Review article

Proper morphometry of degenerative changes in brain aging

Morfometría adecuada de los cambios degenerativos en el envejecimiento cerebral

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ABSTRACT

Introduction: A complex pattern of behavioral and cognitive changes characterizes the development of adults during aging. Knowledge of the biological roots of these changes is based on an understanding of age-related brain transformations.

Objective: To offer an overview to neuroscience and neuroimaging professionals about brain aging, its morph functional patterns and morphological changes in the brain, and will highlight the morphometric studies currently used to the detection and study of these structural changes.

Methods: The publications were reviewed, both in PubMed and in other data bases. The main text books referring to brain aging, neuroanatomy, neurophysiology, and neuroradiology and brain morphometry were consulted.

Conclusions: that age is a factor that affects brain morphology and that the morphological changes that appear depend on factors such as the individual

variability of individuals. Voxel-based morphometric studies are a useful tool to describe these differences, with signs of cerebral atrophy being observed to a greater or lesser degree as age advances.

Keywords: brain aging; morphometry; neuroscience.

RESUMEN

Introducción: Un patrón complejo de cambios conductuales y cognitivos caracteriza el desarrollo de los adultos durante el envejecimiento. El conocimiento de las raíces biológicas de estos cambios se basa en la comprensión de las transformaciones del cerebro relacionadas con la edad.

Objetivo: Ofrecer una visión general a los profesionales de las neurociencias y las neuroimágenes sobre el envejecimiento cerebral, sus patrones morfo funcionales y cambios morfológicos cerebrales y resaltar los estudios morfométricos que se emplean en la actualidad para la detección y estudio de estos cambios estructurales.

Métodos: Se revisaron las publicaciones, tanto en PubMed como en otras bases de datos. Se consultaron los principales libros de texto, referentes al envejecimiento cerebral, neuroanatomía, neurofisiología, neuroradiología y morfometría cerebral.

Conclusiones: La edad es un factor que afecta la morfología cerebral y los cambios morfológicos que aparecen dependen de factores como la variabilidad individual de cada persona. Los estudios morfométricos basados en voxel son una útil herramienta para describir estas diferencias, observándose imagenológicamente en mayor o menor grado signos de atrofia cerebral según avanza la edad.

Palabras clave: envejecimiento cerebral; morfometría; neurociencias.

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Introduction

A complex pattern of cognitive and behavioral changes characterizes adult development during aging. Knowledge of the biological roots of these changes is based on an understanding of age-related brain transformations. Pronounced differences, both morphologically and cognitive/behaviorally, abound among individuals. Macroscopic variations in brain anatomy are maintained long enough for comparative research. In fact, morphological analyzes comparing brains at different healthy or pathological stages can reveal important information about the progression of normal or abnormal development. Characterizing focal brain morphology and its association with age-related neurodegenerative development, function, and processes in healthy humans, as well as local morphological abnormalities found in psychiatric disorders and neurological diseases is crucial to the development of modern neuroscience.[1]

Brain morphometry as a discipline is primarily concerned with developing tools and strategies for measuring the structural properties of the brain according to the type of imaging data used, whether addressing ontogenetic, pathological or phylogenetic issues, and spatial scales of interest. Furthermore, shape feature comparisons have long been limited to simple measurements and primarily based on volume or cut, but have greatly benefited from the digital revolution, as all kinds of shapes in any number of dimensions can now behave numerically.[1]

In this sense, many have been the procedures used in order to know the structural variations of this important organ. In past decades, there were great difficulties in conducting studies on the morphology of the brain in vivo, since there were no diagnostic methods capable of providing extensive information. The methods used included both microscopic and macroscopic techniques, the latter include autopsy. It was not until 1974 with the introduction into medical practice of Honsfield's computed axial tomography (CAT) and later with nuclear magnetic resonance imaging (MRI), that these objectives were achieved.[2]

The rapid evolution in terms of spatial resolution and signal / noise ratio in magnetic resonance scanners, computed tomography and improvements in new imaging techniques and data processing algorithms have helped to develop studies capable of detecting and quantifying initially gross structural abnormalities, but even subtle that appear when comparing different populations.[1,3]

However, there are still several questions to be answered in medical practice about involuntary changes in the brain related to aging in the natural course of life and brain morphometry changes in neurological diseases. This fact becomes more relevant if we consider that population aging is a phenomenon that affects many countries in the world and especially Cuba. Reason why we carry out this review that will address the social phenomenon of population aging, the effect of age on the brain, its morphological changes, the morph-functional patterns of brain aging, as well as voxel-based morphometry studies as a tool in the image processing.

