C. R. Biologies xxx (2015) xxx–xxx

Contents lists available at ScienceDirect

Comptes Rendus Biologies

www.sciencedirect.com

Biology and the technological future of man / Biologie et devenir technologique de l'homme

# Sciences of the brain: The long road to scientific maturity and to present-day reductionism

## *Sciences du cerveau : la longue route vers la maturité et le réductionnisme du temps présent*

Michel Le Moal [a,b,*], Joël Swendsen [b,c,d]

[a] *Neurocentre Magendie, Inserm U862, Bordeaux, France*
[b] *Université de Bordeaux, 146, rue Léo-Saignat, 33077 Bordeaux cedex, France*
[c] *CNRS UMR 5287, Bordeaux, France*
[d] *École pratique des hautes études, Paris, France*

ARTICLE INFO

Available online xxx

*Keywords:*
Conceptual Neuroscience
Psychiatry
Reductionism
Brain and Society

ABSTRACT

When examined in a long-term perspective, brain sciences demonstrate certain conceptual consistencies as well as theoretical oppositions that have lasted for centuries, ever since Ancient Greece. The neurosciences have progressed more on the basis of technological than conceptual advances, and the constant recuperation of new techniques from other sciences have led to a continually reductionist view of the brain and its functions. In a different perspective, if not opposite to the reductionism, are the psychological constructs and those that constitute the functional unity of individuals, which are still mysterious. In fact, the gap between these two approaches has never been larger than it is now. This chapter discusses the enduring nature of some of these problems and their recent consequences.



*Mots clés :*
Neurosciences théoriques
Psychiatrie
Réductionnisme
Cerveau et Société

RÉSUMÉ

Dans une perspective inscrite dans le long terme, les sciences du cerveau laissent apparaître quelques constantes conceptuelles et des oppositions théoriques qui perdurent au cours des siècles. Les neurosciences avancent en raison des progrès technologiques et ces derniers conduisent à un réductionnisme sans fin des approches. Dans une perspective différente, sinon opposée du réductionnisme, se trouvent ce qui constitue les grandes fonctions psychologiques et ce qui constitue l'unité fonctionnelle des individus, dont les comportements restent dans le mystère ; la séparation de ces deux approches n'a jamais été aussi nette. Ce chapitre discute quelques-uns entre ces problèmes dans leurs permanences et dans leurs récentes dérives.



### 1. From antiquity to Descartes: origins of the present concepts

The roles we attribute to the brain that have endured for over a century, with its specific scientific vocabulary related to psychological attributes and functions or in

* Corresponding author. Neurocentre Magendie, Inserm U862, 146, rue Léo-Saignat, 33077 Bordeaux cedex, France.
*E-mail addresses:* michel.le-moal@inserm.fr (M. Le Moal), joel.swendsen@u-bordeaux.fr (J. Swendsen).

http://dx.doi.org/10.1016/j.crvi.2015.06.014
1631-0691/

relation to specific brain regions, are the result of conceptual debates originating in antiquity. Indeed, it is interesting to note the consistency in human thinking and beliefs about the ways we behave and react to the surrounding world. The concept of the brain, or encephalon, was not clearly described in the Bible, but the Greek philosophers opened the debate on this topic by proposing two different approaches accounting for the materialistic origin of human behavior within the body.

In brief, it is possible to distinguish between those who considered the soul as a totality and who refuted its division, and those who were interested in the different causes of human behavior and therefore in a division of the soul into different related skills. Whatever the possible roles of the cerebrum (a soft mass enclosed under the skull, intestine-like and undifferentiated), the existence of its connected ventricles was observed. The first position inspired by Aristotle (384–322 BC) and followers, and later by Alexander of Aphrodisias (150–215), was totally holistic. The heart was the seat of a non-divisible soul that included all the abilities, skills or faculties located in a single and unique part of the body. The second approach stipulated that different parts of the soul were localized in cavities. With Plato (428–347 BC), Hippocrates (460–356? BC), and Democritus (460–370 BC) and followers, the soul was believed to be divided into three parts corresponding respectively to desire and sensuality (located in the belly), to bravery, will and devotion (located in the heart) and to wisdom, reason and knowledge (located in the head). Later, Galen (130–201) proclaimed that the soul with its different properties and aptitudes was localized, together with animal spirits, in different ventricles. In other words, Cardiocentrism was opposed to Cerebrocentrism. Whatever the location, the main opposition was between a conceptualization of human beings as being composed of different, separated functional attributes, or rather as an all-in-one, complete unit, and non-divisible soul. It is important to notice that the different semantics and meaning of the word "heart" still dominate everyday conversation, art and literature, spanning the diverse concepts of love, temper, mood, goodness, generosity and nobility, private thoughts, bravery and spirit, fervor and fullness. As written by Helen Keller (1880–1968), "the most beautiful things in the world cannot be seen, or even touched, they must be felt in the heart." She was expressing a universal understanding about a feeling of wholeness, an inner feeling of subjectivity that is frequently a residual of dualism.

