A Review of the Definition and Significance of the Brain Health

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Abstract – The human brain is considered a remarkable evolutionary feat due to its intricate functionality, encompassing cognitive processes such as reasoning, memory retention, motor control, and emotional experience. The primary objective of adopting a healthy lifestyle is to ensure the optimal functioning of the brain throughout an individual's entire lifespan. As the global population ages, there is an increasing prevalence of neurological diseases and a growing challenge in safeguarding brain function due to its intricate nature. Therefore, it is imperative to comprehend the concept of brain health and its significance. This article marks the commencement of a sequence of scholarly publications aimed at delineating the concept of brain health, scrutinizing the ramifications of significant neurological illnesses on the health of the brain, and deliberating on prospective interventions and preventive measures for these ailments.

Keywords – Human Brain, Brain Health, Neurological Disorders, Transient Ischemic Attacks, Traumatic Brain Injuries, Central Nervous System.

I. INTRODUCTION

As people age, it is imperative to prioritize the preservation of both cognitive and physical well-being. A recent study conducted by the Centres for Disease Control and Prevention (CDC) has found that subjective cognitive decline (SCD), commonly referred to as memory loss, is more prevalent among individuals with one or multiple chronic health conditions [1]. The analysis encompassed a diverse array of chronic conditions, including but not limited to cardiovascular disease, diabetes, stroke, arthritis, chronic obstructive pulmonary disease (COPD), renal disease, and asthma. People who are afflicted with COPD, cardiac disease, or have a prior history of stroke tend to exhibit an increased propensity for the development of sudden cardiac death (SCD). Maintaining autonomy can pose a significant challenge when confronted with escalating disorientation or memory impairment, as well as enduring health issues. These circumstances can impede the ability to perform essential tasks such as cleaning, cooking, medications, and managing health conditions and attending medical arrangements. Possible outcomes could encompass deterioration in physical well-being, avoidable admissions to medical facilities, or an exacerbation of cognitive impairments such as memory decline or confusion. There exists a correlation between sickle cell disease (SCD) and an elevated risk of developing Alzheimer's disease under specific circumstances.

The establishment of a universally accepted definition for mental health remains a subject of ongoing debate and has yet to be reached. The existing definitions of brain health tend to either offer a general overview or concentrate on a limited number of specific facets. According to the United States Centres for Disease Prevention and Control, mental wellness is defined as the ability to effectively participate in various cognitive processes, including but not limited to learning, decision-making, interpersonal communication, and memory retention [2]. As per a presidential advisory released jointly by the American Stroke Association and the American Heart Association, the concept of "optimal brain health" is characterized by the average cognitive performance exhibited by individuals of a particular age group who do not have any

diagnosed brain or organ system disorders [3]. This average performance level can be calculated on the basis of the extent of decline from normal cognitive function or the ability to adequately engage in desired activities.

The brain is a complex organ that performs various interconnected functions, such as processing sensory information and controlling motor functions, regulating cognitive processes and emotions, and maintaining social awareness and behavioural patterns. Hence, brain health can be delineated as the state in which there is an absence of evident brain disorders that impede typical cognitive and mental functioning at a given stage of life, while concurrently upholding the utmost level of brain soundness. It is advisable to seek guidance from a healthcare practitioner or medical professional. According to GBD 2021 Sickle Cell Disease Collaborators [4], only 50% of individuals with sickle cell disease (SCD) and a chronic illness indicated that they had engaged in conversations regarding their memory impairment with a healthcare professional. Individuals who experience chronic health conditions derive significant advantages from the timely identification of memory impairment. Dementia, encompassing Alzheimer's disease, exhibits a diverse range of manifestations, underscoring the significance of seeking medical consultation when encountering symptoms that elude clear explication. An additional advantage of an early diagnosis is the opportunity to participate in clinical studies and enhance preparedness for future outcomes.

Regular physical exercise has been shown to effectively mitigate the age-related decline in cognitive function. Regular physical activity not only decreases the likelihood of developing hypertension, vascular disease, and stroke, but also promotes unimpeded blood circulation to the brain. Engaging in activities such as walking, participating in sports, and attending fitness classes are a few illustrative instances of uncomplicated methods to maintain physical fitness. The advantages of engaging in mental exercise are similar in magnitude to those associated with physical activity. Puzzles and other forms of coursework focused on logic development serve as effective illustrations of cognitive exercises. Games such as chess and sudoku, which necessitate the utilization of strategic planning, have been found to be highly beneficial for cognitive development. The impact of sleep quality on cognitive functioning is significant. The maintenance of a healthy brain necessitates the inclusion of sleep, which typically accounts for approximately one-third of the total duration of each day. The adequate functioning of the nervous system, immune system, and various physiological processes heavily relies on the essentiality of sleep. One can rely on experiencing wakefulness, attentiveness, and the ability to make sound decisions following a restful night's sleep. The optimal duration of sleep varies depending on age, however, it is recommended by experts to strive for a nightly sleep duration of approximately six to seven hours. The adherence to a consistent sleep schedule facilitates the elimination of metabolic waste in the brain and promotes the improvement of memory.

This paper provides a review of the definition and significance of the brain health. The remaining paper of the paper has been organized as follows: Section II provides a discussion of the major brain health neurological disorders. Section III is about the burdens of neurological disorders and ageing. Section IV focuses of the challenges and opportunities for future research. Lastly, Section V presents final remarks to the paper.

II. MAJOR BRAIN HEALTH NEUROLOGICAL DISORDERS

Numerous neurological disorders have been associated with compromised cognitive function and adverse health consequences in individuals. The following section discusses neurological illnesses, which are among the medically recognized causes of brain dysfunction.

Cerebrovascular diseases

Cerebrovascular disease can lead to sudden, focal weakness or paralysis in specific regions that are innervated by the affected blood vessels, due to vascular damage in the brain. Toximetabolic diseases, vasovagal syncope, and cerebral hypo perfusion are more commonly observed as causes of impairment or loss of consciousness compared to the occurrence of simultaneous, extensive, or numerous hemorrhages or ischemic infarctions. Both migraines and epileptic seizures can result in transient, localized neurological impairments that could potentially be misinterpreted as cerebrovascular pathology. Following cancer and heart disease, cerebrovascular disease ranks as the third most prevalent cause of mortality and disability in the United States.

Transient ischemic attacks (TIAs) are characterized by the abrupt onset and subsequent resolution of neurological symptoms within a 24-hour period. Although transient ischemic attacks (TIAs) have a short duration of only a few minutes, they have been consistently demonstrated to be a dependable indicator of future strokes. A stroke is characterized by a sudden and localized impairment in neurological function that does not fully resolve within a 24-hour period. The extent of recovery can vary and may improve gradually over several weeks or months. Ischemic infarction is the primary etiology of cerebrovascular accidents. Both transient ischemic attacks (TIAs) and strokes require immediate medical intervention in order to prevent complications, minimize neurological damage, and reduce the risk of recurrent strokes. The etiology of transient ischemic attack (TIA) or stroke, along with its anatomical distribution within the vascular system, will dictate the optimal therapeutic approach.