Methods

A documentary analysis on the subject was carried out in national and international publications, using an information search system through Infome, in PubMed and in other data bases, were reviewed, mainly selecting the one from the last 5 years and others that, even when they were made in previous years, constitute a mandatory source of consultation. Classic textbooks related to the topics covered were studied. The images were taken from two female patients of 75 and 82 years olds, respectively, that came to the imagenology ward of Juan Bruno Zayas Alfonso Hospital, with previous indications for simple skull CT, are shown, who, by signing the informed consent of the patient and legal representative, expressed their authorization to publish them with research purposes.

Aging and brain

Aging cannot be seen only as a stage of decline. To understand the structural and functional changes of the brain, research in the field of neuroscience in the 21st century has been an excellent contribution, but it is still insufficient.[4]

This fact becomes more relevant if we take into account that more and more people are reaching more advanced stages of life. According to data from the United Nations (UN) in 2020 it will reach 1200 million elderlies. This panorama is particular to developed countries, Cuba is an example of a developing country, given the aging of its population, it is estimated for

2025 that 25 % of the Cuban population will be over 60 years old. This phenomenon brings with it an increase in the rate of conditions typical of the elderly, among which degenerative neurological diseases, Alzheimer's disease and other stand out.[5, 6]

A frequent finding is that the brain, particularly some areas, changes more than others. However, this issue is far from clear. Since age-related brain changes and reported differences differ between the studies and methods used. Pakkenberg and Gundersen[7] evidenced the effect of age on the brain in their research, in which anatomically combining data from six different samples in post-mortem studies, revealed that the frontal cortex, and the medial temporal gyrus and parietal cortex are subject to thinning cortical age-related. In contrast, the inferior and anterior temporal lobe, the crusts of the cingulate gyrus were relatively less affected by age.

Oliveira [8] and researchers who suggest that reductions in the cortical area of the pre-frontal region occur during the last decades of life. Dotson[9] and collaborators in their casuistry revealed that age-related brain changes are not limited only at the cortical level, but affect sub cortical structures, however, no significant changes were evidenced in the sub-cortical nuclei.

The complexity of age-related brain morphological differences may be related to lamellar organization and regional evolutionary history of the cerebral cortex. The age of around 60 years is a breaking point for increased negative associations between age and brain morphology in neurological diseases. Novel relationships of age-related cortical differences with individual sex factors, cognitive functions, reaction time and prospective memory, cigarette smoking, alcohol consumption, sleep disturbance, genetic markers of Apo lipoprotein E, the brain-derived neurotrophic factor Catechol-O-methyl transferase, further reveal the joint effects of cognitive functions and life style.[10-13] Reduced cerebral perfusion found in the elderly which could potentially be explained by physiological variations in the carbon dioxide.[14,15]

The aging of the population is accompanied by a significant increase in the prevalence of obesity, metabolic syndrome; type 2 diabetes and neurodegenerative diseases. Despite being different nosological entities, they have a common characteristic, insulin resistance. Insulin signaling pathway modifications are a common phenomenon in aging along the phylogenetic scale.[16]

In humans, one of the fundamental characteristics of successful aging is related to the maintenance of insulin sensitivity. Centennial studies show

increased insulin sensitivity, decreased adiponectin secretion, and decreased inflammatory component. Similar phenomena appear in studies of especially long-lived families. Finally, insulin plays a central role in cognitive processes such as attention, executive functions, learning and memory, direct administration of insulin in the human SN having been shown to improve cognition and memory. Therefore, insulin and its metabolic pathways participate in a multitude of processes essential for healthy brain aging.[16]

Neural aging is a universal, continuous, heterogeneous, slow and complex process. During this, the gradual deterioration of functional capacities and the loss of homeostatic capacity make individuals particularly susceptible and vulnerable to a variety of neuropathological disorders. At the population level, aging shows notable regularities in characteristics such as the mortality rate and the probability of survival. However, these regularities are masked at the individual level, due to interpersonal variability, which suggests the idea that individuals of a species differ in their biological age in morph-morbid-functional aspects (range of heterogeneity). It can check between the systems and organs that form it, since the different cell types "age" at different rates, the result of a complex interaction between genetics, the environment and stochastic factors.[16]

