Brain Health
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What is brain health and why is it important?

Yongjun Wang and colleagues discuss the definition of brain health and the opportunities and challenges of future research

The human brain is the command centre for the nervous system and enables thoughts, memory, movement, and emotions by a complex function that is the highest product of biological evolution. Maintaining a healthy brain during one’s life is the uppermost goal in pursuing health and longevity. As the population ages, the burden of neurological disorders and challenges for the preservation of brain health increase. It is therefore vital to understand what brain health is and why it is important. This article is the first in a series that aims to define brain health, analyse the effect of major neurological disorders on brain health, and discuss how these disorders might be treated and prevented.

Definition of brain health

Currently, there is no universally recognised definition of brain health. Most existing definitions have only a general description of normal brain function or emphasise one or two dimensions of brain health. The US Centers for Disease Control and Prevention defined brain health as an ability to perform all the mental processes of cognition, including the ability to learn and judge, use language, and remember. The American Heart Association/American Stroke Association (AHA/ASA) presidential advisory defined optimal brain health as “average performance levels among all people at that age who are free of known brain or other organ system diseases in terms of decline from function levels, or as adequacy to perform all activities that the individual wishes to undertake.”

The brain is a complex organ and has at least three levels of functions that affect all aspects of our daily lives: interpretation of senses and control of movement; maintenance of cognitive, mental, and emotional processes; and maintenance of normal behaviour and social cognition. Brain health may therefore be defined as the preservation of optimal brain integrity and mental and cognitive function at a given age in the absence of overt brain diseases that affect normal brain function.

Effect of major neurological disorders on brain health

Several neurological disorders may disrupt brain function and affect humans’ health. Medically, neurological disorders that cause brain dysfunction can be classified into three groups:

- Brain diseases with overt damage to brain structures, such as cerebrovascular diseases, traumatic brain injury, brain tumours, meningitis, and communication and sensory disorders
- Functional brain disorders with detectable destruction of brain connections or networks, such as neurodegenerative diseases (eg, Parkinson’s disease, Alzheimer’s disease, and other demen- tias) and mental disorders (eg, schizophrenia, depression, bipolar disorder, alcoholism, and drug abuse)
- Other brain disorders without detectable structural or functional impairment, such as migraine and sleep disorders

These neurological disorders may have different or common effects on brain health and function. For instance, Alzheimer’s disease is the main type of dementia, with a decline in different domains of cognitive function. Mood disorders may cause dysfunction in execution, reward processing, and emotional regulations. In addition to physical disability, aphasia, gait and balance problems, and cerebrovascular diseases may lead to cognitive impairment and dementia, which are neglected by both patients and physicians.

Ageing and burden of neurological disorders

Human ageing is mainly reflected in the aspects of brain ageing and degradation of brain function. The number of people aged 60 years and over worldwide was around 900 million in 2015 and is expected to grow to two billion by 2050. With the increases in population ageing and growth, the burden of neurological disorders and challenges to the preservation of brain health steeply increase. People with neurological disorders will have physical disability, cognitive or mental disorders, and social dysfunction and be a large economic burden.

Globally, neurological disorders were the leading cause of disability adjusted life years (276 million) and the second leading cause of death (9 million) in 2016, according to the Global Burden of Diseases study. Stroke, migraine, Alzheimer’s disease and other dementias, and meningitis are the largest contributors to neurological disability adjusted life years. About one in four adults will have a stroke in their lifetime, from the age of 25 years onwards. Roughly 50 million people worldwide were living with dementia in 2018, and the number will more than triple to 152 million by 2050. In the following decades, governments will face increasing demand for treatment, rehabilitation, and support services for neurological disorders.

Opportunities and challenges of future research on brain health

Opportunities and challenges exist in the assessment of brain health, the mechanism of brain function and dysfunction, and approaches to promote brain health (box 1).

Defining and promoting optimal brain health require the scientific evaluation of brain health. However, it is difficult to comprehensively evaluate or quantify brain health through one metric owing to the multidimensional aspects of brain health. Many structured or semistructured questionnaires have been developed to test brain health by self-assessments or close family member assessments of daily function or abilities. In recent decades new structural and functional neuroimaging techniques have been applied to evaluate brain network integrity and functional
Brain health is that age, culture, ethnicity, and connectivity. However, these subjective or objective measures have both strengths and weaknesses. For instance, scales such as the mini-mental state examination and Montreal cognitive assessment are simple and easy to implement but are used only as global screening tools for cognitive impairment; tests such as the digit span, Rey-Osterrieth complex figure test, trail making A and B, Stroop task, verbal fluency test, Boston naming test, and clock drawing test are used mainly to assess one or two specific domains of memory, language, visuospatial, attention, and executive function; and neuroimaging techniques, although non-invasive and objective, still have disadvantages of test contraindications, insufficient temporal or spatial resolution, motion artefact, and high false discovery rates, which limit their clinical transformation.

Another difficulty in measuring brain health is that age, culture, ethnicity, and geography specific variations exist in the perception of optimal brain health. Patient centred assessment of brain function, such as self-perception of cognitive function and quality of life, should also be considered when measuring brain health. Universal acceptable, age appropriate, multidimensional, multidisciplinary, and sensitive metrics or tools are required to comprehensively measure and monitor brain function and brain health.

To promote optimal brain health, we need a better understanding of the mechanisms of brain function and dysfunction. Unfortunately, little is known about the working mechanism of the brain. Although we have made considerable developments in neuroscience in recent decades, we still cannot totally decipher the relations between spatiotemporal patterns of activity across the interconnected networks of neurons and thoughts or the cognitive and mental state of a person. Recent progress in brain simulation and artificial intelligence provides a vital tool to understand biological brains, and vice versa. The development of brain inspired computation, brain simulation, and intelligent machines was emphasised in the European Union and China Brain Project. Meanwhile, the mechanisms behind the brain dysfunction in some neurological disorders are still not well understood, especially for mental and neurodegenerative disorders. Further investigation of the mechanisms of brain diseases may indicate approaches to treatment and improve brain function. Brain imaging based cognitive neuroscience may unravel the underlying brain mechanism of cognitive dysfunction and provide an avenue to develop a biological framework for precision biomarkers of mood disorders.

Most common neurological diseases, such as cerebrovascular diseases and Alzheimer’s disease, have complex aetiopathologies, typically involving spatial-temporal interactions of genetic and environmental factors. However, a single genetic factor could account for the disease progression of monogenic neurological disorders. These diseases could be more readily investigated by simplified cross species modelling, leading to better understanding of their mechanisms and greater efficiency in testing innovative therapies. Such research may provide a window to promote the investigation of common neurological disorders and general brain health, as discussed by Chen and colleagues elsewhere in this series.

Few effective approaches are available to prevent and treat brain dysfunction in some major neurological disorders, such as dementia. Neurons are not renewable, and brain dysfunction is always irreversible. Recent trials targeting amyloid clearance and the selective inhibition of tau protein aggregation failed to improve cognition or modify disease progression in patients with mild Alzheimer’s disease. More attention has focused on other potential therapeutic targets, such as vascular dysfunction, inflammation, and the gut microbiome, as discussed by Shi and colleagues. In particular, recent studies showed that the early impairment of cognition was induced by the disruption of neurovascular unit integrity, which may cause hypoperfusion and the breakdown of the blood-brain barrier and subsequent impairment in the clearance of proteins in the brain. Physical activity, mental exercise, a healthy diet and nutrition, social interaction, ample sleep and relaxation, and control of vascular risk factors are considered six pillars of brain health. The AHA/ASA presidential advisory recommended the AHA’s Life’s Simple 7 (non-smoking, physical activity, healthy diet, appropriate body mass index, blood pressure, total cholesterol, and blood glucose) to maintain optimal brain health.

Pan and colleagues discuss how this may indicate a new dawn of preventing some cognitive impairment and brain dysfunction by preventing vascular risk factors or cerebrovascular diseases. For other neurological disorders with potential therapeutic approaches, the main aim is to preserve brain function. Impaired brain function due to anatomical structural damage is underestimated in patients with neurosurgical diseases such as brain tumours, trauma, and epilepsy. In recent years, treatment targets for neurosurgical diseases have changed from focusing on survival or life expectancy to balancing brain structures and functions. Precise preservation of brain function requires an understanding of the exquisite relation between brain structure and function and advanced technologies to visualise brain structure-function relations.

Another example of the predicament associated with protection of brain function is uncertainty in the treatment response in epilepsy management. Current standard care for epilepsy relies on a trial and error approach of sequential regimens of antiseizure medications. The time delay due to this treatment approach means that such treatments may be less effective and irreversible damage may occur. Chen and colleagues describe how recent advances in personalised epilepsy management based on artificial intelligence, genomics, and patient derived stem cells are bringing some hope to overcome this predicament in epilepsy management and promise a more effective strategy.

Brain health is the maintenance of multidimensional aspects of brain function. However, several neurological disorders may affect brain health in one or more aspects of brain function. Deciphering and promoting the function and health of the brain, the most mysterious organ in the human body, will have a dramatic impact on science, medicine, and society. In the past seven years, a number of large scale brain health initiatives have been launched in several countries to promote the development.
of neuroscience, brain simulation, and brain protection. However, further challenges are raised by the different key research directions of brain projects in different countries. In the face of these challenges, Liu and colleagues argue that collaboration on brain health research is urgently needed. As the other articles in this series describe, coordinated research has enormous potential to improve the prognosis of brain disorders.

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Alzheimer’s disease beyond amyloid: strategies for future therapeutic interventions

Jiong Shi and colleagues discuss recent evidence of clinical trials for Alzheimer’s disease and new development strategies

Neurodegenerative diseases encompass a variety of medical conditions that affect the survival and function of neurons in the brain. Neuronal loss often results in a decline of cognitive function and advances to dementia. Dementia is the common denominator of neurodegenerative diseases. The World Health Organization estimated that the number of people living with dementia worldwide in 2015 was 47.47 million. As the population ages, this number is expected to reach 75.63 million in 2030 and 135.46 million in 2050. Alzheimer’s disease is the most common cause of dementia in older people. The natural course of dementia, particularly Alzheimer’s disease, results in significant disability and dependence. The effect on care givers and the public health system is staggering. The total estimated costs of dementia were $604bn (€471bn; £519bn) in 2010, roughly 1% of the world’s gross domestic product (www.who.int). No disease modifying treatment exists for dementia.

Pathology
Alzheimer’s disease is characterised by progressive memory decline and deficits in at least one other cognitive domain that significantly impairs normal occupational and social function. Pathologically, in addition to neuronal and synaptic loss, the disease is defined by pathological hallmarks—namely, amyloid β accumulation as diffuse and neuritic plaques and hyperphosphorylated tau protein in the form of neurofibrillary tangles.

Amloid β peptide was first sequenced in 1984 and later identified as the main component of neuritic plaques. Amyloid β is a product of the larger transmembrane amyloid precursor protein. Acting together, β-secretase and γ-secretase break down and slice amyloid precursor protein into smaller fragments. Amyloid β monomers are formed by backbone hydrogen bonds between their β strands. These monomers are prone to misfolding and are considered critical to the neurodegenerative process. The misfolded proteins trigger production of further misfolded proteins, which accumulate into aggregates or plaques.

