Review

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Posted Date: 7 December 2023

doi: 10.20944/preprints202312.0489.v1

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Abstract: The brain being arguably the most complex organ in the human body, its detailed functioning is yet to be fully deciphered, let alone accurately modeled. Nonetheless, the medical community has gathered quite a remarkable amount of studies about the consequences of illnesses and injuries on its development and functioning. This bibliographic review aims to cover mostly the findings related to the changes in the physical distribution of neurons and their connections - the connectome -, both structural and functional, as well as their modelling. It does not intend to offer an extensive medical description of all injuries and diseases affecting the brain, rather presenting the most common ones succinctly so the need for accurate brain modelling can be fully understood and pondered, offering propositions to this aim

Keywords: connectome; brain injury; neurodegenerative diseases; parkinson; alzheimer; dislexia

1. Introduction

The brain acts as an animal's central computer: it gathers all information obtained through the senses (as a result of external stimuli) and processes it to generate knowledge (through memory) and act upon its surroundings, on top of regulating physiological behaviour and constants like breathing, body temperature or heartbeat; or more vaguely-defined aspects like emotions and conscience. It sends and receives signals through the spinal cord, forming the Central Nervous System (CNS). It is the most energy-consuming organ in relation to its size (a fifth of the total in a resting state), despite undergoing evolutionary optimization for ages in different animal species. [1] Its correct functioning is crucial to the point that a person is considered dead if their brain does not work, although their heart and vital organs could be kept active via artificial means.

According to the World Health Organization (WHO), two of the ten principal causes of death globally in 2019 were directly related to brain malfunction: strokes (also called Cerebrovascular Accidents, CVA) and dementia (including Huntington's chorea, Parkinson's, Alzheimer's and Lewy's bodies, among many others) [2]. Strokes, ranking second on the list, are caused either by a lack (ischemic, 85% of total [3]) or excess (hemorrhagic) of blood flow in the brain, and thus closely related to the leading cause, Coronary Artery Disease (CAD). Dementia, on the other hand, is an umbrella term for most neuro-degenerative illnesses, resulting in the loss of previously held mental capabilities, especially affecting speech, memory and orientation. They can be age-related (Alzheimer's, Parkinson's) or not (e.g.: Huntington's chorea) and they are not to be mistaken with neurodevelopmental disorders, which affect the brain in its first stages of growth.

 doi:10.20944/preprints202312.0489.v1

Cancer is another prominent cause of death worldwide. Whereas brain tumors are not the most common ones (around one-in-fifty diagnoses [4]), they are amongst the most fatal (one in three five-year survival rate on average in the US, around 5% for the most aggressive types, such as glioblastoma [5]) and alarmingly prevalent in children under 14 (about one sixth of total cases as of 2019, second only to leukaemia [6]). In less lethal but arguably as concerning terms, neurological illnesses varying in cause (including injuries induced by tumors) are the leading cause of crippling disability, and their incidence is increasing, especially affecting ever-aging populations in the developed world [7]. In Psychiatry, the freshly emerged field of Pathoconnectomics explores the links between a defective brain wiring degeneration [8] and disorders like depression [9], schizophrenia or autism [10] or the association between Cerebral Small Vessel Disease (CVSD) and cognitive impairment leading to Alzheimer's [11].

Neurological disorders are very costly not only in ethical terms but also on an economical level, higher - in absolute terms - dealing in billions of € per year in developed countries where diagnoses are more prevalent [12–15] but relatively more expensive in underdeveloped countries where means are scarce [7,16,17]. - which poses an inequality issue. Although data itself is relatively abundant, although maybe not representative enough [18–20]. In order to manage such valuable and variable data, new approaches have become widespread, such as Data Mining [21–23] and Machine Learning [24,25] - especially Graph Neural Networks [26–32]

Considering all this, it comes as self-evident that the study and characterization of the brain is a great need not only for scientific purposes but also, and most importantly, for health reasons, such as the study and treatment of related injuries and diseases for a sooner and more accurate diagnose and hopefully a more effective treatment. The purpose of this review article is to very succinctly present the most relevant information gathered about such health issues in relation to the brain's structural and functional architecture. After this introduction underlying the relevance of brain-related illnesses and trauma in Section 1, a brief note on the brain's structure and function will be introduced in Section 2. Section 3 will present a general overview of the most prominent causes of brain damage, while Section 4 contains some modelling propositions for the connectome. Finally, Section 5 acts as a summary of this article accompanied by some line research suggestions.

2. Mapping the brain: the connectome

The first known reference to the brain is the Edwin Smith Surgical Papyrus (Egypt, 1700 BC), although back then its functions were thought to be carried out by the heart instead, as Aristotle reckoned. Although there were some anatomical studies of the brain during Roman and Baghdad Caliphate times, not much else could be done until the invention of the microscope in the late 1500s AD. Some nerves (especially related to the senses, such as sight or hearing) were correctly identified, but it was not until the second half of the 19^{th} century that the field work by Broca, Wernicke and many others began to correctly associate specific areas of the brain with certain tasks (muscles of speech and language comprehension, respectively).

It became apparent that patients having undergone injury or surgery affecting certain brain zones saw some of their cognitive abilities lessened or fully missing, and so doctors began to fill the blanks in the brain map. One of the first attempts to fully map the brain by function was made by Korbinian Brodmann in 1909 [33], as seen in Figure **??**. Staining neurons with Nissl's method, he divided the primate brain in 52 areas (44 present in current human beings and 8 remaining only in related primates) based on cytoarchitectural (cell-level structure) criteria.

Brodmann's map has served as the main guide for decades, and it is still used on an educational level today, but evidence of its incompleteness is abundant and continuously growing. On the one hand, it is possible to live - albeit in an altered state and with great difficulty - with a fraction of a brain, as in severe cases of hydrocephalus - partially substituted by water [34] -, lobotomies - extraction of part of it - [35] or even anencephaly - absence of it altogether - [36]. That can - at least, partially - be explained through the concept of neuroplasticity: the brain's ability to rewire its functional and structural connections to overcome injury's effects, hinting that the spatial distribution of functional

 doi:10.20944/preprints202312.0489.v1

areas is more flexible than charts like Brodmann's would suggest. Neuroplasticity allows for a certain regenerative capacity as well, although humbler in the Central Nervous System than in the Periferic one (PNS) [37], which often helps patients recover motor coordination after strokes, for instance [38].

How the brain really works is only partially known to this day, although significant progress has been made since the dawn of Magnetic Resonance Imaging (MRI) in the 1970s, especially its functional variant (fMRI), able to track brain activity in quasi-real time by measuring changes in blood flow [39], assessing pre-surgery conditions [40] and parcelling brain functional [41] and structural areas [42–44]- even on a city- [45] or nationwide basis [46,47]. Although relationships between specific tasks and areas in the brain do exist (ref), there is plenty of experimental data suggesting that such a strict function-area mapping framework might not be a good-enough approach. Many individual actions require the activation of multiple areas in the brain (like language and perpetual decision [48]), and the coordination between them (co-activation [49], newly studied with a plethora of techniques [50]), so no area is univocally nor individually responsible for a given action, but rather correlated to it.