If the aging process is complex at a general level, it is even more so when we refer to the nervous system (NS). In neurobiology, as in other fields, there is a natural attraction to the idea that neural aging is a programmed process, because the programming of developmental processes is the basis of life. Although, in fact, only some neurodegenerative processes related to aging, such as familial Alzheimer's disease (AD), appear genetically programmed with a classic Mendelian heritability pattern. There are 2 characteristic biological facts of NS: first, that neurons are post mitotic fixed cells and once they have formed in the initial stages of development they no longer divide; second, its maturational development implies, among other processes, the growth of the soma, dendrites and axons, the establishment of the appropriate neural connections and the synthesis of specific neurotransmitters (NT). This high degree of differentiation causes multiple cell types with important morph-functional differences.[16]

Changes in response to stimuli have been observed when evaluating age-related changes in neuronal activity. The conflicting results of these types of experiments have been attributed to differences in brain blood flow and brain metabolic rate of oxygen.[17]

These brain changes, from birth to the most advanced age, provide the NS with a great adaptive capacity to influences and transformations of the environment, both internal and external. This process is what is known as neural plasticity, or neuroplasticity, and is considered one of the key biological mechanisms in successful aging. During brain aging, alterations of some cognitive functions, such as memory, may appear. The most relevant observations indicate that cognitive decline is not only due to the death of neurons, the functional changes that occur over time play a fundamental role. Taken together, modifications in synaptic plasticity, interneuron communication, trophic factors, and the different circuits that interrelate brain activity could represent the key to the process of cognitive aging. [16]

Brain aging from a morphological point of view

The brain, from the neural point of view, is a post mitotic organ, although we known that neurogenic phenomenon persist in certain regions. As a consequence of this characteristic, when neurons are lost for any reason, they are difficult to recover, so the total number of neurons and the overall weight of the brain decrease progressively with aging. Starting at age 60, the brain loses 2 to 3 g annually. These general morphological changes are also attributed to changes in the white matter of the most involved phylogenetically-derived regions. Weight loss is accompanied by volume loss, which is evaluated by comparing brain volume with intracranial volume, or evaluating the progressive width of the grooves and fissures that reveal brain atrophy. [16, 18]

Normal values are considered 4 mm of cranioencephalic distance and 6 mm of the inter-hemispheric width (fig. 1). There are neurodegenerative disorders and diseases such as diabetes, hypertension and some drugs that can cause atrophic brain disorders. [18]