These perspectives experienced an enormous diffusion until the 17th century with varied, but only small, modifications. The two fundamentals remained globally the same: the soul with three different parts (Plato), the cerebrocentrist (Galen) with its localization of animal spirits and functions or abilities, the cardiocentrist uniqueness, etc. Science in these times had to conform to the dominant religious ideology, to the power of the church and to the notion of a separation of soul and body. The ventricles were the common place for these components to meet. Famous drawings of the time illustrate the concept. For example, Leonardo da Vinci's representation, drawn in about 1490, shows three connecting ventricles (or cells) in relation to the eyes. In his *Encyclopedia of grammar, science and philosophy*, Gregor Reisch (1503) depicted the three connected ventricles containing the primary mental faculties: sensation, fantasy and imagination for the first (in front); imagination, cognition, and judgment for the second (in the middle); and memory for the third (in the back of the head) [1]. However, in the 16th century, the great anatomist Vesalius (1524–1564) felt compelled to write "I am not able to understand how the brain can fulfil its proclaimed abilities to imagine, to think, to remember." It was possible on the one hand that some high-level abilities, functions, or qualities existed, but perhaps also that something more general existed in human beings, something that was characterized by a coherent unity and wholeness. The impact and significance of the changes brought by Descartes (1596–1650) was in part due to the feeling of impasse shared by scholars during this period.

For Descartes, matter and soul (or spirit) had to be separated as incompatible, and the human being should be seen as a mixed composite of both of them. Descartes replaced the localization of the various faculties by another theory linking the action of an indivisible soul, meaning a subjective holistic experience that was localized in a unique organ in the head. For that, he proposed that the soul was acting by means of the only uneven and solid part of the brain (as believed at the time): the pineal gland. The gland was receiving and then transferring the flow of animal spirits according to the arrangement of the different components of the bodily machine and its mechanisms. Importantly, the human body and brain were conceived as being nothing else than machines, with the sort of mechanics that are found in automata and timepieces [1] with the language of mechanics and engineering of the 17th century. Descartes revisited parts of the Aristotle–Plato's tradition and, being lucid about the prevailing religious doctrines, he had to find a seat for the soul. Descartes had a dualistic approach of the soul–mind–spirit vs. body dichotomy, but the machine concept was also of a materialistic and rationalistic nature.

In his perspective, thoughts exist and cannot be separated from us and vice versa. From his famous sentence (written in various forms through his books) "I think, therefore I am", Descartes determined that he was a thinking thing, in such a way that he was immediately conscious of the particular thought or judgment that was in mind. The sentence also reflected a subjective experience of totality and wholeness.

In brief, the role of the pineal gland did not survive the 17th century. However, Descartes' proposition to divide the machine in parts in order to reduce complexity was considered as a general methodological principle that is still visible today. Nicolas Stenon (1638–1686), the great anatomist and one of most admired scientists of the time, conceded in a famous talk on brain anatomy given in Paris in 1665 that there were only two ways to approach the organ: "either the Master who had created it could provide the means to approach the organ, or to dismantle it piece by piece in order to examine them separately". In this way, he proposed to proceed with the organ as with that of other machines and then to consider what their pieces were able to do when put together. The language and metaphors of the time, engineering, mechanics and automatons is meaningful. Stenon was expressing clearly what would happen during the next three and a half centuries with the reductionistic and top-down approach to the brain, with the hope for a possible bottom-up reconstruction. In parallel, he sent another strong message at the Paris meeting: "Concerning the anatomy of the brain, I must confess that I still continue to understand nothing." Stenon was reminding his colleagues that the main problem was methodological: how to dissect this mollusk-like organ and how to denominate what was observed. Stenon has also been credited to have distinguished white matter from grey matter, but it would take time before the nervous system could be dissected: formaldehyde would be discovered only in 1859 and the identification of neurons by adequate staining only at the end of the 19th century [2–4].

During the 18th century, the relations between soul and matter, conceived as two separated and incompatible substances, would be challenged with the rise of materialist philosophers such as J. Offray de la Mettrie, C. Bonnet, S.T. Soemmering, and P.J. Cabanis.

## 2. 18th–19th centuries: between localizationism and connectionism

A significant amount of research, mostly on sensory organs and their physiology, characterizes this period. The working hypothesis was to split and reduce the system as a whole in order to examine its fundamentals and their functioning. However, longstanding debates and opposition persisted at this time, dominated by two major theories. The first (chronologically speaking) is the phrenology movement as initially proposed by F.J. Gall (1758–1828) and J.G. Spurzheim (1766–1832). It represented a complete break with the past and, for that reason, had merited the label of revolutionary [5]. Moral qualities and intellectual faculties were considered as innate. Their expression and manifestation were seen as contributing to cerebral morphology. The brain was considered as the organ of all faculties and inclinations, and it was composed by as many selective and localized organs as were existing functions and qualities specific to the human species. Phrenology was a materialistic approach to the localization of functional mental organs, and the soul was absent. Moreover, with the phrenologists, the functional organs migrated from the ventricles towards the cortex, the cerebral lobes, and the grey matter. Importantly, they created a new functional order within the mind and behavioral modularities by considering that attention, perception, imagination, and memory were not primary faculties, but only some sort of working modalities of one or another type of behavior or mental capacity. This concept was of great significance and remains pertinent today when the relations between brain and behavior are considered. The endeavor to which the phrenologists were committed through their international scientific journals and societies was to define common and universal human abilities, qualities and behavioral modalities in all of their complexity, such as cautiousness, combativeness, sublimity, conjugality, parental love, conscientiousness, self-esteem, language, time, color, human nature, etc., and dozens more, and to localize them on the cortical surface, sometimes in relation to cranial bumps or head configurations. The phrenological enterprise was prominent during the first part of the 19th century. Later, and in retrospect, what had been localized was met with derision by historians or philosophers of science. It was for certain a "pseudo-science" without an experimental basis.

