Perspective

The Brave New Brain World

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Abstract

Brain research constitutes an interdisciplinary endeavor ranging from computer science, mathematics, physics and chemistry to cell biology, animal behavior, psychology and the humanities. This perspective article discusses current neuroscience topics of utmost interest including the conquest of aging, evidence-based education, the epidemic of psychiatric medication, the prohibition of certain drugs, the resurgence of depth psychology (e.g. psychoanalysis) and the mechanisms underlying consciousness.

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Introduction

This perspective article highlights some of the neuroscience topics that have in the past decades motivated the most intense discussion in society at large, due to their potential significance for the improvement of human life. It updates and extends to a wider audience a series of considerations previously published in Portuguese (1).

From Clinton's "Decade of the Brain" in the 1990s to Obama's "Brain Initiative" at present, funding for neuroscience research has been elevated to unprecedented levels, raising the interest worldwide on issues related to the nervous system.

This cannot be explained solely by the fact that we all have a brain. After all, there is no market for the dissemination of magazines on nephrology or biochemical targeting the lay public. At the meeting between mathematics, physics, biology, psychology, philosophy, anthropology and the arts, neuroscience fascinates more and more people with the possibility of understanding the mechanisms underlying emotions, thoughts, actions, disease and madness, learning and forgetting, dreams and imagination, phenomena that altogether define and conform the mental life of our species. In particular, health professionals, therapists, teachers and legislators can now begin to take practical ownership of the vast mass of empirical data on genes, proteins, cells, circuits and whole organisms accumulated in the past century. But the translation of novel experimental findings into new techniques and innovative processes is not simple, and the knowledge recently generated nearly always remains opaque to non-specialists. How to interpret the new findings of neuroscience? What do they mean, which changes they may cause, and how far may they lead us?

The conquest of senescence

Multiple factors combine to make the longevity of human life increase over time. In Brazil, life expectancy rose from 60.5 years in 1980 to 74.9 years in 2013, according to the Brazilian Institute of Geography and Statistics. Most countries underwent similar changes. With the increasing elderly population in recent decades, it has become common among families to have older members develop degenerative disorders such as Alzheimer's or Parkinson's disease, both progressive and severely debilitating in the long run. Understanding the mechanisms underlying neurodegenerative diseases became of wide public interest and significant resources have been invested on basic research of the neurodegenerative mechanisms, as well as translational research that seeks to transform discoveries made in the laboratory bench into effective therapeutic solutions.

Parkinson's disease is caused by the degeneration of the dopaminergic circuits controlled by neurons located in the mesencephalic nucleus substance nigra. These neurons send projections to subcortical regions that play a key role in coordinating muscle activity. Degeneration of the substantia nigra can be caused by genetic and/or environmental factors. When the degeneration reaches most of the neurons, the patient begins to display motor symptoms such as stiffness, tremors, slowness of movement and postural instability (2). Although a cure for the disease is yet to be found, various palliative measures have been used to halt the disease’s advance and relieve its symptoms.

The first line of action is typically treatment with drugs that increase dopaminergic transmission, such as precursors of dopamine synthesis, dopamine analogs or inhibitors of enzymes that degrade dopamine. While quite effective initially, the pharmacological strategy tends to run out of options as the disease progresses, since the containment of symptoms demands increasingly higher doses, which in turn produce undesirable side effects(3). Patients that become refractory to pharmacological treatment are often referred to brain surgery, either to lesion deep brain regions as usual in the past, or more recently to implant electrodes for electrical stimulation of the same deep regions (neural pacemaker). Although the mechanisms responsible for such treatments are still unclear, they can frequently eliminate certain motor symptoms of Parkinson’s disease (4). But they may also trigger undesirable side effects such as hallucinations, cognitive impairment, depression and personality perturbations. A very promising alternative is the use of dopaminergic cell grafts to repair the substantia nigra, but the viability of this strategy is yet to be proven (5).

