ORIGINAL ARTICLE

DRAWING NEW FRONTIERS IN BRAIN LIMITS

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ABSTRACT

Introduction: From the beginning of knowledge to these days, the encephalon is considered to be the most fascinating and complex organ of the human body. Scientist over centuries tried to unravel the mysterious complex insights of the brain and their efforts concludes to what we now consider to be our understanding of this organ.

Content: Last past decades were marked by a scientific revolution in brain research simultaneously with other important advancements in the field of molecular and cell biology, informatics and neuronavigation. Molecular investigations and cell biology show us how brain molecules interact with each other as the foundation of neuroplasticity – brain ability to restructure itself as a response to stimuli and neurogenesis – which nowadays is considered to take place not only in foetus but also in adults. Many cognitive disorders such as dementia or Alzheimer's Disease could today be anticipated and treated because of the advancements of mechanisms understanding and markers identification. Informatics and computational biology exhibits an important role in artificial intelligence and machine learning, which nowadays help doctors around to globe to manage clinical information and response to task efficiently. Last but not least, neuronavigation has been developed enormously in the last decades with the introduction of the operatory microscope, MRI and other brain investigations. These favourable agents lead to a better understanding of the brain mapping and an accurate localisation of the areas involved in brain cognitive functions.

Conclusions: Our review purpose is to analyze the most important aspects about brain, drawing to the conclusion that brain still remains an uncovered field of medicine with many discoveries yet to come. All the reviewed aspects were classified specifically into few categories: Brain History, Brain Anatomy, Brain Function, Brain Mapping, Modern Brain Investigations, Brain Plasticity and Recovering, Neurogenesis and Future/Artificial Intelligence.

Key words: brain anatomy, neurons function, brain mapping, neuroplasticity, neurorecovery, neurogenesis, artificial intelligence;

BRAIN ANATOMY-HISTORY

What nowadays scientist know about the brain could be considered work of generations of neuroanatomists, neurosurgeons, physicians and other personalities who influenced the medical world by their legacy.

According to the evolution of knowledge about the brain, we can classify our history in 5 major periods of time: Ancient times, Renaissance, Classicism, Modernism and Contemporary Period.

Ancient time was marked by Hippocrates (1) (460-379 B.C) who was the first who stated that the brain is responsible interpreting the outside world, is the seat of intelligence, and thought epilepsy is a disturbance of the brain. Erasistratus of Chios (2) (280 B.C.) noted the divisions of the brain. Aulus Celsus (3) (25 B.C – 50 A.D) was a great encyclopedist whose scientific work had a great influence over time in surgery. His work "De Medicina" was the first written and printed Latin medical textbook. Galen from Pergam (4) (190-200 A.D) performed vivisections and anatomical demonstrations, he proved hegemonic theory of the brain and elaborated the theory about the cerebral ventricles as the modulators of conscious awareness filled with "pneuma".

Renaissance brought great changes in the history of surgery, primary due to the possibility of making daily human dissections. Leonardo da Vinci (1452-1519) (Figure 1) was the first who elaborated the diagram of the cranium nerves, optic chiasms, brachial plexus and the first one who reproduced the ventricular system by injecting hot wax directly into the brain of an ox (5) .

Figure 1: Leonardo da Vinci, Self-portrait, circa 1512. Source: Barnett, R. (2019). Leonardo da Vinci. The Lancet, 393(10179), 1409–1410.

C. Varolio (6) (1573) who named the pons and the first who examine the brain from its base up. It is known that, Franciscus Sylvius (7) (1641) described fissure on the lateral surface of the brain, while the association of Sylvius's name with the cerebral aqueduct is still problematic. Th. Willis (8) (1621-1675) described the striate nucleus, the internal capsule, the cerebellar peduncles and claimed that pain receptors are found in the meninges and not in the brain itself.

Classic period is the great period of the scientific conquests in neuroscience. This included the discoveries of Broca (9) (1824-1880) who discussed about the cortical localization of speech centre and published the work on the "great limbic lobe". Eduard Hitzig (10) (1838- 1907) and Gustav T. Fritsch (1838-1927) discovered cortical motor area of dog using electrical stimulation. Richard Caton (11) (1875) discovered the electrical waves of cerebral cortex that nowadays lead to the establishment of electroencephalography. Max von Frey (12) (1896) tested the somatosensory system and discovered discrete tegumentary pain points when examining it with fine needles. Wilhelm von Waldeyer (13) (1891) coined the term "neuron" and Charles Sherrington (14) (1897) coined the term "synapse". Santiago Ramon y Cajal (15) (1889) described the dendritic spines as true cellular components and made numberless contributions to neuroscience (Figure 2).