The cortical localization of brain functions became a materialist and forceful concept that led, decades later, to the Penfield's homunculus and to the discovery of the cortical localization by P. Broca (1824–1880) of the component of articulated speech. Based on clinical studies from 1862 to 1866 on language disorders in order to separate them from psychiatric conditions, Broca concluded his anatomical-clinical investigations by stating: "We speak with the left hemisphere." This discovery, whereby the location of cortical lesions became a fundamental event for clinical and experimental neuroscience and to which we owe the birth of neuropsychology (a discipline where a specific neuronal organ or region was associated with a given psychological attribute), inaugurated a new sort of phrenology, but only this time on solid scientific and experimental grounds. A few years later, Wernicke (1848–1905) discovered in aphasic patients other language disorders related to sensory receptivity (1874) with other lesion localizations, and then later another syndrome due to lesions of cortical fibers connecting the cortical area corresponding to "Wernicke aphasia" and to Broca's area known as "conductivity aphasia." Language resulted not only from brain localizations, but also from connected fibers explaining the complexity of language in real life and seen in its totality. For Wernicke, connections were both a functional reality and a concept about brain functioning by associations. It has been proposed that associationism, as a theory, was expressing the major phenomenon of the time in Wernicke's country (Germany), with towns (nodes) linked by systems of communication.

Despite these advances, the first decades of the 20th century were the theatre of violent controversies about the realities of brain functions and their possible localization. Political opinions and religious beliefs, science and naturalism that opposed the church and its power, immateriality and unity of mind or soul against materiality of different mental functions, were all the causes of radical opposition. For many of the eminent neurologists of that period, the unity of mental functions and their subjective reality on the one hand, and physiology on the other, corresponded to two separated worlds. Either the brain was operating globally as a whole with each part contributing to subjective experience or to some kind of internal sense that was revealed by introspection with consciousness, mind, spirit, etc., or each part of the brain was built to perform a precise function or role, independently of the other parts of the brain according to the laws of nature and the materiality of physics.

In summary, Broca and Wernicke were in opposition and this opposition is visible today. There exists to this day a penchant of neuroscientists for the naming of psychological constructs and for the use of a vocabulary

Please cite this article in press as: M. Le Moal, J. Swendsen, Sciences of the brain: The long road to scientific maturity and to present-day reductionism, C. R. Biologies (2015), http://dx.doi.org/10.1016/j.crvi.2015.06.014

corresponding to significant behavioral "universals", and they appear to feel obliged to localize each of these lexical elements in the brain. These localizations are consequential and the constructs are primordial, as phrenologists believed. However, it would be of interest to question the reality of such psychological characteristics represented by words, the possible causality related to the words and what they are really supposed to characterize and describe. For Wernicke, cerebral organizations were not dictated by psychological categories. The psychological categories were simply acting one on the other by associations to finally mold and shape larger behavioral and psychological realities: language (for example) was the instantaneous sum of the different existing capacities and was a unique whole, resulting from connections between the sub-parts and specific capacities. Associationism–connectionism was thereby opposed to localizationism.

These oppositions and their significance are at present at the heart of neuropsychology and behavioral neuroscience. Interestingly, by means of new imaging methods it has been proposed that brain functioning should be considered by means of connectomes [6].

## 3. Modern neuroscience and its concepts

The end of the 19th century and the subsequent decades were a rich period for the development of experimental and comparative psychology, and for the scientific psychology in general [7]. In parallel, field observations of animal behavior and ethology became more rigorous. These two disciplines would benefit from their cross-fertilization, for instance for laboratory ethology and scientific methods in animal psychology. Behaviorism, whatever the criticisms of its concepts raised later, had the merit of imposing technical rigor, including mathematical and statistical approaches allowing one to reproduce experiments from laboratory to laboratory. Constructs such as learning, memory, emotional responses, approach or avoidance, motivation, etc., have been addressed in rodents by ingenious laboratory designs, appropriate apparatus and recording techniques. Ethology and behavioral studies in general, especially when founded on evolutionary principles, were concerned by the biological programs designed for species survival and individual adaptations in relation to environmental changes; behaviors were studied and analyzed as phylogenetic universals and indivisible entities, triggered and organized on biological bases believed to have a complex genetic background (in fact, involving the entire genome) and transmitted through evolution. This perspective reminds us of phrenological constructs, especially when Spurzheim considered that "attention, perception, memory, imagination were not primary faculties, but merely modalities to act for any intellectual faculty." The "modalities to act" were those studied (and that still are) in laboratory or clinical settings as physiological-psychological abilities or functions.

At the turn of the 20th century, besides refinement in descriptive clinical neurology and the relations between structures, functions and diseases, laboratory research focused mainly on anatomy and physiology at the neuronal level, thanks mainly to appropriate staining methods and advanced microscopy. Several Nobel prizes have consecrated these fundamental discoveries. While scientific psychology was investigating brain functions from the "outside", new techniques based on solid anatomical descriptions of rodent and human brains allowed researchers to localize functions from the "inside" [2]. Precise stereotaxic approaches of selective regions with electrodes for stimulation of lesions, or with cannulae for local chemical administration allowed researchers to investigate in more detail the physiology and pathophysiology of the central neurons system [3,4]. The discovery of neurotransmitters in the 1960s opened a new pathway to explore brain functioning in addition to the classic electrophysiological approach; it permitted notably the birth of neuropharmacology. To illustrate a few examples of the discoveries of the time (1950–1970), we cannot consider that knowledge of the physiology of vigilance and sleep was found to be linked to the reticular formation; approach-avoidance functions were localized within the so-called reward system; the mode of action of psychotropic drugs was elucidated by the mapping of neurotransmitter systems, etc. The first departments of neuroscience were founded in the 1960s and the American Society for Neuroscience was created in 1968; its first congress took place in Washington, D.C., in 1971.