Numerous risk factors, such as coronary artery disease, hypertension, tobacco use, hypercholesterolemia, diabetes mellitus, and a familial predisposition to vascular disorders, collectively contribute to the pathogenesis of advanced atherosclerosis in the majority of individuals afflicted with cerebrovascular disease. Obesity, physical inactivity, and excessive alcohol consumption are additional variables that have been found to be associated with the phenomenon under

study, albeit to a lesser extent. Atherosclerotic vascular changes become more common in older individuals, even when significant risk factors are not present. The treatment approach for this vascular disease varies depending on whether it has impacted the major arteries or the smaller arterial branches. Atherosclerotic alterations are commonly observed at the bifurcation points of prominent cervical and cerebral arteries, likely attributed to the heightened turbulence of blood flow in these regions (see **Fig 1**).

Arterial plaques, referred to as intravascular atheromas in academic literature, develop through a process involving the accumulation of lipids in the subintimal layer, proliferation of smooth muscle cells, and subsequent fibrosis. This progression typically takes place over an extended period of months to years. Atheromas and plaques that attain excessive size possess the potential to impede the circulation of blood within an artery, thereby inducing arterial obstruction. Additionally, they may also give rise to the development of ulcers, either independently or in conjunction with the aforementioned obstruction. The obstruction of smaller arteries located downstream can occur due to the activation of blood clots, platelets, fibrin, cholesterol, or calcified components (emboli) following ulceration. This activation can lead to either local occlusion (thrombosis) or distant propagation (embolization). Hence, the main etiologies of ischemic infarction are atherosclerotic plaque thrombosis and embolic occlusion of arteries originating from proximal locations (see **Fig 2**).

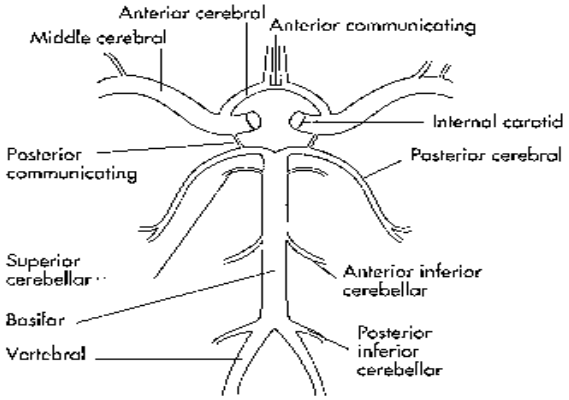

Fig 1. Anatomical structures of the arteries located at the base of the brain. Atherosclerosis commonly manifests at arterial bifurcations, characterized by the presence of shaded regions

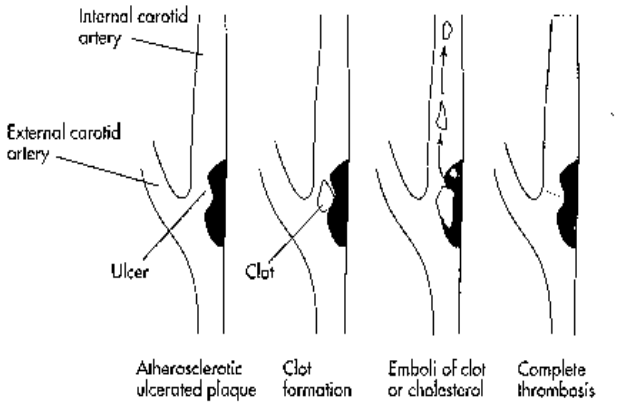

Fig 2. The presence of atherosclerosis at the cervical internal carotid artery

Certain individuals who have a gradual formation of a blood clot in a cerebral artery may potentially avoid experiencing an infarction and the subsequent neurological impairment that would typically arise from the interruption of blood flow to a specific region of the brain or brain stem. The presence of a congenitally intact circle of Willis at the base of the brain is associated with an increased probability of possessing advantageous collateral blood flow. The presence of collaterals originating from the external carotid artery, the vertebrobasilar arteries, or both, has provided assistance to individuals with an asymptomatic occlusion of the cervical internal carotid artery. Retrograde blood flow, also known as blood flowing in the opposite direction, has been observed to occur from the branches of the external carotid artery, specifically through the ophthalmic artery, leading into the circle of Willis. The presence of patent posterior connecting branches within the circle of Willis facilitates the uninterrupted flow of blood from the posterior cerebral arteries to the middle and anterior cerebral arteries, thereby maintaining the vertebrobasilar circulation. The occurrence of efficient collateral flow is less frequent when artery branches are abruptly obstructed by emboli.

In cases where there is partial ischemia in the brain, the neurological impairment resulting from an ischemic infarction caused by thrombotic or embolic mechanisms may exhibit improvement within a span of hours to days. Alternatively, the recovery process may occur at a slower pace over the following weeks or months as various regions of the brain compensate for the impairment. The cerebral cortex, which has experienced a significant artery infarction, exhibits macroscopic characteristics such as increased volume and softness, as observed under a microscope. Additionally, there is a diminished distinction between the boundaries of gray and white matter, along with sporadic instances of hyperemia caused by the leakage of blood. Over time, this particular region undergoes a process of atrophy. Following a clinical stroke, ischemic neurons exhibit morphological changes within a timeframe ranging from 12 to 36 hours, characterized by a reduction in size and a pinkish appearance, commonly referred to as "pink neurons." Following a brief period of time, macrophages undertake the task of removing the necrotic debris, while astrocytes proceed to encase the infarct's periphery with cysts. The basilar artery, along with the proximal anterior and middle cerebral arteries, abruptly gives rise to multiple notable smaller arteries.

The absence of the typical, gradual decrease in artery diameter observed in this case indicates a rather atypical anatomical structure. The structures known as the basal ganglia, internal capsule, thalamus, and corona radiata receive their blood supply from the perforator or lenticulostriate arteries. The presence of a lesion in the internal capsule has the potential to result in significant hemiparesis, despite the fact that the blockage of a relatively small artery may only cause

an ischemic infarction of a few millimeters in diameter. The term used in the medical field to refer to these small lesions is lacunar infarcts. The occurrence of these minor blockages in the arteries is attributed to thrombosis rather than emboli.

Traumatic brain injury

Traumatic brain injuries (TBIs) have a significant impact on individuals across various age groups and are a prominent contributor to mortality and disability. It is projected that about 10 million people are affected by TBIs annually. Both penetration injuries, characterized by the breaking of the skull and dura, and closed-head injuries, characterized by the absence of such fractures, fall under the category of traumatic brain injuries (TBIs).Clinical factors, including the severity and duration of awareness (if available), the availability of neurological and amnesia symptoms, and the findings from structural brain imaging approaches such as MRI or CT, can be utilized to categorize traumatic brain injuries (TBIs) into mild, moderate, or severe classifications. The provision of neurosurgical and intensive care services is essential for patients diagnosed with modest to criticalTBI.