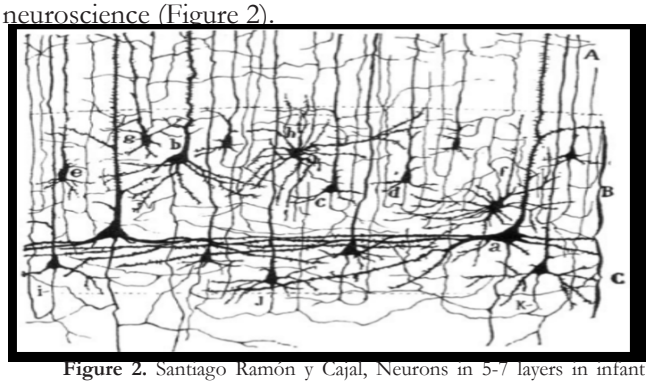

Figure 2. Santiago Ramón y Cajal, Neurons in 5-7 layers in infant visual cortex. Source: Andres-Barquin, P. J. Ramón y Cajal: a century after the publication of his masterpiece. Endeavour 25, 13–17 (2001).

Modern period is marked not only by the discoveries of major functionality insights regarding the nerve cell but also by the lives of the greatest fathers of neurosurgery. There should be mentioned Oskar Vogt (16) and Cecile Vogt (1902) who played a key-role in brain research and established one of the largest and most modern centers of their times.

Ivan Pavlov (17) (1903) mentioned the term "conditioned reflex". Alois Alzheimer (18) (1906) described the senile dementia. Korbinian Brodmann (19) described the cortical areas, being the pioneers of brain mapping (1909). Wilder Penfield (20) (1891-1976) expanded brain surgery's methods and techniques, introducing the notion regarding the cortical homunculus. Victor Horsley (21) (1857- 1916) was the first who successfully removed a pituitary adenoma using a transcranial approach. (Figure 3).

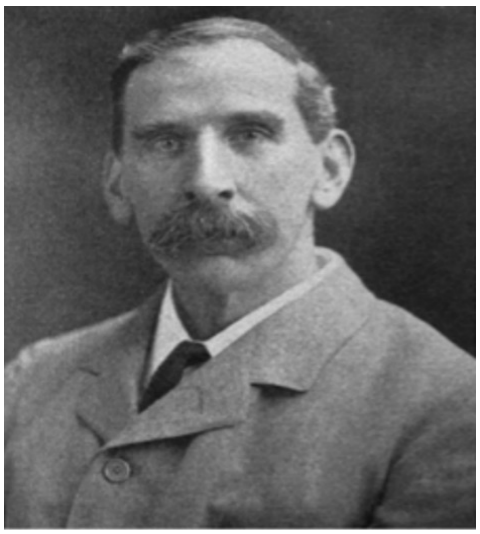

Figure 3. Pioneering neurosurgeon Sir Victor Horsley (1857 - 1916). Source: Tan, T. C. & Black, P. M. L. Sir Victor Horsley (1857-1916): pioneer of neurological surgery. Neurosurgery 50, (2002).

Among the founders of the modern neurosurgery should be mentioned 5 important personalities. Harvey Cushing (22) (1869-1939) (Figure 4) was the father of American neurosurgery, one of the most recognized neurosurgeons in history, the one who established many of the current used techniques and who described Cushing Syndrome.

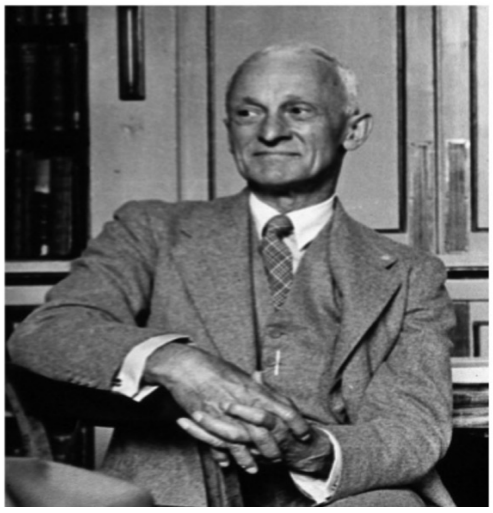

Figure 4. Harvey Cushing. Source: Doyle, N. M., Doyle, J. F. & Walter, E. J. The life and work of Harvey Cushing 1869–1939: A pioneer of neurosurgery. J. Intensive Care Soc. 18, 157–158 (2017).

Figure 5. Fedor Krause – the father of German neurosurgery. Source: Laios, K. et al. Fedor Krause (1857-1937) and His Innovations in Neurosurgery. Surg. Innov. 26, 633–635 (2019).

Walter E. Dandy (23) (1886-1946) was the first neurosurgeon who performed clipping of an intracranial aneurysm (1937), the one who described brain endoscopy and performed total excision of acoustic tumors. Fedor Krause (24) (1857-1937) (Figure 5) - father of German neurosurgery, being the first surgeon who operated cerebral angiomas and who successfully approached the fourth ventricle for tumor resection. Clovis Vincent (25) (1879-1947) with Thierry de Martel (1875-1940) were the founders of French neurosurgery.

In terms of Imagistics, Conrad Roentgen (26) (1895) discovered X-rays and paved the way for novel means of investigating the skull. Ernest Speigel and Henry Wycis (1947) were the first to use stereotactic surgery (27).

