been shown that this is not always the case. Everybody is inclined to provide wrong estimates and evaluations for some specific questions and this is largely independent of the degree of intelligence and education of the person tested. These questions mostly deal with evaluation of probability and risk. These phenomena are surprising and their study revealing, and it is not impossible to make sense of them, if not to account for them. Our brain is essentially similar to that of at least 200 000 years ago, when life conditions were quite different from the present. Our brain evolved to take rapid relevant decisions to ensure the survival and reproduction of our ancestors. We cannot understand the functioning of our mind if we do not take into consideration these requirements. Genetically, we are not born to be insurance agents or chess players. Our central nervous system is perfectly fitted for allowing us to escape a danger, to chase a prey or reach a mate. We need not be perfectly logical for these actions but, more importantly, we are able to take rapid decisions on relevant issues. How we make judgements of relevance is not known and represents a formidable task for future studies, whereas the rapidity of decision-making is achieved through the adoption of a variety of intellectual short-cuts, often termed *heuristics* or *heuristic procedures*, and is generally understandable in terms of the generally parallel nature of information processing in our central nervous system.

We could consider many more aspects of mental life, such as representation, language, reasoning, imagination and creative thinking, but this would require an extended treatment. Let us conclude by considering, briefly, the issue of consciousness, probably the most difficult subject to confront, since it is possibly too late for philosophy and too early for science. Nevertheless, many – possibly too many – books have recently been published on this topic and many ideas have been aired. I think that all this can be better approached if one makes some qualifications. First, there is the fact that the word *consciousness* is commonly used with at least three different meanings:

Awareness. Many higher animals are more or less aware of what is happening and what they are about to do. This awareness is common to several animal species and small children, and shows many degrees of amplitude and clarity. It can be best studied by observing their behaviour, with the help of our own theory of the mind, a mental function we all share. There is preliminary but suggestive evidence that awareness may imply synchronization of neural signals in some selected cortical areas.

Shared self-consciousness. There is a form of shared consciousness, common to all of us. Humans are able to communicate through language. Therefore, their consciousness can be studied not only by observing their behaviour (as is the case for the awareness of animals and infants), but also through speech and conversation. This renders human self-consciousness somewhat different from simple awareness, at least from the point of view of the range of possibilities to approach it. Consciousness requires awareness, but the converse does not hold true.

Phenomenal consciousness. Humans also have private sensations, feelings and emotions that are not always easy to communicate. From a rigorous point of view, they are accessible exclusively through introspection. Every individual is aware of his/her own ideas and private feelings and mental states. Let us call this mental property *phenomenal consciousness*, as opposed to a general concept of shared self-consciousness. It is a property of one single subject: me. On these grounds, some philosophers claim that it is operationally impossible to penetrate the phenomenal consciousness of individuals and this private mental state will remain for ever outside the realm of observation and henceforth of scientific investigation. Many illustrations of this concept have been put forward and it certainly looks apparent to me that I can never penetrate completely the inner phenomenal consciousness of another person. It is, by the way, not even clear whether phenomenal consciousness is necessary for our mind to work.

With this distinction in mind, we may hope to reach some understanding of consciousness in its first and second meaning and this needs to be actively pursued. As far as the third meaning is concerned, there is probably nothing to do, but who really cares? The impossibility of studying private, phenomenal consciousness should not prove to be an obstacle to the scientific study of common aspects of consciousness. This is a field of great interest and difficulty, where only a limited number of successes have been so far reported. Nevertheless, there is a metaphor I like to illustrate consciousness at work. According to this view, consciousness is a sort of ideal funnel transforming a fraction of the parallel processes taking place in our central nervous system into something intrinsically serial and sequential. In this process a collection of neurostates is transformed into a psychostate. This happens continually and most of the time we do not even realize that this is actually an operation and has precise requirements. Only when something goes wrong, due to drugs, tiredness or age, do we realize the existence of this great mechanism and related problems. Linguistic utterances are serial by definition and this is even more true for written statements. In this light, it is conceivable that language, whenever it first appeared, contributed over time to shape our own form of consciousness and that literate people develop in their life additional unique features that shape and characterize a number of working details of their own consciousness. It is evident that there is still a great deal to investigate and learn, but I can hardly imagine anything more interesting and stimulating than the scientific study of the brain and mind.

About the Author

Edoardo Boncinelli, a member of the European Molecular Biology Organization (EMBO), for many years headed a research laboratory of Molecular Biology of Development, first in the International Institute of Genetics and Biophysics in Naples and subsequently in the Scientific Institute San Raffaele of Milan. He is at present director of the International School for Advanced Studies in Trieste. His experimental work has been mostly devoted to the analysis of the genetic control of body plan and brain development in higher organisms, although recently his interests have gradually shifted toward the study of the mind and cognition.