Approximately 80% to 90% of traumatic brain injuries (TBIs) are categorized as mild commonly referred to as a concussion. Numerous groups have devised clinical criteria to establish the parameters for classifying mild TBIs, and these criteria generally exhibit a high degree of concordance.Blunt, non-penetrating head trauma is the prevailing etiology of mild TBIs, with its temporary symptoms being discernible through medical observation, patient self-report, or witness annotations, if applicable. Various physical symptoms, including nausea, vomiting, dizziness, and headache, as well as cognitive symptoms such as memory issues and poor attention, and behavioral symptoms like irritation and emotional lability, may manifest. Additionally, loss of consciousness is also a potential outcome.

Fig 3. Various categories of forces integrated in mild TBIs

Fig 3 depicts the primary factors contributing to mild TBIs namely the biomechanical forces of acceleration and deceleration. Diffuse axonal damage is a result of the application of shearing and strain pressures to the brain axons by external forces. Forces that induce movement of the head in the anterior-posterior locus, such as effects to the back or the front of the head, result in linear (translational) acceleration. The application of external forces, such as a lateral impact to the head, induces rotational (angular) acceleration resulting in the rotation of the head towards one side. The phenomenon of the head experiencing a sudden decrease in velocity, such as when it comes into contact with the ground, is referred to as impact deceleration. Numerous traumatic brain injuries arise from a combination of the aforementioned factors.

The American Congress of Rehabilitation Medicine may classify both a standard neurological examination and a CT scan of the brain as normal, depending on the interpretation of the results. BOX1 comprises the medical criteria employed for the categorization of mild traumatic brain injury (TBI). At present, there is a lack of a universally accepted diagnostic tool of optimal accuracy for mild traumatic brain injury (mTBI) that can be effectively employed in a clinical environment.The majority of individuals experiencing post-concussion symptoms typically observe a positive progression in their condition within a timeframe ranging from 1 to 12 weeks. Additionally, it has been observed that in approximately 80% of cases, symptoms associated with mild traumatic brain injury tend to diminish within a period of 7 to 10 days. It is possible that athletes may experience a faster recovery from sports-related concussions compared to individuals with non-sports-related mild traumatic brain injuries due to their typically superior physical condition.

While it is true that sports-related traumatic brain injuries (TBIs) may occur due to lower mechanical forces compared to non-sports-related TBIs, individuals with non-sports-based mild TBI are more prone to having pre-existing behavioral, psychiatric, or/and substance abuse issues. These pre-existing conditions can heighten their vulnerability to injury and potentially prolong the recovery process. Patients who experience persistent symptoms following a concussion are clinically diagnosed with post-concussion syndrome (PCS).According to Kelmendi et al. [5], it is estimated that post-concussion syndrome (PCS) may impact approximately 10-15% of individuals who have experienced a concussion. This prevalence can be attributed to the diverse array of symptoms that can manifest following a head injury.

Chronic traumatic encephalopathy (CTE) has been found to be associated with a prior occurrence of mild traumatic brain injuries (TBIs) and subconcussive head impacts, particularly among individuals involved in contact sports or with a military background10. While there have been recent suggestions for criteria regarding traumatic encephalopathy syndrome (TES) in clinical settings, it is important to note that CTE refers to a diagnosis, which could only be determined using post-mortem examination. This is due to the lack of validated or established medical criteria and biomarkers, which have the capacity to support diagnosis before death. The year 1928 marked the initial documentation of a degenerative neurological disorder observed in retired boxers, commonly referred to as "punch drunk syndrome." Subsequently, this

condition was designated as "dementia pugilistica", while the term chronic traumatic encephalopathy (CTE) did not emerge until the 1940s.

Neurofibrillary tangles (NFTs) refer to the accumulation of paired helical filament (PHF)-tau. The association between NFTs and dementia pugilistica was initially established in a neuropathological study conducted in 1973. The initial documentation of chronic traumatic encephalopathy (CTE) pathology can be traced back to the year 2005, as referenced in source 18. This report highlighted the case of a former American football player [6]. Subsequently, De Los Reyes, University of the East Ramon Magsaysay Memorial Medical Center, Quezon City, and Villamayor [7] have revealed the presence of CTE pathology in a considerable number of athletes engaged in contact sports like soccer, ice hockey, rugby, and wrestling. The presence of pathological findings consistent with CTE has also been documented in military personnel who have been exposed to explosive devices and subsequent explosions. The presence of amyloid-beta (Aβ) plaques in CTE patients has been found to have a significant association with the inheritance of the apolipoprotein E (APOE) 4 allele and advanced age. According to Tang et al. [8], approximately 50% of individuals diagnosed with CTE exhibit the presence of these plaques.

Brain Tumours

A brain tumor is considered to be among the most severe forms of human neoplasms. It is accountable for approximately 1.35% of the total cancer cases and contributes to 29.5% of the mortality associated with cancer. Neoplasms affecting the central nervous system encompass a range of tumors that can arise in various anatomical structures, such as the brain, cranial nerves, spinal nerves, spinal cord, and meninges. Malignant and benign tumors represent the principal classifications of neoplasms. Based on the categorization system established by the World Health Organization (WHO), cancers are assigned a grading scale ranging from 1 to 4. Notably, malignancy is attributed to grades 3 and 4. The term "brain tumor" encompasses both primary brain tumors and secondary malignancies that have metastasized to the brain. Glioblastoma, the most prevalent form of malignant brain tumor, originates from glial cells. Metastasized brain tumors (MBTs) are prevalent among the adult patient population with intra-axial brain tumors. It is widely believed that approximately one-third of individuals diagnosed with a primary cancer will develop metastatic lesions in the central nervous system (CNS). Tumors affecting the CNS are the prevailing form of solid tumors observed in children and rank as the second most prevalent malignancy in the juvenile population.

In order to mitigate the risk of permanent neurological impairment or fatality, it is imperative to promptly identify and address brain tumors.Medical data analysts heavily rely on the process of feature selection and categorization when determining the normality or abnormality of patient data. The identification of indicators that facilitate early detection of tumors is crucial, as the prognosis of patients is closely linked to the stage of the disease at the time of detection, often rendering therapeutic interventions less effective at later stages. The treatment options for patients diagnosed with brain metastases include the administration of corticosteroids, surgical resection, chemotherapy, whole-brain radiation therapy, or stereotactic radiosurgery. The presence of brain tumors has been observed to have a significant impact on individuals, leading to the development of neurocognitive impairment. In order to optimize neurocognitive rehabilitation, it is imperative to develop novel approaches for the timely identification of neurocognitive impairment resulting from brain tumors. Raman spectroscopy can be employed to differentiate between various types of brain tumors. The successful removal of gliomatumors in brain surgery is contingent upon the accurate identification of two critical factors: the delineation of the tumor border and the determination of the extent of resection.