Contemporary period started with the introduction of CT (28) in the medical practice (1971 - Godfrey N. Hounsfield, 1972 – commercially available) and continued further with the use of microscope fMRI and neuronavigation. M. E. Phelps and his colleagues developed the first PET scanner (29) (1975). Raymond Damadian (30) (1977) built the first MRI scanner by hand and achieved the first MRI scan of a healthy and cancerous human bodies. Gazi Yaşargil (31) is one of the fathers of micro neurosurgery, treating brain tumors with instruments of his own design. Important advances in this period included the introduction of surgical microscope, real time scanning, Doppler blood flow, Pulsed Doppler, Color flow imaging, etc.

BRAIN ANATOMY AND FUNCTION

Brain structure involves the surface or cerebral cortex which is easily visible after craniotomy and some other deep structures essential for metabolism, movement, five senses. Based on the most prominent sulci and fissures, brain cortex could be divided in 4 lobes: frontal, temporal, parietal and occipital lobe, each of them with specific function, yet interconnected and working conceptually as a whole.

Frontal lobe is the largest lobe of the brain, anterior to the central sulcus, consisted of a medial, lateral, polar and orbital part. Frontal cortex includes prefrontal cortex involved in long-term memory and the processing of internal states - motivation (35), personality (33), social behavior and emotional regulation (34).

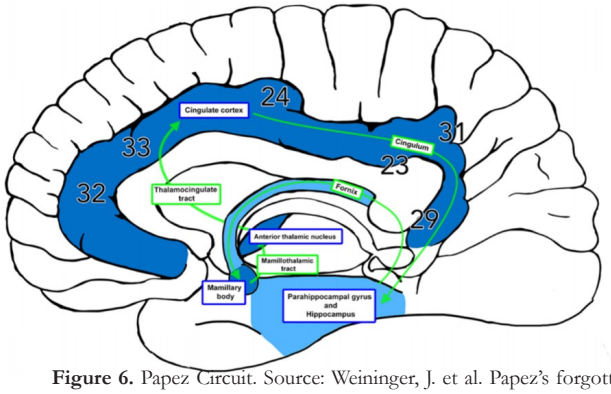

Figure 6. Papez Circuit. Source: Weininger, J. et al. Papez's forgotten tract: 80 years of unreconciled findings concerning the thalamocingulate tract. Front. Neuroanat. 13, 1–11 (2019).

The ontogenic gradient of myelination starts from the primary sensory and motor areas to the associative areas, thus the prefrontal cortex is the last part to be myelinated, simultaneously executive functions are matured lately (36). Also, it includes Broca's area which is involved in language production and comprehension (37).

Broca aphasia is a non-fluent aphasia which is remarkable for partially losing the capacity to produce both spoken and written. In addition, frontal cortex includes the primary motor area and premotor area that are involved in movement control, etc.

Parietal lobe contains an anterior part which includes the primary sensory cortex (S1) responsible for interpreting the simple somatosensory (38) signals – touch, pressure, temperature, pain, etc. The posterior part is one of the main 3 associative areas in the brain (along with PFC and temporal cortex) and plays an important role in sensorimotor integration, spatial navigation, working memory, early motor planning (39). An infarct at this level will cause 3 major symptoms consisting the "Bálint's syndrome": oculomotor apraxia, ataxia and simultagnosia - inability to perceive more than one object at a time highlighting the important role of this area in building the representation of the surrounding space and orientation into it (40).

Temporal lobe is subdivided into superior, middle and inferior parts and hosts hippocampus and amygdala. Temporal lobe process information into memories, language and emotions. The connection between middle temporal lobe, hippocampus and parahippocampal areas plays an important role in declarative memory (episodic/events memory and semantic/facts memory) (41,44,45). Also, the Papez circuit (Figure 6) initially thought to be involved in emotional expression, today it is well-known to be involved in learning and episodic memory (48). Increasing age with a decrease in blood perfusion of its components (e.g mammillary bodies, anterior thalamus) have been associated with Alzheimer's Disease (49,50). Besides, temporal cortex includes the primary, secondary auditory cortices and Wernicke's area. The role of the last one is debatable today, scientist reaching to the conclusion that WA is involved in phonological representation (identification of each phonemes of each stimulus with the memorization of them) and retrieving an associated word concept (42). Amygdala is the most involved in fear processing, avoidance behaviour and emotional responses, being the structure where neutral stimuli and aversive unconditioned stimuli emerge to form the conditioned fear (51,52,53).

Occipital lobe is the smallest lobe of the brain, situated posteriorly to the others. Occipital cortex is responsible for visuospatial perception, color identification, distance estimation, face recognition. Bilateral infarction of the occipital lobe leads to Anton's Syndrome manifested by visual anosognosia – denial of loss of vision, with cortical blindness and confabulation

(43). Visual ventral stream between occipital and temporal lobe play an important role in core object recognition – the ability to rapidly label the images around humans which involves the detection and classification of thousands of objects basing on a big sets of images that were integrated into the neural circuits via past experiences (46,47).