Seemingly related (directly or inversely) tasks may be performed by different areas within a brain region, such is the case of facial recognition and evaluation [51]. Activity patterns for the same task can differ [52] and even change with age [53] or illness. Although there's a certain consensus on a "default" network configuration in resting states [54,55], it is still subjected to individual variations, some of them associated to illness [56]. One must also bear in mind that structural and functional pathways in the brain influence each other. On top of that, most brain mappings show correlation between task and activations, rather than causation of such patterns [57].

Thanks to the experimental work of Santiago Ramón y Cajal in the 1880s, using Nissl's method, the neuron doctrine gained recognition to become the widely accepted theory that it is today. It conceives the brain (and the whole CNS by extension) as a network of intertwined but independent neurons, a specific type of cell receiving and transmitting electric signals. Neurons are mainly composed of a nucleus (soma), a thin extension covered by myelin (axon) ending in appendices (dendrites) responsible for communication between them (synapse). This connectivity between neurons can be structural - physically existing links between neurons - or functional - the links actually used during neural activity -.

These two sides can be mutually affected and/or change due to injury and/or disease, or even with mere biological age. Neurons themselves can be classified along these lines: structurally as uni/bi/multipolar/anaxonic, etc. or functionally as afferent (sensory), efferent (motor) or interneurons (transition). Furthermore, these connections are subjected to neuroplasticity: rewiring (structural [58]) and alternative paths (functional [59]) life-long [60], especially during and after growth [61], age [62,63], injury [64,65] or disease [66]. The connectome is also affected by diaschisis, by which an area distantly connected to another damaged area might see their functions deteriorated by the latter - a sort of negative functional plasticity [67].

3. Brain Damage

Neural cell death takes place "naturally" in the brain: unneeded neurons are disposed of in a programmed, foreseeable and controlled way - known as apoptosis [68], by which the dying cell implodes collapsing its cytoskeleton and liberating broken nuclear DNA, its remains being eaten by other cells (phagocytosis). This can be a result of brain development [69,70] - well studied and measured [71,72] - and/or due to structural neuroplasticity (axon retraction, i.e. "pruning" [58]) due to redundancy [73]. Apoptosis, be it intrinsic (mitochondrial, BH3-Bax-APAF-1-caspase-9) or extrinsic (death receptor, caspase-8-Bid) [74], is a complex process regulated by multiple internal mechanisms involving various mollecules such as p75, Bcl-2 or caspase-1 [75] and crucial in fighting cancer - which is, at the end of the day, an out-of-control cell multiplication [76–78].

Brain damage comes into picture when the unforeseen deterioration or destruction - necrotic death - of brain cells (neurons) takes place. By this process, the cell's mitochondria and endoplasmic reticulum swell and break the external membrane, due to a plethora of different mechanisms

 doi:10.20944/preprints202312.0489.v1

(necroptosis, parthanatos, ferroptosis, pyroptosis, oncosis, lysosomal, autophagic, phagocytic, MitoPore - mitochondrial permeability transition) [74], thus affecting neighbouring neurons though inflammatory expansion - unlike apoptosis. Some of these processes (parthanatos, oncosis, MitoPore) result in ATP (Adenosin-TriPhosphate) depletion - which in turn produce the failure of sodium and calcium channels through the neuron membrane, and with them come cell swelling and degradation via proteases and phospholipases, respectfully. Be it this way or by Mixed Lineage Kinase domain-Like (MLKL: necroptosis), Reactive Oxygen Species (iron: ferroptosis) or inflammation (pyroptosis, lysosomal), the result is abnormal neuron necrosis [74]. As it will be explained in the following subsections, these necrotic mechanisms are linked to the advent of various neurodegenerative diseases [79,80] and other neurological disorders such as sleep apnea [81,82].

3.1. Acquired Brain Injury

Acquired Brain Injury (ABI) is any brain injury caused after birth, and so excluding birth-related trauma and all hereditary or congenital diseases. This exclusion obeys to the fact that the connectome takes years to fully form, so the study of early or pre-natal damage is rather case-dependent, no general procedures having been established. This damage can have an internal (e.g.: tumor growth, mental disorder) or external origin (e.g.: concussion, accident). The first kind are usually - but not exclusively - caused by injuries and are known as to Traumatic Brain Injuries (TBI), while the latter, Non-Traumatic Brain Injuries (NTBI), normally involve a brain illness - not necessarily neurodegenerative. Both have in common widespread destruction of the cortical ribbon and white matter tracts and deep brain damage (thalamus, basal gmanglia) [83]. Other complications incluse hydrocephalus, pneumo-encephalus, ventricular enlargement, skull fracture, unconsciousness, sores, bladder infections, pneumonia and/or multiple organic faliure [83].

Their symptoms can be physical (paralysis, headaches, seizures, insomnia, loss of consciousness, aphasia - speech impediment), cognitive (memory loss, impaired information processing, comprehension or expression), perceptual (disorientation, lack of equilibrium, sight/hearing/touching/smell/taste disfunction, hyperalgesia - extreme pain sensitivity) or behavioural (irritability, aggresiveness, lethargy/apathy).Neural damage, on the other hand, is more difficult to quantify, as most imaging techniques can only identify and count dead neurons [84]. Nonetheless, some techniques do exist [85]. ABI can be primary -shear/tear of tissue, complete right after the impact - or secondary -more complex chemical, biological or biomechanical changes hours after the insult, including blood barrier damage, excitotoxicity (glutamate release), mitochondrial disfunction, Na+/Ca+ influx- [83]. In the most severe scenarios (GCS < 8), it can lead to prolonged coma states or even death.

3.1.1. External: Traumatic Brain Injury

This category includes brain damage caused by physical trauma, i.e. accelerations, shocks, concussions, incisions, etc. caused by a foreign agent. It is responsible for more than 1-in-3 annual injury related deaths in Europe - accounting for 2 million yearly hospitalizations [86] and it affects around 70 million people globally [87] (around 1% of the world's population), typically young males [88]. TBI can be classified into mild (13-15 points), moderate (9-12 points) or severe (3-8 points) via the Glasgow Coma Scale (GCS), composed of three areas (4 verbal points, 5 ocular and 6 motor). Depending on its causes, it can be further divided into closed (unbroken skull: fast movements, shaking) and penetrating brain injury (open head, e.g. bullets). There are concluding signs of comorbidity with several mental conditions such as Major Depression (MD), Post-Traumatic Stress-Disorder (PTSD), general anxiety and suicidal behaviour [89] - and even sleep disorders, back pain, high cholesterol, osteoarthritis and diabetes [90].