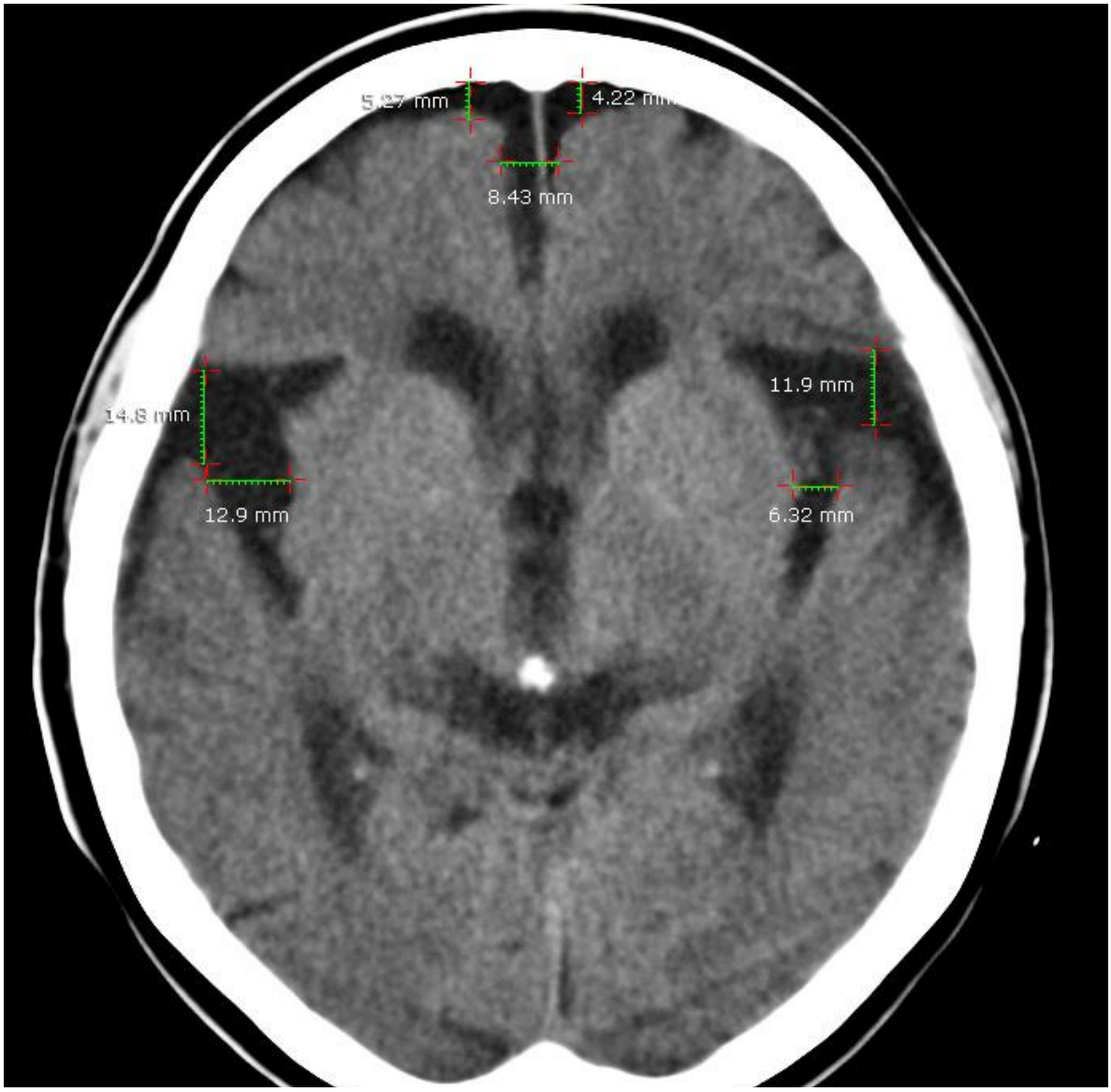

Fig. 1 - Computed tomography image of the simple skull of a 75-year-old patient that came to the imagenology ward of Juan Bruno Zayas Alfonso Hospital , without neurologic focalization signs, it showing signs of cerebral atrophy, with deepening of the grooves at the frontal level (5.27 and 4.22 millimeters respectively), of the anterior portion of the interhemispheric fissure (8.43 millimeters) and dilation of the grooves of Silvio (11.9 and 14.8 millimeters on both sides) and Rolando (6.32 and 12.9 millimeters on both sides).

An increase in the total volume of the ventricles (especially the third and hemispheric) is also observed, which can go from 15 ml in young to 60 ml in elderly controls.[16] In relation to the lateral ventricles, the analysis of their increase is It is done mostly qualitatively in our environment, from the simple visual analysis of the topographic study. It can also be done quantitatively from

the Evans ventricular index (IVE), which must be greater than 0.3 and increases in hydrocephalus and secondary ventricular megaly in sub cortical atrophies (fig. 2).[19] It is obtained according to the formula:

