The German Brain Plan
Agenda 2030

Supporting brain health.
Treating brain disease.

The roadmap to a brain healthy future in Germany.

Der Deutsche Gehirnplan
Agenda 2030

Die Gesundheit des Gehirns fördern.
Krankheiten des Gehirns behandeln.

GBC GERMAN BRAIN COUNCIL

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German Brain Council

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It's time to act for brain health!

The German Brain Council has prepared the "German Brain Plan – Agenda 2030" because human health is not possible without brain health.
Currently, 25 percent of all people worldwide have a neurological or mental illness, and these illnesses result in costs of more than 800 billion euros annually in Europe alone. Five examples covering the entire human lifespan, from stroke to depression, are presented to highlight these facts and ask for quick and effective help from policymakers and society to support research on better prevention and treatment.

Contents

The German Brain Plan

Germany needs a concerted national strategy to maintain health and combat brain diseases throughout the human lifespan. This strategy must be embraced by society and supported by policymakers. To this end, we have to define objectives for research, prevention, care and follow-up care and facilitate the achievement of these objectives. This paper provides analyses and selected examples as a framework for discussions.

This draft German Brain Plan is directed towards decision-makers in society, politics and the healthcare system. It outlines important steps in the areas of prevention, diagnosis, treatment and research and aims to act as a catalyst for public discussion and concrete political measures.

Large potential for innovation. Every day, well over 100,000 people are involved in the fields of neuroscientific, neurological and psychiatric research and medical treatment of the brain. They work in disciplines such as neurobiology, psychiatry and psychotherapy, neurology, neurosurgery, child and adolescent psychiatry, child and adolescent neurology, neurorehabilitation, neuroradiology, clinical neurophysiology, neuropathology, neuroanatomy and psychology. In addition, countless people care for neurological-psychiatric patients, either as employees or volunteer caregivers. Germany is one of the world's leading locations for these specialized fields, all of which are represented in the German Brain Council. Every day, we gain experience and knowledge that may represent the beginning of new types of treatment and care.

Agenda 2030: a roadmap for brain research. What is missing, however, is a unified, concerted strategy for performing research on the most important and complex human organ and for coordinating the numerous findings. The 2020s offer the chance to fundamentally improve the treatment of brain diseases. Therefore, with its 2030 agenda the German Brain Council is calling on policy makers to quickly make decisions that will enable the latest findings in science and medicine to be translated into effective measures for the good of the population.

In contrast to research on most other organs and disease areas, neuroscientific and neurological-psychiatric research encounters numerous, as yet undeciphered functions because of the complexity of our brain and its continuous interaction with its environment – and this research thus needs to use new approaches to understanding and treating diseases. A well-known example is Alzheimer's disease, which affects well over a million people in this country. Its origin is still unclear, even though the underlying pathology was described over 100 years ago.

The example of Alzheimer's disease illustrates another problem: the common public perception of brain diseases as age-related diseases. However, psychiatric and neurological diseases often occur in early and very early phases of life, when the course is set for the entire lifetime. For this reason, the German Brain Plan considers the whole lifespan of a person, from birth to old age. It is therefore tailored to the lifespan and covers the areas of prevention, acute treatment, rehabilitation and lifelong follow-up care.

The Executive Committee of the GBC

THE ROADMAP – AGENDA 2030

2022/2023

Raising of public awareness of the German Brain Plan. Networking. Identification of deficits in care.

2024/2025

Pilot projects on traumatic brain injury and depression. Promotion of early diagnosis, treatment and rehabilitation.

2026/2027

For all diseases, implementation of research findings in clinical practice: improvement of treatment success and recovery of functions.

2028/2029

Continuous expansion of project topics.

Reasons why a German Brain Plan is important

Brain health is of great societal importance because ...

- Physical and mental health is not possible without a healthy brain.
- One in three people is affected by a brain disease. This means individual suffering, loss of quality of life and autonomy and reduced productivity of hundreds of millions of people in Germany alone.
- Brain health is the most important national resource for our society and a prerequisite for education, creativity, innovation and international competitiveness.
- Brain diseases cause a high economic burden. In Germany, brain diseases result in direct costs of over 60 billion euros per year for the health care system. This amount corresponds to almost 20% of all health spending. The total costs of brain diseases for the German national economy are at least three times higher.
- Disorders at an early age can have effects throughout life, e.g., on education or life expectancy.