Alzheimer's disease is a degenerative illness characterized by progressive neuronal death and atrophy of several brain regions. The initial symptoms of the disease are memory deficits that evolve over time into mental confusion, irritability, aggressiveness, mood instability and severe cognitive problems that end up isolating the patients from society, and eventually lead to dementia and death. The causes of Alzheimer's disease are not well established, and there are at least three major theories not necessarily exclusive to explain the phenomenon. The oldest hypothesis about Alzheimer's disease is that it stems from a decrease in the synthesis of the neurotransmitter acetylcholine. In the 1990’s a new hypothesis proposed that the disease comes from the accumulation of beta-amyloid plaques made of fragments of proteins which integrate cellular metabolism during non-pathological conditions, performing enzymatic, transcriptional and neuroprotective roles. A third hypothesis postulates that the cause of Alzheimer's disease is the hyper-phosphorylation of the tau protein, which would lead to protein aggregation fibrils able to arrest the intracellular transport of molecules via microtubules. Recent studies in animal models indicate that the initial progression of Alzheimer's disease depends on the trans-synaptic propagation of the pathology related to the tau protein, starting from the entorhinal cortex (6).

Although immunization against beta-amyloid peptides is capable of eliminating amyloid plaques (7), significant effects on dementia were not observed (8). Experiments with transgenic mice indicate that mnemonic deficits related to the tau protein can be reversed by interruption of its synthesis (9). Pharmacological treatments had so far limited success in controlling the cognitive symptoms of the disease. As a cure for Alzheimer's disease is still unknown, much of the research on this subject focuses on preventive measures that can delay the onset of the disease. Studies of elderly twins in which only one individual has dementia caused by Alzheimer's disease indicate that the daily practice of mental activity slows the onset of the disease (10).

With the advent of cell reprogramming and stem cell therapy (11), it is not hard to imagine that, in the future, medicine will routinely perform the replacement and renewal of organs. Such new medicine will necessarily have to deal with neurodegenerative diseases. Cure for such diseases would raise the health and quality of life of seniors in a way that humanity has never known. We live the dawn of a new generation of elders, mentally and physically agile people that will expand the boundaries of longevity. The promise that is drawn is the conquest of old age. Whether such blessing shall extend to all or only to those who can pay dearly for it, will depend on what we do about the education of children.

Evidence-based education

The advent of computers and the internet led to an unprecedented expansion of the frontiers of human cognition. In contrast, the gap between production and distribution of knowledge grows the chasm between the elite and the destitute. Although everyone seems to agree that a reversal of the world's stark economic inequality can only be achieved through broad access to high quality education, in reality much of the planet is far from achieving that. The future demands an educational revolution: The universalization of learning opportunities.

With regard to the comparison of different types of pedagogies, it is forceful to recognize that most schools teach the natural sciences, mathematics, languages and humanities in a quite unscientific way. Teaching is nearly always based on theoretical options, traditions, ideologies or qualitative judgments. The educational science of the future will come from quantitative empirical tests, and will strive to continually improve over time, in pace with research.

To overcome the educational gap between the different nations, across classes, genders and ethnicities, we will need to better understand the biological, psychological and pedagogical foundations of school learning. Several lines of research point to practical modifications of great potential impact regarding two major physiological bottlenecks of learning: nutrition and sleep.

Every morning, malnourished children and teenagers are directed to schools. Not surprisingly, these students often have learning disabilities. The brain is the organ that most consumes glucose (12), and glucose administration before learning has been shown to strengthen memories (13). Irrespective of which pedagogical method is employed, malnutrition will always affect learning negatively. Caloric ingestion is not the only nutritional requirement for learning. Meal composition matters in ways that we are yet to unravel, as indicated by experiments in which mice fed high fat diets learned less and more slowly than animals fed low-fat chow(14). The phenomenon is caused by a dessensitization of glutamatergic NMDA receptors(15), which are necessary for long-term learning. Class-room research with randomized design, large samples and adequate controls is in order to establish how school learning is affected by factors such as hydration, caloric intake, meal composition, micronutrients, serving sizes, frequency of eating, and the use of edibles as reward.