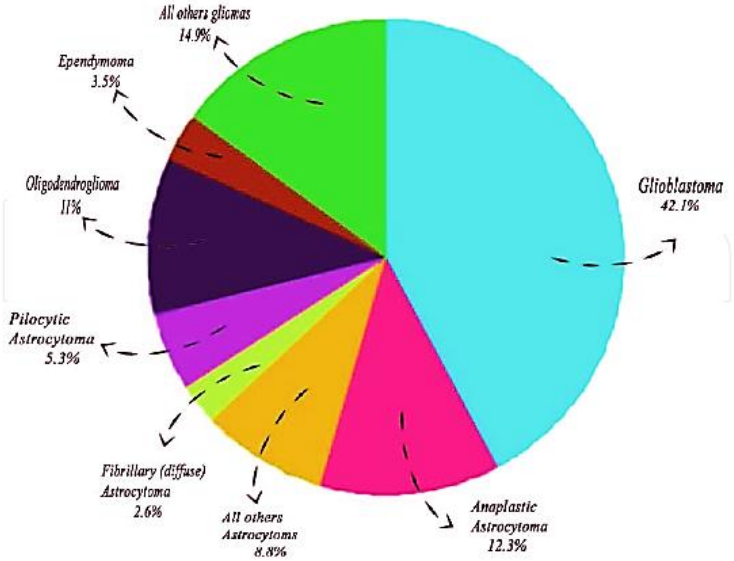

Fig 4. The epidemiology of central nervous system (CNS) tumors, specifically examining the incidence rates of brain tumors across various regions of the brain

Population-based studies are generally considered to be more dependable and less prone to bias compared to clinical or autopsy-based series due to their utilization of larger sample sizes. The precise incidence of brain metastases remains uncertain. Epidemiological analysis utilizes hospital data, tumor registries, and death certificates as primary sources of information. According to Mărginean et al. [9], there appears to be a comparable occurrence of gliomas and brain metastases. **Fig 4** presents a comprehensive overview of the survival rate categorized by histology.

Alzheimer's disease

Alzheimer's disease (AD) is medically featured by a transition from impairments in episodic memory to a progressive degeneration in cognitive abilities. In 2013, it was projected that the global prevalence of dementia would affect approximately 44 million individuals. However, it is anticipated that this figure will significantly increase to approximately 136 million individuals by the year 2050 [10]. At present, there exists no pharmacological intervention for Alzheimer's disease that has demonstrated efficacy in decelerating or halting the advancement of the condition. The pathology of Alzheimer's disease involves various factors, including alterations in amyloid precursor metabolism of protein, changes in tau protein phosphorylation, impaired energy production, increased oxidative stress, inflammation, mitochondrial dysfunction, dysregulation of membrane lipids, and disruption of neurotransmitter pathways.

It is currently recognized that metabolic dysfunction plays a vital obligation of the advancement of Alzheimer's disease (AD), and that a majority of the clinical symptoms associated with AD can be attributed to this malfunction. One example of a consistent feature of Alzheimer's disease (AD) is the reduction in cerebral glucose uptake, which becomes apparent many decades before the beginning of cognitive decline.The interaction between A42 and mitochondrial enzymes results in an increased generation of ROS (reactive oxygen species). This, as a result, impacts glycolysis, the tricarboxylic acid (TCA) cycle, and the activity of the respiratory chain within the mitochondria. The build-up of dangerousintermediary metabolites in the mitochondria is responsible for these effects. The neurotoxicity of A42 has been extensively documented and is believed to play a role in the disruption of neuronal energetics through the initiation of a series of pathological processes.

The individual who is widely acknowledged for initially describing Alzheimer's disease is Dr.Alois Alzheimer, a famous German psychiatrist, and Auguste D, a neuropathologist, diagnosed with a unique cerebral cortex disorder, exhibited a range of symptoms including disorientation, language and memory impairment, behavioral symptoms such as delusions, paranoia, and hallucinations, including psychosocial impairments. These symptoms were documented by Alzheimer in his influential conference lecture in 1906 and further elaborated upon in his subsequent article in 1907. Dementia is a complex disorder that necessitates an initial description of the processes associated with normal aging, followed by an identification of potential deviations that can lead to abnormal conditions such as dementia. There exists a significant degree of overlap and interplay among the biological, social, and psychological viewpoints pertaining to the process of aging. In the context of arthritis, for example, decreased mobility can result in a decline in engagement in social activities and other previously enjoyed endeavors. When conducting a comparison between the cognitive skills of an individual in the past and present, it is crucial to consider the interplay between different aspects of aging.

The frequency with which the boundaries between behaviors and perspectives categorized as "normal" and "abnormal" become indistinct is noteworthy, considering the inherent challenges in establishing a clear definition of what is considered "normal." The dissolution of boundaries between communities, ecosystems, and individuals is a common phenomenon. A prevalent misconception exists regarding the definition of "normal," wherein it is mistakenly equated with "not abnormal." However, the accurate interpretation of "normal" alludes to the range encompassing the central values of a given dimension (such as height), with dual extremes founded at opposite sides (i.e., very short and very tall), instead of one extreme. Given the subjective nature of individual perceptions, life expectancies in relation to aging can vary significantly. Due to significant advancements in medical science and technological innovations, individuals are experiencing increased longevity, leading to heightened exposure to the elderly population and a greater awareness of the diverse aging phenomena observed among their own familial relations. Consequently, the criteria utilized to evaluate ourselves and others, along with our understanding of the definition of "typical" aging, remain in a constant state of change. Alterations in higher cognitive functions, commonly referred to as higher mental capabilities, are an inherent aspect of the aging process and coincide with even the most subtle modifications in physical attributes.

The individual's ability to effectively acquire information may have been compromised, resulting in inadequate encoding or retention of knowledge, thereby potentially impairing memory function. The manifestation of memory decline due to the aging process is often one of the initial cognitive alterations that become apparent to others, thereby engendering significant concern for the individual affected, as well as their social network comprising friends, family, and colleagues. Dementia is distinguished by deterioration in cognitive functions, particularly in the realm of memory. Nevertheless, it is crucial to consider the possibility that it may also indicate additional dysfunctions.

Schizophrenia

Schizophrenia is a highly debilitating psychiatric disorder characterized by profound disturbances in an individual's perception of reality. Symptoms such as hallucinations, delusions, and marked cognitive and behavioral disorganization can manifest in individuals with schizophrenia, significantly impeding their functional capacity in daily activities. Individuals diagnosed with schizophrenia will require continuous medical care. The long-term prognosis may be enhanced

if symptoms are effectively managed in the early stages, prior to the emergence of more substantial consequences. Schizophrenia is influenced by various factors, including cognitive, behavioral, and emotional disturbances. The manifestation of impaired functioning is evident in the observed indicators and manifestations, which encompass, but are not restricted to, delusions, hallucinations, and incoherent speech. **Table 1** enumerates a range of potential symptoms.