Brain research must be adequately strengthened and better financed because ...

- The complexity of the brain is nowhere near fully understood.
- The translation of research findings into therapeutic strategies is still unsatisfactory and needs to be improved.
- New, ground-breaking ideas and treatments (e.g., antisense therapies, molecular therapies, network therapies) have been applied only in individual cases but most of them are still waiting to be implemented and promise great leaps in knowledge.
- New treatment concepts can be improved through translation and back translation.
- Interdisciplinary configurations must be better promoted, for example between neuromedicine and data engineering or in the transition from adolescent to adult medicine.
- Structured promotion of the excellent academic potential in Germany could lead to a significantly better expansion of research.
- The roughly 4 million people with approx. 6800 rare diseases (orphan diseases) should also benefit from research.

We need modern care concepts for brain diseases to …

- Reduce individual suffering, improve quality of life and decrease the duration of each individual's disease and the burden on their families.
- Use funds more efficiently so that innovative, sometimes very costly treatment strategies can also be financed.
- Adapt care structures to both the existing need and modern treatments (e.g., new therapies for patients with 5q-linked spinal muscular atrophy or anti-amyloid therapies).
- Improve availability of telemedicine approaches, e.g., video treatments.

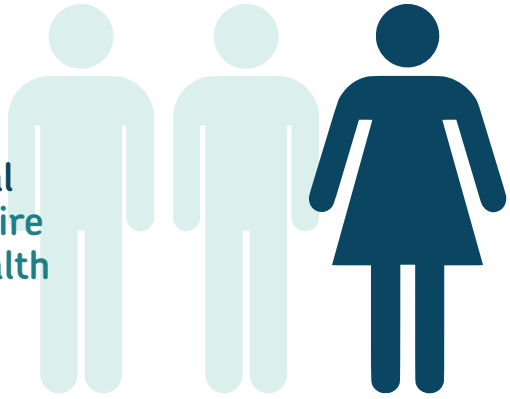
Promotion of brain health and education about brain diseases are necessary …

- To improve the general public's understanding of brain research.
- To reduce stigma about diseases of the central nervous system (CNS) so that, as a consequence, more people seek diagnosis and treatment.
- Because patients often cannot or do not want to speak for themselves.
- To make inclusion and participation a reality (e.g., at school and work, as opposed to high early retirement rates because of depression).

THE SITUATION

Disease burden of brain diseases

About 29 million people in Germany, i.e., about a third of the population, fulfil the criteria for a psychiatric or neurological diagnosis. This places a burden on our entire society: on patients, their families, the health system and the economy.



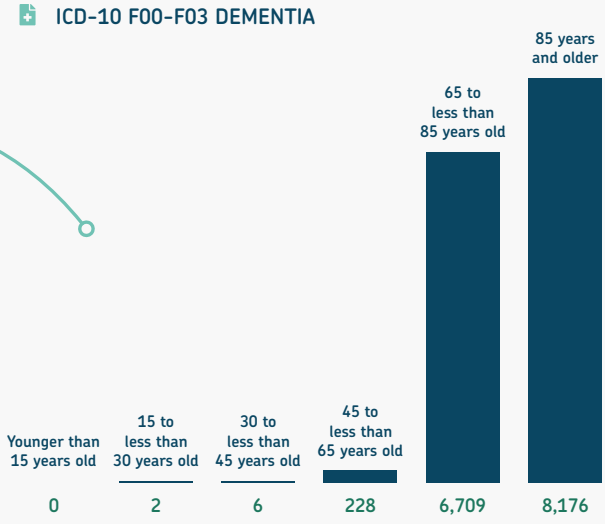
11 million people

In Germany (approx. 15 percent) have a neurological disease: about 1.2 million people have Alzheimer's disease, about 400,000 have Parkinson's disease and about 260,000 have a first or repeated stroke.