Besides the principal lobes and cerebral cortex, there are a bunch of other important brain structures that are not discussed here, but will be the main themes of other reviews in the future. In this list should be included: ventricles, brainstem, thalamus and hypothalamus, pituitary and pineal gland, cerebellum, reticular network.

NEURONS FUNCTION – CEREBRAL ACTIVITY

The normal human brain contains about 20 billion (1013) neurons, which give birth to a very complex network containing of 164 trillion synapses (54). These synapses are further sustained by a 40-130 billions of glial cells (astrocytes, oligodendrocytes, and microglia) with

Glia-Neuron ratio less than 1 rather than 10:1 as it was thought in the past (55). Today, some of the glial cells, especially the astrocytes which were considered for a long time just a sustaining part of the neuronal network are thought to have an important role in demarcating

gray matter regions in functional areas and controlling the thresholds of these areas (56).

This great number of neurons, glial cells and synapses give us the specific human behavior. While animals with smaller brains are primary adapted to feed themselves, attack the prey and survive, human intelligence is established on the brain capacity to process and integrate a huge amount of information in a minimum of time via several complex sensorial and motor systems. Thus, human brain capacity is determined by efficient spatial organization of neuronal system and by a-low-time transfer of information via the interconnected fibers (57). According to PET data association areas in human brain with higher aerobic glycolysis are less myelinated than the sensory and motor areas which suggests that association areas are more intensively active than the other, favoring the conceptual process in humans to the sensorial or motor processes in other animals (58). An example of this integrative function of human brain is found in the prefrontal cortex which is responsible for selecting a weaker but relevant task-response, for a stronger but irrelevant task-response (59).

It is good to mention that these functions as brain complex processes are interconnected based on a complex neural network, which only in this form could serve for solving humans' daily tasks. According to literature specific information tends to segregate into small network within a specific region of the brain that some authors (60) called it resting-state network RSN. To understand how brain functions is important to acknowledge that these RSNs are connected to each other through a central backbone called "rich club" an information integrator, which plays the role of a global efficient workspace (61).

About the organization of neurons, these distributed in layers on a horizontal scale, but also in columns in a in a vertical scale. Adjacent neurons from the same column are interconnected vertically, but also share their extrinsic connectivity and tuning patterns acting as basic units in cognitive processing (62). Further, information is transmitted by a sequence of rhythmic action potentials along the dendrites, cell body and axon. Human cortical brain uses synchronous spike events propagation between different groups of neurons found within the six-layered neocortex as the primary efficient transmission practice (63). An increase in stimuli rate leads to an increase in intensity of firing, till the limiting frequency of transmission is achieved and synapse becomes saturated or could no longer transmit the presynaptic information (64).

BRAIN MAPPING

Brodmann areas were originally defined and numbered by the German anatomist Korbinian Brodmann based on the cytoarchitectural organization of neurons he observed in the cerebral cortex using the Nissl method of cell staining. Brodmann published his maps of cortical areas in humans, monkeys, and other species in 1909 (Figure 7), along with many other findings and observations regarding the general cell types and laminar organization of the mammalian cortex (65).

Similar, but more detailed cortical map was published by Constantin von Economo (66) (Austrian psychiatrist and neurologist of Romanian origin) and Georg N. Koskinas in 1925. Many Broadmann areas have been associated with brain functions (67).

For example, Brodmann areas 3, 1 and 2 are the primary somatosensory cortex, area 4 is the primary motor cortex, area 17 is the primary visual area, and areas 41 and 42 correspond closely to primary auditory cortex.

Higher order functions of the association cortical areas are also consistently localized to the same Brodmann areas by functional imaging and other methods.

However, building the brain map just on the anatomical landmarks exhibited on neuroimaging is not a reliable source because neuroanatomy and cortical functions are just partially associated. The real localization of brain areas with their wholly functional patterns representation requires high-resolution MRI that enables the visualization of the differences between intracortical myelin density and some myeloarchitectonic features specific for certain brain area (Cajal-Retzius stripes) (68).

In a number of cases, brain areas are organized into topographic maps, where adjoining bits of the cortex correspond to adjoining parts of the body. A simple example of this type of correspondence is the primary motor cortex or primary somatosensory cortex – representing the motor, respectively, sensory homunculus (69).

In 2016, a new map based on brain scans data collected by the Human Connectome Project was released by Matthew F. Glaser and David C. Van Essen. (Figure 8) These scientists created the map using a semi-automated analysis of high-quality neuroimaging that included 180 areas, representation of cortical thickness, myelin tracts and functional connectivity (70). This task was realized using tfMRI, architectural modalities of cortical thickness, T1w/

/T2w myelin maps, and resting-state-based visuotopic maps. To build the representation of an area, they selected multiple modality maps, drew an initial trajectory of a specific border, and then adjusted using the others modalities maps71. The results were validated according to an average correspondence of the localization of brain areas, yet the brain regions differ between people. Other scientists built the human Brainnetome Atlas (72), a pioneering-work which aims to identify the areas of the entire brain. This atlas contains around 210 cortical and 36 subcortical subregions. This mapping provides biologically plausible brain fine-grained parcellation revealing some subdivisions never discussed before.