Currently, at the beginning of the 21st century, the field is now split into dozens of disciplines, many autonomous (it is fashionable to add prefix "neuro" to any substantive to create a new discipline), and most of the data is being obtained from animal models. There are different levels of investigation, including that of molecular and genetic level, cellular level, circuit level, region level, and whole organ analysis. Neuroscience benefits from the dominant sciences of the moment, including physics, chemistry, computer science, molecular biology, and genetics, in such a way that the researchers explore the brain in its minute details and reveal its incredible complexity.

In brief, this organ is conceived as a computing machine with 100 billion neurons connected by $10^{12}$ synapses exchanging 1 billion signals per second; it uses 20% of the body's oxygen and needs 50% of our genes. It is now the most important discipline in life sciences (at least in terms of PhDs produced per year worldwide) and the subject of more than 300 international journals that are now publishing data from both basic and pathological neurosciences.

This program has enriched our knowledge of brain functions, cognitive abilities and the different types of memory. In practice, however, the discipline is now dominated by founding dogmas relevant to reductionistic causality. First, for its basic dogma, everything the brain does (behavior, thought, mind) is explained by its basic components and results from the functioning of a given set of neurons. Second, a corollary identity dogma holds not only that knowledge of the brain is necessary for knowledge of the mind — everyone agrees — but also that it is sufficient [8]. However, at least for now, nothing in the literature provides sound scientific data for a demonstration of such sufficiency. This problem is also related to the distinction between "knowing" and "understanding." To have a causal exploration for a phenomenon is not enough to "know" that phenomenon; some kind of familiarity or experience with it is also needed for its understanding. As far as we can go in intuition, inference, imagination, there is always a limit.

Reductionism is not the birthright of the causal molecular-genetic approach. Considering integrated functions at the regional or whole organ levels, the so-called "cognitivist revolution" (1960–1980) is therefore interesting to analyze. This movement was born from the theories of information and its specific language: i.e. "the brain computes." It concerned all the mental processes at the basis of perception and knowledge acquisition; it assumed the existence of logical reasoning. Later and consequently, cognitive neuroscience has been governed by the search for the molecular and neural bases of knowledge, reasoning, consciousness, and decision-making. Dozens of papers are published every month on this latter construct, a product of business management. However, these approaches have not brought significant understanding of the more fundamental behaviors as discussed above. The conscious and reasoning individual is not the adapting subject in a real world [9,10]. From 1980 on, the so-called affective revolution [11] has demonstrated — quite obviously — the central role of emotions, intuition, beliefs and affect in reasoning and decision-making. This research is at the crossroads of social psychology and evolutionary psychology, and allows for a more integrated and global approach to behavioral neuroscience. Most of our decisions, judgments and choices are managed unconsciously [9]. Emotions and cognitive functions are intertwined to constitute personal characteristics of the individual, whether in humans or in animals, and notably concerning temperament and personality. When dysfunctional, they can manifest themselves as some of the most disrupting psychiatric conditions. Amusingly, our contemporary "rational" man continues to consult all sorts of shamans, sorcerers, and faith-healers to solve personal problems or to predict the future as if they were modern oracles.

For most of neuroscientists, localizationism is dominant and concerns abilities and psychological functions, i.e. different types of memories, control processes, emotions, decision-making, etc., constructs that are mapped onto selective parts of the brain and responses that are organized by neuronal entities. For others, experience is analyzed at the whole organ level, and the brain is built to integrate this reality with cohesion and binding [12].

## 4. Neuroscience tomorrow: problems at the interface of science and society

Some recent evolutions of disciplines relevant to the brain as an organ will be discussed for their relative impact on society and their association with the dominant working hypotheses mentioned above. The neurosciences are characterized by the dramatic presence of powerful technologies, and by a relative weakness in guiding conceptualization. There is, at present, no general theory describing the brain functions for an individual immersed in his environment.

Examples of difficulties raised by this situation will be briefly exposed: one concerns the processing of the enormous amount of data that is published, another concerns the pathology of the organ and the consequences of dominant reductionism. The question of the relation between brain and behavior is an additional important issue to be discussed, followed by a brief description of the technological avatars.

### 4.1. The brain chip

Whatever the words used to characterize our present-day situation, crisis or impasse, neuroscientists are confronted with a wall of data that accumulate in an exponential manner. There is no coherent strategic plan to figure out what is possible to do with this mass of knowledge, how to make use of it coherently or to build a unifying anatomo-functional cerebral model. More and more researchers in the field admit that it is currently impossible to reach such a goal and to construct a representation of cerebral connectivity by classic experimental methods.

Following all the changes that have been observed in the field, it seems that neuroscience is now ready to embrace the currently dominant and appealing sciences of our times: that of computer science, big data, networks, etc. [13]. A methodological paradigm shift is now being proposed, and it is opening the gate to a revolution in understanding the brain through information technologies. These technologies are growing and expanding so fast that no one is able to figure out what they will be in the near future. The notion is that microprocessors will be modelled on networks of nerve cells, and that the endless data obtained during the last 40 years will be integrated through powerful advances of computer science. The main goal is to understand the different forms of existing neurons at the genetic level and then to design their connections by means of "neuromorphic" super-computers with appropriate algorithms that permit the prediction of communication between the neurons. The final objectives are to model all the connections within the human brain and their functioning in order to understand all forms of human characteristics and abilities from decision-making to consciousness [14]. With this objective, the European "Human Brain Project" began in 2013 with a grant of one billion euros. A US counterpart, Brain ("Brain Research through Advancing Innovative neurotechnologies"), quickly followed, but with lower funding [15].

