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EDITORIAL

From *Homo sapiens* to *Homo in nexu* (connected man): could functional imaging redefine the brain of a "new human species"?

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The old times (about 30 years ago)

Older readers will certainly remember the great emotion when they first saw a picture sent by fax, probably in the early 1980s. It would have been an image with a very low resolution, printed on a roll of carbonless paper, becoming unreadable in a few days. The oldest of the authors (L.M.) remembers his first publication in 1976, defining threshold values for tumour markers based on a statistical analysis of 1,000 normal subjects. The only available computer for scientific purposes was in Naples; it occupied a large room at the Faculty of Engineering. The analysis took a week, including reservation of the slot, perforation of punch cards for programming and statistical analysis, and was performed exclusively by engineers. Those who were young in the late 1970s remember the first video games, frequently Pong, a table-tennis simulator in black and white utilizing extremely simple graphics. Little more than 30 years have passed since then, but they seem like centuries. The "digital revolution" based on computers, the internet and mobile phones has been the fastest in human history.

The "internet gaming addicted"

In this issue Tian et al. [1] report that PET can be used to reveal brain functional changes in subjects with internet gaming disorder (IGD), using either *N*-methylspiperone (^{11}C-NMSP), to assess the availability of D2/5-HT2A receptors, or ^{18}F-fluoro-D-glucose (^{18}F-FDG). Twelve drug-naive men who met the criteria for IGD and 14 matched controls were studied under both resting and internet gaming task states, playing World of Warcraft, one of the most widely recognized "massively multiplayer online role-playing games" (MMORPG), which showed a compulsive behaviour in many people worldwide. IGD is a "pathological state" which, in the fifth edition of the Diagnostic and Statistical Manual of Mental Disorders (DSM-5), is identified in Section III as "a condition warranting more clinical research and experience before it might be considered for inclusion in the main book as a formal disorder" [2]. This state is difficult to categorize because of heterogeneity, since it also debated whether compulsive use of the internet (gaming, gambling, social media, blogging, pornography, shopping, work and so on) is a mental disorder in itself or is related to another form of addiction. This "addiction" may also be considered part of the obsession with technology, already identified in relation to radio and television, but exploded in the digital era [3]. Furthermore, abuse may not depend on the internet, as in the case of overuse of video games and mobile phones [4], but may represent a compulsive need similar to social networking addiction [5].

In the study by Tian et al. [1], individuals with IGD showed a significant decrease in glucose metabolism in the prefrontal, temporal and limbic systems together with dysregulation of D2 receptors in the striatum, correlated with the number of years of overuse. Low levels of D2 receptors were significantly associated with decreased glucose metabolism in the orbitofrontal cortex, suggesting that D2/5-HT2A receptor-mediated dysregulation of the orbitofrontal cortex could be the underlying mechanism for loss of control and compulsive behaviour in IGD.

Similar alterations of certain pathways and/or brain structural changes have been observed in individuals addicted to

Homo sum, humani nihil a me alienum puto (I am human, therefore nothing human is foreign to me); Publius Terentius Afer, 163 BC

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chemicals and individuals compulsively overusing the internet for study or work [6]. Compulsive behaviours are frequently associated, there being many internet gamers also addicted to alcohol, drugs, tobacco, or sex [7]. Although internet is a pro-social interactive medium, internet addiction disorders may significantly reduce human interaction. Consequently, interpersonal difficulties can lead compulsive gamers to depression and the hope of avoiding reality, frequently when playing Second Life games involving avatars. Virtual engagements do not stimulate release of neurotransmitters responsible for feelings of satisfaction and relaxation, such as oxytocin and endorphin, as do real interactions [8].

Human evolution

We belong to the species *Homo sapiens*, which emerged about 200,000 years ago, and is the only human species still living. The major distinction with respect to both other primates and extinct humans is represented by the higher degree of development of the nervous system, which shows a more complex and functional neural organization. Our brain is not larger and does not show a higher ratio with respect to the whole body; our "human quality" depends on a higher percentage of cortical mass, primarily of the frontal lobes. During the evolutionary process over many centuries our brain developed without a further increase in volume; the number of interneuronal connections multiplied, with the number of neurons remaining substantially constant, resulting in the creation of the most refined and efficient logical network yet seen. The cerebral structure of the human brain is dictated by function, and the characters that most identify us as human (not universal among all animal species) may be considered as upright posture, binocular vision, ability to manipulate objects using prehensile hands with opposable thumbs, circadian cycle, abstract thinking and creativity allowing technological progress and production of diverse cultures.