Table 1. Signs of Schizophrenia	
Negative symptoms	This defines an absent or reduced capability to perform routine tasks. For example, they could not hand their individual hygiene or show a deficiency of emotions by avoiding eye contact, speaking monotonously, or changing facial expression.
Extremely abnormal and disorganized motor behavior	This phenomenon can be seen in different ways, such as erratic restlessness, or juvenile levity. The deficiency of goal-directedness in behavior poses challenges in task execution. Behavior can encompass various manifestations such as defiance towards instructions, displaying inappropriate or peculiar body postures, exhibiting a complete absence of response, or engaging in purposeless and excessive movements.
Disarranged thinking (speech)	The availability of disarranged speech may be indicative of disarranged thinking. The impairment of effective communication can result in answers to questions that are completely or partially unrelated. Occasionally, verbal communication may involve the construction of incoherent sequences of words that lack semantic coherence, colloquially referred to as "word salad."
Hallucinations	These frequently encompass perceptual experiences of visual or auditory nature that lack correspondence to objective reality. The complete magnitude and impact of a typical occurrence, nevertheless, are present for the individual diagnosed with schizophrenia. While hallucinations may be seen in different sensory modalities, auditory hallucination, specifically hearing voices, are the most commonly observed type.
Delusions	These represent erroneous views, which are not considered the reality. For example, individuals might feel tormented or threatened; feel as a target of particular remarks or gestures; feel gifted or famous; feel in love with someone else; or feel a critical disaster is yet to occur. Most people with schizophrenia tend to have delusions.

The various manifestations and severities of symptoms may undergo changes and variations over time. Certain signs and symptoms have the potential to endure indefinitely. Schizophrenia typically presents in males during their early to mid-20s. Typically, symptoms manifest initially during the late twenties in women. The prevalence of schizophrenia is significantly lower among individuals in younger age groups and even more infrequent among those aged 45 and above.

Bipolar disorder

Bipolar disorder, earlier known as manic depression, is a psychiatric condition distinguished by cyclic episodes of elevated mood (mania or hypomania) and depressive states. Symptoms commonly associated with depression include a pervasive sense of sadness and hopelessness, as well as a diminished capacity for experiencing pleasure in various aspects of life. Possible symptoms of manic or hypomanic states include feelings of euphoria, heightened energy levels, and atypical irritability. Mood fluctuations can pose challenges in terms of initiating sleep, maintaining wakefulness, accomplishing tasks, making sound judgments, and engaging in effective cognitive processes. Mood fluctuations may occur on an annual basis or manifest multiple times. The majority of individuals are likely to experience emotional consequences during the interim periods between episodes, although there may be exceptions. Medication can effectively manage mood swings and other symptoms associated with bipolar disorder; however, it is important to note that the condition itself is chronic and enduring. The primary modalities of treatment for bipolar disorder encompass pharmacotherapy and psychotherapy.

Table 2 enumerates a variety of bipolar and related disorders. Mania, hypomania, and sadness are all potential manifestations. The occurrence of unpredictable fluctuations in mood and behavior resulting from symptoms can lead to significant discomfort and challenges in one's daily functioning.

Table 2. Different forms of bipolar and related	
Bipolar I disorder	The individual in question has experienced at least one episode of mania, which may be followed or preceded by episodes of hypomania or major depression. In certain instances, the presence of mania has the potential to induce a departure from reality, commonly referred to as psychosis.
Bipolar II disorder	The individual in question has experienced a minimum of one significant depressive episode and a minimum of one hypomanic episode, yet they have not encountered a manic episode.
Cyclothymic disorder	Individuals have experienced a minimum of two years, or one year specifically in the case of children and teenagers, characterized by recurring episodes of hypomanic symptoms as well as moments of depressive symptoms, albeit of lesser intensity compared to major depression.
Other types	Examples of such disorders encompass those induced by specific substances, such as alcohol or drugs, as well as those arising from medical conditions, including but not limited to stroke, multiple sclerosis, or the Cushing's disease

Contrary to prevailing beliefs, it is fundamental to consider that bipolar II disorder should not be regarded as a less severe manifestation of bipolar I disorder. The presence of severe mania is a defining characteristic of bipolar I disorder, while the persistent depressive episodes commonly associated with bipolar II disorder can be equally incapacitating. While bipolar disorder can present itself at any stage of life, it is commonly diagnosed in individuals during their early adulthood. Symptoms may exhibit variability among individuals and may also undergo temporal fluctuations.

Additional symptoms, including feelings of anxious discomfort, sadness, psychosis, and various others, may manifest in individuals diagnosed with bipolar I and bipolar II disorders. There are two potential diagnostic classifications for symptom timing, namely mixed cycling and rapid cycling. Manic-depressive episodes can also be triggered by pregnancy and seasonal changes. The identification of bipolar disorder in young individuals poses a significant challenge. Distinguishing between natural mood fluctuations, stress or trauma-induced effects, and other mental health conditions that may or may not be associated with bipolar disorder can pose a challenging task. In contrast to the observed pattern in adults diagnosed with bipolar disorder, children and adolescents may exhibit notable episodes of depression, mania, or hypomania. During episodes, emotions may exhibit rapid fluctuations. Certain adolescents may go through extended periods without encountering any mood disturbances whatsoever. The prominent characteristic of bipolar disorder in young individuals is the presence of pronounced and atypical fluctuations in mood.

Individuals diagnosed with bipolar disorder frequently fail to access the necessary therapeutic interventions due to a lack of awareness regarding the profound impact of their emotional instability on both their personal lives and the well-being of their close relationships, irrespective of the severity of their mood fluctuations. Individuals diagnosed with bipolar disorder often describe experiencing a heightened sense of euphoria and increased levels of productivity during their manic episodes. However, this elevated state is typically succeeded by a subsequent period of decreased mood, which may induce feelings of despondency, fatigue, and potentially result in legal, financial, or interpersonal complications. It is advisable to promptly seek medical or mental health assistance in the event that one exhibits symptoms indicative of depression or mania. The absence of a natural remedy for bipolar disorder is evident. The management of symptoms associated with bipolar disorder can be effectively achieved through the assistance of a mental health professional who possesses specialized expertise in the treatment of individuals with this condition.

The potential impacts on cognitive well-being and neurological functioning of specific neurological disorders can exhibit both distinct and overlapping characteristics. Dementia is typified by a pervasive decline in cognitive abilities, with Alzheimer's disease being the prevailing manifestation of this condition. Mood disorders have been associated with dysfunctions in these areas, as well as impairments in emotional regulation. The potential association between cognitive impairment and dementia and physical impairments such as gait balance problems, and aphasia, and cerebrovascular illnesses is frequently disregarded by both medical professionals, and patients.

III. BURDENS OF NEUROLOGICAL DISORDERS AND AGEING

The manifestation of cognitive decline and the aging of the brain are widely recognized as the primary indicators of the aging process in humans. According to available data, the global population of individuals aged 60 and above was estimated to be approximately 900 million in the year 2015 [11]. Projections indicate that by the year 2050, this figure is expected to increase significantly, reaching a projected population of two billion. The prevalence of neurological disorders and the challenges associated with maintaining optimal brain health are increasing significantly in correlation with the growing and aging populations. Individuals afflicted with neurological illnesses impose a significant economic strain as a result of the physical disability, cognitive impairment, and social dysfunction they experience.