People with brain disorders are more likely to be placed on medical leave and to be unemployed; they retire earlier and have a significantly lower life expectancy than the general population.

Dementia is a typical disease of old age

Medical expenses in Germany, 2015, in million euros



Source: Federal Statistical Office (Destatis), status: 2015

The German population is getting older. Neurodegenerative diseases, such as Alzheimer's dementia, increase with age.

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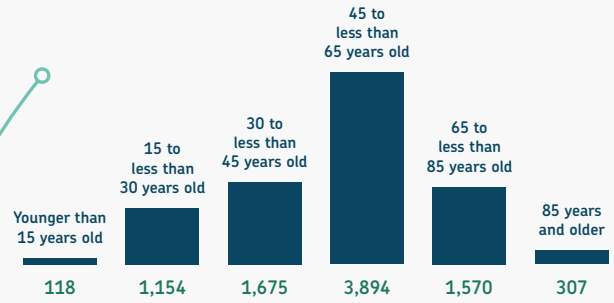
18 million people

in Germany, have a mental illness, of whom about 10 million have an anxiety disorder and about 5 million have depression.

Depression affects people of all ages

Medical expenses in Germany, 2015, in million euros

ICD10-F32-F34 DEPRESSION



Source: Federal Statistical Office (Destatis), status: 2015

Psychiatric and neurological diseases affect all age groups – from childhood to old age, e.g., depression, which must be increasingly treated in young people aged 15 and younger.

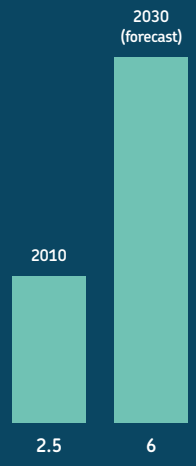
798 billion euros

In 2010, the total cost of brain disorders in Europe was 798 billion euros, of which 37% were direct health costs, 23% direct non-medical costs and 40% indirect costs. The average cost per citizen was €5,550.

Global costs of mental and neurological diseases

2010 and 2030 (forecast), in trillions (US$)

According to estimates from the World Economic Forum, in 2010 mental and neurological diseases caused costs of 2.5 trillion US dollars.



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The German Brain Council

The alliance against diseases of the nervous system

The German Brain Council (GBC) was founded as a non-profit association by 14 organisations in Berlin in 2018. Today it comprises 20 organisations and represents well over 60,000 members of medical and scientific professional associations and patient organisations. The German Brain Council develops solutions for a brain healthy future.

As an umbrella organisation, the German Brain Council bundles the competencies of all experts in diseases of the brain and nervous system from clinical medicine, basic research and patient groups.

www.braincouncil.de

The German Brain Council is a member of the European Brain Council.

The European Brain Council: a voice for the brain in Europe

The EBC is a non-profit organisation based in Brussels. It campaigns on the European level to ensure that policymakers do justice to the social relevance of neurological and psychiatric diseases and that research activities are funded accordingly. To this aim, it also bundles the activities of the national Brain Councils in Portugal, Spain, France, Belgium, the Netherlands, Germany, Croatia, Serbia, Ireland, Norway and Finland. The countries Czech Republic, Poland, Slovenia and Turkey are also represented in the European Brain Council even though they do not have a national Brain Council.

www.braincouncil.eu

Aims and areas of activity of the GBC

We advocate ...

- Life-long, good brain health, prevention and better quality of life,
- Patient-oriented health and care services that also consider the environment of patients and their relatives,
- Good care and the best possible participation from the start of symptoms to diagnosis, treatment and rehabilitation,
- Improved knowledge and quality through research and innovation.

To do this, we need ...

- Political support for a **national strategy for brain health** throughout the human lifespan,
- Prioritisation of funding for the development of **translational health programmes** for the treatment of brain diseases,
- **Long-term and adequate funding** of research on brain functions and diseases amounting to 10% of the overall public health research funding,
- **Destigmatisation** of people with brain diseases,
- **Support programmes for relatives** of people with brain diseases,
- **Greater awareness** in society of the topic of brain health.