$$VIE = \frac{\text{diameter of the front horns}}{\text{brain diameter}}$$

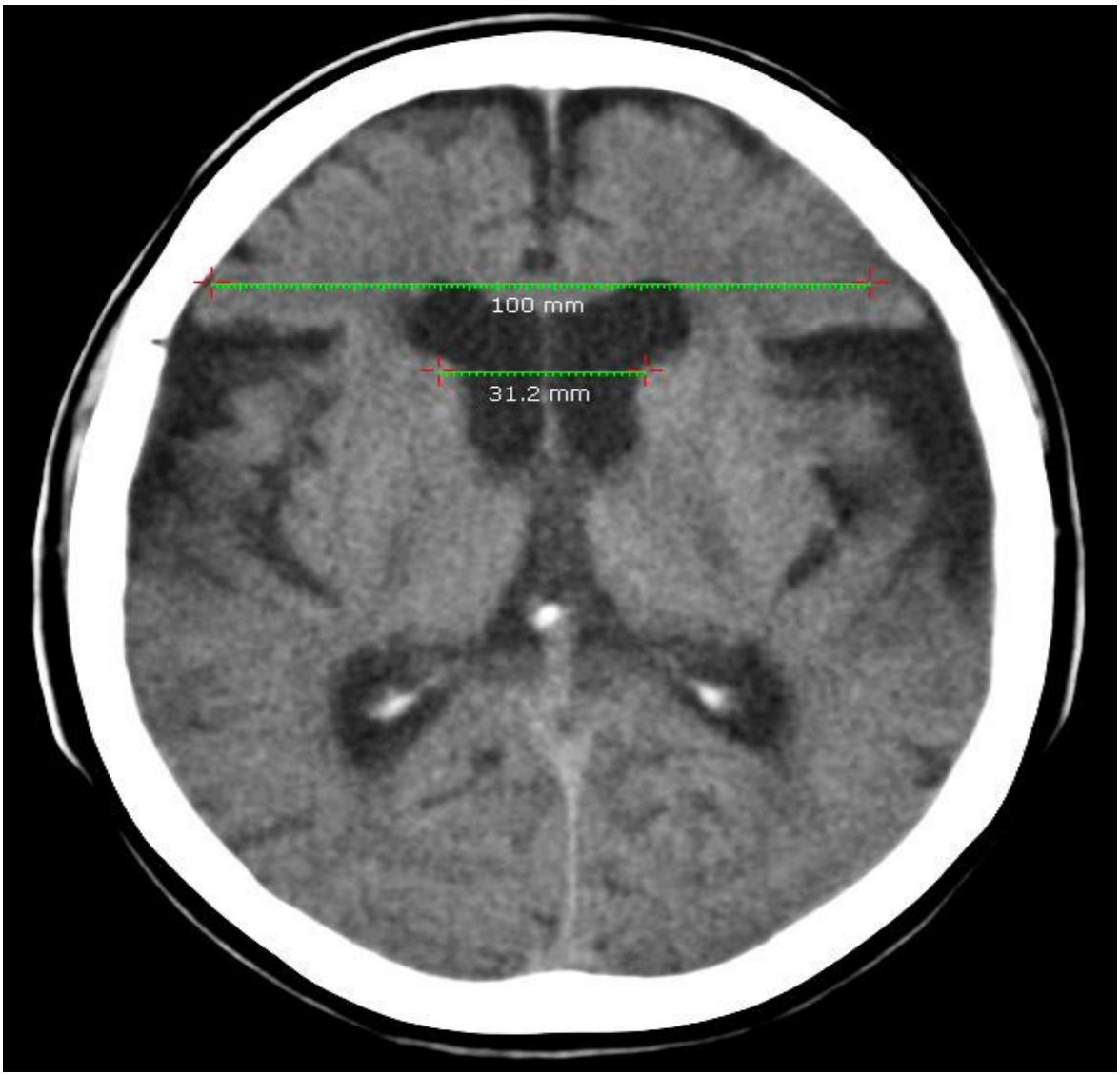

Fig. 2 - Simple skull CT image of a 75-year-old patient that came to the imagenology ward of Juan Bruno Zayas Alfonso Hospital , without neurologic focalization signs ,it showing signs of cerebral atrophy and an IVE at the level of the frontal horns of the lateral ventricles of 0.31mm.

Special attention in radiological practice is given to the morphometry of the frontal horns of the lateral ventricles, at the level of the Monro hole, in people younger than 40 years < 12 mm, and in those older than 40 years < 15 mm.[20]

The same atrophic phenomenon is verified in the hemispheric volumes that can drop up to 3 % per decade from the beginning of adulthood. These cortical and/or white matter decreases are interpreted as loss of interneuron's. Recent studies with neuroimaging performed on living people, however, are not as conclusive, the variability is important and many elderly people do not present significant changes from the macroscopic point of view.[16]

Regarding the cellularity of the brain, various works support the idea that some loss of neurons associated with gliosis occurs, although the precise moment in which these changes are initiated is not well established. However, the quantification of possible losses in the number of neurons associated with age is complex. The macroscopic changes reported, the different cyto cortical or nuclear architectures, the biases of the measurement method itself or the differences in tissue retraction depending on the method of brain fixation, the differences in the changes according to the different regions analyzed and, of course, the differences by sex and interindividuals of aging itself increase the methodological complexity of quantification and influence the results.[16]

Regarding cortical thickness, a neuronal loss of up to 35 % was estimated in the largest cells; however, these numbers may over-overestimate the neuronal decline, due to the actual decrease in the size of the cell cytoplasm with aging. The published data is inconclusive regarding whether or not to confirm neuronal loss. These problems, both regarding the estimation of brain volumes and compartments and the global quantification of the number of neurons, have been tried to solve with the analysis of smaller and more defined structures such as the hippocampus, the Meynert basal nucleus, the cerebellar cortex. And through the use of quantification techniques based on stereology. Today it is assumed with respect to the number of neurons that, in most brain regions, including the hippocampus, remains quite stable throughout life.[16]

However, there may be exceptions in certain regions of the brain. Purkinje neurons in the cerebellum have been shown to be one of those areas were neuronal cellularity can be affected by the aging process. A reduction of up

to 40 % in the number of Purkinje cells and granular cells in the anterior lobe of older males is estimated.[16]