Human genetic studies on autosomal dominant early onset familial Alzheimer’s disease have shown that mutations in one of the three genes encoding amyloid precursor protein, presenilin 1, or presenilin 2 result in increased production of amyloid β. Apolipoprotein E ε4 allele is the strongest genetic risk factor for late onset sporadic Alzheimer’s disease. It increases the risk of the disease by three to four times in heterozygotes and by around 12 times in homozygotes. The apolipoprotein E ε4 allele has been shown to reduce the clearance, and increase the seeding, of amyloid β. These data from human genetic studies led to the hypothesis of the amyloid cascade. Evidence from transgenic amyloid β mouse models provided mechanistic support for the hypothesis, in which amyloid β accumulation is the critical initial step in the pathogenesis of Alzheimer’s disease. Amyloid β triggers subsequent hyperphosphorylation and accumulation of tau protein, neuronal and synaptic loss, and, ultimately, results in clinical symptoms.

Additionally, Alzheimer’s disease is a tauopathy as shown by abnormal levels of hyperphosphorylated tau protein. The pathological aggregation of these proteins lead to neurofibrillary tangles. The non-pathological tau protein is involved in stabilising microtubules, which make up the cytoskeleton of the cell. When the tau protein is hyperphosphorylated, it induces the breakdown of microtubules and the formation of insoluble aggregates of neurofibrillary tangles in the brain.

In Alzheimer’s disease, neurofibrillary tangles emerge from the internal brain structures to more distal regions—namely, from the transenthorinal cortex to the hippocampus and then the neocortex. Cognitive impairment is evident only after tau pathology manifests in the neocortex. In contrast to amyloid β, tau pathology has shown a strong correlation with declining cognitive performance based on longitudinal pathological and imaging studies.

Pathological hallmark targeted clinical trials for Alzheimer’s disease
During the past two decades, treatments targeting amyloid β have been designed to lower amyloid β concentrations and prevent the amyloid β triggered cascade. Several compounds have been developed to target various forms of amyloid β, monomeric, oligomeric, aggregates, and plaques. The initial trial (AN1792) attempted to achieve active immunisation by injections of a full length amyloid β peptide in patients with Alzheimer’s disease. This study was terminated early owing to complications of encephalomeningitis. Additional treatments were designed to increase amyloid β clearance from the brain, including inoculations with amyloid β antigens (ABvac40, CAD-106), anti-amyloid β monoclonal antibodies (bapineuzumab, solanezumab, ...
and crenezumab), and anti-amyloid β polyclonal antibodies (immunoglobulins). Trials to decrease the production and aggregation of amyloid β included amyloid β aggregation inhibitors (traminostat, scyllo-inositol, PBT2), γ-secretase inhibitors (avagacestat and semagacestat), γ-secretase modulators (tarenflurbil), and β site amyloid precursor protein cleaving enzyme inhibitors (LY2886721, umibecestat, elenbecestat, verubecestat, atabacestat, and lanabecestat). No clinical efficacy was shown in any of these studies. The β site amyloid precursor protein cleaving enzyme inhibitors worsened cognitive function, probably because they have other functions critical to neuronal development. Furthermore, the use of γ-secretase inhibitors caused adverse effects because of their function on Notch signalling pathways.

Recognition of the clinical significance of tau pathology in comparison with amyloid β has resulted in a resurgence of interest in targeting tau protein. Treatments designed to inhibit production of phosphorylated tau protein have been investigated. Leucotox-methylthioninium (hydromethanesulphonate) is a methylene blue derivative that reduces fibrillation and aggregation of tau protein. Tidiglutirib is a glycogen synthase kinase 3 inhibitor that blocks tau kinase and thus the abnormal hyperphosphorylation of tau protein. Neither of these treatments was found to be clinically efficacious. Immunotherapies targeting tau protein (AADVac-1, ACI-35, BIIB092, and ABBV-8E12) are currently in phase II trials for patients with early Alzheimer’s disease.15 ABBV-8E12 has already been studied in patients with progressive supranuclear palsy. Progressive supranuclear palsy is considered a “pure” tauopathy because it has abundant tau pathology but lacks amyloid pathology. This study of progressive supranuclear palsy was terminated early owing to inefficacy.

Analysis of clinical trials targeting biomarkers
Several reasons have been proposed for the lack of efficacy of pathology targeted treatment in clinical trials. Firstly, it has been suggested that the dose used to affect the disease could be inadequate or result in unacceptable adverse effects. One of the earliest clinical trials (AN1792) was effective in reducing amyloid β concentrations in the brain. Unacceptable levels of encephalomingitis developed, however, and the trial was terminated. This set the tone for future investigations, and subsequent trials focusing on amyloid β immune treatments have used doses to minimise the adverse effects rather than maximise the benefits. Many trial regimens were terminated early as a precaution when there was evidence of inflammatory changes or microhaemorrhages in the brain, although some argued that this could have been early evidence of the immunotherapy efficacy rather than a risk of future encephalitis. Additionally, the human blood-brain barrier is much more discriminating than that of lower species. Therefore, higher concentrations may be required to achieve the therapeutic effect seen in animal models. For instance, solanezumab penetration into the central nervous system is only 0.1% to 0.3% of the concentration measured in plasma. Aducanumab and gantenerumab showed a better and more clinically meaningful outcome when higher doses were used.14

Secondly, considerable controversy exists about the stage at which Alzheimer’s disease is reversible. Most of the failed phase III trials enrolled patients with mild to moderate disease. Longitudinal clinical imaging/pathological correlation studies have disclosed a preclinical phase of Alzheimer’s disease that precedes the onset of symptoms by a couple of decades.16 It has been hypothesised that the onset of pathological deposition is the time when the disease may be amenable to immune treatments. Thus several large scale prevention trials, such as the Anti-Amyloid Treatment in Asymptomatic Alzheimer’s (A4) trial, Alzheimer Prevention Initiative (API), and the Dominantly Inherited Alzheimer Network Trial (DIAN-TU), were designed to capture patients in the presymptomatic stage. These clinical trials test anti-amyloid treatments in cognitively normal patients who are at high risk for developing Alzheimer’s disease.

Thirdly, amyloid β and tau protein may synergistically and simultaneously cause pathological changes in Alzheimer’s disease. Amyloid β enhances phosphorylation, truncation, and aggregation of tau protein, whereas tau protein further induces the production of amyloid β species. The effective suppression of only one of these two factors is probably insufficient to produce a clinical benefit. Thus an approach targeting them simultaneously or sequentially may be necessary to affect the course of the disease.

Finally, although the amyloid hypothesis and tau pathology are supported by considerable genetic and biomarker studies, the data from failed clinical trials suggest that other potential targets should be explored.

Non-biomarker targets
In most patients, Alzheimer’s disease is late onset, and the most common risk factor for Alzheimer’s disease is ageing. Ageing in the industrialised world is associated with cardiovascular and cerebrovascular diseases, as well as an increased incidence of risk factors such as hyperlipidaemia, hypertension, hyperhomocysteinaemia, and diabetes mellitus. Autopsy studies have shown that more than half of patients with Alzheimer’s disease have mixed vascular pathology. Amyloid β generates reactive oxygen species, which cause capillary constriction in the human cortex, resulting in reduced cerebral blood flow. Hypoxia can also increase amyloid β production, thus generating a vicious cycle. Vascular impairment can ultimately lead to hypoperfusion, oxidative stress, inflammation, and dysfunction of the neurovascular unit. The Finnish Geriatric Intervention Study to Prevent Cognitive Impairment and Disability (FINGER) focused on the treatment of modifiable vascular and lifestyle related risk factors. The intervention was effective in reducing the risk of cognitive decline. Similarly, the Multidomain Alzheimer Preventive Trial (MAPT) has shown that a multidomain intervention alone or in combination with omega-3 fatty acids improved cognitive outcome in subjects with positive amyloid status.17 The validity of these results will be further tested by the worldwide FINGERS network, which shares core methodology with consideration of local culture and adaptations. Hyperhomocysteinaemia is a modifiable risk factor for cognitive impairment. The relative risk of dementia is up to 2.5 in older people with moderately raised homocysteine. Homocysteine lowering treatment with B vitamins could slow down the rate of brain atrophy and cognitive decline.17

The role of inflammation, also significant in cerebrovascular disease and ageing, has been studied for its effect on Alzheimer’s disease. Systemic inflammatory markers such as C reactive protein and interleukin 6 are associated with neuronal and synaptic loss and poor cognitive performance in older people.18 However, anti-inflammatory treatment, including low dose prednisone, low dose aspirin,
non-steroidal anti-inflammatory drugs, selective cyclo-oxygenase-2 inhibitors, and etanercept, has failed to show clinical efficacy in patients with mild to moderate and preclinical Alzheimer’s disease. One explanation for the lack of efficacy of systemic anti-inflammatory agents could be their poor penetration across the blood-brain barrier. In the central nervous system, there is a growing body of evidence linking the role of immunogenicity to pathology and the clinical manifestations of Alzheimer’s disease.

Whole genome analysis studies have disclosed the evidence leading to clinical trials. They identified several immune related genetic risk factors which may contribute to the inflammatory process and increased cytokine production in Alzheimer’s disease, including triggering receptor expressed on myeloid cells 2 (TREM2) and CD33. Both are involved in microglial activation, cytokine production, and inflammation. The TREM2 activating antibody and CD33 blocking antibody are in phase I trials. Although microglial activation is related to the pathology of Alzheimer’s disease, further work is needed to examine the Janus faced effects of microglia and associated cytokines. Furthermore, increasing evidence has shown that interactions between the gut microbiome and the central nervous system innate immune system (gut-brain axis) may be involved in the pathogenesis of Alzheimer’s disease. Microglial activation and function are regulated by the microbiome via microbiome derived metabolites.

Conclusion

Biomarkers for Alzheimer’s disease have been clearly identified yet the disease remains a complex and multifaceted disorder. Few would argue against the value of biomarkers for diagnosis and tracking the course of Alzheimer’s disease. As our understanding of these biomarkers advances, however, the limitation of these signature proteins as targets of treatment also emerges. We have delineated several promising strategies, which may improve the clinical outcome of future trials. Firstly, the use of higher concentrations of monoclonal treatments to adjust for poor penetration of the blood-brain barrier; secondly, early identification and treatment of patients at high risk for Alzheimer’s disease, and targeting treatment at asymptomatic patients with limited biomarker deposition; and finally, the simultaneous or sequential targeting of both biomarkers with monoclonal treatment to determine whether synergy is needed to achieve efficacy. In the meantime, we need to explore promising areas of research that target pathological changes associated with Alzheimer’s disease and affect cognitive performance, such as vascular and inflammatory risk factors. Whether or not these cognitive benefits directly correlate with, or significantly affect, biomarker deposition requires further investigation. Cerebrovascular parameters, which may affect clinical outcome in monoclonal trials, should be evaluated. The combination of cerebrovascular risk modification and monoclonal treatments targeting amyloid β/tau protein could have a therapeutic effect not seen in isolation.

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Precision biomarkers for mood disorders based on brain imaging

Identification of biomarkers could facilitate earlier diagnosis and better treatment, say

Runsen Chen and colleagues

Mood disorders are a global public health problem because of their high prevalence, chronicity, and recurrence throughout the lifespan as well as increased risk of mortality. They also impose a heavy economic burden on society because of lost work productivity (occupational disability) and increased use of health services. Early diagnosis and effective treatment are therefore essential.