The paradigm shift is based more on technological than conceptual advances. Whatever the criticism that may be expressed concerning this initiative, its solutions are largely technology-dependent. All this might reflect a fascination towards human-like robots or related artefacts, or perhaps some sort of hope of accomplishing human enhancement. More fundamentally, it reflects a lack of interest for the real, flesh-made human, with his or her beliefs, passions, irrationality, affective reactions and emotions, and all that guides unconscious and conscious decisions in daily life.

### 4.2. Neuroscience as the science of psychiatry

Psychiatry is the discipline that gathers the most fascinating phenotypes of medicine and constitutes a group of invalidating syndromes that have enormous health care costs. It is common to admit that knowledge of an organ, its anatomy and physiology, are the bases for explaining its pathology and, reciprocally, deciphering the mechanisms of diseases help shed light on normal functioning. This endeavor has been at the heart of experimental medicine since Claude Bernard.

Psychiatry might be proud to have been honored by two Nobel prizes: for the therapeutic role of malaria in general paralysis (1927) and for the use of lobotomies in psychosis (1949). These decisions are of interest to those interested in scientific evaluations. The first molecules with therapeutic efficacy were discovered by chance in the 1950s; ten years later, the first published reports appeared concerning the main neurotransmitters that were supposed to provide chemical support for their action. Since that time, and despite the mountains of publications on the topic, including neuropsychopharmacology (which adds to over 400 forms of psychotherapy), progress in psychiatric treatments and in the understanding of the neuropathological bases of its various syndromes has been negligible. Since the USA's Decade of the Brain (1990–2000), tens of billions of dollars have been spent on both sides of the Atlantic to establish neuroscience as the basic science of psychiatry, in particular in its molecular and genomic aspects. It is worth noting that most of its publications are based on animal models whose relevance is rarely questioned.

While some leaders in the field continue to voice claims that the solutions are for tomorrow (and of course that more grant money is urgently needed), there is now a general feeling of impasse with the inability to shake off the poor image of being "medicine's least respected branch", and still the only one with no biological markers. No strategy currently exists to aggregate these countless and endless bits of information or to bridge the gap between mice and humans into a coherent view of the pathophysiology of these conditions. No dramatically new discoveries in drugs have occurred since the 1950s and most of the big pharmaceutical companies have closed their neuroscience departments. From the perspective of nosology, symptoms and syndromes continue to be described in an atheoretical way (at least for the DSM series), without reference to brain physiology or physiopathology. This influential system of nosology is also characterized by great instability, changing every fifteen years or so, and thus rendering epidemiological studies impossible in the long-term [16].

An additional important paradox of psychiatry is that, while implicitly permeated by the dominant neuroscience perspective that the subjective experiences of the individual are only vague reflections of more precise, more fundamental, and even more "legitimate" means of defining mental disorders (i.e. genetics and physiology), the field does not know how to use these markers should they ever be found. For example, there is currently no blood test or other reliable biological marker for depression (one of the most debilitating and costly of all mental illnesses). However, if there was, we can imagine the given physician who could announce with great satisfaction to his/her patient that the blood test was "clear" and that there were no signs of this illness. It is difficult to accept this reassuring biological certainty; however, if that same patient responds to that physician that he "nonetheless still *feels* terribly depressed, and can't stop thinking about suicide." Is the subjective experience of depression in this patient less valid (or serious) because of a lack of biological markers? This remains an important and unresolved question for the field, specifically regarding what should be the gold standard for disorders defined currently (and perhaps appropriately) by subjective experience.

In medicine, causality is a construct used with caution, but this is even truer in psychiatry. What causes schizophrenia, bipolar disorder, obsessive-compulsive disorder, addiction etc. The answer for neuroscience is (too) simple of course: genetics. Dozens of contributing genes have been proposed for each condition, but with large overlaps between diseases. As suggested above, these data have not been integrated into a comprehensive model of pathophysiology, and they certainly have not been integrated into a comprehensive model of etiology. As one salient example, numerous genes have been repeatedly associated with the risk of alcohol dependence. From a biological perspective, neuroscientists may, and do, try to identify the specific function of these genes (whether they influence the metabolism of alcohol, or influence its reinforcing effects, etc.). However, efforts to understand these genetic correlates with an environment or system, and as a function of evolution, are painfully absent. And yet there is no doubt that most of these genes have existed in our human genome and in those of our ancestors for hundreds of thousands of years, and some for millions of years. It is in fact only since about 4000 years (a drop in the ocean of time) that there exists a "toxin" in the environment — alcohol — that negatively interacts with these genes to influence the risk of addiction. In this context, can we say with any certitude that these genes are in themselves "pathological"? The easy solution of course is to accept these biological markers as the cause of alcoholism and pursue research in the goal of genetic therapy or other purely biological solutions. The less reductionist approach would obviously be to understand these genes as part of a dynamic system that must necessarily take into account the individual within his or her environment. Such is not the current zeitgeist of the neurosciences. For the patient the "when", the "why", the "where" are still unknown or unexamined; the "how" is the only matter of debate [17]. In other words, mental diseases are surrounded — still — by deep mystery, with the only one thing we know being that they are at some point biologically embedded [18].