Functional morph patterns of brain aging

Normal aging is characterized by a gradual decrease in cognitive processes such as executive functions, episodic memory, working memory, and brain processing speed. However, there is substantial heterogeneity in the cognitive abilities of healthy people, and some show surprisingly high levels of cognitive function regardless of age, leading to the general hypothesis of the cognitive reserve mechanism. The idea holds that the adaptive capacity of neural networks helps some individuals cope with aging better than others, and therefore maintain their cognitive performance. In recent years, functional magnetic resonance imaging, in a resting state, has influenced the understanding of the complex model of brain functional organization by analyzing the synchronization of the signals of the levels of dependent blood oxygen in the different regions of the brain.[16]

An important feature of the functional organization of the brain are the axes of highly functional and interconnected neural networks such as the insula, anterior cingulate cortex (CCA) and posterior (CCP), superior frontal cortex, and medial pre-frontal cortex. These systems form the central structure of communication between different brain regions and play a crucial role in adapting behaviors in response to the demands of cognitive changes. These axes are also the structure of the neurocognitive base of functional networks.[16]

Neural network clusters are the first group of structures susceptible to AD and other disorders. It has been hypothesized that brain function problems in these neurodegenerative processes tend to be concentrated in centers of neural connectivity networks. Various studies have shown that these connectivity axes have a higher metabolic rate and blood flow than other brain regions. This increased functional requirement could represent greater vulnerability to deficits in the supply of energy substrates, resulting in greater sensitivity to neurodegenerative diseases. Furthermore, regions with high connectivity present the morphological characteristics of neurodegenerative disorders. The age-related interruptions in connectivity that appear in these brain areas produce detrimental effects on episodic memory and executive functions in older adults, underscoring the

importance of these neural connectivity networks in understanding aging. normal brain. Among these regions, the insula and the CPC and their role during aging stand out, both for people with good and poor cognitive performance. Subjects with poor cognitive performance related to age have interruptions in the functional connectivity of the right insula with PCC. Furthermore, these people also presented alterations in the connectivity between the left CCP, the prominence network and the CCA. In contrast, the elderly with good cognitive performance when comparing both hemispheres, only showed deficits in the connectivity of the left insula, the PCC and the left hemisphere.[16]

These results suggest a differential adaptation of these centers of neural connectivity between people with good and bad cognitive performance as age increases. The lobe of the insula appears as a fundamental structure in the processes of intracerebral communication, both among people with normal and altered cognitive performance, the insula functioning as an integral center to help the brain regions involved in generating appropriate behavioral responses to stimuli, as well as their participation in attentional processes.[16]

Morphometric studies based on voxel

Advances neuroimaging techniques allow exploratory analyzes of structural abnormalities that can be used as evaluations of such changes related to age and sex. Examples of such techniques include voxel-based morphometry (VBM), tensor-based morphometry (TBM), region-based hybrid strain-based morphometry (DBM) (MBR), and surface morphometry (MBS) that allow detection of even subtle changes in the structure of the brain.[1,14]

Using modern machine learning techniques in the neuroimaging community, they have made it possible for researchers to discover biomarkers of aging and develop automatic classification systems. Furthermore, it can be useful for delineating a typical anatomy pattern, including for estimating brain age, which is of great importance in predicting biological age in health informatics, with an application to the early prediction of neurocognitive disorders.[21,22,23,24]

Today, the combination of different methods of imaging, data processing, statistics, and physics creates the possibility of describing and building understandable brain networks. Data processing, statistical methods,

mathematics and physics often play an important role in achieving safe results in such scientific studies.[25]

Medical images are an essential tool in clinical practice since they allow early detection of pathologies (fig. 3), knowing of the existence of cerebral sexual dimorphism. Studies reveal that it appears in stages as early as post-puberty, invoking as causes the hormonal effect and its action on the brain structure, differences in abilities according to gender and gender behavior.[26,27]