Just as children cannot learn when hungry, no learning can be achieved when children come to school with a major sleep deficit. Laboratory research has now firmly established that various kinds of learning are benefited by sleep, before as well as after training (16). Experiments conducted in classrooms show that post-training sleep benefits memory consolidation as in the laboratory (17, 18). Further research in the school setting is required to optimize the pedagogical use of sleep (19). For instance, it is important to compare the effects of resting versus having short naps (rich in slow-wave sleep) or long naps (which may include rapid-eye movement sleep).

Sleep and nutrition are potential game-changers for the future of education in developing countries, due to their critical importance for memory acquisition and consolidation, low-cost of implementation, and high scalability. Another scientific fact of great relevance to increase teacher motivation is the way people respond to reward. The relationship between incentive and motivation follows a sigmoid function, so that for very small as well as very large incentives, motivation does not change linearly in response to gains in incentive (20, 21). Any salary policy capable of increasing the motivation of teachers needs to happen in the middle range, well above the current low levels, where increases in incentive lead to proportional increase in motivation.

Several recent scientific discoveries feed the debate on the relationship between neuroscience and education, such as evidence that directing the student's attention to specific points on the studied material favors the retention of memories, that nonverbal gestures precede cognitive leaps, and that the language-based learning morpheme and grapheme is more effective than teaching whole words. The role of computer games in education is still controversial, but some studies suggest that the practice of customized computer games can reverse learning deficits characteristic of dyslexia, and lead to the transfer of skills across different cognitive domains. In Uruguay, the project "One computer per student" allows the acquisition of massive school learning datasets comprising all the students in the country. The promise of the global computer network is the dissemination of knowledge without barriers. If we learn how to navigate these new possibilities, we will have the chance to promote the greatest educational leap in the history of the species.

The epidemic of sadness

As necessary as it is, educational revolution will not suffice to eliminate human suffering. The advent of psychopharmacology and the development of the pharmaceutical industry were followed by major increase in the number of people who take medicine daily. In particular, millions of people began using drugs to act on mental categories such as "mood" and "attention", setting an epidemic of psychiatric disorders that were not even defined at the time of our grandparents. The widespread use of tranquilizers, sedatives and antidepressants was driven by heavy advertising, and by a close association between doctors and drug companies. In recent years, many widely prescribed psychiatric drugs are having their effectiveness challenged (22, 23). Research reporting high clinical efficacy of a drug, required for approval of commercial production, often comes from scientists funded by the very companies that market the drugs. Unfortunately, in a large number of cases the initial results are not confirmed by follow-up studies (22, 23).

The prohibition of certain drugs

Parallel to the explosion in the use of patented and marketed psychiatric drugs, several natural substances that have existed for millennia in various parts of the world were banned in the 20th century (24). Unfortunately, neither the war on certain drugs nor the commercial promotion of other drugs are minimally related to the potential physical or mental damage that may result from their use (25).

From the perspective of neuroscience, any substance capable of altering biological parameters is a drug whose effect stems from the interaction of three factors: The specific substance used, the body in which it acts, and the physical and social context in which the use occurs (26). Prohibition exacerbates the potential harms of drugs in all three factors. With regard to the specific effects of substances, prohibition necessarily creates an unregulated black market that not only precludes control of chemical composition, but in fact tamper with the drug, adding substances unknown by the user. With respect to the body upon which a drug acts, prohibition hinders the protection of risk groups, for it is impossible to teach people - and especially young people - about variations in the degree of risk associated with the consumption of substances that are banned even from conversation. Finally, with respect to the social context of drug use, prohibition induces states of fear and persecutory paranoia that are themselves harmful (27).

Through the prism of neuroscience, no drug should be criminalized and all drugs should be regulated in a case-by-case manner, according to their specificities and according to criteria free of moralism and politico-ideological trends. Scientific rationality requires harm reduction, equal treatment for drugs with similar harmful potential, and the termination of public policies that punish those who rather need acceptance and medical help. This discussion leads to the current controversy about compulsory hospitalization of drug users in major cities of the world. Of dubious effectiveness (28), this measure tramples individual freedoms and treats people as automatons devoid of subjectivity-the main focus of the depth psychology founded by Sigmund Freud and Carl Jung.