### 4.3. Behavior, a neglected complexity

Behavioral sciences classically examine animal or human activities in order to demonstrate recurrent patterns and to discover the rules of adaptation to a changing environment leading to the preservation of individuals and species. This definition is quite selective given the numerous meanings of the word behavior. Behavior is thus considered here as a biological construct shaped by evolution.

There is a serious resistance to evolutionary concepts in behavioral neuroscience and behavioral research in general [19,20]. Behavior is the means of individual or species adaptation. There are universals, most being commonly shared with other animals and typical behaviors being shared by non-human and human primates. Behavioral research and causalities in the domain are the realm of ethology, anthropology, psychology, sociology, etc. In a classic paper [21], Mayr proposed a distinction between two different kinds of causalities, the ultimate and the proximate. The proximate causalities concerned the environmentally-released (or triggered) mechanisms existing along the life span and accumulated through learning and memories and shaped by the various sensorimotor pathways. However, the ways to respond are what makes us human as a biological species and which depend on ultimate, phylogenetic causes shaped by evolution. All of what the brain does is evolved aspects of our species [22]. Everyday laboratory investigations with animal models aim to discover neurobiological substrates for a given response with selective environmental settings, with their goal finally being to generalize to humans, are both implicit to proximal and distal causalities (implicit, but generally never clearly formulated).

It is not the topic of this manuscript to detail the reasons behind the resistance to appropriate evolutionary theory. Religious beliefs raise the most radical objections and denial about the Darwin–Wallace theory. A second objection, while less critical, denies that evolution is relevant to study behavior, cognition, or the mind, as if the human brain needed its own science separated from the non-human, animal world. This is reminiscent of Cartesian dualism. Frequently, neurobiological functions and behavior, two different constructs, are confusingly mixed together; for behaviors to be performed, they need to integrate appropriate physiological functions (memory, vigilance, sensori-motricity, etc.). A third objection comes from the environmentalists. Here, biology has a very limited role in explaining human behavior because, fundamentally, human beings are products of environmental influences whatever the name given to these roles: tabula rasa, environmental determinism, or the standard social science model. The manner in which individuals are affected by social situations defines social psychology for many supporters of this discipline, focusing on proximate mechanisms and ignoring the ultimate biological ones, in brief human nature (the classic nurture–nature opposition). Needless to say, scientific disciplines concerned by evolution are also environmentalist disciplines. Finally, the brain estimates relatedness from cues experienced through development and learning, giving adaptive diversities to genetically-determined systems in order to construct both mental and internal models. Here, the brain, the organism and its Umwelt are deeply intertwined and interrelated. They have created through evolution a global, highly dynamic system including active internal forces producing adapted behaviors for survival. Living systems can only be understood by assuming an interrelation between a supervening whole and its lower-scale components. Organisms maintain their identity within a meaningful Umwelt [23]. This approach is globally neglected.

As one example among many, social attachment and pair bonding are complex behaviors whose goals result from distal-evolutionistic influences [24]. In the case of monogamous mating systems, species have evolved strategies in response to selective forces from their environment. Recent research has shown that in spite of the reductionistic and localizationist languages used by many neuroscientists "oxytocin (or dopamine) as the social peptide (or amine)", these behaviors reflect the working of complex circuits that interconnect several large regions of the brain.

To conclude, it is time to face up to these complexities, these genetically engraved behaviors and consider their neurobiological and bodily substrates. Let us consider an example, trivial but essential: motherhood. Motherhood is an extremely complex, integrated, and precise behavior that is fundamentally a result of evolution. It is a complex behavioral program that is constantly reproduced all over the world, so close to what exists in animals around us, and with its three phases of before, during pregnancy, and after birth. The question to be asked is how the brain processes and manages the program, where is it in the organ, what are the relations between body and environment? The truth is that nobody knows.

### 4.4. *At the interface of brain and society: two recent developments*

If we can fix hearts and we can fix badly broken bones, why cannot we fix part of the brain? [25]. Have no doubt, it is on its way: cells are implanted to regenerate neuronal systems, brain stimulation technologies are proposed for repairing networks affected by diseases or trauma in order to rehabilitate the damaged functions, etc. These methods also lend to "neuroenhancement" [26] in healthy individuals, helping them to improve memory and cognition and to control emotions. Finally, intra-cortical detectors are inserted at the interface between brain and machines for helping movement in handicapped persons. Here, each type of signal recorded on the cortex necessitates a detector selected according to the region of the cortex where the signal is emitted. The nervous signal is decoded and then transformed in command in order to act upon a machine and produce an action; the signal can also be sent to a muscle and redirected through a stimulating machine in order to reconnect the brain with the muscle and restore a voluntary act. It has been estimated that there are now more than 700,000 individuals having stimulation/recording devices in use worldwide for various neurological conditions, whether involving the spinal cord or cortical areas [27]. In Parkinson's disease, it is now a common treatment for tremor and dystonia. Needless to say, the future of these technologies is without limit [28], at least in the imagination of engineers and computer scientists. Brain–computer interfaces, computer–brain interfaces, computer-mediated brain-to-brain interfaces, etc., will allow communication between subjects with conscious transmission of information between two human brains [29]. Those in charge of these programs envision a profound impact on the social structure of our civilization.