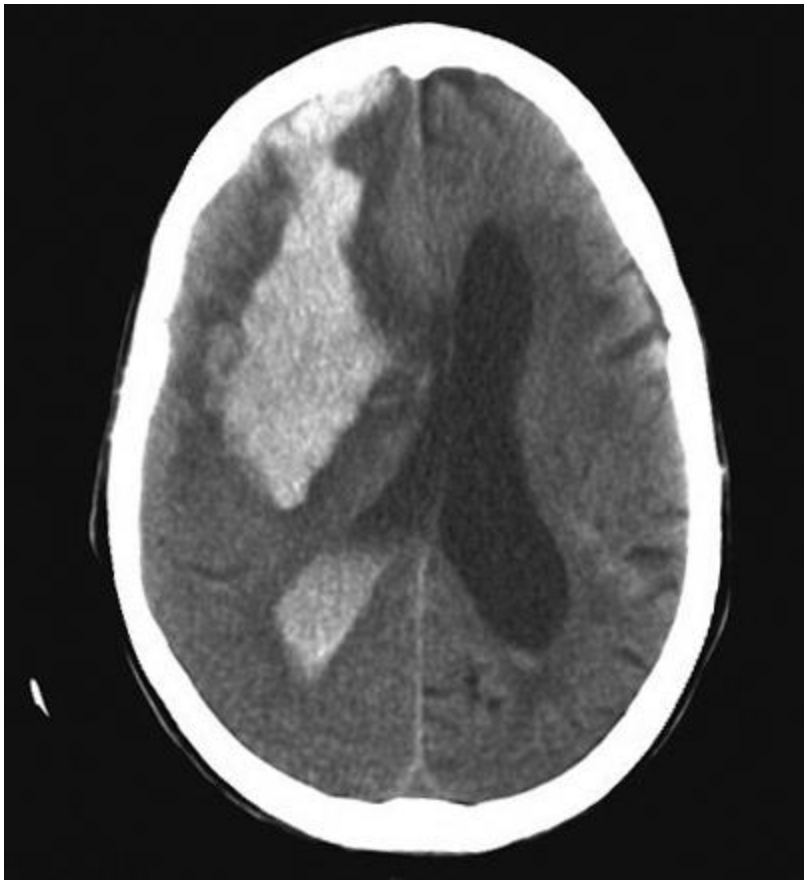

Fig. 3 - CT image of the simple skull of an 82-year-old patient that came to the imagenology ward of Juan Bruno Zayas Alfonso Hospital, with neurologic focalization signs related to full down, it showing a recent hemorrhagic focus of 82 right front parietal HU, measuring 93.6mm x 41.4mm that floods the ventricular system, note the blood content in both occipital horns a predominance of the right side, associated with perilesional edema that clears the cerebral sulci at that level, collapsing the right frontal horn and compressing the body of the right lateral ventricle, which displaces the midline to 8 mm to the left.

Its use is not relegated only to the field of radiology; it is increasingly common to use image-based computing elements in other medical specialties. With such tools, decisions are made in real time. Other applications not only refer to medical diagnosis, but also to medical planning, development, and subsequent evaluation of surgical and radiotherapy processes.[25] We cannot forget that it is in the brain that superior nervous activity occurs.[28]

Brain morphometry studies show that the largest changes within an individual occur during early development, the subtlest changes continue into adulthood, and, again, dramatic changes occur in the latter part of human life: aging. Neuroimaging studies clearly show that it is not possible to specify an age at which development stops or when aging begins, and that it is not the case that the brain is static at any age, but is characterized by experience dependent lifelong neurocognitive plasticity.[1]

The brain continues to change throughout life, with the positive and negative processes of assuming that it occurs alongside others as we age. Interestingly, there is a growing recognition of how early influences of life and cognition on the brain can affect all life time, and how neurocognitive changes at different periods of life can be related. For example, recent studies provide evidence supporting the hypothesis that normal brain degeneration in aging in some respects reflects brain development.[1]

Currently, however, most applications of MRI or CT-based brain morphometry have a clinical objective. Advances in neuroimaging progressively led the scientific community towards a new understanding of neurological diseases, as well as psychiatric disorders based on their underlying neurobiology, facilitating diagnostic classification, improving our ability to predict treatment outcome, and improving our understanding of the genetics and environmental causes of these disorders.[29,30]

With the development of imaging, new modalities of tomography imaging have emerged, such as computed tomography (CT), magnetic resonance imaging (MRI), and positron emission tomography (PET), which offer images of different organs free of overlaps with precision without precedents. You can even record the three-dimensional (3D) structure of the organs by taking a sequence of parallel cross sections.[30]

For many clinical tasks such as surgical planning, complex and often malformed 3D structures need to be understood and communicated (fig. 4). Experience has shown that "mental reconstruction" of objects from cross-sectional images is extremely difficult and highly dependent on the observer's training and

imagination. For these cases, it is advantageous to present the human body as a surgeon or anatomist would see it.[30]