Mood disorders are characterised by a significant change in a person’s state of mood and include two main subtypes: depressive disorders (major depressive episode and dysthymia) and bipolar disorders (hypomania, mania, or cyclothymia—that is, cycling between depressive and manic states). In 2015, over 300 million people were living with major depressive disorder worldwide, representing 4.4% of the global population. A world mental health survey reported that the lifetime and 12 month prevalences of bipolar disorders in the general population were 2.4% and 1.5%, respectively.

Mood disorders are associated with a widespread cognitive dysfunction, involving higher-order executive function, reward processing, and emotional regulation (fig 1, box 1). These deficits are associated with abnormalities in both the structure and function of specific brain circuits. Interest is growing in developing precision biomarkers for mood disorders based on a deeper understanding of their biological bases by integrating multilevels of data, such as brain imaging, clinical symptoms, and cognitivebehaviours. Structural and functional magnetic resonance imaging (MRI) can detect subtle deficits in brain structure and function. For example, structural MRI data from more than 20 cohorts worldwide showed that, compared with healthy controls, patients with major depressive disorder had thinner cortical grey matter in the orbitofrontal cortex, cingulate cortex, and insula, while patients with bipolar disorder had thinner cortical grey matter in the left pars opercularis, left fusiform gyrus, and left rostral middle frontal cortex (fig 1).

Using resting state functional MRI (fMRI), Satterthwaite and colleagues found that the severity of major depressive disorder was associated with diminished connectivity between the amygdala and frontal areas, including both the dorsolateral prefrontal cortices and anterior cingulate cortex. Studies using task based fMRI showed that patients with mood disorders exhibited atypical neural responses to emotional processing in the medial prefrontal cortex, amygdala, and insula, as well as decreased neural responses to emotional regulation in the dorsolateral prefrontal cortex. Multimodal brain imaging therefore offers the potential to identify biomarkers for mood disorders that could improve diagnosis and treatment.

Diagnostic confusion
Current diagnostic systems, including the Diagnostic and Statistical Manual of Mental Disorder and International Classification of Diseases, were developed based on clinical symptoms and signs. The acquired diagnostic categories do not align with the underlying psychopathology or predict treatment response. The diagnostic categories of major depressive disorder and bipolar disorder, for example, share many clinical symptoms, while patients with these diagnoses present with heterogeneous symptoms.

Clinical symptoms may be shared across mood disorders or with psychiatric disorders. For example, major depressive disorder is commonly associated with anxiety symptoms, but these also occur in bipolar disorder and schizophrenia. Recent studies have used brain imaging and transdiagnostic approaches to characterise the neural basis of the shared symptoms. Resting state fMRI data showed that patients with major depressive disorder, bipolar disorder, and schizophrenia had common brain functional deficits. More generally, recent studies proposed a general psychopathology factor (p factor) to describe a shared vulnerability to a broad range of symptoms across mental disorders, and a higher p factor was associated with diminished activation of the frontal pole, anterior cingulate cortex, and anterior insula during executive tasks. The imbalance in these brain circuits is believed to confer vulnerability to mood disorders as well as other mental disorders, which could be the underlying mechanism of the shared symptoms. Other specific brain circuits related to factors such as anhedonia may therefore give rise to specific diagnoses such as major depressive disorder.

Heterogeneity is also a problem in the current diagnostic system. Mood disorders are increasingly viewed not as a unitary disease but as a heterogeneous clinical syndrome that encompasses multiple subtypes with distinct pathophysiological deficits. Interest is therefore growing in parsing the neurobiological heterogeneity of mood disorders. Drysdale and colleagues subdivided major depressive disorder into four discrete biotypes using a clustering approach, each type defined by distinct patterns of dysfunctional connectivity in the limbic and frontostriatal systems. Rather than dividing mood disorders into discrete categories, dimensional approaches are able to parse them into several dimensions using brain imaging, with each dimension representing loadings onto symptoms.
Accurate identification of the time of onset of a disorder is essential for achieving this goal. Clinical symptoms of mood disorders usually begin in youth, with the mean age of onset being 14.9 years for major depressive disorder and 20.2 years for bipolar disorders. Therefore, youth—defined as ranging from childhood to early adulthood—is a critical period for diagnosis and implementation of suitable interventions.

Youth is also a period of considerable brain development, and atypical brain developmental trajectories are related to clinical symptoms and cognitive dysfunction in patients with mood disorders. For example, longitudinal high resolution MRI showed that relative to healthy youths, those with bipolar disorder had a greater grey matter volume contraction and less white matter expansion in the prefrontal cortex during development. Xia and colleagues found that mood symptoms were related to dysconnectivity within the frontoparietal system and the pattern of dysconnectivity was strengthened from childhood to adulthood. Based on these findings, scientists increasingly conceptualise mood disorders as neurodevelopmental disorders. An understanding of the atypical brain development in patients with mood disorders could allow identification of a biologically informed time of onset for mood disorders, which might be earlier than the onset of clinical symptoms.

Dense sampling shows particular promise for precise characterisation of the atypical development of brain functional organisation in patients with mood disorders. Typical fMRI acquisitions last 5-10 minutes, and may be adequate for characterising group average functional organisation. However, such short acquisitions have limited reliability for describing an individual's brain functional organisation in detail. Recent studies have shown individual variations in the topography of brain organisation that are obscured in group level organisation and can only be reliably detected using dense fMRI scanning data. Dense fMRI protocols acquire a much longer time series of fMRI data on one person, which can be acquired by repeated scanning in multiple sessions. Such protocols reveal specific topography details for individuals that are both reliable and reproducible and could be useful in identifying precision biomarkers for mood disorders.

Recently, Cui and colleagues used 27 minute fMRI acquisitions, which is much longer than traditional acquisitions, to show that the topography of brain functional organisation is refined during youth. Such characterisation of typical brain development in youth is a prerequisite for understanding differences in brain development in mood disorders. Results also showed that the individual variation in brain functional organisation predicted executive function, which is typically impaired in mood disorders. These findings suggest that the topography of functional organisation revealed by dense fMRI scanning could be helpful in understanding the atypical neurodevelopmental trajectories of mood disorders. However, dense fMRI scanning data are still lacking for healthy youths as well as for youths with mood disorders.
and the neuroscience and psychiatry communities should concentrate on this effort.

As well as dense fMRI scanning data on individuals, data from large samples are also essential to characterise how mood disorders differ from the typical brain developmental trajectory. The research community has publicly released several youth datasets with large sample sizes, such as the Philadelphia neurodevelopmental cohort (box 2). The Philadelphia cohort includes young people representing a spectrum from a healthy to a diseased state and is therefore a great resource for identification of the time of onset of mood disorders. Future efforts should collect datasets with both a large sample size and dense fMRI scanning to better characterise the time of onset.

**Early biomarkers of treatment outcomes**

Identifying early biomarkers of treatment outcomes is vital for evaluating treatment strategies for mood disorders. A recent theory of antidepressant drug action—the cognitive neuropsychological model—suggests that drugs do not act primarily on mood but rather modify biases in the cognitive processing of emotional information in the brain (fig 2). fMRI has been used to study changes in the brain associated with positive or negative biases in emotional processing that occur when patients with mood disorders and healthy volunteers take antidepressants. For instance, Godlewska and colleagues found that, compared with placebo, treatment with the antidepressant escitalopram for 7 days normalised neural responses in patients with major depressive disorder by reducing the response of the amygdala to negative stimuli (fearful facial expressions). Importantly, the neural changes seen during the early stages of antidepressant treatment were independent of subjective mood changes, suggesting that antidepressant drugs act directly on neural functions that are relevant to major depressive disorder before producing any effects on mood.

Interestingly, studies have consistently shown that antidepressant induced early changes in neural response to emotional processing tasks predict treatment outcomes. A recent study assessed changes in neural response to emotional facial expressions before and after 7 days of treatment with escitalopram in 35 patients with major depressive disorder who had not previously had drug treatment. Based on the criterion of 50% reduction in depressive symptoms at the end of six weeks’ treatment, 22 patients were classified as responders to the treatment and 13 as non-responders. Compared with the non-responders, responders showed decreased neural activity to fearful versus happy faces in the amygdala, insula, anterior and posterior cingulate cortices, bilateral supramarginal gyrus, and thalamus. These results suggest that early changes in neural responses to fearful faces are predictive of clinical response to treatment for major depressive disorder.

Studies of neural responses could therefore be useful in testing the efficacy of novel drugs in both patients and healthy volunteers. Neural responses could also serve as an early biomarker of treatment efficacy and improve understanding of mechanisms of action, including those underlying drugs targeting N-methyl-D-aspartate receptors (such as ketamine). Candidate drugs are typically screened in translation to humans is the main reason for failure in drug development. Ensuring that new drugs affect the core measures of emotional or cognitive function during the early phase of drug development could reduce costs of failed clinical trials. A better understanding of the cognitive neuropsychological effects of psychopharmacological drugs and using neural assessment to predict treatment response may in future allow better patient stratification for mood disorder treatment.

**Conclusion**

Development and validation of precision biomarkers for mood disorders is urgently needed for early diagnosis and treatment evaluation. However, the overlap and heterogeneity in mood disorders impede this progress. Brain imaging, which can detect brain structural and functional changes, is one promising way to solve this problem and identify biomarkers that can cut across different facets of disorders of mood and emotion. This will require a combination of brain imaging, cognitive neuroscience, experimental modelling, and computational techniques (box 3). We encourage the close collaborations between a diverse research community for this endeavour.

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**Box 2: Open access brain developmental datasets in youth**

- Adolescent Brain Cognitive Development: https://abcdstudy.org
- Human Connectome Project Development: https://humanconnectome.org/study/hcp-lifespan-development
- Pediatric Imaging, Neurocognition, and Genetics (PING) Data Repository: http://pingstudy.ucsd.edu/
- Healthy Brain Network Biobank: https://data.healthybrainnetwork.org/main.php
- IMAGEN: http://www.imagen-europe.com/
Box 3: Future directions in precision biomarkers for mood disorders

- Understand the neural substrate underlying shared symptoms using transdiagnostic approach, which cut across the diagnostic categories
- Identify biologically informed biotypes of mood disorder and their distinct brain deficits
- Characterise how the brain development of patients with mood disorders deviates from the typical trajectory in youth
- Use brain imaging data to predict the emergence of patients disorders and treatment outcome
- Advance the cognitive neuropsychological model with improved experimental designs to better evaluate the treatment outcomes of psychopharmacological therapies

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BRAIN HEALTH


A new dawn of preventing dementia by preventing cerebrovascular diseases

Yuesong Pan and colleagues discuss the relation between cerebrovascular diseases and impairment of cognition, with an emphasis on a chance to prevent dementia by preventing cerebrovascular diseases

Cerebrovascular diseases and dementia are two leading contributors to impairment of brain health and neurological disability in older people. The prevalence of these two neurological disorders has increased in recent years as the population has aged and grown. Globally, an estimated 42.4 million cases of stroke occurred in 2015, and approximately 50 million cases of dementia (including Alzheimer’s disease, vascular dementia, and other dementias) occurred in 2018. Strategies for preventing and treating stroke have progressed substantially in recent years, but no effective treatment yet exists for Alzheimer’s disease. Recent studies have shown that many vascular risk factors and unfavourable lifestyle factors are shared predictors of stroke and dementia, and incident cerebrovascular diseases may precipitate a decline in cognitive function or dementia. This suggests that some cognitive impairment and dementia might be prevented by preventing cerebrovascular diseases.