Depth psychology resurges

The scientific study of the human mind is rooted in depth psychology, as recognized by Nobel prize winner Konrad Lorenz (1948):”Another, far more significant branch of psychological research that originated from medical psychiatry remains remarkably isolated and disconnected, although it deserves more than any other field of psychology to be labeled as scientific. However much we may reject the theoretical edifice constructed by Sigmund Freud and Carl Jung (29), there can be no disagreement that both of these depth psychologists are observers, indeed gifted observers, who saw for the first time certain facts that are irrevocable, inalienable components of collective human behavior.

In the late 19th century, psychiatrists Sigmund Freud and Joseph Breuer replaced the use of hypnosis by listening attentively to the words produced spontaneously by the patients themselves, creating the method of free association of ideas for the exploration of mental representations (30). The method proved to be particularly useful when patients were encouraged to talk about their dreams, which were soon recognized as a rich source of revealing unconscious associations (31). It was postulated that pathological symptoms of psychosomatic nature reflect the existence of impenetrable regions of the mind, indirectly mapped by the analyst as a systemic exclusion of certain memories. According to psychoanalytic theory, a "talking cure" would occur when the patient consciously reached the repressed content, illuminating the genesis of the traumatic memory. A central concept of this paradigm is the notion that the unconscious is a thriving source of intrusive thoughts that appear more easily in the context of relaxation and reverie brought about by psychoanalysis (32).

Interest in spontaneous word associations also motivated parallel efforts by Carl Jung, even before his encounter with Freud. The young Dr. Jung focused his research on the recording of large numbers of word pairs freely associated by volunteers (33). In contrast to the qualitative survey conducted by Freud, Jung's study was quantitative and reached dozens of people of different genders, ages and socio-cultural backgrounds. The expectations were ambitious, aiming at classifying people based on the idiosyncratic relationships between words produced by free association. Despite its broad scope, the pioneering effort produced a single concrete result, nearly a truism today: people with high education levels had much larger lexical repertoires than subjects deprived of formal education.

Freud and Jung made many fundamental discoveries about the human mind but were rejected by the science of his time. Treated throughout the twentieth century as frauds, their contributions have returned to the center of neuroscience research, re-emerging in many different fronts. One of the central themes is the Freudian day residue, namely the dream reverberation of waking events (31). Such "daytime remains" have been widely observed in humans and rodents during both phases of sleep, both at the molecular (34-37) and electrophysiological levels (36, 38-40). We now know that the interruption of sensory interference promoted by sleep allows for mnemonic reverberation that is crucial for the consolidation of memories (16, 41).

A neurobiological translation of classic concepts of psychoanalysis updates the famous Freudian statement that " dreams are the royal road to the unconscious", for the unconscious can be understood as the collection of all memories acquired by the individual, as well as all their possible combinations. Two other concepts closely associated with Freud's work are the unconscious repression and conscious suppression of memories. Studies using functional magnetic resonance imaging showed that the suppression of unwanted memories correlates with the deactivation of hippocampus and amygdala, brain regions devoted respectively to declarative memories and emotions, and with the activation of prefrontal cortical areas related to intentionality (42).

One of the most controversial parts of Freudian theory is the notion that early psychological trauma can cause severe behavioral symptoms, becoming determinant for behavior. For decades science has remained skeptical about it, but the discovery of inheritable changes in gene expression by chemical modifications of DNA gives tangible meaning to traumas. An important example of such epigenetic regulation was the demonstration of an association between abuse during childhood and decreased glucocorticoid receptor expression in the hippocampus (43). In this study of post-mortem tissue, a group of subjects with history of abuse during childhood and suicide during adulthood was found to express abnormally low amounts of glucocorticoid receptors in the hippocampus, in association with promoter methylation of the gene encoding the glucocorticoid receptor. By reducing gene transcription rate and thus decrease glucocorticoid receptor levels, DNA methylation may turn individuals less tolerant to stress, possibly leading to suicide.