An impediment in building the brain map could be the association (73) between regional brain activity and transient emotional states. Esslen et al (74) presents that there are a few brain structures that are both involved in brain cognition

such as temporal cortex – involved in

memory but also happiness and sadness or anterior cingulate cortex – involved in attention

but also in depression and emotional regulations. Thus, literature presents that a better brain computational organization is obtained when analyzing non-emotional tasks such as motility than emotion-involving tasks such as speech.

Moreover, studies (75,76) have reported that not only that emotional word processing is

prioritized to neutral words when persons are aware of these words, but also that there are specific parts of the brain – in addition to the usual language centers - that report increase of the neuronal activity in case of emotional words such as dorsomedial prefrontal cortex and anterior cingulate cortex. However, this situation is somehow avoided when analyzing the motility which is less emotional related.

Brain mapping is far more impactful than we have ever thought before. By comparing patterns between normal and abnormal brains, scientist today could have a better management of the evolution of the disorders. Such an example is the management of Alzheimer's Disease (77) when by providing special information about the extent and trajectory of the disease. The most studied parts in AD may be considered to be hippocampus and entorhinal

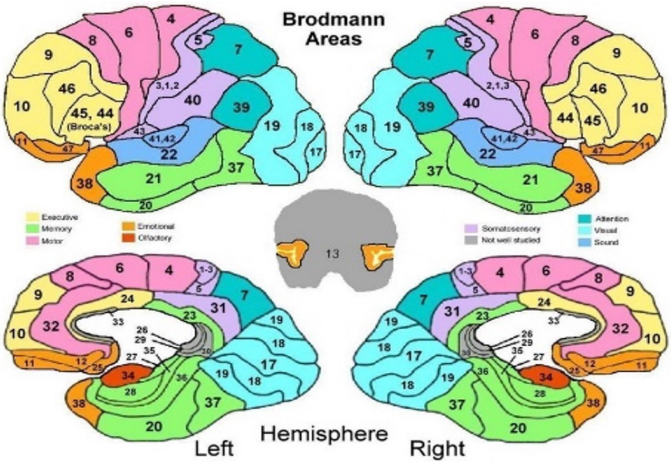

Figure 7. Mapping of the brain areas depicted by Korbinian Brodmann in 1909. Source: Liu, Y. et al. What Strikes the Strings of Your Heart? - Multi-Label Dimensionality Reduction for Music Emotion Analysis via Brain Imaging. IEEE Trans. Auton. Ment. Dev. 7, 176–188 (2015).

cortex, however there are still other different brain parts like temporal, posterior cingulate and precuneal cortex which report progressively atrophy as the disease advances.

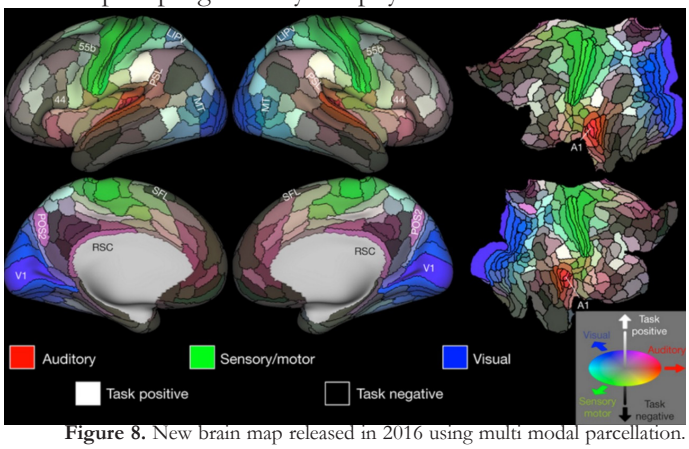

Figure 8. New brain map released in 2016 using multi modal parcellation. Source: Glasser, M. The Human Connectome Project: Progress and Prospects. Cerebrum Dana Forum Brain Sci. 2016, 1–16 (2016).

MODERN BRAIN INVESTIGATIONS

Brain investigations include a wide range of methods that are used in diagnosis and treatment of brain diseases. The development of these technologies have led over time to considerable achievements in neurosurgery, neurology, psychiatry and other areas related to cerebral domain.

CT (Computed Tomography) plays an important role in nowadays practice especially in the treatment and investigations of trauma and SAH patients. From its origins in 1972, Nobel award ceremony in 1979 (Hounsfield with Cormack), CT suffered a long-way of developments - from the slow-scan time and artefact-problem caused by movement or breathing in spiral scanner CT to large areas gathered by a single shot and faster acquisition in multislice CT (78). While the spiral scanners use only one single row of detectors to pick up the x ray, multislice scanners use 8 active rows of detectors.