Cognitive impairment in cerebrovascular diseases

Cerebrovascular diseases include a variety of medical conditions that affect the blood vessels of the brain and the cerebral circulation. These include conditions that may cause acute interruption of cerebral circulation and subsequent acute neuronal damage, such as ischaemic or haemorrhagic stroke, and disorders that may cause chronic pathological changes in small vessels and neurological dysfunction, such as cerebral small vessel diseases. Patients with cerebrovascular diseases, both acute and chronic, usually have multidimensional functional impairments to the brain and an increased risk of cognitive impairment and dementia.

Globally, approximately one in four adults will develop stroke in their lifetime from the age of 25 years onwards. Functional impairments to the brain due to stroke vary, but physical disability, aphasia, and dysphagia are common and have received the most attention from stroke specialists to date. However, many patients who survive stroke go on to experience cognitive decline, including vascular cognitive impairment and other dementias, and these aspects have received less attention from either stroke specialists or dementia specialists. This is unfortunate, as incident stroke is associated with an acute decline in cognitive function, especially in global cognition and executive function.

The incidence of post-event dementia at one year in patients with the mildest stroke symptoms (that is, transient ischaemic attack and minor stroke) ranges from 5-8% to 19% but may reach more than 34% in those with severe stroke, nearly 50 times higher than in the general population. Cognitive decline also accelerates and persists over many years, and it could be as high as 44% at three years after a minor stroke and be the main factor preventing independence or return to work.

Another form of cerebrovascular disease that has received less attention from neurological specialists is chronic damage to the small vessels in the brain. The features of cerebral small vessel diseases seen on brain imaging include lacunae, white matter hyperintensity, and cerebral microbleeds, as well as various other features. A population based study showed that more than 70% of people aged 50 years or older presented with at least one kind of cerebral small vessel disease. Cerebral small vessel disease is not fully understood, but it is associated with chronic damage to small vessels that may lead to blockage or leakage of small vessels in the brain. As the chronic damage accumulates, patients with cerebral small vessel disease can present with acute stroke syndromes, mild cognitive impairment or dementia, gait and balance problems, mood disorders, and urinary incontinence, depending on the location of the lesions. Cerebral small vessel disease is one of the most common causes of vascular dementia and is also frequently found alongside Alzheimer’s disease pathology. Cerebral small vessel disease is estimated to contribute 45-50% of all cases of dementia.

The cognitive consequences of cerebrovascular disease may substantially affect patients’ quality of life and cause a considerable disease burden for patients and their families. Compared with other brain dysfunctions such as movement disorders, cognitive impairment and dementia due to cerebrovascular diseases are neglected by both patients and physicians in all countries, but especially in low income and developing countries such as China.

Mechanisms of cognitive impairment in cerebrovascular diseases

Given the high prevalence of cognitive impairment, understanding the mechanisms of cognitive impairment in cerebrovascular diseases is pivotal. Understanding impairment of brain function due to neuronal damage after stroke is not difficult. A recent study suggested that multiple infarcts in one hemisphere; involvement of strategic regions such as the middle and inferior frontal gyri, parietal region, and middle temporal gyrus; larger stroke lesion volume; and lesions on the left hemisphere were associated with a higher risk.
of dementia after stroke. Further studies are needed in large populations to confirm these findings and enable application of a personalised approach in the clinic.

Despite cognitive impairment after cerebral small vessel disease being a common cause of impairment of brain function, its underlying pathogenesis and mechanism are poorly understood. Recent studies showed that early impairment of cognition may be induced by disruption of the glio-neuro-vascular unit. Small vessel pathologies due to vascular risk factors may induce breakdown in the integrity of the blood-brain barrier and cerebral blood flow deficits. Although not yet tested in prospective longitudinal studies, structural and functional alterations of cerebral small vessels may trigger the cascade of molecular signals (for example, activation of innate immunity, vascular oxidative stress, and inflammation), leading to disruption of the glio-neuro-vascular unit. Neurovascular dysfunction alters the homeostasis of the brain microenvironment and promotes accumulation of amyloid and tau protein in regions involved in cognition, leading to early vascular and neurodegenerative cognitive impairment. Accumulation of amyloid and tau protein in cerebrospinal fluid and changes in their concentrations in the brain may contribute to pathophysiologic progression from no cognitive impairment to mild cognitive impairment to early vascular and neurodegenerative cognitive decline, which abnormalities are reversible, and why lesion progression and symptomatology are so variable (box 1). Clarification of these questions may facilitate identification of potential therapeutic targets to improve brain function after cerebrovascular diseases.

Preventing dementia by preventing cerebrovascular diseases

Screening for cognitive impairment using scales such as the Montreal Cognitive Assessment (MoCA) is easy. However, although the US Food and Drug Administration recently accepted an application for the first biological treatment (aducanumab) of Alzheimer’s disease, treatment of the disease is still disappointing owing to the failure of most recent trials targeting clearance of amyloid and selective inhibition of tau protein aggregation to improve cognition in Alzheimer’s disease. Increasing evidence points to a failure of amyloid and tau rather than overproduction as a main problem in Alzheimer’s disease, and this failure is related to hypertension and other vascular risk factors through functional alteration of perivascular space clearance, implicating new directions to prevent dementia by preventing cerebrovascular diseases. This may help to identify new therapeutic targets to prevent cognitive impairment, including protection of the glio-neuro-vascular unit (box 1).

Cerebrovascular diseases and dementia share some, largely modifiable, risk factors and protective factors. Growing clinical evidence shows that vascular risk factors contribute to cognitive impairment. General cardiovascular risk was shown to be associated with longitudinal cognitive decline in clinically normal older adults, both alone and synergistically with β-amyloid burden. Adherence to the Life’s Simple 7 advice for ideal cardiovascular health (stop smoking, eat better, lose weight, control cholesterol, get active, reduce blood sugar, and manage blood pressure) in midlife was associated with a lower risk of dementia later in life in the Whitehall II cohort study and was recommended by the American Heart Association/American Stroke Association Presidential Advisory to maintain optimal brain health. The Lancet Commission on Dementia Prevention, Intervention, and Care proposed a life course model of dementia risk that reflects how lifestyle factors across the lifespan contribute to risk of dementia. They estimated that 12 modifiable lifestyle factors across the lifespan accounted for approximately 40% of worldwide dementias, among which vascular risk factors (midlife hypertension, alcohol misuse, and obesity; later life smoking, physical inactivity, and diabetes) accounted for approximately 11%. A recent study showed that vascular risk factors (diabetes, midlife hypertension, midlife obesity, physical inactivity, and smoking) accounted for approximately 21% of Alzheimer’s disease and 17% of vascular dementia. Assuming a 20% reduction in the prevalence of above vascular risk factors, depression, and low educational level implied a 6.4% and 6.5% reduction in the prevalence of Alzheimer’s disease and vascular dementia. Considering that approximately 90% of stroke is attributable to modifiable risk factors, preventive dementia by controlling vascular risk factors and cerebrovascular diseases may be promising. Nevertheless, a systematic review conducted by the Agency for Healthcare Research and Quality concluded that insufficient high strength evidence existed to justify a public health campaign to encourage people to adopt lifestyle interventions to prevent or slow cognitive decline and dementia.

Box 1: Advances in research on preventing dementia by preventing cerebrovascular diseases

Where we are
- Early impairment of cognition may be induced by disruption of the glio-neuro-vascular unit
- Neurovascular dysfunction may promote both early vascular and neurodegenerative cognitive impairment
- Vascular risk factors, such as diabetes, midlife hypertension, midlife obesity, physical inactivity, and smoking, are associated with both vascular dementia and Alzheimer’s disease
- Insufficient high strength evidence exists for lifestyle interventions to prevent or slow cognitive decline and for drugs to improve cognitive impairment after cerebrovascular disease

What the prospects are
- In-depth research is needed on the types of vascular dysfunction that initiate or propagate small vessel disease pathogenesis, which abnormalities are reversible, and why lesion progression and symptomatology are so variable
- Ways need to be found to prevent dementia by improving management of vascular risk factors and testing drugs that may improve the glio-neuro-vascular unit
As cerebrovascular diseases and dementia are so closely interlinked, amelioration of vascular risk and vascular damage offers a new dawn for preventing not only vascular dementia but also mixed and even Alzheimer’s dementias, and it may even offer alternative routes to clear amyloid and tau protein aggregation. Neurons are not renewable, and impairment of brain function is often irreversible. Therefore, very few effective approaches are available for patients with cerebrovascular diseases and cognitive impairment, although scope for repurposing exists. For example, one study suggested that nimodipine might reduce memory impairment after acute ischaemic stroke.22 Similarly, drugs with endothelial and glial protection and anti-inflammatory properties, such as cilostazol, are being trialled to prevent and treat cerebral small vessel diseases and reduce cognitive impairment (for example, http://www.isrctn.com/ISRCTN14911850). As cerebral small vessel disease is associated with vascular risk factors, particularly hypertension, intensive control of vascular risk factors such as hypertension has been evaluated, although with mixed results.23 For example, a substudy of the SPRINT MIND (Systolic Blood Pressure Intervention Trial Memory and Cognition in Decreased Hypertension) trial showed that intensive blood pressure reduction decreased progression of white matter hyperintensities, mild cognitive impairment, and probable dementia.24 The results of these trials indicated that patients with cerebrovascular disease or vascular risk factors might be a potential target population to prevent dementia. As cerebrovascular disease and vascular risk factors are so common, these converging epidemiological and clinical trial results justify further efforts to find ways to prevent dementia by improving management of vascular risk factors and testing drugs that may improve the function of the endothelium and other parts of the glo- neuro-vascular unit.

In summary, patients with cerebrovascular diseases have a substantial risk of cognitive impairment. Vascular factors contribute to the pathophysiological progress of cognitive impairment, providing new opportunities for preventing not only vascular dementia but also mixed and potentially even Alzheimer’s dementias by testing prevention strategies that work for cerebrovascular diseases. Further studies are needed to understand the mechanism by which cerebrovascular disease accelerates Alzheimer’s, mixed, and vascular dementias and to test interventions targeting vascular risk factors and people with cerebrovascular diseases to prevent dementia.

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New era of personalised epilepsy management

The trial and error approach to epilepsy treatment has not changed for over a century but machine learning and patient derived stem cells promise a personalised and more effective strategy, argue Patrick Kwan and colleagues

Epilepsy affects 50 million people worldwide with no age, ethnic, or geographical boundary. Patients have recurrent seizures that can lead to injuries, cognitive decline, psychosocial dysfunction, and even death. Epilepsy is caused by brain insults such as trauma, stroke, tumour, inflammation, and infection as well as systemic changes resulting from genomic variation. Patients with epilepsy have increased comorbidities, including cerebrovascular, neurocognitive, and psychiatric diseases. Better epilepsy control will therefore improve overall brain health.