A strong network

The member organisations of the German Brain Council

AADHD Germany (ADHS Deutschland, ADHS)
Alzheimer Research Initiative (Alzheimer Forschung Initiative, AFI)
German Association for Biological Psychiatry (Deutsche Gesellschaft für Biologische Psychiatrie, DGBP)
German Association for Bipolar Disorders (Deutsche Gesellschaft für bipolare Störungen, DGBS)
German Association for Epileptology (Deutsche Gesellschaft für Epileptologie, DGfE)
German Association for Child and Adolescent Psychiatry, Psychosomatic Medicine and Psychotherapy (Deutsche Gesellschaft für Kinder- und Jugendpsychiatrie, Psychosomatik und Psychotherapie, DGKJP)
German Association for Clinical Neurophysiology and Functional Imaging (Deutsche Gesellschaft für Klinische Neurophysiologie und Funktionelle Bildgebung, DGKN)
German Association for Neurosurgery (Deutsche Gesellschaft für Neurochirurgie, DGNC)
German Association for Neurology (Deutsche Gesellschaft für Neurologie, DGN)
German Association for Neuromodulation (Deutsche Gesellschaft für Neuromodulation, DGNM)
German Association for Neuropathology and Neuroanatomy (Deutsche Gesellschaft für Neuropathologie und Neuroanatomie, DGNN)
German Association for Neuroradiology (Deutsche Gesellschaft für Neuroradiologie, DGNR)
German Association for Neurorehabilitation (Deutsche Gesellschaft für Neurorehabilitation, DGNR)
German Association for Neurotraumatology and Clinical Neurorehabilitation (Deutsche Gesellschaft für Neurotraumatologie und klinische Neurorehabilitation, DGNKN)
German Association for Parkinson's and Movement Disorders (Deutsche Gesellschaft für Parkinson und Bewegungsstörungen, DPG)
German Association for Psychiatry, Psychotherapy and Psychosomatics (German Deutsche Gesellschaft für Psychiatrie und Psychotherapie, Psychosomatik und Nervenheilkunde, DGPPN)
German Federal Parkinson Association (Deutsche Parkinson Vereinigung Bundesverband, dPV)
Association for Neuropaediatrics (Gesellschaft für Neuropädiatrie, GNP)
Neuroscientific Association (Neurowissenschaftliche Gesellschaft, NWG)
RLS e.V. German Restless Legs Association (RLS e.V. Deutsche Restless Legs Vereinigung)

The Advisory Board of the German Brain Council

Prof. Peter Falkai, Director of the Department of Psychiatry and Psychotherapy at the LMU Hospital Munich
Prof. Bernd Huber, President of the LMU Munich
Prof. Veronika von Messling, Head of the Life Sciences Department at the Federal Ministry of Education and Research (Bundesministerium für Bildung und Forschung, BMBF)
Prof. Bernd Sommer, CNS Research at Boehringer Ingelheim
Prof. Ottmar Wiestler, President of the Helmholtz Association