DSA (Digital Subtraction Angiography) is an emerging technology (79), widely use in the diagnostic of arterial diseases and injuries, by combining digital data collection and computer

processing to obtain vascular images. With DSA doctors could analyse the patency of the vessels, find arterial insufficiency. The disadvantage may be the invasive nature.

MRI (Magnetic Resonance Imaging) provides 3 types of data: cortical regions (T1/T2 flair), structural connectivity (Diffusion Tensor MRI) and functional connectivity (resting- state fMRI). While T1/T2 flair are used on a daily basis in neurosurgery, the other 2 types of MRI are used more for building the neural networks within the brain (DT MRI) or in brain mapping. DT MRI (80) could detect the developmental or aging pathologies in CNS that influence the neural architecture by analysing the abnormal distribution of water within the tissue

fMRI (functional Magnetic Resonance Imaging) bases its functionality on the analysis of oxygen (81) consumption and metabolic activity. fMRI brings life to the anatomic structures, evaluating the basal and higher functions in different neurological diseases and also the behaviour of cerebral structures under drug administration. Other types

of investigations that could be performed are: PET, DTI, TMS.

PET (Positron Emission Tomography) is an investigations focused on the detection of photons elimination released when radionuclides produce positrons that suffer annihilation with electrons. PET could detect the malignancy in brain before the appearance of macroscopic alterations visible with CT or MRI, based on the analysis of abnormal brain metabolic activity (82).

DTI (Diffusion Tensor Imaging) (Figure 9) analyses the microstructure (83) of white matter tracks by the diffusion pattern of water molecules.

Thus, the image captured are furthered displayed in a MRI projection and certain injuries could be localized at axonal level. However, this brain investigation seems to have the disadvantage for not being so accurate in mild lesions, not being able to distinguish very clearly between the lesions and normal brain structure. Another important aspect is that DTI analyses not just the interested tracks but also the surrounding tracks which may be unaffected thus leading to false negative results.

TMS (Transcranial Magnetic Stimulation) is an important investigation (84) in a way that by stimulating one scalp region, this brain area found under the scalp could further lead to motor-evoked potential (MEP) on electromyography, examining the corticospinal tract functionality. Contrary to TMS, rTMS (repetitive TMS) can increase or decrease the excitability of the cortical neurons playing an important role in the treatment of neurological and psychiatric disorders.

BRAIN NEUROPLASTICITY AND NEURORECOVERY

Neuroplasticity can be defined as the ability of the brain to adapt and modify its structure according to experience and significant stimuli. Understanding this process could mark a major step for clinicians and researchers willing to treat several neurodegenerative and neurological disorders. In our review, we were looking on the factors that influence this ability, describing the direct impact on the cortical sensory areas, and how neuroplasticity could lead to brain recovery.

One important factor in neuroplasticity is age, specifically the critical periods, defined as the periods of time when specific sensitive functions develop promptly. In case of vision, Wiesel and Hubel (85) reported that occlusion of one eye in the first hours of infants could lead to contralateral eye dominance in children. Regarding the other senses, language is accurately analysed today in terms of critical periods. Even though, the language process is not developed as a whole at once, it is important to mention that researches marked specific periods of time when aspects of language are developed. Vocabulary (86), for example, is developed throughout life, while syntax and phonology at the age at which the baby is exposed to the verbal stimuli. Moreover, babies experience something called perceptual shift, a process that occurs between 6 and 12 months. By this process, the neural representations of specific and used sounds are strengthened, while non-important surrounding stimuli are neglected.

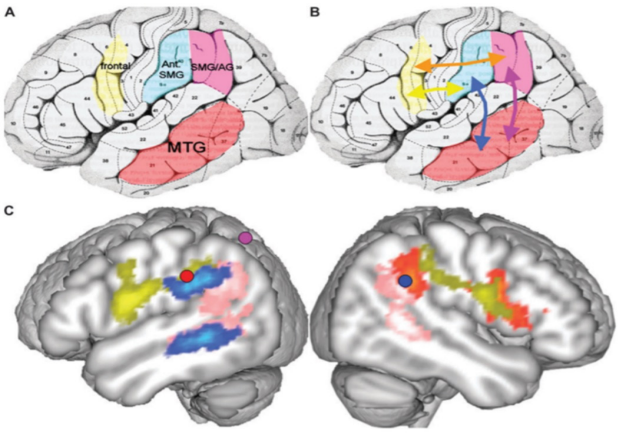

Figure 9. Four brain segments are tracked using tractography. Source: Ramayya, A. G., Glasser, M. F. & Rilling, J. K. A DTI investigation of neural substrates supporting tool use. Cereb. Cortex 20, 507–516 (2010).

Critical periods have been encountered also in olfaction (87). Even though are few studies in this area, one important (88) done in 2007 mentioned that the first 3 hours after birth may be essential for developing olfactory memory. The study suggests that infants may memorise the trace of the stimulus for 3 days. Also, there are reported in literature some important aspects about the relationship between mothers and babies based on olfaction critical periods in the first hours of life.