Based on the findings of Zhan et al. [12], it was determined that neurological disorders had an increased number of DALYs (disability adjusted life years) of about 275 million and ranked as the second leading cause of mortality (9 million) in the year 2016. The primary contributors to neurological DALYs encompass migraine, stroke, Alzheimer's disease, other forms of dementia, and meningitis. Approximately 25% of individuals will experience a stroke upon reaching adulthood, typically around the age of 25. In 2018, the global prevalence of dementia was estimated to have impacted more than 50 million individuals, with projections indicating a significant increase to approximately 152 million individuals by the year 2050. The anticipated increase in demand for government funding to support programs aimed at treating, rehabilitating, and providing assistance to individuals with neurological illnesses is expected to occur in the coming decades.

Global Burden of Disease 2016 Greece Collaborators [13] provide a comprehensive compilation of the neurological conditions that are encompassed within the estimates provided by the Global Burden of Disease (GBD) study. It also offers explanations on how to appropriately interpret these estimates, along with the inclusion of data from the year 2016. Additionally, the GBD Compare Viz Hub website offers an interactive tool for data visualization, enabling users to independently explore and analyze the results. The data presented in this study includes absolute numbers and age-standardized rates, which are adjusted to the age distribution of the global population. This adjustment allows for comparisons to be made across different populations and over time. The variables examined in this study include deaths, DALYs, incidence, and prevalence, all of which are measured per 100,000 individuals. The data specifically pertains to neurological disorders and is based on the year 2016. The confidence interval, representing a 95% level of confidence, is provided alongside each GBD estimate to indicate the plausible range of values within which the true estimation of health

loss for a particular cause is likely to fall. Estimates of neurological burden are derived by extrapolating data from countries with similar etiology in cases where primary data is not accessible.

The accuracy of estimations plays a crucial role in influencing policy and research funding decisions at the global, regional, or national level based on the findings of the GBD. The implications of these findings can be observed in various domains, such as population-wide prevention measures, social development objectives, health-care service planning, and workforce development. For example, the utilization of absolute figures can be employed to approximate the requisite quantity of community services and hospital beds obligatory to provide adequate patient care diagnosed with neurological illnesses. This estimation can be conducted on both a collective level and for specific disorders on an individual basis.

The incidence, prevalence, and fatality rates of non-communicable neurological illnesses, alongside their alliedDALYs, have experienced a notable rise. This is in spite of a decline in age-adjusted rates of prevalence, incidence, mortality, as well as DALYs for all neurological illnesses examined between 1990 and 2016. A significant proportion of fatalities (78.5%) and DALYs (77.3%) are disproportionately concentrated in low- and middle-income countries (LMICs). In the year 2016, neurological diseases were responsible for the second highest number of deaths, totaling 9.0 million (with a 95% uncertainty interval of 8.8-9.4 million), and the highest number of DALYs, amounting to 276 million (with a 95% uncertainty interval of 247-308 million) globally [14].

The observed reduction of age-standard DALYs and rates of death from 1990 through 2016 can be attributed to advancements in the management and prevention of stroke and communicable neurological illnesses. Low- and middle-income countries (LMICs) exhibited comparatively slower rates of decline in comparison to high-income countries (HICs), thereby underscoring regional discrepancies in the magnitude, accessibility, scope, and efficacy of preventive involvements. The incidence and prevalence of noncommunicable neurological illnesses have indicated an upward trend, indicating that current efforts in prevention and management have not adequately addressed the challenges posed by population growth and aging. The significant increase in the prevalence of non-communicable neurological diseases is widely attributed to global demographic changes. However, it is worth noting that enhanced case identification and reporting methods implemented over the past three decades may also play a role in this trend.

Decision-makers often assess the effects of various injuries and diseases by considering not only the number of premature deaths they cause, but also the extent of suffering they inflict. To quantify this impact, they rely on DALYs, which serve as the principal metric in Global Burden of Disease (GBD) research. According to the data presented in **Fig. 5**, stroke accounted for the highest proportion of Disability-Adjusted Life Years (DALYs) at 42.2%. This was followed by migraine at 16.3%, meningitis at 7.9%, AD and other dementias at 10.4%. These findings indicate that these particular health conditions were the primary contributors to the burden of disease in terms of DALYs. The occurrence and impact of AD, headaches, multiple sclerosis, and other dementias were found to be more prevalent among women compared to men. The ratio of male to female ranged from approximately 0.54 (95% uncertainty interval (UI) 0.53 to 0.56) for migraine to about 0.90 (0.88 to 0.92) for other neurological disorders. However, when considering all neurological disorders together, the combined rate of DALYs in 2016 was notably more in males compared to females. The global distribution of the three primary neurological causal factors of death, namely AD and other dementias (20.3%), meningitis (3.7%), and stroke (66.4%), is illustrated in **Fig 5**.

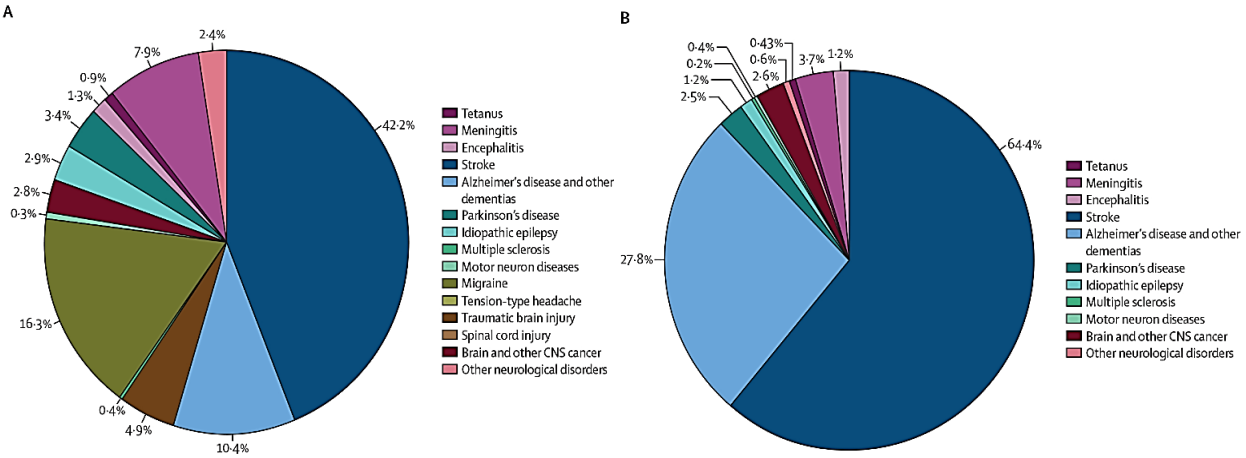

Fig 5. Comparative influence of specific neurological conditions on the overall burden of neurological disease. The measurement of disabled life-years (A) and overall deaths (B) expressed as a percentage.