Closed Head Injury

 doi:10.20944/preprints202312.0489.v1

The most common type is mild TBI - meaning not immediately life-threatening (around 80% of all diagnoses [86]), a sub-type of closed head injury (CHI) - occurring within an intact skull - caused by bumps to the head or any other action causing fast skull movement (acceleration/deceleration, especially rotational [91]) which may result in physical strain to the brain and/or chemical changes. These accelerations usually involve coup - contrecoup: back-and-forth jarring of the brain against the skull's inner walls shearing tissue and resulting in blood vessel rupture, bruising and swelling.

It is relatively common in any physically intensive activity (sports, military practice), acts of violence or accidents (traffic, falls), and can cause some of the aforementioned physical or behavioural symptoms, normally immediately after injury (peaking within the first 24h, during which the brain undergoes gliosis - scar-like multiplication and/or growth of glial cells [91], hindering healing) but entailing potential long-term effects [92–94] such as Chronic Traumatic Encephalopathy (CTE) in the case of recurrent milt TBI, typical in sportsmen (up to 90% of athletes in the US [95]) who may experience memory and attention impairments, suicidal behaviour or even cardiovascular complications [96,97].

TBI usually produces three major effects: acute subdural hematoma -associated with traumatic cerebrovascular injury (TCVI) in a limited number of cases (less than 2% [97]), brain contusion and diffuse axonal injury [98]. Contusions involve brain bruising as a result of coup - contrecoup accelerations, mostly affecting the basi-frontal and anterior temporal lobes [99]. Not to be mixed with concussions, an umbrella term for closed-head, mild TBI involving transient mental effects ranging from confusion to loss of consciousness.

Hematomas are extended contusions causing blood overflow from multiple broken blood vessels (due to brain bruising), common in physical trauma. It can be epidural (EDH) or subdural (SDH). The former involves a rapidly leeking broken artery - middle meningeal - between the dura mater (third and most external layer in the meninges) and the skull; whereas the latter takes place when a bridging vein ruptures and slowly seeps between the arachnoid (second meningeal layer) and the dura mater. Traumatic Subarachnoid Hemorrhage (SAH) can also take place if capillaries break and flood the region under that layer. Such blood volumes (be it arterial or venous) may interfere with the Monro-Kellie principle (the total intercranial volume remains constant) [100,101], meaning pressure on the rest of intercranial components, namely brain tissue cerebrospinal fluid (CSF). That could lead to cerebral edema (fluid accumulation), disruption of the blood-brain barrier and/or diffuse axonal injury, among other undesirable effects.

Diffuse axonal injury (DAI) is a the strain/tearing of axons all across the brain due to the stress combination (compression, tension, shear) occurring during and after TBI in 1-15 mm stretches within a particular distribution [83]. It is provoked by both strain (10-50%) and strain rates (10-50 Hz) [98]. This phenomenon is more acute at the junction of gray and white matters with different densities, where the axons are covered in thicker myelin sheaths and surrounded by a drier environment. While and after undergoing stretching, the axon could swell, detach, fracture, increase its permeability and calcium influx and even die (necrosis). [99]. It can also have long-term effects such as a greater chance of developing neurodegenerative diseases such as Alzheimer's [102–105]. DAI is usually detected by MRI, although it takes time, so CT may be preferred for fast hemorrhage identification if the patient needs urgent treatment [106], despite CT being less detailed than MRI [83,107], which can be further enriched by Gradient Echo (GRE) [108] or Susceptibility-Weighted Imaging (SWI) [109]. A major problem when modelling DAI is the fact that it is unlocalized, all over the brain (hence "diffuse"), and thus difficult to predict an injury pattern in a deterministic way given a certain traumatic origin.

Penetrating Brain Injury

Penetrating Brain Injuries (PBI), although far less common than Closed Head Injuries (CHI), are also fairly more lethal. They are caused by an external collisions against the skull, which is often fractured - resulting in hematoma and/or intercranial hemorrhage, mostly fatal in the basilar area [88]. Its origins are various (assault, murder/suicide attempts), usually involving physical violence and/or

 doi:10.20944/preprints202312.0489.v1

projectiles such as bullets and its consequences harsher: short-term outcomes such as severe trauma in 55% of cases [110] (GCS < 5 for gunshots [111]), generalized hemorrhage, CSF leaking, intracranial infection and aneurysm (50 % lethal [112]) and often death (around 40% [110] - up to 90% if neurological status is poor [112]); and long-term effects like post-traumatic epilepsy and/or seizures for 1 in 2 cases [113].

PBI's effects vary greatly according to the kinetic energy liberated by the weapon used to inflict the damage $E = mv^2/2$, which varies linearly with mass (the heavier the object, the greater the damage) and quadratically with its speed (low if under 300 m/s, medium up to 600 m/s and high upwards). Thus, light, low velocity objects like nails or knives are less likely to cause severe damage, and such damage is localized closely to their trajectory. Bullets and shrapnel, on the other hand, travel much faster and can increase their already devastating effect - direct by penetration or indirect by shockwaves (causing cavitation) - depending on shape, angle, deformation or shredding of the skull and/or projectile inside the cranium.

After PBI, rapid evaluation is vital in increasing the chances of patient survival, undergoing CT to determine if surgical intervention is viable, be it to heal wounds and/or extract the projectile (except knifes at first [114]), and act ipso facto to prevent worsening scenarios related to hypoxia, anemia, CSF leaks, hypotension (systolic under 90 mm Hg) or hyperpyrexia (extreme fever over 41,5ºC). Prophylactic anticonvulsants are used to prevent seizures and special attention is paid to aggravating factors: old age, severe coma (GCS = 3), high intracranial pressure, coagulopathy, thrombosis [115]. The prognosis depends greatly on the foreign object's trajectory, being mostly reserved if it crosses the midline, ventricles or posterior fossa [114] or if it affects the brainstem, both lobes and/or hemispheres [112]. Self-inflicted wounds and pre-hospital intubation and craniotomy/craniectomy are positively correlated with the mortality rate in PBI [110]. Laceration and crushing of tissue as a result of bumping or projectile disintegration enhance damage.

As a result of PBI, neural tissue can be either physically broken (sectioned by the foreign object), impaired or dead (insufficient blood flow due to leakage, hypotension, etc.). Damage is usually more localized than in CHI but also more severe, often meaning lasting neurological consequences and perhaps death. Infections by lack of prophylaxis are another common complication, better explained in the next section as they are largely non-traumatic derived.

3.1.2. Internal: Non-Traumatic Brain Injury

This category includes any brain injury with internal origin, especially involving infections (meningitis, encephalitis, etc.), poisoning (radiation, lead), lack of oxygen (aneurysm, stroke, heart attack) or any other event increasing internal cranial pressure (e.g.: tumors). Sometimes, they can be broadly referred to as ABI, being acute (mainly anoxia/hypoxia-induced: stroke, heart attack, drowning) or chronic (migraines). In general terms, they can potentially stretch all across the brain (diffuse injury) since they target the neuron's structure [83]. It can have similar effects to TBI, including coma states [116].