Perhaps the strongest objection to psychoanalysis is the claim that its research object, the world of memories and mental images, is intrinsically opaque to direct observation. But even this criticism has been refuted by recent neuroscientific research, in the face of technological advances that allow the noninvasive study of the mind. The unconscious was completely intangible for many decades after its inception. Nowadays, understanding the brain's unconscious processes constitutes a major research program (44, 45). The arrival of fast affordable computers, capable of crushing large data sets and quickly implementing complex calculations, completely changed the dynamics of neuropsychological research, enabling sophisticated mathematical algorithms and brute force approaches for data analysis and classification. Today it is possible to classify mental states using brain imaging data, i.e., it became possible to read minds. This was demonstrated in the visual cortex during visual image presentation (23, 46), as well as throughout the cerebral cortex during the word mentation (47).

This new scenario rescues research programs that have long been abandoned, such as the research on word associations (48, 49). Now it is feasible, for example, to use structural and/or semantic analysis to differentially diagnose psychosis (50, 51), and even to predict its onset (52).

The potential usefulness of the method extends far beyond psychiatry, reaching the various mental states induced by education, hypnosis, meditation and dream states. The investigation of joint structures between distinct languages is also promising, such as the existence of words in different languages with identical polysemic use, presumably rooted in the invariant relationships of these words with the human body. What now appears to be within the reach of science is indeed profound: To evaluate the dynamics of individuality, which develops from infancy to old age, through longitudinal studies of speech capable of distinguishing mere mood fluctuations from consistent drifts of personality traits.

The heart of the matter

The great synthesis of knowledge that characterizes contemporary neuroscience inevitably faces the problem of consciousness. Over the past century, biology and psychology supported the unity between body and mind with very different focuses: While the former privileged the study of the brain, the second concentrated its efforts on the understanding of mental phenomena. Now we begin to understand that consciousness is not a thing or a place in the brain, but rather a process of ionic fluxes distributed by various brain regions (45). Of course, all the interactions with the environment, conscious or not, depend on these flows. What differentiates consciousness from unconscious perception or action is above all its enormous capacity to evoke the past and simulate the future, creating parallel narratives based on imagination (9). The brain research program to understand consciousness advances in a gradualist and reductionist way, isolating phenomena such as binocular rivalry - the perceptual alternation of different images presented to each eye - to understand how specific aspects of our subjective experience are added to generate awareness(53, 54).

Part of the difficulty in addressing the problem of consciousness is derived from the Cartesian postulate of separation between subject and object. It is possible that the more direct and revealing path to understand consciousness is not the "third person" study of experimental subjects exposed to stimulation paradigms, but rather the simultaneous cerebral and mental investigation of the researcher himself, in "first person". The concept of self-research sounds strange to the traditional biologist, but in the training of psychoanalysts, for example, it is actually a requirement.

One of the pioneers of self-research in neuroscience is the Chilean neurobiologist and philosopher Humberto Maturana. For more than four decades he has investigated cognition as a sum of interdependent and recurrent relations between body and environment (55, 56). In the 1960s, he published an article on color vision in which the experiments were performed by the reader himself, using overlapping transparencies and an overhead projector (55, 56). The feasibility of experiments stems from the fact that visual images are easily accessed by the conscious self.

People are keenly aware of their external physical limits, but perception of the internal organs is an entirely different matter. Such perception is nearly nonexistent in the West, in contrast with the importance given to the subject by Indian and Tibetan Yoga, and by the Chinese Qiqong. The control of important physiological functions through meditation is recognized by science (57). Similarly, voluntary dream control is a skill that begins to be scientifically understood (58-61).

Closer to the mainstream of neuroscience research, neurofeedback experiments in which the experimental subjects train control of brain activity are performed for various rehabilitation and therapeutical purposes (62). Although these approaches are still in their infancy, self-research gradually progresses through the mysterious confines of the mind, equipped with the experimental method and the precise quantification of self-observed phenomena. This brave new brain world portends important changes in the way we grow, live and die. The challenge of integrating all this knowledge for the common good of humankind is the challenge of our time.

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