Uncertainty in treatment response is major problem
Numerous drugs are available to treat epilepsy as well as non-drug interventions such as resective surgery, neuromodulation, and dietary therapies. Yet the current standard of care still relies on a trial and error approach of sequential regimens of antiseizure medications. Although there are guidelines on drug selection based on broad seizure type (focal or generalised onset) many drugs have similar efficacy when analysed on a group basis. For any given patient, it is impossible to predict which drug will be most effective and should be selected as the initial treatment. Nor are there surrogate biomarkers that can reliably predict treatment responses or risk of drug resistant epilepsy in the routine clinical setting. The upshot is that patients must simply wait and see whether their epilepsy will be controlled, usually defined as an absence of seizures for at least one year. Despite an explosion of new drugs, with over 20 on the market, antiseizure medications fail to control seizures in one third of patients.

Across much of the world most patients newly diagnosed with epilepsy are treated by primary care physicians (box 1). If seizure control is not achieved with initial treatment, patients are referred to a general neurologist who, if further drug treatments fail, then refers them to an epilepsy centre. This sequential care pathway means critical time is lost before patients who may be at high risk of drug resistant epilepsy can be assessed by epilepsy specialists. Other treatment options, such as surgery, are widely considered a last resort. Sadly, the associated time delay means such treatments may be less effective. The result is often years of reduced quality of life, lost productivity, and increased mortality.

This predicament might be solved by a reliable method to find patterns linking treatment outcomes to a patient’s personal characteristics. Patients with high risk of drug resistant epilepsy could be triaged early, expediting access to the precious resource of specialist care. Recent advances in artificial intelligence (AI) and stem cell research are raising hopes that personalised epilepsy management could soon be a viable alternative to this sequential treatment pathway (fig 1).

Medical artificial intelligence
Recent advances in machine learning, a subset of AI, offer novel ways to develop prediction models that are more accurate than traditional statistical modelling. Machine learning is being explored in epilepsy to forecast and detect seizures through recognition of electroencephalography (EEG) patterns. A recent study used 9571 routinely collected scalp EEG records to train a deep neural network that outperformed experts in detecting interictal epileptiform discharges. Researchers have also used time series based algorithms (for example, the line length algorithm used in responsive neurostimulation systems) to analyse controlled, continuously acquired, intracranial EEG signals to develop seizure warning systems. If shown to be effective in large scale clinical trials, such systems could help patients pre-empt and reduce injury from seizures.

Recent studies have used drug dispensing databases to develop models to predict drug treatment responses. Although these are large datasets, the models do not capture detailed information about the individual or the disease and therefore lack potential importance data on treatment outcomes. Medical records, on the other hand, include comprehensive clinical information on epilepsy management and are a fuller repository of factors potentially linked to treatment outcomes.

In the past five years a more advanced subfield of machine learning, called deep learning, has achieved impressive gains in the areas of image recognition, natural language processing, and speech. The superior performance of deep learning over traditional machine learning mainly arises from its depth of architecture and the capacity to scale massive amounts of data and continuously improve with more observations. Extended graphical models have shown superiority in modelling dynamic and complex graph structured data, such as clinical data. These models can unravel the hidden structure and reveal the complex links between clinical variables to derive predicted probabilities of the outcome of interest.

In medical AI, models have been shown to be capable of automatically discovering and learning from complicated “hidden (latent) spaces” by encoding multiple observed features to fewer representation variables that are optimised for predicting the outcome of interest. For instance, graphical models recently identified the spatiotemporal evolution of epileptic seizures by leveraging spatial and temporal information in structural longitudinal data.

KEY MESSAGES
- For more than a century the approach to epilepsy treatment has been trial and error because there is no reliable way to predict which medications will work
- Advances in machine learning promise more accurate models to predict treatment outcomes for individual patients
- Genome-wide screening and sophisticated disease models using patient derived stem cells may allow precision epilepsy treatment in future
Biomedical Bidirectional Encoder Representations from Transformers (BioBERT)\(^{21}\) is the latest pretrained biomedical language representation model based on deep learning techniques and designed for biomedical text mining. BioBERT, released in early 2020, supports model training by facilitating use of unstructured data from many additional sources, such as electronic health records and clinical reports. This is combined with powerful deep learning graphical models, allowing researchers to include more granular and potentially useful information in the analysis of treatment outcomes, something not possible with traditional statistical analysis.

These AI advances raise the hope of robust models to predict drug treatment responses. A study at the Stanford Epilepsy Center is developing AI models to predict outcomes of antiseizure medication treatment from participants’ seizure, genetic, physical, physiological, medication, and environmental data.\(^{22}\) The ideal AI algorithm and input data to predict drug treatment responses are not yet known. Future studies should therefore explore more advanced and complex graphical AI models and use data from large, longitudinal epilepsy registries so that comprehensive information can be mined from patients’ medical records. Those studies might enhance the models by applying natural language processing tools to extract unstructured data.

Although clinicians may be getting used to software being incorporated into their workflow, the “black box” nature of deep learning based AI systems could still hamper uptake. There have, however, been recent advances in the visualisation of AI based support of clinical decisions in clinical practice. To address that knowledge gap, a randomised controlled trial is investigating the clinical utility and cost effectiveness of whole genome sequencing in patients with refractory epilepsy.\(^{29}\)

If genetic knowledge is to translate into better treatment it is critical to have a clearer understanding of the functional role of genetic variation. Researchers have traditionally studied this using animal and cellular disease models that insert the errant gene into an organism’s DNA. Pathophysiological changes are then established by comparison with a control, or wildtype, state.

In epilepsy, disease modelling studies of SCN1A mutations (a gene responsible for most cases of Dravet syndrome\(^ \text{30}\)) have pinpointed the pathology as a reduction in the sodium ion channel function of inhibitory interneurons.\(^ {31}\) That finding has led to a reassessment of drug selection in Dravet syndrome, avoiding drugs that block sodium ion channels as they could further reduce interneuron function and aggravate seizures.\(^ {32}\)

In most cases, however, the pathogenicity of SNVs has not been established because of the limited scope of disease modelling studies. If precision medicine is to be widely adopted in epilepsy, patients identified as having a genetic variant must get expedited testing. The genetic variant should be investigated using in vitro models to assess its pathophysiological consequences and tailor testing and selection of drug treatment.

One promising disease model uses neurons derived from induced pluripotent stem cells (iPSCs) generated from the patient. iPSCs carry the patient’s genetic information and can be grown...
or “differentiated” into a variety of cell lineages, including multiple neural subtypes (fig 2). These patient derived neural models allow the study of genetic variation for a broad range of neural phenotypes, such as abnormal neural morphology or synaptic transmission, which is not possible with traditional models. The models have been used to identify the abnormal behaviour of neurones that carry highly pathogenic gene variants, as seen in early developmental encephalopathies.33

The advantages of iPSC based disease models include the ability to explore the combined effects of multiple SNVs in a single patient and cases where the genetic lesion is unknown.34 There are, however, important hurdles to be overcome before these models can be used routinely in clinical decision making. More research is needed to show whether a hyperactive network phenotype, a hallmark of clinical epilepsy, can be reproduced in a dish. More study, too, is required to establish the relation between electrical activity measured in these in vitro models and epileptiform activity observed on EEG.

Current iPSC based neural models lack sufficient cellular complexity to establish seizure-like activity. Researchers are therefore turning to cerebral organoids that contain organised, multicellular tissue structures found in the brain.35 More complex disease models will be essential to accurately model dysfunction in the broad range of cell types and brain regions that cause epilepsy in humans. In addition, multielectrode arrays, which record the coordinated interplay of networked neurones, have been used to detect EEG-like signatures from cultured cerebral organoids.36

Since iPSC based models can be grown indefinitely without risk to the patient, they will be important for high throughput screening of candidate compounds in patient specific conditions. The aim is to identify novel, targeted antiseizure medications. Indeed, these models have been successfully used for high throughput drug screening in other central nervous system diseases.37 Such drug screening platforms could overcome our heavy reliance on traditional rodent models, which has hindered the development of antiseizure medications and helps explain why more than a third of patients with epilepsy lack effective treatment.

Future of personalised epilepsy management

If personalised epilepsy management is to become a reality technological advances must be coupled with improved health education and access to specialist care. The Australian Epilepsy Project (https://epilepsyproject.org.au) aims to build a network of centres to improve access for people living with epilepsy, especially in rural regions. It will recruit 8000 patients over five years to develop clinical decision support models by training AI algorithms on advanced imaging, neurocognitive functions, genetics, and other clinical features. The outcome prediction models will not only be of value to specialists but help general practitioners, who can use them to triage patients for early referral to epilepsy centres (box 2). Instead of the current trial and error approach physicians will consult decision support software that incorporates multimodal data for machine learning modelling. Personalised disease models derived from patients with drug resistant epilepsy will integrate clinical data for decision making and screen for novel, approved compounds as precision treatment. Fields such as oncology38 have shown that combining in vitro models with clinical char-

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acertistics can yield predictive models more powerful than those using either data type alone. Our hope is that a convergence of technologies could, within five to 10 years, make personalised epilepsy management a clinical reality.

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Rethinking monogenic neurological diseases

Studies on monogenic diseases can provide valuable insights into the mechanisms of other neurological disorders, say Wan-Jin Chen and colleagues

Monogenic diseases result from modifications to a single gene. Over 10,000 monogenic diseases have been identified, around 17% of which are neurological disorders, covering a broad spectrum of brain syndromes. They affect hundreds of millions of people globally and present a substantial health threat and care burden in ageing societies. Notably, monogenic neurological disorders have been estimated to account for up to 40% of the workload in hospital paediatric practice, with over 1% of children affected at birth.

Many different forms of brain impairment are associated with monogenic neurological disorders. These include effects on brain development from birth (eg, fragile X syndrome, Huntington’s disease, or monogenic autism), progressive degenerative neuronal deficiency that manifests in later life (eg, some forms of Parkinson’s disease or amyotrophic lateral sclerosis), and young or late onset of abnormal functioning in people with brains that appear structurally normal (eg, dystonia). On a structural level, the manifestations of monogenic neurological disorders range from microcircuit impairment to nuclei degeneration or even vast brain atrophy and result in problems including cognitive decline, motor deficits, and psychiatric dysfunction.

Importantly, monogenic neurological disorders share a wide spectrum of symptoms with common neurological diseases, including cerebrovascular disease and Alzheimer’s disease. The pathological mechanisms of some monogenic neurological disorders are known to have a role in more common idiopathic forms of disease (eg, neuronal injury in familial and sporadic Alzheimer’s or Parkinson’s disease). However, the aetiopathologies of common neurological diseases typically involve complex spatial-temporal interactions of internal genetic factors and external environmental stimuli, making it extremely difficult to understand their fundamental pathogenic mechanism(s) and develop treatments. Investigation of monogenic neurological disorders is more straightforward as a single genetic factor drives disease progression. This provides several unique prospects for neurologists and neuroscientists for diagnosis, innovations in treatment technologies, and development of relatively simple experimental models for hypothesis-driven mechanistic research.

We believe that medical thinking about monogenic neurological disorders urgently needs a major update. Historically, given their often overwhelming disease burdens and limited treatment options, attitudes to them in the research and clinical communities have been largely pessimistic. This reflects the long standing dogma that heritable monogenic neurological disorders are incurable, although a few, such as Wilson’s disease, can be treated. However, attitudes are beginning to shift as the potential of monogenic neurological disorders as a tool for investigating the mechanisms of more common neurological disorders is increasingly recognised.