Another problem worth mentioning has been produced not only by the progress in imaging methods but even more by data interpretation. As these methods improve and change the views about brain functioning, they are supposed to reveal more about our conscious control, to what extent our actions are governed by processes related to free will [30]. The legal system, the moral basis for many institutions, requires an understanding concerning when people are — and are not — responsible for what has been done. The neuroscientists are now invited as experts to participate in court verdicts. Neuroscientists are supposed to understand the processes that connect sensation and action because they are supposed to reveal the neurobiological mechanisms by which decisions are made, and more and more professionals in the field agree with that notion [31,32]. The neurobiological problem to be solved is how to interpret the data, to explain limitations in order to provide materials for an informed decision, given the differences between the legal and neuroscientific fields [33]. "It is not me, it is my brain"; it is not because neurons fire without being aware of it that a decision has not been made, and unconsciously as for most of what is done during the day.

These examples — brain stimulation and neuroscientists in court — suggest that our knowledge is still so fragile, that the brain is such a special and peculiar organ and also that it is far too precious for us to risk abandoning it into the hands of neuroscientists only.

### 4.5. Reductionism and its discontents

Another aspect of contemporary neuroscience worth discussing is the consequence of reductionism, which is at times radical for some of its most prominent proponents. The working hypotheses or dogmas have been mentioned previously (see "Modern neuroscience and its concepts"). For every neuroscientist and educated person (it is not worth raising sterile arguments relative to the social and human sciences that still follow the tabula rasa or constructivist approaches), the brain is unquestionably a biological organ that is wholly responsible for mind, thinking, spirit, consciousness, and behavior. It is also true that a vast majority of neuroscientists have a materialistic approach to their science, just as they do for the world, at least by considering that everything exists from matter and from the activity of its constituents.

The vocabulary used here and its semantics, as old as when humanity began to think, to speak and then to write, makes no reference to biological causality, as it has been summarized above in the historical section. Moreover, the real meaning of these constructs remains vague; they represent global activities recognized by all of us and their precise localization within the organ remains the Holy Grail of neuroscience research. The problem is nevertheless the levels of analysis, to accept or not that the brain is the proper level to formulate psychological theories. By analogy, some biologists would not accept the proposal that chemistry is the right level of analysis at which biological theories should be formulated. The fact that the mind depends on the brain's activities does not prove that psychology is not an autonomous science. The assumption is that psychology and psycho-sociology can be translated into brain activity, beyond its physical components (i.e. "after all, brains are made of matter and physics is the science of matter"). This sort of logic, supported by some neurophilosophers and leading neuroscientists, is a matter of debate.

Brain sciences are still in a state of great ignorance, trivial for such a young enterprise. It is not because we are ignorant of the mechanisms of conscious awareness, of reason, of the sense of truth, the sublime and the beautiful, etc., that they will not be one day explained and that they will not be in the end, after decades, finally fully understood. The incredible pace of scientific discoveries will also be the source of paradigmatic changes that are presently unknown. As discussed above, more and more neuroscientists believe such changes are long-awaited and necessary. Nevertheless, some philosophers consider that there are specific features of our intelligence that make it ill-equipped to understand some subjective features, the phenomenal unity of consciousness, or pain, or social exclusion, or how the world is experienced by a blind man and what colors are to him, even if it is believed that the underlying neurobiological substrates are objective. To take a classic example, one may ask what is like to be a bat [34], considering of course that the specialist of these species may claim to "know" it; or what it is like for a woman to be pregnant but from her male partner's experience and point of view. To understand and to know belong to different worlds, and philosophers are entitled to remind us of these limitations, i.e. that in some cases at least, there might be a logical error to pretend that our present ignorance will not be ignorance in the near future and that the imagination in our possession is constrained.

To discover the localized electrical activities corresponding to social exclusion, pain, or consciousness [8], and to demonstrate brain correlates do not tell us what it means to be rejected or in pain. The notion of causality is inherent to the scientific language claims of some contemporary neurophilosophers and neuroscientists: they are engaged in some sort of homunculus representation of the human brain. It is claimed that there are neurons or groups of neurons for reason, for having intentions to perform a given activity, for taking decisions about what we do, and let us not forget the "mirror neurons" [35] whose role is to reflect the actions of others (in fact they are only part of larger circuits). This scientific language is not just a way to speak, but real avatars of a conception about the bilateral relations between human beings and their neuron systems.

In brief, it is not sufficient to understand the brain to understand the mind, according to "identity theory", even if it one admits that the mind depends causally on the brain. Having a good theory and scientific knowledge of vision is not sufficient for a blind man to see: a causal explanation for a phenomenon does not produce the phenomenon.

## 5. Conclusions

In brief, there is a consistency of the main concepts and theoretical opposition spanning from the Greeks, who argued about the tripartite decision of the soul and localization in three ventricles or, on the contrary, a unique localization of the various agencies (desire, morality, rationality) within a unique seat, the heart, to the beginning of the 21st century, with whole vs. parts, localizations vs. connectivity. Recent evolutions of technology have allowed investigations at elementary levels to which functions have been attributed, while new imaging methods propose new aspects of brain functioning, connectomics with "nodes" linked by pathways for a given function: localization and connections are still in vogue.

It is obvious that science at a given period of its development uses the methods of the dominant science of its time, but also language as a means to interpret. Computer science, numerical worlds, network theories, etc., dominate current language and the methods of neuroscience. The brain is a computing machine. The brain has not been shaped through Evolution to conform to the scientific methods of the 21st century. It has been suggested that, as for all the other sciences at one period of their lifespan (and frequently at their maturity), neuroscience is facing a kind of crisis or impasse and perhaps needs paradigmatic changes. In this case, it is necessary to analyze the symptoms and, if possible, the causes. More and more practicing neuroscientists are aware of these problems: To solve them by means of computer science has been proposed with mixed feelings.