The occurrence of neurological diseases exhibited considerable variation across different age groups. For example, while common communicable neurological illnesses, mostly meningitis, were the primary factors contributing to neurological DALYs in young children, migraine and tension-type headache made notable contributions among individuals in the younger and middle age groups. The highest occurrence rate of stroke was observed within the age range of 60 to 84, while the highest occurrence rate of AD and other dementia was observed within the age range of 85 to 95. Murthy and S. Prabhakar [15]found that there was a higher prevalence of stroke, epilepsy, and meningitis in parts with low

degrees of socio-economic developed, as evaluated by the SDI (sociodemographic index). This was reflected in the age-standardized DALY rates, showing the burden of these diseases in these areas. There was a positive correlation observed between the rise in SDI and the increase in DALY rates for brain and other central nervous system malignancies, Parkinson's disease, motor neuron illnesses, and multiple sclerosis. However, no significant associations were found between the SDI increase and the occurrence of AD and other types dementias, including tension-type headaches, and migraine.

IV. CHALLENGES AND OPPORTUNITIES OF FUTURE RESEARCH

The evaluation of brain health, comprehension of the underlying approaches of the brain function; including its dysfunction and the formulation of strategies to enhance brain health have distinct opportunities and challenges. The definition and promotion of optimal brain health necessitate scientific evaluation. Given its complex and multifaceted characteristics, the assessment and quantification of brain health using a singular indicator is widely recognized as a challenging endeavor. The assessment of one's own abilities or the evaluation of the functional capacities of immediate family members is a prevalent approach in measuring cognitive well-being.

To this end, numerous questionnaires, both structured and semi-structured, have been developed. In recent decades, there has been a notable utilization of advanced structural and functional neuroimaging techniques in the examination of functional connectivity and brain network integrity. The utilization of objective or subjective metrics presents both advantages and disadvantages. For example, scales like the Montreal cognitive evaluation and the mini-mental state evaluation are straightforward and convenient to administer. However, their primary purpose is to serve as broad screening equipment for cognitive impairments. Contrarily, tests like digit span, trail making A and B, Rey-Osterrieth complex figure test, verbal fluency test, clock drawing test, Stroop task, and Boston naming test, are major utilized to assess particular memory domains, visuospatial abilities, language, executive functions, and attention.

The optimal brain health perception is subject to variation based on factors such as age, culture, ethnicity, and geographical location, thereby introducing an additional level of intricacy to the process of measuring brain health. Patient-centered assessments of brain health, like self-report measures of quality of life and cognitive ability, has to be visualized in conjunction with conventional clinical assessments. There is a requirement for universally accepted, multidimensional, age-appropriate, interdisciplinary, and sensitive methodologies or metrics to systematically track and assess brain health and brain function.

In order to enhance individuals' mental well-being, it is imperative to undertake further investigation into the intricacies of brain functionality and dysfunction. Unfortunately, there exists a limited understanding regarding the true functioning of the brain. Despite considerable advancements in neuroscience in recent years, the precise relationship between concepts, an individual's cognitive and mental state, and the spatiotemporal patterns of activity within interconnected neural networks remains an enigma. The advent of brain modeling and artificial intelligence in recent years has emerged as a pivotal tool for investigating biological brains. Zheng, Yang, Sun, Liu, Wang, and Zou [16]have prioritized the advancement of brain-inspired computing, brain simulation, and intelligent technologies.However, the understanding of the underlying mechanisms responsible for brain dysfunction, especially in the context of neurodegenerative and mental disorders remains limited. More research into the etiology of neurological disorders has the potential to yield novel therapeutic interventions and augment cognitive functioning. Cognitive neuroscience, which utilizes brain imaging techniques, has the potential to elucidate the neural underpinnings of cognitive dysfunction and establish a solid scientific framework for the development of precise biomarkers pertaining to mental health conditions.

The aetiopathologies commonly observed in prevalent neurological disorders, such as Alzheimer's disease and cerebrovascular diseases; often involve complex interactions between genetic and environmental factors in both spatial and temporal dimensions. Nevertheless, the progression of illness in monogenic neurological disorders can be elucidated by a solitary genetic element. The utilization of simplified cross-species modeling has the potential to enhance research efforts pertaining to these disorders, thereby enabling a more profound understanding of the fundamental causes and expediting the assessment of potential therapeutic interventions. Belkacem, Jamil, Khalid, and Alnajjar [17]have previously emphasized the potential of this research direction to provide novel opportunities for investigating prevalent neurological disorders and gaining a broader understanding of the human brain.

Certain neurological disorders, such as dementia, present limited viable interventions for the prevention or management of cognitive impairment. The regeneration of neurons is currently deemed unattainable, and any impairment to the brain is considered irreversible. The recent studies conducted with the objective of improving cognitive function and slowing disease advancement in people with mild AD based on the amyloid clearance and targeted inhibition of tau protein combination did not yield positive outcomes. Čoma, Manning, Kaltner, and Gál [18]underscore the shift in recent research focus towards alternative therapeutic targets, including inflammation, vascular dysfunction, and the gut microbiota. In this particular case, recent research has demonstrated that the neurovascular unit integrity disruption leads to early cognitive impairment. This impairment, in turn, could contribute to hypoperfusion, collapse of the BBB (blood-brain barrier), and impaired clearance of proteins within the brain.

The six fundamental components of brain health encompass physical exercise, cognitive stimulation, a well-balanced diet and optimal nutrition, active social involvement, relaxation and sufficient sleep, effective management of vascular risk elements, and the mitigation of stress. The presidential advice from the American Stroke Association and the American Heart Association emphasized the significance of observingtheAmerican Heart Association Life's seven guidelines in

order to safeguard cognitive function. These guidelines encompass abstaining from smoking, participating in regular physical exercise, consuming a nutritious diet, sustaining a healthy body mass index, and maintaining optimal levels of blood pressure, total cholesterol, and glucose.Namakin et al. [19] postulate that this phenomenon could potentially mark the advent of a novel era characterized by the amelioration of cognitive impairment and brain dysfunction through the eradication of vascular risk factors and other conditions affecting cerebral blood vessels.

The principal objective of therapeutic interventions for diverse neurological disorders is to sustain brain functionality. Individuals suffering from neurosurgical conditions, such as brain tumors, trauma, and epilepsy, frequently experience compromised cognitive abilities due to structural damage within the brain. However, this impairment is often overlooked or underestimated. In recent years, there has been a notable shift in the objective of neurosurgical therapy, transitioning from a primary focus on extending life expectancy to a renewed emphasis on the restoration of normal brain structure and function. Gaining a comprehensive comprehension of the complex interplay between brain structure and function, as well as employing state-of-the-art technology to visualize the interactions between brain structure and function, are imperative for the accurate preservation of brain functionality.