The widespread deployment of DNA sequencing methods in hospitals has greatly increased our ability to identify and accurately diagnose monogenic neurological disorders. For example, targeted genetic testing followed by next generation sequencing has been shown to be a cost effective approach to molecular diagnosis in patients with genetically heterogeneous ataxia, resulting in detection rates of up to 75% in familial cases with adolescent onset. Once monogenic neurological disorders cases are identified, the long duration of the pathogenic processes enables focused, long term studies across generations of families with relevant mutations and development of research models to support mechanistic insights. Since monogenic neurological disorders have a single causal factor, they are also excellent targets for innovative, specific, biotechnology enabled therapies.

Advances in diagnosis

Developed in 1977, Sanger sequencing was one of the first methods for determining nucleotide sequences in DNA. It quickly became the standard in both research and commercial applications because of its technical ease and reliability of results. Low throughput and labour intensive procedures make Sanger sequencing less useful for large scale applications such as screening of whole human genomes or exomes, and it has been replaced by next generation sequencing that allows whole genome sequencing in short times and at low cost.

The introduction of these modern DNA sequencing practices into hospitals has initiated a new era for genetic diagnostics and discovery of causes of monogenic neurological disorders. There are ample data to support the use of next generation sequencing to reduce diagnosis time. For example, clinical exome sequencing in patients with adult onset and sporadic presentations of ataxia is a high yield test, providing a definitive diagnosis in more than 7% patients and suggesting a potential diagnosis in more than 30% to guide additional phenotyping and diagnostic evaluation. Indeed, it seems likely that patients with hereditary monogenic neurological disorders will soon be able to get an accurate diagnosis when they first seek medical attention.
Linking pathological mechanisms to common neurological disorders

Each newly identified genetic variation associated with a monogenic neurological disorder is a chance both to improve medical care and to discover more about the mechanisms neurological disorders more generally. When genetic testing on a patient identifies a previously unknown mutation in a locus associated with a monogenic neurological disorder, this candidate causal genetic variant can be investigated in the proband’s family and in patient derived biological materials (eg, cultured fibroblasts or induced pluripotent cell (iPSC) derived neurons). Genetically modified animal models can then be used to investigate the molecular, cellular, and circuit level mechanisms underlying the disorder. This research path is now common and has increased our mechanistic insights into monogenic forms of cerebral vascular disease, Alzheimer’s disease, and Parkinson’s disease.14

Importantly for brain health generally, research into the mechanisms of monogenic neurological disorders is already reshaping our understanding of neurodegenerative disease. For example, insights into causes of the monogenic disease CADASIL (cerebral autosomal dominant arteriopathy with subcortical infarcts and leukoencephalopathy) may contribute to our understanding of the mechanisms underlying other forms of cerebral small vessel disease. In particular, the monogenic forms of cerebral small vessel disease share overlapping clinical phenotypes (eg, cognitive dysfunction) and thus may help understand how dysfunction in the small arteries in the brain can cause neural injury.11

Developing research models and early intervention strategies

Many brain diseases progress relatively slowly, arising from a long term process that starts with subtle molecular dysregulation and proceeds to the cellular and tissue levels before manifesting as clinical symptoms.12 Given the single genetic causal factors underlying monogenic neurological disorders, it is possible to conduct longitudinal observation of patients as well as use experimental models, including cell models, rodent models, and even non-human primate models. Imagine, for example, a family with a monogenic neurological disorder in which the first case is a father, who develops symptoms needing medical attention at the age of 60. His 30 year old son, a carrier without symptoms, may then be available for long term follow-up observations combining, for instance, imaging and electrophysiology data acquisition over several decades.

A major barrier to the development of effective therapies for patients with amyotrophic lateral sclerosis is that treatment is typically only initiated at a relatively late stage of the disease course. However, presymptomatic amyotrophic lateral sclerosis could be explored in a family with a monogenic form of the disease. This would allow researchers to study the disease process before it manifests clinically, including identification of biomarkers to predict when symptoms are likely to emerge.13

Disease models for translating gene therapies to preserve brain health

Broadly speaking, gene therapy involves the use of nucleic acids to alter the course of a disease. This can be achieved either by delivery of a functional, therapeutic gene as a substitute for the defective or missing endogenous counterpart or by reducing the levels of a harmful defective gene product by, for example, using sophisticated biotechnological tools such as antisense oligonucleotides (ASOs). An ASO is a small piece of synthetic DNA that is complementary to a segment of the target mRNA and may be used to stop translation, trigger mRNA degradation, or alter splicing.14 Several targeted, genotype specific gene therapies are on the horizon15 and offer hope for improved treatment or cure of monogenic neurological disorders.

Most gene therapies have focused on overcoming detrimental monogenetic defects. As an example, spinal muscular atrophy—a neuromuscular disease caused by an abnormality in the survival motor neuron (SMN) gene—was previously incurable and fatal but can now be treated with ASOs. The treatment was approved by the US Food and Drug Administration in 2016 and enhances the abundance of the full length SMN2 mRNA, substantially reducing the motor deficits of affected infants.16

More recently, the FDA approved a therapy that uses an adeno-associated virus to deliver complementary DNA encoding a functional SMN gene, which effectively restores motor function.17

Genome editing techniques have also been used to disrupt SMN2 intrinsic splicing silencers to successfully restore SMN function in mice models of spinal muscular atrophy and patient derived induced pluripotent stem cells.18 Additionally, there are exciting recent examples of using of a patient derived oligonucleotide treatment for neuronal ceroid lipofuscinosi 7, suggesting that personalised treatment of monogenic neurological disorders is possible.19 Use of these techniques could facilitate treatment of many monogenic neurological disorders in future and end the traditional view that they are incurable.

New potential

The growing number of successful demonstrations of gene therapy approaches to treat monogenic neurological disorders suggests a promising future for the clinical practice of neurology. The clinical understanding and experience with regulatory hurdles gained from innovative treatments of monogenic neurological disorders are paving the way for the wider application of gene therapies to treat common neurological disorders. Furthermore, basic models of common neurological disorders may be advanced by future treatments for monogenic neurological disorders. An advanced CRISPR gene editing system targeting RNA (CasRx) has been used to convert glial cells into functional neurons to alleviate motor symptoms in a mouse model of Parkinson’s disease.20 It is becoming increasingly clear that the rational use of gene editing strategies can modify pathological processes shared by monogenic and common neurological disorders to improve brain health generally.

We believe that the ongoing development, regulatory approval, and clinical deployment of new therapies to treat monogenic neurological disorders represents the vanguard of neurological therapeutics. It is time to stop thinking of these disorders as incurable and exploit the opportunities they provide to understand the nervous system more deeply and to facilitate the development of new methods of treatment.

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Improving brain health by identifying structure-function relations in patients with neurosurgical disorders

Use of new technology to map which parts of the brain control different functions is leading to better treatment of patients with neurosurgical disorders, say Liwei Zhang and colleagues

Brain diseases amenable for neurosurgery comprise a group of conditions that are caused by damage to identifiable brain structures. These diseases threaten long term brain health and cause a large burden on both individuals and societies. Tumours originating in the brain, for example, are the most common fatal cancers in children as well as the third most commonly occurring cancers in adolescents and young adults (15-39 years old). Epilepsy is another common neurological disorder that is often caused by specific brain structural abnormalities. Around 10 million patients are thought to have epilepsy amenable to surgery, with 1.4 million new cases globally each year.

Neurosurgery can repair structural problems in the brain that cause dysfunction but may itself affect brain function. A substantial proportion of patients with neurosurgical disorders have some functional impairment. Patients with glioma may experience postoperative impairment of language, emotional, and psychological processing when the tumours are located in areas controlling those functions (eloquent areas), and roughly 46% of long term survivors have a cognitive impairment, especially in memory and executive function. Psychiatric or neuropsychological testing would probably show that the current data under-report the extent of impairment caused by neurosurgical disorders.

These neurological deficits are challenging because many patients will live for decades and require supportive care, particularly since young patients are disproportionately affected by neurosurgical disorders. For malignant brain cancers, the global disability adjusted life years (DALYs) were estimated at 7.7 million in 2016, roughly 3.4 times the number of deaths, which was 227,000. Greater use of advanced imaging technology offers the potential to reduce the harms arising from surgery.

Multidisciplinary approach to protect and restore brain function

Maintaining brain function is vital for quality of life, but in practice, insufficient attention is paid to protecting brain functions when developing plans for neurosurgical intervention. Neurosurgical disorders are complex, and interdisciplinary collaboration is advocated when treating patients. For example, the UK National Institute for Health and Care Excellence suggests referring patients with brain tumour for neurological rehabilitation assessment, including physical, cognitive, and emotional function after diagnosis and at each follow-up.

A typical multidisciplinary team includes neurosurgeons, neurologists, neuroradiologists, neuropsychologists, intraoperative neurophysiologists, monitoring professionals, anaesthesiologists, neuropsychologists, psychiatrists, and therapists. A well functioning multidisciplinary team can provide neurosurgeons with proper techniques to assess brain function and its implications for long term brain health. Effective strategies to protect and restore brain function depend on a more fundamental understanding of the relation between brain structures and their various functions, as well as advanced neurosurgical and imaging techniques. Advanced multimodality techniques, such as navigation, awake craniotomy, and intraoperative cortical stimulation mapping have decreased the rate of postoperative neurological deficits in patients with gliomas (box 1). According to a meta-analysis of 90 studies, cortical stimulation mapping decreased the rate of late severe neurological deficits from 8.2% to 3.4% while also enabling a more extensive resection in glioma patients with tumours in eloquent areas.

Other non-invasive imaging techniques—for example, functional magnetic resonance imaging (fMRI) and diffusion tensor imaging—enhance the detection of eloquent areas. These techniques have shown that vital functions are often distributed across the brain, with many eloquent areas identified outside the brain structures suggested by historical brain atlases. Improved identification has also facilitated serial monitoring. Invasive and non-invasive techniques have converged to propel neurosurgery into the modern era of precision medicine, to further improve patients’ brain health.

Multidisciplinary teams have the strength of overcoming the intrinsic limitations of professionals from a single discipline. For example, neurosurgeons often use preoperative fMRI to guide surgery. However, fMRI has a sensitivity of 44% and specificity of 80% and cannot be a substitute for cortical stimulation mapping in patients having awake brain surgery, which requires input from intraoperative neurophysiological monitoring professionals.
monitoring professionals. In one study of patients with gliomas in areas that were assumed to be unresectable based on functional imaging, most were able to have maximal safe resection guided by cortical stimulation mapping without experiencing any functional deficits. This shows how multidisciplinary working can help minimise the probability of brain functional damage and maximise life expectancy.

**Novel insights into brain function from neurosurgical patients**

Although neurosurgical procedures have traditionally focused on targeting specific abnormal brain structures, new knowledge about the pathophysiology of brain changes has been achieved by examining the effects of surgery on patients. For example, study of patients with brain tumours has discovered more refined structural areas related to language, emotional, and psychological processing.

Novel insights into the functional distribution of critical brain structures, especially language, have been attained from patients who received cortical stimulation mapping during awake neurosurgery. This process requires a multidisciplinary team, including the neurosurgeon operating the handheld brain probe, the anaesthetist keeping patients awake but pain free, and the intraoperative neurophysiological monitoring expert assessing language function.