Infections

Neurological infections, although almost eradicated in Europe and North America, are relatively prevalent in developing countries. They involve contamination of the cerebrospinal fluid (CSF) in the Central Nervous System (CNS) via blood (hematogenic), contiguity to infected organs or bones or neural transmission [117]. Hematogenic contagion is by far the most usual process, caused by pathogenic agents (bacteria, fungi, protozoa or parasites) in the blood stream, mainly arterial through the junction of white and grey matters (parasitic/bacterial, some viruses) with chances to metastasize elsewhere, although neurotropic viruses (such as herpes or measles [118]) get into the CNS through the blood brain barrier (BBB), transcytotic epithelial passage or leucocyte infestation.

Venous infections are rare, disseminating schistosomiasis (trematode worms) and (micro)thrombophlebitis (blood clot induced vein swelling). Transosteal infections originating in adjacent frontal (face, e.g. sinusitis) or temporal areas (such as otitis affecting the petrous bone) can

 doi:10.20944/preprints202312.0489.v1

generate intracerebral abscesses or pericerebral collections (extra-/sub-dural empyema). Neural propagation, although unusual, is a vector for viruses (herpes simplex, varicella, rabies) and bacteria (listeria). Lastly, infection can also occur in direct contact with the cranium or vertebrae after a PBI or surgery (such as nosocomial meningitis). About 1 in 5 brain infection cases have unknown origin [117].

Most common infections imply inflammation (meningitis - meninges, encephalitis - brain parenchyma) or other alterations of intercranial pressure such as abscesses (intracerebral pus accumulation), which of course implies shear and compressive stresses on axons. Some of them (pyogenic or tubercular abscesses, Aspergillosis, Whipple disease, mucormycosis, cryptococcosis, blastomycosis, histoplasmosis, toxoplasmosis, cytomegalovirus, etc.) can complicate diagnosis mimicking space-occupying lesions (SOL, i.e. tumors), losing valuable and timely treatment opportunities [119]. In case of sepsis, damage (inflammation, BBB disruption, hypoperfusion) can have long-term effects (cognitive impairment) [120].

Immunosuppressed patients are particularly vulnerable and carry a worse prognosis. Some Sexually Transmitted Diseases (STDs) such as HIV, herpes, candidiasis, syphilis can have deep neurological impact, most commonly meningitis, but also more severe like Progressive Multifocal Leukoencephalopathy (PML). Some other prominent infections are those related to helminthic worms, provoking angiostrongyliasis, gnathostomiasis, (neuro)cystercosis or schistosomiasis, among others [121]. Over 300 parasites can infect human brains causing eosinophilia (abnormally high concentration of eosinophils in blood [122]). Infections affecting other organs can reach the brain (e.g. tubercolisis expansion causes 6% of all meningitis [123]. Animals can be carriers of viral infections causing encephalitis (rabies by dogs and bats, toxoplasmosis by cats).

Autoimmune diseases

Autoimmune diseases are associated with myelin loss and hemorrhage, come from within [124] or outside the brain (such as lupus erythematosus [125]) and can cause very similar effects to those of infection (meningitis, encephalitis, epilepsy, vasculitis) [126]. Like infections, they often result in brain damage via anoxia, shear/compression or chemically-induced necrosis [124].

Toxic/Metabolic

Neurotoxins causing Toxic Encephalopathy (TE) can be classified into metallic compounds (iron [127], lead, mercury, arsenic, aluminum), nonmetallic inorganic (sulphur, bromine-derived), industrial/environmental (nitric oxid, carbon monoxid, aliphatic hydrocarbons [128], cyanide), nerve agents (gases like sarin, liquids like Novichok), drugs and pharmaceutical products (alcohol, tobacco, cannabis, opiates, cocaine, methamphetamine) and biologic origins (mushrooms - A. Muscaria, A. Phalloides -, animals - snakes, spiders, scorpions -, microorganisms - botulism [129], tetanus, diphtheria -) [130]. Its consequences vary greatly, but often include cerebrovascular accidents (infarct, hypoxia/ischemia, hemorrhage, vasogenic cerebral edema), infection, (astro)glial abnormalities, diffuse neural necrosis and dementia in the long term [131].

This toxins can target the soma (especially heavy metals and Toxic Metabolic Encelopathy), axons (degeneration by industrial chemicals), myelin sheath (separation or loss of myelin sheets resulting in abnormal transmission of nerve impulses), astrocytes (abnormal ionization in membrane activation, processing of toxins). Drugs have a great negative impact on neurotransmission - MDMA disturbs serotonin, methamphetamine kills dopamin [132] - and blood flow in the brain - cocain and heroin are linked to hypoxia and ischemia [133] -. Toxic Metabolic Encephalopathy (TME) can acutely alter neurotransmitters as a result of drug-induced hypoglycemia, anemia, sepsis, anoxia and other organ failures (liver, kidney, lungs), syndromes (withdrawal) [134] and nutritional/endocrine deficits [135].

Radiation poisoning, either accidental or planned (e.g.: radiotherapy as a treatment for tumors) exposure to ionizing agents, can have dreadful effects in brain tissue by four main mechanisms: vascular damage, astrocyte extinction, cytokine alterations and stem cell death (mainly in the hippocampus [136], cerebellum and cortex) [137]. Acute symptoms include edema, headache and drowsiness; mid-term memory loss and attention deficit and long-term vascular hyalinization, myelin depletion, inflammation, ischemia, necrosis, functional damage, dementia [136,138] and even tumor

 doi:10.20944/preprints202312.0489.v1

progression instead of its remission - a common adverse effect in oncological radiotherapy [139,140], dose-dependent [141] not so easy to identify [142].

Vascular

Although they can occur after trauma (TCVI [97,143]), cerebrovascular injuries can also be originated from inside the skull by obstruction, breakage, and/or defective oxygenation (hypoxia/anoxia) of blood vessels within brain tissue, leading to necrosis: a stroke, the second leading death cause worldwide [2,144]. Also known as Cerebrovascular Accident/Insult (CVA/CVI) or apoplexy, its incidence is steadily increasing (especially for population over 75 years old). It can be ischemic (brain infarction due to insufficient blood supply via vessel occlusion) or hemorrhagic (intracranial blood spilling via vessel or aneurysm rupture).

The former are by far the most common - around 85% of all cases [144,145] - and it is sometimes anticipated by Transient Ischemic Attacks (TIA) [145], falling into several etiological categories: large-artery artherosclerosis, cardiogenic embolism, small vessel occlusive disease, determined or undetermined cause. Hemorrhagic stroke can be further classified into intracerebral (ICH, within brain) and subarachnoid (SAH, between inner and outer meninges), as previously mentioned. Its symptoms include half-body paralysis, high blood pressure, arm stiffness, headache and incoherent speech or motor impairment. Risk factors can be fixed - age, genetics (race, family history), sex - or modifiable - hypertension (causing hemorrhagic strokes), diabetes, nutrition (diet, obesity), alcohol, sedentary lifestyle or cardiac conditions among others - [144,145].