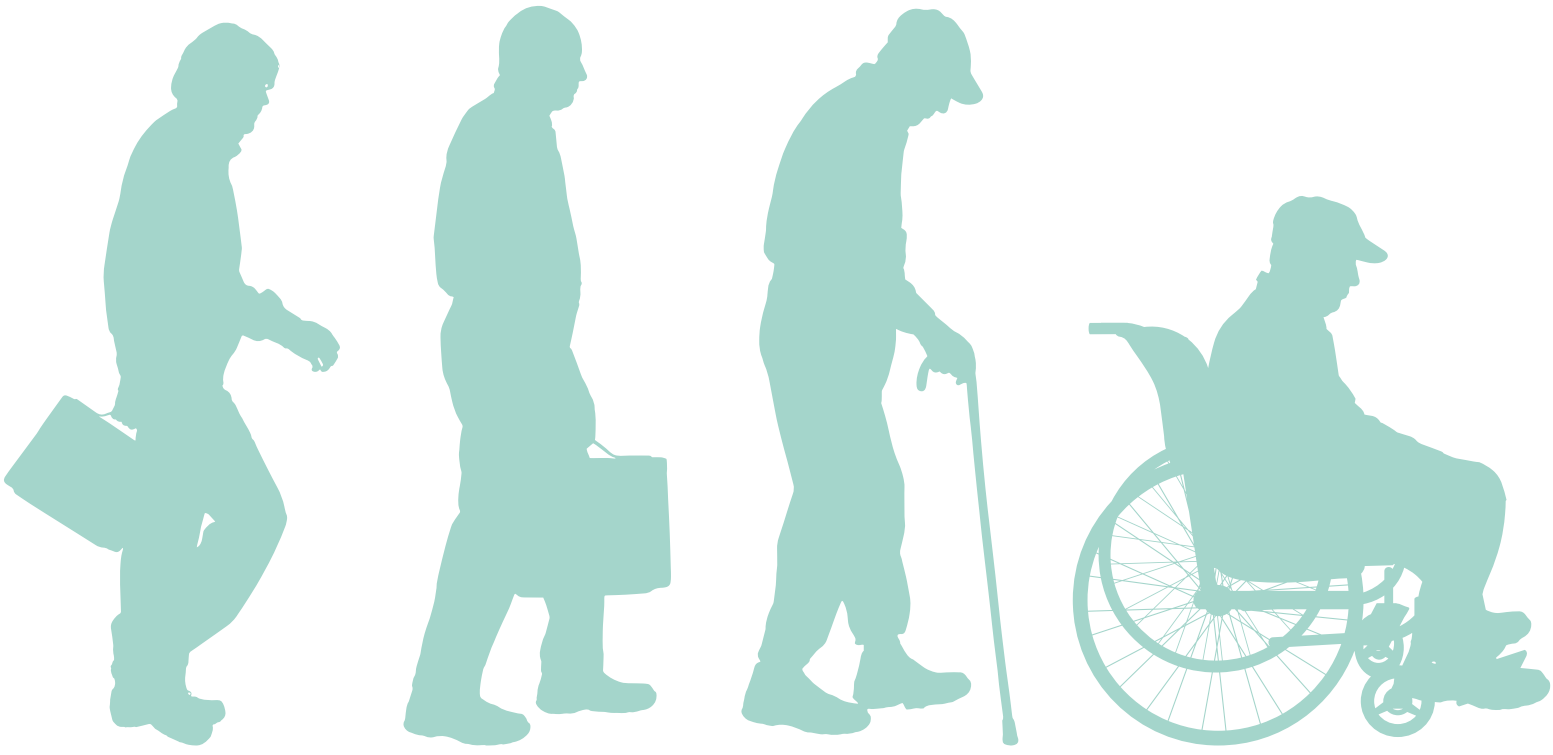
Brain health over the human lifespan exemplified by 5 brain diseases

The fields of neurology and psychiatry perform research on, diagnose and treat several hundred diseases, including numerous well-known diseases such as Parkinson's disease, multiple sclerosis, epilepsy and alcohol dependence, to name just a few. In addition to the widespread diseases, there are also thousands of rare diseases. New challenges, such as long COVID, add to the spectrum of brain diseases.

5 diseases – 5 representative examples

In the following chapters, experts – from adult, paediatric and adolescent medicine – summarise the existing knowledge on 5 brain diseases and describe the current research needs until 2030.

Contents



Traumatic brain injuries in children, adolescents and adults

U. Schara-Schmidt (children and adolescents)
N. A. Terpolilli and J.-C. Tonn (adults)

State of knowledge

Traumatic brain injuries (TBIs) include head injuries that affect the cranial bone (fractures) and brain tissue (concussions, injuries). Depending on the damage mechanism, TBIs are classified as diffuse or focal, open or closed, primary or secondary. These distinctions involve different pathomechanisms, clinical symptoms, courses, treatment options and prognoses. The severity of a traumatic brain injury is normally categorised with the Glasgow Coma Scale (GCS) score.