The first bilateral map of human language function in both hemispheres was built from 165 patients having awake mapping for resection of low grade glioma. Interestingly, speech arrest was localised to the ventral premotor cortex, not the classic Broca’s area (inferior frontal gyrus), and the right hemisphere was also found to have a role in language processing. Some bilingual patients with brain tumours experience language disturbance or bilingual switching preoperatively or postoperatively. The structural locations of name switching were found across the left middle frontal gyrus by using cortical stimulation mapping to identify language function in awake brain surgery. These important findings broaden our anatomical based understanding of Broca’s area. Insights obtained from these procedures not only extend our conceptualisation of the traditional Brodmann area maps but also reduce damage to patients’ language function.

The psychological changes in some neurosurgical patients could provide evidence to update our understanding from preclinical studies. For example, neurosurgeons and psychologists collaborated to find that patients with focal anterior insular cortex lesions displayed decreased empathetic responses to others’ pain. By thoroughly assessing the change in patients with insular gliomas, they clarified this psychiatric processing was localised in the anterior insular cortex rather than the anterior cingulate cortices, as suggested by neuroimaging.

Treatment of other neurological disorders also provides an opportunity to better understand brain function. For example, brain mapping and intraoperative stereoelectroencephalography at the cortical-subcortical level is used to detect areas responsible for epileptogenesis, and this technique can also be used to reveal brain functions that need to be preserved. For patients with Parkinson’s disease, precise stimulation of nuclei through deep brain stimulation has been shown to substantially improve motor control and quality of life, leading to a new area of research in neuromodulation.

With ethical approval, neurosurgeons working in collaboration with other disciplines to study brain function could provide important advances for brain health.

**Challenges in brain health**

Brain scientists confront many challenges in research and the clinic. A new brain atlas of advanced human brain functions would meet the demands of clinical and scientific communities and could be achieved through multidisciplinary research. The historical atlases of brain functions are based on non-human models that do not accurately predict the long term effects of neurosurgical disorders on human brain function. The functions of animal brains are different from those of humans, especially for functions unique to humans such as advanced cognition and language.

Although current multimodality imaging and intraoperative techniques benefit neurosurgical patients by preserving their brain functions, the level of evidence supporting their routine use is not high, mostly at level III. A shortage of multidisciplinary teams, brain disease heterogeneity, and insufficient numbers of patients eligible for large clinical trials at a single institution have hindered high quality studies. In addition, because of the limited resources for brain protection techniques and an insufficient number of experts in underdeveloped regions, some neurosurgical skills and research approaches have not been widely implemented. International collaboration is therefore essential to overcome these challenges.

Preserving additional brain function in neurosurgical patients while also prolonging life expectancy is often a difficult balance because of the robust evidence that more extensive resection of the tumour and aggressive treatment correlates with better survival for patients with gliomas. Despite emerging knowledge of the relationship between tumour location and the corresponding brain functions, evidence suggests that these relations, and their long term implications, may still be underappreciated. The high incidence of postoperative cognitive decline in patients with low grade glioma could be explained by some functional activity remaining within the tumour mass. Focal brain tumours produce global changes in the functionally complex and networked brain architecture, which may aid in our understanding of patients’ larger scale...
neurological manifestations and provide a framework for improving plasticity. Of note, recent reports have linked neuronal excitability with growth of gliomas and brain metastases. These and other findings highlight the need for a deeper understanding and clearer visualisation of the relations between abnormal brain structures, lesions, and functions from the neurosurgical perspective, which can create new insights in brain health.

Further multidisciplinary research will create an understanding of the pathophysiology of brain function impairments as well as brain plasticity. This will enable greater therapeutic targeting while maintaining function to achieve optimal brain health.

**Future directions**

Neurosurgical disorders directly damage specific brain structures and lead to large individual and societal burdens in the long term. Research that focuses on the patient’s brain functions during and after surgery should be prioritised to reduce these burdens. This represents a major opportunity for neurosurgery to collaborate with other disciplines to advance our knowledge of brain health.

Establishing a multidisciplinary research alliance, using multimodality technologies, and studying more long-term functional changes in neurosurgical patients, will improve our understanding of brain functional localisation and mechanisms of damage in brain disorders. By taking part in research approved by ethics committees, neurosurgical patients can help provide unique insight into brain function and health that could in turn benefit the broader clinical, scientific, and patient communities.

International, large, and diverse prospective trials are also needed to assess changes in patients’ brain function attributed to damaged structures in neurosurgical disorders. Initially, the reproducibility and generalisability of brain function observed in patient case series could be validated in a large global population. Such evidence based understanding of brain function and protection techniques could then be used to tailor treatments for a variety of brain disorders.

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Decoding the brain through research—the future of brain health

David Z Wang and colleagues look at the latest advances in brain research and how they might affect treatment of brain disorders

The world has come a long way in solving the mystery of the brain, understanding its fundamental role in human consciousness and discovering methods to treat its disorders. In *The Sacred Disease* in ~430 BC, Hippocrates wrote that the brain served to house the ventricles, whose main purpose was to be a container and transit point for the breath or air (pneuma) from outside the body—the force that brought to life our joys, pleasures, laughter, and grief. Thus, the brain was a reservoir for an animated substance that produced the human experience of consciousness and personality rather than the source of that activity itself. Our knowledge of the brain and its functional complexity remained at the level of three ventricles where our soul lies (Nem­esius, da Vinci) for hundreds of years until modern neuroscience began to uncover the fine network of neuronal circuits that made up the solid substance of the brain.

With the advent of modern neuroimaging, the complex structure of the brain has been brilliantly revealed, and this has helped greatly in the treatment of many brain related disorders. Other articles in this series have provided updates on a wide range of topics, including neurodegenerative diseases, mental disorders, cerebrovascular diseases, epilepsy, monogenic neurological diseases, and in vivo brain function testing. With help from gross anatomy to electronic microscopy, tissue staining to profiling, cell physiology, and synaptic chemistry, neuroscientists have elucidated the mechanisms and pathophysiology of many common brain diseases. For example, trinucleotide repeat expansion is now known to be responsible for many genetically inherited degenerative diseases such as Huntington’s disease, and amyloid precursor gene or presenilin gene mutations can cause Alzheimer’s disease.

On the other hand, despite centuries of discovery on mechanisms of brain disease, treatment options remain limited. Most treatments still provide only alleviation of symptoms, though recent breakthroughs in gene therapy such as onasemnogene abeparvovec-xioi to treat children with spinal muscular atrophy and reperfusion therapy for acute ischaemic stroke hold the promise to truly revolutionise treatment for neurological disease. While options are available to modify disease expression with medications—such as in the treatment of Parkinson’s disease, multiple sclerosis, and epilepsy—we are far from curing them.

Entering the 21st century, perhaps we now have better ways to understand the mechanism of those brain disorders that are still a mystery and find the precise treatment. The key will likely be interdisciplinary research. Many ongoing brain health research programmes have already been multidimensional, combining neurobiology, physics, engineering, big data science, and artificial intelligence.

**Imaging advances**

In the future, it is likely that humans will be able to live longer, and do so with augmented capabilities supported by machine-human interactions. One exciting advance is new ways of observing in vivo brain-wide activities at the cellular level. A real time, ultra-large scale, high resolution (RUSH) macroscope has recently been developed that can provide video-rate gigapixel imaging of biological dynamics at centimetre scale and micrometre resolution, with a data throughput of up to 5.1 gigapixels a second. RUSH has enabled in vivo functional imaging of neural networks across the whole mouse brain at single dendrite resolution and brain-wide tracking of leu­cocyes during pathological processes, and the technology opens up a new horizon for large scale brain imaging to study various brain diseases at a systematic level.

Another example is the better understanding of the precise number of brain cells needed to complete a particular task. By constructing an explicit model of face selective cells that could decode an arbitrary realistic face from face cell responses and predict the firing of cells in response to an arbitrary realistic face, Chao and colleagues identified that macaques require only 200 cells to remember a face. These findings have far reaching significance. For the first time, a specialised task of the brain can be attributed to a specific number and type of brain cells in a specific circuit. This may allow scientists to build artificial models of explicit brain functions and experiment with mechanisms of injury and repair at a cellular or molecular level. Such mapping may aid our understanding of brain function and recovery and guide the rebuilding of brain circuits or resection of dysfunctional brain cells rather than whole tissues. It may also help us pinpoint the cells and circuits that are responsible for addictive behaviours, from smoking to substance use disorders to gambling.

**Resilience and plasticity of brain cells**

The common belief is that when a brain has been removed, brain death is imminent. However, such belief has recently been shattered. Sestan and colleagues collected brains of 6-8 month old pigs four hours after death and bathed them in specialised perfusate solutions. They found that brain cells and synapses of certain areas of brain began to recover and show signs of cellular activities. Their finding suggests that there may be a late window of treatment after onset of brain anoxia when brain tissue can recover, analogous to the
benefit of late window thrombectomy. This discovery has taught us that brain cells can survive and recover after loss of circulation, and that favourable conditions may preserve a reservoir of resilient brain cells that are slow progressors to ischaemic necrosis.

Evidence is also emerging on how brain cells can adapt. A recent report of functional neuronal connectivity in adults without apparent loss of function after brain hemispherectomy sheds new light on brain plasticity. The study provides the first comprehensive analysis of whole brain functional connectivity across the full repertoire of resting state networks after hemispherectomy and shows preservation of resting state networks but an increase in internetwork connectivity with other functional brain networks. When hemispheric resection occurred in patients younger than 11, the retained hemisphere was able to protect the jeopardised functions by enhancing cellular interaction and synaptic activity.11

Harnessing the power of big data
Artificial intelligence (AI) has been widely applied in clinical diagnosis and patient monitoring. Recent studies have attempted to classify or detect Alzheimer’s disease and other cognitive impairment,12-14 acute neurological events,15-18 focus of epilepsy, autism spectrum disorder, and attention deficit/hyperactivity disorder by using deep learning based algorithms. The data in these AI models include not only medical images but also clinical scores, in vitro diagnostic test results, and other functional and structure information.19-25 These studies showed high sensitivity and specificity from their test set, and work is ongoing on how to incorporate the routine use of these AI systems into a clinical setting.

The lack of a large dataset from multiple centres, the limited coverage of a disease spectrum, and unclear risk of using AI are major limitations of these blackbox systems. In contrast, Wang and colleagues have recently proposed a “vascular aware” unsupervised learning technique, VascadeNet,26 which provides the end users with explainable images, including both vascular structures and multidimensional features such as anatomical, physiological, biochemical, and cellular details. The enriched outputs could augment human decision making on treating vascular diseases and contribute to the emergence of the next generation of healthcare engineering.

The US Food and Drug Administration has already approved several automatic quantitative measurement software systems for disease classification (eg, NeuroQuant, Quantib, RAPID). Brain morphometry analysis software can automatically examine segments of brain tissue and detect minute changes. This technology can help early detection of degenerative brain diseases by comparing the results from individuals with a large dataset and images of healthy people. To take racial differences in the brain into account, some Asian companies have developed software based on datasets acquired from Asian populations (http://quant-health.com). Use of a deep learning based segmentation algorithm could improve the accuracy and test-retest stability in segmenting and measuring the volume of brain structure, abnormal lesions, perfusion deficit area, and other characteristics. The resulting quantified values could be used to assign a clinical score automatically, avoiding the variation arising from subjective measurement and interobserver inconsistency.