Strokes disturb the brain's functional connectivity within minutes [146], either by tissue loss (necrosis) or diaschisis, as well as abnormal patterns such as trading interhemispheric connectivity for intrahemispheric among usually unrelated local networks [147]. It is as well a key element for recovery [148–150] by promoting small-worldness in neural networks, i.e. high nodal clustering (specialization) and short inter-nodal path lengths (efficiency, integration) [151]. Studying the brain's angiome (blood vessel network) can provide meaningful information when facing stroke detection and therapeutics, since its mappings are easier and more developed than those of the connectome [146] - which it directly affects.

Cancer

Tumors, also known as neoplasms, are lumps of abnormally - and uncontrollably - growing cells. The can be benign (non-cancerous, slowly growing and unlikely to spread) or malign (cancerous, rapid growth and prone to propagate). Brain tumors originate mainly in intercranial tissue or the meninges (meningiomas), although they mostly [152] come from different adjacent organs (metastasis); such is the case of melanoma (skin cancer), prostate/breast cancer, lung cancer or Hodgkin's lymphoma (lymphatic system cancer). Although rare amongst cancers (2% of total [4]), brain tumors have a great potential to be lethal (around 10% 10-year survival rate [4]) or produce long-term sequels. Risk factors include ionizing radiation, genetics (hereditary syndromes: neurofibromatosis, tuberous sclerosis), immunosupression (infection, allergy), chemicals (N-nitroso compounds are mutagenic and trespass the BBB) and head trauma.

Symptoms are very generalistic (nausea, headaches, fatigue), although the apparition and evolution cognitive impairment (aphasia, hemiparesis, motor dysfunction) and seizures are usually more telling [153]. Diagnosis is made through gadolinium-contrasted MRI - commonly when the BBB barrier is already broken by a malignant neoplasm, since most radiotracers used for other tumors - which, of course, poses a limitation to act upon the injury. Nonetheless, some alternatives like fluorodeoxyglucose (FDG) and labeled aminoacids might be able to detect low-grade gliomas in time before they develop into glioblastomas [154].

There are more than 100 types of brain tumors, and their classification is difficult, having undergone recent restructuration to include molecular biology - namely, mutations related to proteins IDH, B-raf or MGMT - in their traditionally histologic criteria [155]. If they originate within the CNS, they are called primary brain tumors, the most common being gliomas (75% of diagnoses [156]) originating in glial cells or supportive tissue in a circumscribed or diffuse manner: astrocytomas on

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astrocytes (anaplastic - grade III, glioblastoma multiforme - grade IV), ependymomas (ventricles, spinal cord), oligodendrogliomas (CNS, myelin production), or brain stem gliomas. Some of them can be localized (astrocytomas), while others are diffuse and can easily extend (glioblastoma multiforme) [153]. Other brain tumors without glial origin are medulloblastomas (developing nerve cells), meningiomas (meninges), schwannomas (Schwann cells), craniopharyngiomas (pituitary, near hypothalamus) and germ cell (gametes) tumors.

Their effects on the connectome are multiple: mechanical (pressure by tumor growth on the remaining healthy brain tissue plus sometimes edema, damaging it), chemical (protein mutation deteriorating synapses), vascular (thromboembolism) and necrosis - with the subsequent functional impairment depending on the area. As mentioned above, neurotoxicity is both a common origin and byproduct of some tumor treatments (radiotherapy, chemotherapy) - identified as a possible trigger for glioblastoma [157].

3.2. Neurological disorders

Diseases are a common origin for brain damage, not injury-related but rather result of a prolonged condition, developing in a mid/long-term basis. They are presented in a separate group to differentiate them from incidental, acute insult (previous section). They include pathologies like epilepsy and dementia, neurodegenerative illnesses and psychiatric/motor disorders.

3.2.1. Epilepsy

Epilepsy is a chronic, non-contagious neurological disorder causing recurrent (at least two within 24 hours) uncontrollable, unprovoked seizures - thus excluding those induced by traumatic brain injury, electrolyte disequilibrium or concomitant diseases. It affects 1% of world population [158] and its onset can be focal, generalized - affecting both hemispheres, motor or non-motor - or unknown. Etiologically, it can be genetic (mutation affects management of voltage-dependent sodium channels [159]), structural (network abnormalities), infectious, metabolic (biochemical changes), immune (induced inflammation) and unknown. Although it is rarely lethal, epilepsy can have long lasting neurological effects [160].

Its incidence depends on age (prominent during childhood - 75% of diagnoses [161] - and adolescence), gender (more common in males), availability of medical devices (compromising in developing countries, more diagnoses and generalized rather than focal seizures [158]), socioeconomic status (the lower the income, the higher the chances) [162] and developmental conditions (autism is correlated). Its symptoms vary greatly with the originating cortex area: visual phenomena - blinking, vision loss, hallucinations - (occipital lobe), clonic/tonic motor responses (precentral gyrus, frontal lobe), sensory - e.g. numbness (postcentral gyrus), etc. [161] They may be preceeded by a warning or omen, known as "aura".

Epileptogenesis involves an imbalance between excitative and inhibitive neuronal pathways as a result of uneven activation potentials creating a synchronized wave of excessive neuron firings [158, 159]. Malfunction in enzymes (ATPase) and/or glia regulating the extracellular ion concentration (e.g.: potassium overload) may produce neuron depolarization and so action potential discharge leading to seizures, which in turn raise even higher the potassium levels; creating a cascade effect (epilepsy) - which also strengthens dendritic echoes, further enabling activation [163]. GABA-ergic synaptic transmission may lead to depolarization if its controlling ions (e.g. chloride) are altered. Aberrant neural network synchronization requires not only the aforementioned excessive discharge but also triggering events such as paroxysmal depolarization shifts (PDS) of cortical pyramidal cells or neuroplasticity itself - for instance, axon collateral sprouting [159]. Although anti-epileptic drugs are effective in 2 out of 3 cases [164], insight in the connectivity implications of epilepsy [165] is greatly needed for effective treatment strategies. Synchronization may be limited to the lamellar axis, according to some studies [166].

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3.2.2. Neurodegenerative diseases

Neurodegenerative diseases are becoming increasingly common worldwide, especially in developed countries where life expectancy is higher and thus dementia is more likely to appear [167]. They entail a progressive, inevitable deterioration and ultimate death of cells within the nervous system (both central and peripheral, though mostly in the brain [168]) causing neurological dysfunction, ranging from memory loss - e.g. Alzheimer's - to motor impairment - sclerosis, Parkinson's -. They can be classified according to etiology into amyloidoses (Alzheimer's, Creutzfeldt-Jakob's), tauopathies (Pick's disease, CTE), alfa-synucleinopathies (Lewy bodies, multiple system atrophy) and TDP-43 proteinopathies (some types of sclerosis) [169].