The issue pertaining to safeguarding brain function is further exemplified by the presence of uncertainty in the therapeutic response within the context of epilepsy treatment. The current approach to managing epilepsy involves a systematic method of experimentation, wherein various anticonvulsant medications are administered sequentially in order to determine the most effective treatment. The concern arises from the potential for reduced efficacy of treatments and the risk of enduring damage due to the temporal delay resulting from the implementation of this approach. Recent advancements in personalized epilepsy management, utilizing genomics, artificial intelligence, and patient-based stem cells, have presented a potential solution to the perplexing challenges in epilepsy therapy. Volarevic et al. [20] have extensively discussed these breakthroughs, offering a glimmer of hope for resolving this conundrum.

V. CONCLUSION

The concept of “brain health” pertains to the maintenance of various aspects of cognitive function. However, it is important to note that several neurological disorders have the potential to impact brain health to some extent. The comprehension and enhancement of brain health will yield extensive implications for the disciplines of medicine, science, and culture. In the previous seven years, numerous international endeavors have been undertaken to promote the progress of brain modeling, brain protection, and neuroscience through the allocation of resources and backing of extensive brain health initiatives. Nevertheless, additional challenges arise due to the divergence in research objectives among different countries' brain programs. Many scholars argue that the necessity for collaboration in brain health research is of utmost importance in light of these challenges. The potential of coordinated research to enhance the prognosis of brain illnesses is highlighted in the preceding articles of this series. Brain health alludes to the condition in which there are no apparent neurological abnormalities and the optimal brain integrity preservation, including cognitive and mental health functioning. The natural process of human aging is correlated with the increased occurrence of cognitive decline and neurodegenerative diseases, which in turn contribute to the escalation of healthcare expenditures. Further research is required in the domains of evaluating the health of the brain, comprehending the mechanisms underlying brain dysfunction and function, and identifying effective strategies to enhance the health of the brain.

Data Availability
No data was used to support this study.

Conflicts of Interests
The author(s) declare(s) that they have no conflicts of interest.

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Competing Interests
There are no competing interests.

References

[1]. K. Dempsey, M. Louise McLaws, S. Jain, A. Pantle, and P. Bradd, “77. Australia’s pathway to a national centres for diseases control - Comparing the current infection prevention and control structures,” Infect. Dis. Health, vol. 27, p. S10, 2022.
[2]. T. Hampton, “United States helps establish African centres for disease control and prevention,” JAMA, vol. 313, no. 20, p. 2014, 2015.
[3]. Stroke Council, American Heart Association and American Stroke Association, “Statins after ischemic stroke and transient ischemic attack: an advisory statement from the Stroke Council, American Heart Association and American Stroke Association,” Stroke, vol. 35, no. 4, p. 1023, 2004.
[4]. GBD 2021 Sickle Cell Disease Collaborators, “Global, regional, and national prevalence and mortality burden of sickle cell disease, 2000-2021: a systematic analysis from the Global Burden of Disease Study 2021,” Lancet Haematol., 2023.

[5]. F. M. Kelmendi et al., "Ability of S100B to predict post-concussion syndrome in paediatric patients who present to the emergency department with mild traumatic brain injury," Br. J. Neurosurg., vol. 37, no. 1, pp. 53–58, 2023.
[6]. I. Mavroudis et al., "A review of the most recent clinical and neuropathological criteria for chronic traumatic encephalopathy," Healthcare (Basel), vol. 11, no. 12, 2023.
[7]. F. V. De Los Reyes, University of the East Ramon Magsaysay Memorial Medical Center, Quezon City, and C. Villamayor, "Comparing differential gene expression in chronic traumatic encephalopathy, Parkinson's disease, and bipolar disorder," Philipp. J. Pathol., vol. 5, no. 1, pp. 30–37, 2020.
[8]. Tang et al., "Inhibitive and destructive mechanisms of chronic traumatic encephalopathy-related R3-R4 tau peptide chains and protofibril by epigallocatechingallate: Evidence from molecular dynamics simulation," ACS Chem. Neurosci., vol. 14, no. 11, pp. 2098–2111, 2023.
[9]. L. Mărginean et al., "CT in the differentiation of gliomas from brain metastases: The radiomics analysis of the peritumoral zone," Brain Sci., vol. 12, no. 1, p. 109, 2022.
[10]. J. F. Uleman et al., "Simulating the multicausality of Alzheimer's disease with system dynamics," Alzheimers. Dement., vol. 19, no. 6, pp. 2633–2654, 2023.
[11]. "Abuse of older people," Who.int. [Online]. Available: https://www.who.int/news-room/fact-sheets/detail/abuse-of-older-people. [Accessed: 01-Jul-2023].
[12]. Y. Zhan et al., "Disability adjusted life years-oriented assessment of Cryptosporidium parvum inactivation with a Point-of-Use ozonation system," Environ. Technol. Innov., vol. 30, no. 103079, p. 103079, 2023.
[13]. Global Burden of Disease 2016 Greece Collaborators, "The burden of disease in Greece, health loss, risk factors, and health financing, 2000-16: an analysis of the Global Burden of Disease Study 2016," Lancet Public Health, vol. 3, no. 8, pp. e395–e406, 2018.
[14]. M. Amini, F. Zayeri, and M. Salehi, "Trend analysis of cardiovascular disease mortality, incidence, and mortality-to-incidence ratio: results from global burden of disease study 2017," BMC Public Health, vol. 21, no. 1, p. 401, 2021.
[15]. J. M. K. Murthy and S. Prabhakar, "Bacterial meningitis and epilepsy," Epilepsia, vol. 49 Suppl 6, pp. 8–12, 2008.
[16]. T. Zheng, W. Yang, J. Sun, Z. Liu, K. Wang, and X. Zou, "Processing IMU action recognition based on brain-inspired computing with microfabricated MEMS resonators," Neuromorph. Comput. Eng., vol. 2, no. 2, p. 024004, 2022.
[17]. A. N. Belkacem, N. Jamil, S. Khalid, and F. Alnajjar, "On closed-loop brain stimulation systems for improving the quality of life of patients with neurological disorders," Front. Hum. Neurosci., vol. 17, p. 1085173, 2023.
[18]. M. Čoma, J. C. Manning, H. Kaltner, and P. Gál, "The sweet side of wound healing: galectins as promising therapeutic targets in hemostasis, inflammation, proliferation, and maturation/remodeling," Expert Opin. Ther. Targets, vol. 27, no. 1, pp. 41–53, 2023.
[19]. K. Namakin et al., "Elderberry diet improves gut-brain axis dysfunction, neuroinflammation, and cognitive impairment in the rat model of irritable bowel syndrome," Metab. Brain Dis., vol. 38, no. 5, pp. 1555–1572, 2023.
[20]. V. Volarevic et al., "Ethical and safety issues of stem cell-based therapy," Int. J. Med. Sci., vol. 15, no. 1, pp. 36–45, 2018.