AI algorithms can also objectively analyse the data collected from a depth camera or wearable devices, assess behaviour, and evaluate facial expressions.27-29 The quantified values produced would not be affected by the physicians’ experiences, and errors can be avoided since the spatial-temporal resolution of the hardware is much smaller than visual evaluation by humans. Such early detection may allow treatment of a disease before a person shows clinical signs of brain dysfunction. Quantified measurements can be used as biomarkers to monitor the progress of the disease and help evaluate the efficacy of precision therapy.

Prospect of cure
One of the potential ways of curing a brain disorder is to correct its diseased protein structure. Many neurological diseases are caused by misfolded proteins, including Huntington’s, Parkinson’s, and Alzheimer’s disease. AlphaFold, a Google company, has successfully predicted a protein structure by using large genomic data. The 3D models of proteins that AlphaFold generates are far more accurate than any that have come before—making significant progress on one of the core challenges in biology. The ability to predict a protein’s shape from its DNA sequence is useful to scientists because it is fundamental to understanding its role within the body, as well as diagnosing and treating diseases believed to be caused by protein misfolding.30

We have entered into an exciting new era of brain science research and discovery. With the advent of AI, advanced imaging, genomics, psychosocial analytics, and protein engineering we may be closer than ever to new precision medicine approaches to treat many brain disorders.

Contributors and sources: DZW drafted the first manuscript. LHS, TYQ, and QHD critically reviewed and revised the manuscript. DZW is an expert in stroke clinical research. LHS is an expert in neuroscience research and stroke care quality improvement. TYQ is an expert in big data and artificial intelligence. QHD is an expert in brain research and artificial intelligence.

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Check for updates

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Brain science is still in a discovery phase because of our limited knowledge of basic nervous system structure and function. We need a broader perspective of delivering meaningful outcomes to patients with neurological disorders and greater understanding of the mechanisms that underlie development of neural circuitry, how neurons encode and retrieve information, and how information interacts from one neuron to another. Knowledge of how brain activity gives rise to complex behaviours and how it adapts to external and internal changes is limited. Superficial understanding of the various senses, emotions, and cognitive functions—thinking, choice, and even consciousness—promises innovative solutions in areas such as health, education, and 21st century economies. With the increasing burden of major brain diseases across the world, we need to find the most effective means to comprehensively apply modern biotechnology and to solve problems in clinical medicine.

Neuroscience is entering a new era of collaboration, in which successful new technologies, generated by large scientific projects across the world, will have a dramatic impact not only on medical science but on economics and society as well. In 2013, the US government launched the Brain Research Through Advancing Innovative Neurotechnologies (BRAIN) initiative and put forward a national brain science project. This initiative complemented the Human Brain Project in the European Union and was shortlisted by the Brain/MINDS programme in Japan and several other national initiatives from Korea, China, Canada, Australia, and the International Brain Research Organization. Coordinating these successful international programmes and encouraging broad distribution of new technologies and open accessibility of the data generated will increase their value, while promoting creativity and expertise from every source. Multidisciplinary science that leverages translational research is critical to the success of these endeavours, along with the establishment of distribution systems and sharing mechanisms of technology on human data. In support of these goals the International Brain Initiative was formed to coordinate global BRAIN projects. This may facilitate comparability of the data and reduce economic and social disease burden. The complexity of the human brain is reflected in how its molecules, cells, circuits, and systems enable humans to perceive, recognise, and communicate with each other, as well as to understand how our brain confers our individual identity and enables us to contemplate our place in the natural world. The ambitious goal of understanding the brain is being approached in various projects. Paramount to this process of tackling all the objectives is the commitment to collaboration between government and non-government organisations and integration of basic and clinical translational brain research.

Clinical promise

Global brain initiatives to map, monitor, and modulate brain activity will lead to a host of clinical applications. Our colleagues from the stroke and neurocritical care community look forward to technologies that can improve ability to diagnose and successfully intervene to prevent and treat severe brain injury as well as enhance the brain’s capability for rewiring for improved function. The Neurocritical Care Society, a multidisciplinary non-profit organisation with thousands of members around the world, is poised to take advantage of the new neurotechnologies. The society undertakes research through the Neurocritical Care Research Network. The fresh impetus for such research initiatives is the desire of clinical scientists to enhance our understanding of complex disease states to improve patient outcomes and maintain brain health. The main goal of the society was to foster collaborative multidisciplinary clinical research and to advance critical care research methods such as using specific integrated chips for monitoring patients with traumatic brain injury. By monitoring the electrocorticography and neurochemical signals of the injured human brain tissue, it might be possible to detect spreading depolarisations, which are associated with poor outcomes in patients with traumatic brain injury. The “behind the ear” wireless microplatform device also enables monitoring of mobile patients with traumatic brain injury for secondary brain injury impact. Recent multidisciplinary collaborative clinical research indicates that a better outcome for patients in the completely locked-in state (severe disability) or with severe stroke may be feasible using brain–computer interface training to improve motor rehabilitation.

Need for standardisation

Further challenges are raised by the varying directions of brain research projects around the world. They have different funding mechanisms, project management structures, and approaches to ethical issues. It is impossible to achieve an understanding of the mysteries of the brain in one project alone—integrated collective intellectual and technological support are needed from different resources. Enhanced standardisation of those elements that enable scientists to compare data and contribute to building a common knowledge base of the brain is urgently needed.

What should be standardised to construct a framework that will bring together...
the results of large scale brain research initiatives from different countries? Examples might include agreement on common core acquisition methods and sharing plans for human brain imaging and data, or common standards for meta data and analysis tools for single cell typing studies. Also included could be approaches to disseminate new neurotechnologies and training programmes to optimise their application to brain projects. Human genetics has already benefited from global team science. An excellent model is ENIGMA (Enhancing Neuroimaging Genetics through Meta-Analysis), a worldwide network of researchers who pool brain imaging and genetic data from over 200 institutions aiming to investigate various aspects of the brain.8

Alzheimer’s disease is one disease where such networks could advance understanding. Amyloid deposition, intracellular tau aggregates, vascular compromise, and immune/inflammatory alteration are strongly implicated in the pathogenesis of neurodegeneration in Alzheimer’s disease. Sleep disturbance, changes in the brain’s lymphatic flow, and even effects of microbiota on brain functioning provide other contributory factors. Yet despite this new knowledge, effective therapies have been elusive. Tools from the global brain initiatives that enable investigators to interrogate the complex circuits affected in Alzheimer’s disease should enable the science to move from associative molecular-structural relationships to treatments that intervene to preserve circuit function.

Common worldwide data may provide insight into additional therapeutic targets, which mainly focus on transforming basic research achievements into clinical prevention and treatment. Further research into degenerative medicine, vascular biology, public health sciences, and clinical trial implementation and organisation is also important.9

As with earlier projects in genomics, astronomy, and physics, the enthusiasm of brain initiatives around the world call for strengthening international collaboration. The aim is to reduce the current and future brain related disease burden through multidisciplinary research and capacity building, promoting the development of effective prevention and intervention for neurological disorders. Box 1 summarises the challenges and opportunities regarding brain research, especially for global collaboration.

**Models of collaboration**

What models for international collaboration might neuroscientists emulate to achieve productive research worldwide? Consultation on all potential elements would require involvement of a wide range of stakeholders from academia, industry, and government.

To tackle this challenging task, we suggest identifying the core areas of research priorities, expanding scientific opportunities, and disseminating discoveries for the benefit of humanity. The most notable example of such collaboration in our area of medicine is the BRAIN initiative, a partnership between the National Institutes of Health, the National Science Foundation, the Defence Advanced Research Projects Agency, private foundations, and researchers.10 We have a limited understanding of brain function and the workings of neural networks. The development and application of innovative technologies that explore brain circuits over the spatial scales that range from molecular interactions at the synapse to electron microscopic level connections, and then to mesoscale imaging of structural and functional neuroimaging will result in a dynamic picture of brain function.

As an example, gait deficits contribute significantly to functional disability after stroke. Recent technological advances in stroke gait rehabilitation have made it possible for robotic devices to provide safe, intensive training through accurate repetitive motion.11 There is evidence that electrical stimulation of the brain, as a means to further engage post-stroke neuromuscular plasticity and enhance functional recovery, may promote recovery and improvement in symptoms. Various neuromodulation techniques are under investigation for stroke patients, including transcranial direct current stimulation, repetitive transcranial magnetic stimulation, motor cortex stimulation, and deep brain stimulation. Existing results show improvement in patients’ paresis in certain circumstances,12 and improved outcomes (such as the International Tourette Syndrome Deep Brain Stimulation Public Database and Registry).13

The most difficult disorders to understand are those without a known pathological signature. Recent evidence suggests that pure circuit diseases such as mood disorders may be better characterised by a combination of dimensions (emotions, cognitions, social) and a novel diagnostic system that cuts across traditional diagnostic classifications. By implementing psychological tasks and various neurovisualisation techniques, the experimental medicine approach has been used to determine specific predictors of neurocognitive and emotional abnormalities and to assess the effects of new treatments in these processes.14 New tools that could identify circuit disturbances that underly these abnormalities could serve as targets to enhance therapeutic development.

Worldwide data and methods portals with common data standards for sharing and data pooling could drive international collaboration. Such projects face huge challenges because of the unique complexity of data from an organ with billions of neurons and trillions of synaptic connections. It is therefore essential that we begin with ambitious but manageable goals—for example, integrating mouse serial electron microscopy connectomic data with light microscopy mesoscale connectomics, single cell census studies to provide scientists with reagents for genomic access to particular cell types so they can precisely monitor or modulate brain circuits. Computer...
technology for informatics platforms are critical to support modelling and theory development. The Human Brain Project’s platforms give scientists a single point of access to neuroscientific method, multiomic clinical data, and analysis tools from around the world. Thanks to the international collaborative projects, the field of functional neuroimaging has advanced substantially, showing the value of big data science. On the clinical side we have seen the value of harmonisation of variables among relevant studies to promote greater comparability across collaborating research projects.

Machine learning and artificial intelligence techniques based on big data are increasingly being used in both understanding and diagnosis of neurological disorders and offer a new model for personalised management. Machine learning techniques could be used to delineate the categories and predict the patients’ outcomes with various conditions. For example, artificial intelligence has been successfully used on pattern recognition of electroencephalogram or neuroimaging abnormalities for diagnostic purposes in patients with epilepsy. However, these efforts are only the beginning. A synergistic international effort could provide greater global impact and better use of precious research funding, including government, industry, non-governmental organisations, and individual contributions. It requires rewarding the groups or team for the collective effort rather than a few lead investigators. In the international brain project, expertise is unlikely to lie in a single country. The removal of national barriers for funding team science seems a desirable goal but is difficult politically and even more difficult when it entails intellectual property claims. The Human Brain Project exemplified team science funding within the European Union; the US BRAIN initiative makes funding available to any researcher from any country, as long as the proposed project is deemed worthy by the study sections that review it.

Importantly, new tools to map, monitor, and modulate brain circuits in humans hold great promise not only for the treatment of neurological disorders but also the ethical challenge to understand how these tools should be used. The answers may depend on cultural beliefs, but the processes for establishing ethical guidelines should be global and transparent. Many countries have incorporated ethical issues into the design of their brain programmes.

In conclusion, the collective success of bridging these projects into a global collaboration that aims to understand the scientific basis of brain structure and function could have a key role in this era of academic development. In addition, it would be of benefit for science as a whole, open up a new strategic direction and promotion for brain disease prevention, create new industries, and ultimately achieve a better life for individuals and the population.

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