Although very diverse in nature, they all share some common features. Firstly, instead of a static neuronal loss - typical for metabolic/toxic NTBI -, necrosis progressively affects certain cells due to their vulnerability and it spreads according to the brain's structural and functional connectivity [169] (neural pathways). Secondly, they are related to a chronic immune malfunction. Lastly, they generally cause inflammation. [170]

Dementia-type Dementia is the gradual loss of mental skills such as memory, thinking, learning and judgement. It affects around 50 million people globally - mainly over 65 years [171] with symptoms such as behavioural changes and/or deficits in communication, orientation and memory. While cell deterioration is part of the normal ageing process, dementia implies There have no definitive cure - the only attainable goal being the slowing of the decay - and ultimately make the patient dependent on others. The main risk factors are lower education, hypertension, hearing impairment, smoking, obesity, depression, sedentary lifestyle, diabetes, isolation, TBI, alcohol and air pollution [172]. Most common illnesses causing dementia are Alzheimer's and Lewy's bodies, although its origins can also be vascular (strokes), STDs or trauma (CTE). Dementia is not to be mistaken for delirium, which is sudden, transitory and mainly distorts attention mechanisms.

Alzheimer's Disease is the most prominent dementia-inducing disease (half of all cases [173]), affecting around 5% of the European population [174] - the most deeply affected continent due to its advanced life expectancy. A-β plaques and neurofibrillary tangles (NFTs) are generated by accumulation of amyloid β-peptides and hyperphosphorilated τ-proteins (and/or demyelinization [175,176]), causing inflammation and degeneration of the brain tissue and so excessive, non-programmed cell death (necrosis) and volume changes (gyri shrink, sulci grow - overall volume loss up to 50%) [80]. It can also be the result of mutation (genes APP, PS1, PS2), though very rarely (less than 1 in 20 cases).

AD deteriorates memory, thinking processes and alters emotions by provoking diffuse neuronal loss, synaptic degeneration (correlated with NFT distribution) and reactive gliosis (abnormal glial and astrocyte growth) [80] altering the complex cellular micro-environment in the brain [177]. It starts as a localized neural loss (locus ceruleus, entorhinal cortex) but eventually becomes diffuse (amygdala, hippocampus, frontal/parietal cortices). As neurons die all over the brain, paths between them get longer while local clustering remains in the unaffected areas, yielding an efficiency loss as "small-world" characteristics fade away [178] - selective hub vulnerability [179] - although that depends on the characterization of such graphs (sample size, brain area, measurements) [180].

The disease's progress can be tracked by synaptic activity, namely the post-synaptic density protein PSD-95 [181–183] and other biomarkers [184]. Enhancing neuroplasticity [66] and some immunotherapeutic drugs [184] or boosting the endogenous cannabioid system (ECBS) in the brain [185,186] can help slow down the advancement of AD, especially in its prodromal (i.e. early) stages. A precocious diagnosis [184] and realistic computational approaches [179] can prove important in treatment.

Dementia with Lewy Bodies (DLB) is the result of the accumulation of the alpha-synuclein protein in the brain, creating deposits (Lewy bodies) which disturb the brain's chemical balance. Although not as common as AD, it represents a sizeable share of cases (around 5-7,5% of all dementias [187]). It is

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one of two diseases caused by Lewy Bodies, the other being Parkinson's (PD), discussed in the next section.

Movement disorders Under a relatively new and phenomenological medical category [188], this section encompasses the most common neurodegenerative diseases affecting motor abilities, i.e. walking, reflexes, standing, etc. as a result of a disruption or dysfunction of coordination between the CNS (brain, spinal cord) and muscles. According to the movement's disruptive expression, they can be further subdivided into hyperkinesias (excessive), dyskinesias (unnatural) - jerky or non-jerky -, hypokinesias (decreased reach), bradykinesias (slowness), akinesias (absence) and abnormal involuntary movements [188]. Although this subsection focuses on prolonged disorders prominent in advanced ages (+65 years), transitory movement disorders - such as tremors, dystonia or tics - are not uncommon in younger patients and can result in early Parkinson's misdiagnosis [189].

Parkinson's Disease (PD) produces hypokinesia and bradykinesia - among other non-motor symptoms - stemming from Lewy's bodies (α-synuclein deposits), presenting high comorbidity with LBD and so greatly hampering an accurate (and timely) diagnosis [187] - which already requires very high-fidelity MRI [190]. This deposits provoke localized necrosis in the ventrolateral substantia nigra - namely targeting dopaminergic neurons - and so dopamine underflow to the striatum within the brainstem [191]. About 10-15% of all cases are genetic, and they can originate from prion diseases and perhaps metabolic iron accumulation [192] as well.

PD results in axonopathy, demyelination [193] (particularly originating in the basal ganglia [194]) and synaptic dysfunction and reduced white matter structural connectivity [195] - especially along certain pathways: nigro-pallidal, frontoparietal-stratal, etc. Some studies suggest this connectivity decrease and subsequent cortico-striatal topological reorganization is present in prodromal symptoms of PD, like rapid eye movement sleep behaviour disorder (iRBD) [195]. It also disrupts functional connectivity, although reliability and reproducibility between patients undergoing different stages, treatments and severities of PD and time evolution is problematic when comparing to healthy individuals [196], although some praiseworthy attempts exist [197]. Treatment usually involves L-DOPA (levodopa or l-3,4-dihydroxyphenylalanine) which crosses the BBB to increase dopamine concentrations in the brain.

Lastly, one must not mistake PD for ataxia, which is an acute lack of coordination of different muscles affecting gait, speech and eye movement among others as a result of nervous damage, mainly cerebellar and reversible in some cases [198].

Huntington's Disease (HD) is a rare, genetic (autosomal dominant) disorder affecting the CNS and showing symptoms like chorea (involuntary, fast and abrupt movements of facial, trunk and/or limb muscles), behavioural and psychiatric degeneration - including dementia -. It can manifest itself at any point in the patient's life, with no noticeable clinical indices until then [199], although most diagnoses happen between 30 and 50 years of age, inevitably leaving to full dependency and death (most commonly by pneumonia or suicide) [200]. It is caused by a cytosine-adenine-guanine (CAG) trinucleotide repeat (more than 36 times) in the huntingtin (HTT) gene on chromosome 4p and frequently treated with dopamine receptor blockers [200].

In terms of structural connectomics, HD greatly decreases nodal betweenness centrality (i.e., reduced relative importance of certain nodes within the network) and the clustering coefficient - meaning an impaired capacity for inter-nodal information processing [201] that can spread throughout the brain as the mutant protein propagates, shaping propagation patterns - with origin in the striatum and explaining white and grey matter deterioration - predictable via graph theory [202]. HD disrupts as well functional connectivity in subcortical and default mode networks. In some brain areas (within putamen, insula-putamen, visual networks), functional connections are further impeded as the CAG repeat length increases; whereas the contrary is true for others (calcarine to middle frontal gyri) [203].