Neuroplasticity equilibrium in brain is based on excitatory and inhibitory processes (89).

Studies reported that an alteration of these processes cause a various of disabilities in learning, memory and cognition. Such an example could be the over-activation of GABAergic receptors (90) during daily phases which are responsible for the inhibition of

neuroplasticity, found also in neurological degenerative disease. Administration of GABAergic solutions in accordance with the maximum activation CNS during day could lead to destabilisation of learning. Other situation in which GABAergic reactions are involved in the reactivation of monocular dominance in adults when one eye is deprived of the vision, situation that is usually seen only in infants.

Regarding the importance of excitatory synapses in neuroplasticity, studies have reported that antagonists of NMDA receptor lead to schizophrenia (91), especially by affecting the memory and cognition. A major reduction of synaptophysin (92) in pyramidal neurones of prefrontal cortex could lead to a disruption of the normal synaptic transmission, an important pathological aspect in schizophrenia.

Traumatic brain lesions could lead to numerous cortical impairments affecting the good functioning of the entire body. However, based on specific studies today it is well-known that neuroplasticity plays one of the most important roles in recovering (93,94). Such example has been reported in the literature for the motor impairment in case of animals and humans, when repeated tasks drives neuromodulation and synaptogenesis to stimulate functional recovery (95). Brain recovery is dependent on the time phase of the intervention. Studies (96,97) reported that early interventions

Studies (96,97) reported that early interventions may be better than the latter, however, the efficiency of these intervention depends on the induced spreading of new dendrites and axons.

Therapy-induced neuroplasticity (98) is an important approach towards treating brain

injured patients, because it allows to evaluate whether any behavioural change is caused by the therapy. Such a situation could be encountered in post-stroke aphasic patients, who need not only to recover from the stroke but also to be reintegrated into society as the majority of those who suffered from this are under 65 years. Constraint-induced aphasia therapy (99) is just an example of the bunch of the therapies that exist today and that have been demonstrated to gain significant improvements over time. The main aspect of this therapy represents the constraints

– aphasic patients often tend to use non-verbal communication, which in CIAT is maximally silenced in favour of verbal communication by using language games with specific rules that may hinder usage of verbal commands (100).

Moreover, brain stimulation should be realized in accordance with the personality of the person. Thus, music (101) or dance (102) could be alternative options, for enhancing the correlations between several neural network with rehabilitative potential.

NEUROGENESIS

Neurogenesis is the process (103) by which nervous cells are formed from the neural stem cells in all species of animals. Neurogenesis is most active during the embryonic period of life, however it continues over time in several places in body. The central nervous system is derived from the neural tube, that will later generate neurons when a certain number of nerve cells is achieved. Neurons do not form neural circuits after the development of axons and dendrites. Otherwise, infant neurons have to migrate long distances to their final destinations and then develop neural circuitry.

Comparing different species of animals, it seems like that the mechanisms of cerebral cortex expansion based on a protracted neurogenesis, while the deposit of neurons is amplified (104).

The rate of neurogenesis depends on several factors such as molecular and genetic components. Many of them are related to Notch signaling pathway (105,106). Neurogenesis varies in time from species to species; literature reporting that brain neurogenesis occurs also at birth (107) and postnatally - subventricular zone (SVZ) of the lateral ventricles (108) and the dentate gyrus of the hippocampus (114). New-born neurons could be found also in the olfactory bulb where their life-span seems to be influenced by the olfactory sensory inputs, studies suggesting that deprivation of olfaction lead to a decrease in this new-born cells (115). These new-born neurons are originated from the astrocytes of the SVZ, then transformed into neuroblasts and finally into neurons which migrate towards the olfactory bulb. In case of CNS lesions, neural stem cells from subventricular zone migrate in the affected areas and are metamorphosed into astrocytes which exhibit a protection role (110). Moreover, SVZ sustains the development of oligodendrocyte, making it a center for directional migration (112). Besides this traditional areas, literature presents also more other sites such as the neocortex, piriform cortex, striatum, amygdala, medial preoptic area which exhibit adult neurogenesis (113).

From the proliferative stage of neurogenesis, human brain goes further to the differentiated divisions, one important key-role being played by the epigenetic modifications as DNA methylation (111). This differentiation can be seen as a fate restriction-based mechanism – firstly spatial limitation, then temporal limitation (109).

The role of adult neurogenesis is widely-discussed. Neurogenesis found in hypothalamus seems to have several important roles. Neurogenesis in the arcuate nucleus and median eminence seems to play a role in metabolism and weight regulation, while formation of new neurons in ventromedial and arcuate nuclei may have an important role in sexual activity (116). Neurogenesis in the other parts of the brain such as hippocampus have an important role in spatial memory, working memory and learning (117). Other cognitive functions such as behavioral inhibition - the process during which animals are halting whatever they are doing in order to reassess a situation in response to a threat – seems to be affected as a result of the disruption of normal cell proliferation in the hippocampus. The lesioned-animals show more defensive responses to potentially threats even though these are not real at all (118).