It has been seen that reductionistic methods and resulting concepts for brain functioning merit careful scrutiny at both scientific and philosophical levels, inside the accepted barriers of materialism and monism.

## Disclosure of interest

The authors declare that they have no conflicts of interest concerning this article.

## References

[1] P. Corsi, La fabrique de la pensée, Electa, Milan, Italy, 1990.
[2] L.H. Marshall, H.W. Magoun, Discoveries in the human brain, Humana Press, Totowa, 1998.
[3] C. Gross, Some revolutions in Neuroscience, J. Cogn. Neurosci. 25 (2012) 4–13.
[4] M.W. Cowan, D.H. Harter, E.R. Kandel, The emergence of modern neuroscience: some implications for neurology and psychiatry, Annu. Rev. Neurosci. 23 (2000) 343–391.
[5] A. Harrington, Au-delà de la phrénologie : théories de la localisation à l'époque contemporaine, in: P. Corsi (Ed.), La fabrique de la pensée, Electa, Milano, 1990, pp. 206–215.
[6] J. Bardin, Neuroscience: making connections, Nature 502 (2013) 428–430.
[7] W. James, The principles of psychology, Harvard University Press, Cambridge, MA, USA, 1981 (first ed. 1890).
[8] F. Pulvermüller, How neurons make meaning: brain mechanisms for embodied and abstract-symbolic semantics, Trends Cogn. Sci. 17 (2013) 458–470.
[9] D. Kahneman, A perspective on judgment and choice: mapping bounded rationality, Am. Psychol. 58 (2003) 697–720.
[10] R.F. Baumeister, E.J. Masciampo, K.D. Vohs, Do conscious, thoughts cause behavior? Annu. Rev. Psychol. 62 (2011) 331–361.
[11] J. Haidt, The new synthesis of moral psychology, Science 316 (2007) 998–1002.
[12] A. Revonsuo, Binding and the phenomenal unity of consciousness, Conscious. Cogn. 8 (1999) 173–185.
[13] H. Markram, The blue brain project, Nat. Rev. Neurosci. 7 (2006) 153–160.
[14] H. Markram, K. Meier, T. Lippert, et al., Introducing the human brain project, Procedia Comput. Sci. 7 (2011) 39–42.
[15] Y. Frégnac, G. Laurent, Where is the brain in the human brain project, Nature 513 (2014) 27–29.
[16] W.W. Eaton, Studying the natural history of psychopathology, in: M.T. Tsuang, M. Tohen, P.B. Jones (Eds.), Textbook in psychiatric epidemiology, Third edition, John Wiley & Sons, Baltimore, 2011, pp. 183–198.
[17] D. Adam, Cause is not everything in mental illness, Nature 511 (2014) 509.
[18] H. Akil, S. Brenner, E. Kandel, et al., The future of psychiatric research: genomes and neuronal circuits, Science 327 (2010) 1580–1581.
[19] D. Burke, Why isn't everyone an evolutionary psychologist? Front. Psychol. 5 (2014) 590.
[20] P.K. Jonason, L.K. Dane, How beliefs get in the way of the acceptance of evolutionary psychology, Front. Psychol. 5 (2014) 1212.
[21] E. Mayr, Cause and effect in biology: kinds of cause, predictability and teleology are viewed by a practicing biologist, Science 134 (1961) 1501–1506.
[22] S.D. Preston, F.B.M. de Waal, Empathy: its ultimate and proximate bases, Behav. Brain Sci. 25 (2002) 1–20.
[23] S. Fresh, How cognitive neuroscience could be more biological-and what it might learn from clinical neuropsychology, Front. Hum. Neurosci. 8 (2014) 541.
[24] Z.V. Johnson, L.J. Young, Neurobiological mechanisms of social attachment and pair bonding, Curr. Opin. Behav. Sci. 3 (2015) 38–44.
[25] E. Underwood, G. Ling, DARPA aims to rebuild brain, Science 342 (2013) 1029–1030.
[26] E. Lane, Will brain stimulation technology lead to "neuroenhancement"? Science 342 (2013) 438.
[27] M. Desmurget, Z. Song, C. Mottolese, A. Sirigu, Re-establishing the merits of electrical brain stimulation, Trends Cogn. Sci. 17 (2013) 442–448.
[28] C. Grau, R. Ginhoux, A. Riera, et al., Conscious brain-to-brain communication in humans using non-invasive technologies, Plos One 9 (2014) e105225.
[29] J.P. Donoghue, Bridging the brain to the world: a perspective on neural interface systems, Neuron 60 (2008) 511–521.
[30] E. Nahmias, Why we have free will, Sci. Am. (2015) 65–67.
[31] N. Scurich, A. Shniderman, The selective allure of neuroscientific explanations, Plos One 9 (2014) e107529.
[32] D.S. Weisberg, F.C. Keil, J. Goodstein, E. Rawson, J.R. Gray, The seductive allure of neuroscience explanations, J. Cogn. Neurosci. 20 (2008) 470–477.
[33] O.D. Jones, A.D. Wagner, D.L. Faigman, M.E. Raichle, Neuroscientists in court, Nat. Rev. Neurosci. 14 (2013) 730–736.
[34] T. Nagel, What is like to be a bat, Philos. Rev. 83 (1974) 435–450.
[35] P.S. Churchland, Looking-glass wars, Nature 511 (2014) 532–533.

Please cite this article in press as: M. Le Moal, J. Swendsen, Sciences of the brain: The long road to scientific maturity and to present-day reductionism, C. R. Biologies (2015), http://dx.doi.org/10.1016/j.crvi.2015.06.014