Prion diseases, also known as transmissible spongiform encelopathies (TSE) are rare neurodegenerative, deadly illnesses caused by misfolded proteins (prions) PrP^{C} mutating irreversibly into PrP^{Sc} and causing neuronal necrosis, vacuolation and abnormal activation of microglia and

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astrocytes [204]. This can take place in humans and other animals (e.g.: sheep, deer, cows), in all organs but mainly the brain and the CNS. Their incubation process is long (up to decades), during which those proteins accumulate and create microscopic holes in the brain, transforming its tissue into a sponge (hence the name).

Prion diseases (PrD) can be divided into sporadic (spontaneous and unpredictable: Creutzfeld-Jakob disease (CJD), fatal insomnia, variable protease sensitive prionopathy), familial (genetically transmitted: familial CJD and fatal insomnia, Gerstmann – Sträussler – Scheinker disease) and acquired (through introduction of contaminated tissue into the patient - ingestion, transfusion, etc.: kuru, variant CJD). CJD is the most common prion disease, affecting 1 in a million yearly (85% sporadic, 10-15% familial [205]), manifesting itself in young adulthood if acquired (vCJD) and senescence if sporadic (sCJD) [206]. Although uncommon and heterogeneous in etiology and diagnosis, the study of prion diseases can potentially shed light on the role of protein misfolding in more widespread neurodegenerative diseases such as Parkinson's and Alzheimer's [207] and its transmission along connected structural pathways, which can be modeled as graph diffusion [208].

Multiple sclerosis (MS) can be also considered a neurodegenerative disease [209,210] in its latest stages, after initial autoimmune inflammation in the CNS [170,211,212]. "Sclerosis" means "abnormal hardening of body tissue". Its ultimate etiology is unclear, but it involves multiple genes increasing susceptibility along some environmental (ultraviolet B exposure), disease (Epstein-Barr virus) [212] and genetic factors (highest incidence among European and North American populations [210,211]). It is usually diagnosed in early adulthood via MRI (several white matter scars/plaques over time, chronic CNS inflammation) and it can be intermittent (relapsing-remitting, 85% of cases) or chronic, with chances of drug-induced remission (secondary progressive MS) or not (primary progressive or progressive-relapsing MS) [211].

MS affects mainly optic nerves, the brainstem and the spinal cord [212]. comprise demyelination and neuronal loss through axon deterioration [211] so, although remission can happen within hours or days, it is never complete because the neuronal reserve is progressively depleted - hence the neurodegenerative nature of the illness, despite partial remyelination [212]. Primary progressive MS entails ataxia and progressive cognitive and visual failure [212]. Lesions appear as the illness advances, affecting the connectome's structure (inflammation, atrophy) and thus also its functioning: abnormal activation of frontal regions or hippocampus for memory tasks and upsetting the default mode network (DMN) in resting states - although its direct links to cognitive impairment have proven difficult to clarify [213,214].

Functional connectivity remains a benchmark for studies about MS nonetheless, with special attention to network efficiency indicators [215,216] - e.g. on working memory, but subjected to patient heterogeneity [217] - with an apparent common ground altogether: altered connectivity in deep-gray matter areas, lower brain modularity, hemispheric skewness and task-independency [218]. Treatment strategies have rapidly improved in a paliative sense but keep failing to put a remedy to continuous neurodegeneration [219].

Amyotrophic lateral sclerosis (ALS) - also known as Lou Gehrig's disease - is a rare (1 in 100000 [220]) neurodegenerative disease targeting mainly motor neurons in the brain (upper, in the frontal lobe) and the spinal cord (lower) and the brainstem. As such, it is incurable and, on average, patients perish 2 to 5 years after diagnosis (usually after 60 years [220]) due to the malfunction of the diaphragm (breath) and/or swallowing muscles (nutrition) - with notable exceptions of longevity such as Sir Stephen Hawking. Although it starts focally, ALS often spreads to other body parts. It etiology can be autosomal inheritance (10 %) by a hexanucleotide repeat expansion of gene C9orf72 (between 1/3 and 1/2 of familial cases, although there are at least other 25 genes involved [221]) or sporadic (unclear). Half of all patients experience extra-motor conditions like behavioural changes, language impairment or executive dysfunction, and 1 in 10 show signs of frontotemporal dementia [222].

It is proven that brain topology worsens quantitatively (leaf fraction, degree divergence and correlation) in terms of efficiency as ALS unfolds, disentangling the multiscale, assortative networks

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- bonding between similar nodes - typical for a healthy connectome [223] - which translates into a functional impairment accordingly, predictably with more intensity within the motor cortex [224]. Overall, patients show a decreased functional connectivity in the cortex (right orbitofrontal, left interior frontal) and the corpus callosum [225] as well as an enhancement in the right angular, parietal cortex and the frontoparietal networks [226]. All this changes could be interpreted as compensatory mechanisms - surrogates for lost or damaged brain regions.

3.3. Psychiatric disorders

This category includes non-neurodegenerative disorders affecting mental health, also referred as mental disorders and illnesses and commonly treated by psychiatrists. They can be defined as clinically significant disturbances in an individual's cognition, behaviour or emotional processes affecting their normal mental function; usually listed on the Diagnostic and Statistical Manual of Mental Disorders (DSM). They are projected to be one of the biggest health concerns during this century and they usually develop from infancy and early adulthood (by mid-20s) [227], while diagnoses peak around 15 years (early adolescence) [228].

An early treatment could very much determine the future evolution of the illness and life quality in the subsequent years. Neurodevelopmental disorders (mental disability) and anxiety are diagnosed in early infancy (around 5 years), while obsessive-compulsive and eating disorders bloom during adolescence (around 15 years) and long-lasting issues like addiction/substance abuse and psychiatric disorders (mood, psychosis/schizophrenia, personality) appear evident in the first 20s [228].

Unlike neurological disorders such as the ones listed in the previous section, they are purely behaviourally diagnosed. Connectomics has shifted the paradigm in psychiatric studies as it allows for the identification of structural and functional measurable changes in the patient's brain during and after illness on a graph-like basis [229], such as local network efficiency, clustering coefficients and global communication path lengths [230]. MRI has been particularly useful in mapping the cortical surface, structural (diffusion, dMRI) and functional (fMRI) connectivity patterns - even in resting state (rfMRI), although coactivations for the same task and a great individual variability must be considered [231]. Alterations in structural and functional connectivity in the brain have been associated to schizophrenia, major depression, bipolar disorder and autism, among other disorders [232].

Schizophrenia is a chronic mental health disorder affecting 1% of the population and growing in incidence in developed countries [233], whose symptoms can be considered "positive" - hallucinations, voices, paranoid delusions - or negative - social handicap, loss of affection, drive or sense of pleasure, incoherent speech, erratic behaviour and diminished cognitive ability - [234]. It may occasionally relapse (via therapy and drugs) or become incapacitating.