Regarding the involvement of neurogenesis in Alzheimer's disease (121), decrease of neurons density was remarked in patients, especially in the regions CA1 and CA3 (122).

Transplantation of neural stem cells to the hippocampus improves memory in patient with AD, when coupled with production of growth factors such as IGF-1119 – molecule with important anti-inflammatory, anti-apoptotic and synapse formation properties. The importance of IGF-1 in neurogenesis was also highlighted in treatment of spinal cord injury patients, when associated with treadmill training better results were exhibited in the IGF-1 group than in the traditional treatment group (120). Besides the impact in AD, altered neurogenesis in the islands of Calleja – aggregation of granular cells in the ventral striatum – could lead to schizophrenia. The mechanism involves dysfunction of D3 receptors and high accumulation of dopaminergic molecules in striatum (123).

FUTURE/ARTIFICIAL INTELLIGENCE

In simple terms, artificial intelligence (AI) (124) refers to systems or machines that mimic human intelligence, to perform various activities and which can be iteratively improved based on the information they collect. AI refers more to processes and functionalities for extraordinary data thinking and analysis than to a particular format or function. Even with increased technological investments, in medicine, AI will not replace humans, but rather make contributions to human health-care delivery (125). AI has different aspects and applications such as machine learning, deep learning,

natural language processing, physical robots, robotic process automation (126).

Machine learning refers to a complex system of processes that predicts the result based on a data set consisted by millions of data points (127). Comparative to the classical statistical modelling, machine learning works with huge mass of data, modern efficient algorithms and greater computational power. A big volume of data fits better with deep learning or neural

networks which is a complex form of machine learning working as an artificial representation of brain structure and functionality (128).

Artificial neural networks (ANN) are composed by nodes, which are widely distributed

and interconnected. Each network has 3 characteristics: node character, network topology and networks rules, which refers to how signals are processed into the node, how nodes are structured and how the weights of inputs are adjusted to obtain a minimum of error (129). After being multiplied by connection weight or coefficients, the inputs are accumulated and transferred via a transfer function to obtain the desired result (130). Thus, the inputs are firstly captures by the superficial layers of data processing which send information further to deep nodes of the network via feedforward (131) or feedbacks regulations, while between these the input and output layers are found one or more hidden strata responsible for data synthesis.

Fixing the coefficients is an important step in order to reduce the error between the outputs and the targets of the network. This is realized by training the ANNs through a mass of known input-target pairs with the aim to find a general rule of processing the data (132).

Information which come into the artificial brain could easily be classified as labeled or unlabeled. Labeled information is usually an association of two items such as the picture with its tag and is part of a great process – supervised learning. The other learning paradigm involves unsupervised learning, which means that unlabeled information is deeply processed based on mathematical annotations of similarities and labeled them into different categories. Computers are looking for similar sequences which are comprised into ethograms – examples: mating, feeding, sleeping(133).

Recently, scientist tried to improve ANNs by adding artificial re-enforcement learning, process based on the rewarding system. Combining these two produced great results especially in video games, poker, chess and multiplayer contests (134). However, it seems that for brains, information processing is easier than to computers and is realized via some simple "proto concepts"(135) that are inherently encoded in humans and guide the progressive acquisition of complex concepts.

One specific application of AI is natural language processing (NLP) that refer to the ability of computers to comprehend human language. NLP include speech recognition, text analysis, translation and other processes that need to transform language into a data form (136).

In healthcare, NLP can produce, understand clinical documentation, prepare reports and conduct conversational AI, especially in chronic disease such as circulatory diseases, neoplasms and metabolic diseases where clinical notes – letters, clinical narratives dominate over structured notes(137).

In the next years, experts indicate massive interest and investment in AI, especially in medicine where is estimated an investment of $6.6 billion by 2021 (138). Ultimately, all of these findings take on a science fiction aspect with possible application in medicine and improvement of the quality of life based on the rapid establishment of diagnosis and better treatment management.

CONCLUSIONS

All these cumulated data about the structural and functional aspects of the brain shows that this specific complex organ has no limits at all. On the basis of cerebral activity and functionality of the whole body lays an ordered, well-established and equilibrated neuronal activity. Negative factors that are the primary causes of diseases are smoking, stress, alcohol and sugar. Healthy alimentation, alkaline water, fresh air, resting sleep are favorable factors that help human live full-filled lives.

Abbreviations:

RSN – resting-state nework;
tfMRI - Task-based functional magnetic resonance imaging;
AD – Alzheimer's Disease;
SAH – subarachnoid hemorrhage;
WA - Wernicke's area;
DSA - Digital Subtraction Angiograph;
PET - Positron Emission Tomography;
DTI - Diffusion Tensor Imaging;
TMS - transcranial magnetic stimulation;
MEP - motor-evoked potential;
CIAT - Constraint-induced aphasia therapy;
NLP - natural language processing;
AI – Artificial Intelligence;
ANN - Artificial neural networks;

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