A B

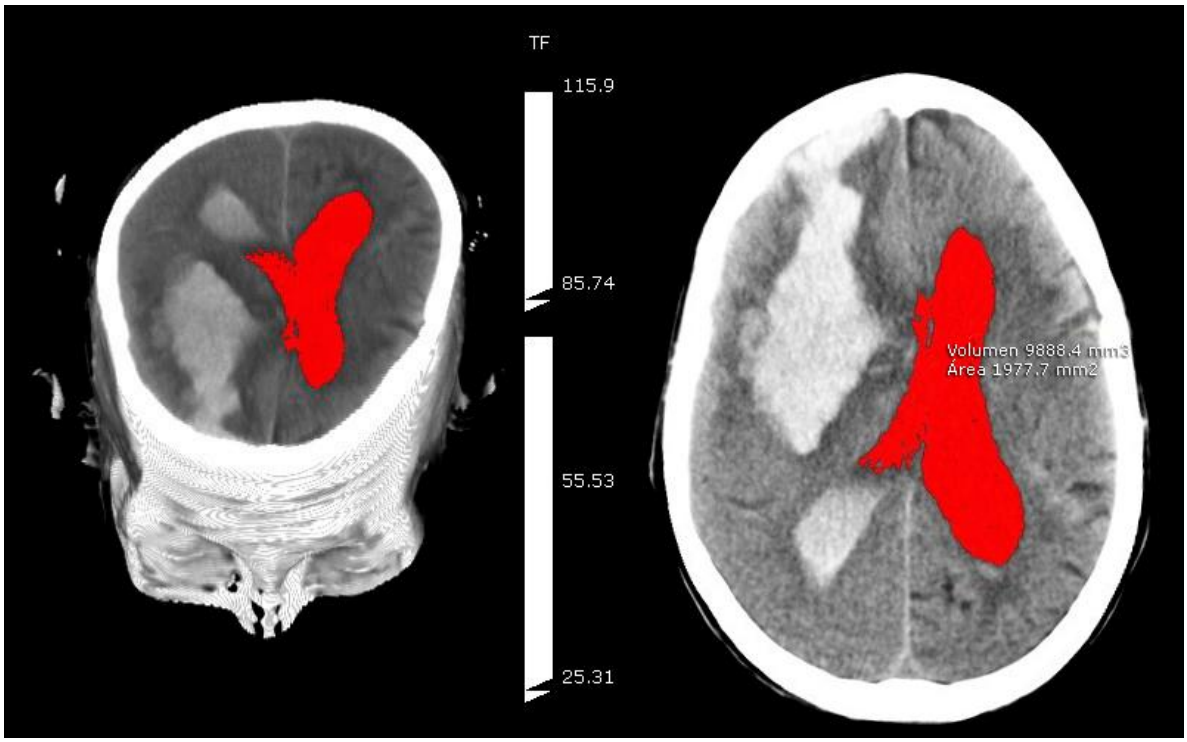

Fig. 4 - Image A represents the 3D reconstruction from the segmentation of the lateral ventricles and the volume 9988,4 cubic millimeters and area 1977,7square millimeters obtained in this tomography slice, were the hemorrhagic focus of 82 front parietal right UH is observed in B image.

As with every scientific approach to the study of a system, morphometry is a continuously evolving discipline. Certainly, access to high-performance computing has dramatically improved the quality of the results, as the technological enhancement of MRI signals equalized the reliability of the data and spurred the production of sophisticated algorithms for analysis. However, there is a long way to go, with the connection between the microscopic and mesoscopic levels of our knowledge about the still distant brain structure. At the same time, a better understanding of the physiology of the brain due to the development of techniques capable of detecting, non-invasively, the local metabolism of the tissue with spatial precision will benefit the characterization of the shapes, thickness and gyrification of the cortex also in terms of its role in

the entire system. Finally, the recent application of complex network science to the clinical and non-clinical aspects of neuroscience will surely help characterize structural differences through age, medication, or dysfunction at the population level, thanks to its ability to discover elusive patterns and trends in big data.[1]

Conclusions

In the differences in the morphometry of the brain, age is a factor that affects its morphology. Different tissue classes, brain regions, and structural features develop differently, and there are large interindividuals differences in brain morphology at any age and in its development.

Brain aging is characterized by having individual variability, depending on the complex interaction between genetics, the environment, and stochastic factors.

Morphologically, there is a decrease in weight, volume, and compensatory dilation of the ventricular system, with an increase in the subarachnoid and subdural spaces; as well as deepening of grooves and fissures.

Today it is assumed with respect to the number of neurons that, in most brain regions, remains stable.

Brain neuroplasticity, property of the SN, is one of the key biological mechanisms in successful aging (cognitive reserve).

Voxel-based morphometry is an effective tool to study structural changes in the human brain, at healthy or pathological stages.

Morphometric studies have shown that despite the most dramatic developmental changes in brain morphology taking place before birth and during the first years of life, the brain continues to undergo substantial structural remodeling during childhood and adolescence and in Adulthood.

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Conflict of interests

The authors declare that there is no conflict of interest.

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