It provokes a neurochemical imbalance by which the normal course of neurotransmitters (dopamine, serotonin, glutamate, perhaps aspartate, glycine or GABA) is altered, mainly along four pathways: nigrostriatal (caudate nucleus to substantia nigra) - linked to motor symptoms -, mesolimbic (ventral tegmental to limbic areas), mesocortical (ventral tegmental area to cortex) - associated with negative symptoms as the dopamine level decreases - and tuberoinfundibular (hypothalamus to pituitary gland) [235].

Its etiology is manifold, from obstetric problems (infections, fetal complications) to genetic factors (parents, monozygotic twins) and environmental triggers (social isolation, trauma). The connectome undergoes important changes during the illness, such as left frontal lobe hyperactivity [236], network randomization as clustering decays due to neural path over-shortening [237] - distortion of the characteristic "small-world" properties in healthy brains [238] and altered hierarchies in functional connectivity [239].

Major Depression (MD), also known as Major Depressive Disorder (MDD), is a persistent (at least 2 weeks) and debilitating sensation - with apparent cause or not - of sadness or melancholy associated with a loss appetite, libido, interests, pleasure sensations (anhedonia) and/or sleep, cognitive impairment and irritability [240]. It affects 1 in 6 people along their lifetimes [241]. It

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is the second most devastating burden in terms of disability-adjusted life years (DALY), which includes years lived with disability (DLY) - which can last all life - and years of life lost to premature mortality (YLL) - mainly due to suicide (50% of them are depression-induced), but also as a result of comorbidity with diabetes, heart diseases and stroke. It has a large genetic component (about 35% [240,241]) - although not attributed to any specific gene single-handedly - which more often than not comes with an array of reinforcing behavioural traits (conflict avoidance, pessimism, anxiousness) [240].

MDD is responsible for a decrease in functional connectivity among fronto-amygdalar [242], somatomotor, dorsal attention [243,244], salience - relevant for treatment [245], executive control and default mode networks in resting state [246] - linked to social dysfunction [247] and potentially recoverable by electro-convulsive therapy (ECT) [248] and medication [249] - predicting relapse [250]. Despite that, this alternations do not affect the global network irreversibly [251].

In combinations with manic episodes (grandiosity, good mood, overconfidence), MDD produces bipolar disorder (BB) [252], which exacerbates this mood swings turning them into extenuating chronic cycles that may become crippling. According to the severity of said manic events, experts separates bipolar I (acute, severe, followed by delusions and hallucinations in 75% of cases), bipolar II (less severe, hypomania) and cyclothimic disorder (recurring depressive and hypomanic states for over 2 years) [253]. In all three versions, it affects 1 in 100 people worldwide and lists among the leading causes of disability for young patients, yielding cognitive and behavioural impairment that can induce cardiopathies [254] lead to suicide during the worst episodes [255]. Connectivity distortions are similar to those of MDD, adding an important decoupling between functional and structural pathways - strongly correlating with suicide attempts [256,257].

Autism Spectrum Disorder (ASD), formerly known as Pervasive Developmental Disorder (PDD) [258,259] or "childhood schizophrenia" [260], encompasses conditions involving a combination of social communication and recurring behaviours, commonly with an early onset (around 3 years of age) and followed by sensory anomaly and perhaps intellectual disability. It concerns about 1 in 100 people [261] worldwide, although prevalence is higher in rich countries [259] as the definition and diagnose methodology has shifted in the last decades [262]. It is namely hereditary - with a plethora of associated genes and proteins [263], some of them locally inhibiting neural connectivity [264,265] - and presents high comorbidity with other neurological (ADHD, epilepsy) or psychiatric disorders (depression, anxiety) [259].

In contrast to most disorders disclosed in this article, it has been found - through fcMRI, MEG and EEG - that ASD appears to enhance functional connectivity excessively (hyperconnectivity) on a network and state base, depending on age as well - although some life-long effects exist, e.g. parietal and frontal hyperactivity (linked to repetitive behaviour in early development) and long-distance hypoactivity [266],depending on the analyzed frequency [264]. Nonetheless, this hyperactivity is not necessarily reflected on a structural basis - apart from higher gyrification, rather the inverse: brain overgrowth during development makes adults with autism have a delayed long-distance connectivity (less efficient). Despite the general tendencies, individual variability [267] and symptom severity [268] play a crucial role on connectivity. In spite of proof of increased network efficiency markers such as betweenness centrality [269,270], there is contradictory evidence in regards to ASD-induced frontal hyperactivity [271].

Asperger syndrome (AS) is a chronic neurodevelopmental disorder related to, if not included, in the autism spectrum [272], presenting similar symptoms and connectivity disturbances to those of broad "autism", except for a greater intelligence on average and general absence of dysphasia (impaired propositional language) [273], rather the contrary as patients develop quite a structured form of language - albeit delivered in uncommon ways [272]. Differential diagnosis from social phobia and schizoid personality can prove difficult [274]. There is no structural difference in the brain between healthy controls and AS patients, while functionally they have higher global efficiency (greater transfer speed) and lower network segregation (transitivity) and resilience (assortativity) [275].

Obsessive-Compulsive Disorder (OCD) is a mental health condition described by repetitive, ritualistic behaviours involving checking tasks and washing excessively; feeling anxiety and fear if they do not perform in such manner. Appearing in early adulthood (22-36 years), OCD involves intrusive thoughts and is often misdiagnosed. It is not curable and may be genetically inherited, though treatment - normally serotonin re-uptake inhibitors and cognitive–behavioural therapy, perhaps surgery [276] - reduces symptoms greatly improving daily life functionality [277].

4. Conclusions and future research lines

Biophysical models, especially those allowing for brain activity tracking, can greatly enhance diagnoses of neurodegenerative illnesses [168,278].

Final objective: customized modelling and diagnose (individual, real-time brain mapping).

Extend analysis to all Central and Periferic Nervous Systems, considering the role of glia, myelin, angiome, etc. Focus on the cortex (most synapses within 20% of the brain's volume) and cerebellum (80% of all neurons contained in 10% volume) [231].

Emphasis on preventive monitoring and more accurate diagnoses (Digital/Hybrid Twins [279])

Funding:

This project has received funding from the European Union's Horizon 2020 research and innovation programme under the Marie Słodowska-Curie Grant Agreement No. 956401

Grant PID2021-126051OB-C43 funded by MCIN/AEI/ 10.13039/501100011033 and by "ERDF A way of making Europe".

Acknowledgments: The authors would like to thank Professor Michel Destrade (Chair of Applied Mathematics, University of Galway) and Sairam Pamulaparthi Venkata (Early-Stage Researcher 8, XS-Meta Project, University of Galway) for their insights on brain modeling as a soft, visco-elastic material, as well as Itziar Terradillos Irastorza (PhD in Neuroscience 2021, UPV/EHU), Hanoi Iván Guillermo Montiel (PhD student, Institut Pasteur) and Edgar Soria-Gómez (Neuroscience Department at UPV/EHU) for their medical guidance.

Conflicts of Interest: The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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