The internet gaming addicted as avant-garde of a new human species: the "*Homo in nexu*" (connected man)

If the brain is expression of human functions, some changes have probably already occurred in younger internet gaming addicted with respect to the identity of *Homo sapiens* [9], giving origin to a new human species, "*Homo in nexu*" (connected man), with web connection as his individuating cornerstone.

Homo in nexu is biped during some of the day, because he moves, works, studies, plays and relaxes sitting or lying. There is less and less side dominance in his hands and prehension is no longer the main function. All fingers participate in gestural actions, tapping or creeping with bilateral movements. Because the field of view is limited to the screen, three-dimensional reconstruction requires binocular activation different from that in the real world because the process of focusing is different. Reality, communication, even sex, are virtual and there is no more idleness, i.e. the time to think and process thoughts, because the brain is constantly subjected to multiple stimuli. There is no longer a circadian cycle since a large part of the day and night is spent indoors. So, has Penfield's homunculus the same distribution as compared to 1953? And is the brain of the "addicted" child organized like our's 30 years ago?

Functional imaging and evolution of the "brain paradigm"

Until a few years ago, the idea of regional cerebral topographical specialization drove neuroscientists to map functions in the context of specific anatomical regions, ascribing neurological symptoms to the prominent involvement of definite areas. Although this is partially true, the assumption has been changed by evidence provided by newer technologies. A striking example is Huntington's disease, considered for many years as a caudate nucleus disease. Only recently, using structural (MRI) and functional (PET) imaging, in subjects genetically predisposed to disease but still far from onset it has become possible to identify brain structures other than the caudate, such as the white matter, involved in the neurodegenerative process many years before symptom presentation [10]. Several studies based on fMRI have revealed a simultaneous activation in multiple cortical regions of different lobes and cingulate cortices suggesting that higher functions involve cortical and subcortical structures [11]. On this basis many researchers now assume that multiple cooperating networks in an energetic state are responsible for cognitive functions and individual responses to environmental stimuli. The paradigm of brain signal processing has been redefined from regional to distributed and from sequential to parallel. These findings have radically changed the scenario by introducing concepts such as brain network activities in the resting state, the so-called default mode, as compared to network activation during cognitive tasks.

A major new understanding is that the brain network changes in response to external stimuli. Specific cortical region signalling can control the neural network activation thus providing individual adaptive and flexible responses to stimuli [12]. The availability of new technologies enables a more accurate characterization of structural and functional brain development. The growth of individual skills may be the unpredictable result of the activation of distribution nodes of brain networks which progress in a nonlinear way in response to the external environment [13]. The impact of early experiences on brain development was assessed by Als et al. who

performed MR diffusion tensor imaging at 2 weeks and 9 months of age in 16 preterm infants undergoing individualized developmental care programs in comparison with 14 preterm controls [14]. Based on these preliminary data, we can consider the world in which we live as a unique laboratory where tools such as the World Wide Web can provide a huge amount of heterogeneous stimuli without comparison in the history of human civilization.

Tian et al. [1] try to evaluate the effects of interaction between individuals on a global virtual scale on brain functions, thus giving the opportunity to reflect on what could be the cerebral development in this new era. Nevertheless, the results have to be confirmed, the study's sample size being too small and the enrolled population too heterogeneous, especially the controls, and not clearly characterized. Moreover, the data were analysed using SPM, which shows false-positives in small populations, and images were not adequately normalized and/or corrected for partial volume effects. Further studies using larger and more homogeneous populations have to be encouraged, eventually working with multimodality approaches such as PET and MRI to assess metabolic and structural connectivity in addicted as compared to controls in major default mode network nodes located in the posterior cingulated, frontoparietal and medial prefrontal cortices. Although hybrid PET/MRI could provide more accurate and better correlated data in a single imaging session [15], separately acquired coregistered studies may also permit identification of the state of structural and metabolic networks at rest and after gaming stress [16].

Together with developments derived from a wider use of fMRI, mainly when strictly correlated with PET, new perspectives may also be derived from nuclear medicine per se. A significant improvement in FDG PET could be achieved from a more rigorous and reliable methodological approach, including quantitative analysis [17] and a better understanding of glucose metabolic rate resulting from the activity of astrocytes/neuroglia, more than of neurons [18]. Further developments could be achieved from a deeper knowledge of mirror neurons, that fire both when an animal acts and when an animal observes the same action performed by another [19]. Finally, improvement could be obtained from PET beyond FDG, including radiotracers for studying cerebral metabolism and for evaluating blood–brain barrier permeability [20] and neuroinflammation [21].

Finally, we have to come back to the early 1980s, when many of the early studies using FDG PET were directed to elucidating neurophysiology. Incredible abilities are now available to rewrite the "in vivo" structure and function of the brain, giving relevance to a network analysis. In this direction we could evaluate whether a new human species is already born: *Homo in nexu*.

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