Nationwide, about 250,000 people suffer a traumatic brain injury every year, including 70,000 children and adolescents

Nationwide, about 250,000 people suffer a TBI every year, 70,000 of them children and adolescents. A first frequency peak is seen in children aged up to two years (often due to falls) and a second in adolescents aged 14 to 18 years (leisure activities, high-risk sports, mobility). From the age of 60, the incidence of falls and thus the frequency of TBIs increases considerably; given the age structure of the population in Germany, the group of older people thus represents the majority of patients with TBI.

Most people (up to 90%) suffer a mild TBI (TBI grade 1, concussion/mild concussion). The damage resulting from a mild TBI is not easy to recognise or assess – but the consequences may be more serious than hitherto assumed.

Some consequences of TBI (fractures, bleeding) can be detected within the first few minutes, but many others (e.g., brain swelling, contusions, infarcts, metabolic disorders, impairment of the fibre tracts in the brain) only develop in the subsequent days or weeks. Even after a mild TBI where imaging tests performed soon after the trauma show no relevant injuries, serious damage can occur over time in some of those affected and sometimes severely impair their everyday lives. For example, after a symptom-free period, bruising of the skull in older patients can result in secondary bleeding between the brain surface and the dura mater of the brain (subdural haematoma) that requires treatment.

Today we also know that – even years after a TBI – active injury processes can be demonstrated in brain tissue and can lead to problems with fine motor skills and balance and to neurocognitive and psychiatric disorders (such

Even mild traumatic brain injuries can result in complications that have a negative impact on the prognosis.

as concentration and memory disorders, avolition, depression and anxiety disorders); in addition, dementia occurs more often and earlier after TBI. This symptom complex is referred to as chronic traumatic encephalopathy (CTE). The development and severity of CTE does not necessarily depend on the severity of TBI. Findings from professional sports show that repeated, mild TBI (e.g., in contact sports, football, American football) can lead in the long term to pronounced brain damage with corresponding severe symptoms. This knowledge is also having an increasing impact on regulations in popular and amateur sports. For example, the German Association for Neurology now recommends that footballers wear head protection for when they head the ball.

One thing is true for all TBI: serious risks may remain hidden at first, so early additional treatment may not be performed. Rapid identification of TBIs and long-term follow-up with appropriate diagnostic tests and rehabilitation are essential, especially in children, to avoid and reduce long-term TBI-related deficits.

State of research

After trauma, brain damage usually happens in several phases. The injuries caused directly by the trauma (i.e., within the first few minutes), e.g., ruptured blood vessels (bleeding) and disruption of the brain's fibre tracts or fractures, are referred to as the primary injuries. This initial damage triggers a series of cellular injury processes that, after a certain period (days to weeks), result in brain swelling, insufficient blood flow and, ultimately, cell death. This secondary brain damage can result in delayed death of brain areas not initially affected by the trauma. Even without further trauma, the brain damage can become much more widespread.

For the above reasons, a TBI may initially not cause significant impairments but later can seriously endanger those affected and cause severe long-term neurological damage.

Many mechanisms of secondary damage have already been studied and elucidated, although this is only true for the acute phase in the first few days after the trauma. This research has identified potential targets for possible drug treatment, e.g., inducible NO synthase, an enzyme that produces nitric oxide (NO), which causes oxidative stress and inflammatory responses.

This research is particularly important for mild TBI because it enables us to identify people early on who initially have mild initial symptoms but may have a serious course of the disease and therefore require timely diagnosis and treatment.

In TBI research it is also important to remember that children are not little adults. The pathophysiology of paediatric TBI is different from that of adult TBI. In children, the brain is not yet well protected by the calvaria. Decreased resistance to shear forces accompanied by incomplete myelination and increased water content lead to diffuse axonal trauma with generalised cerebral oedema. In addition, the immature blood-brain barrier reacts more sensitively. Lastly, secondary metabolic neuronal damage plays a major role in children: a higher density of NMDA receptors, greater calcium influx into the cell and lower glutathione peroxidase activity and glutathione stores with higher levels of oxidative stress.

Gaps in basic research

It is not sufficient to treat patients with TBI only in the acute phase. Even after mild TBI, brain damage can continue to accumulate for a long time – for years or maybe decades – after a trauma. However, the mechanisms of this chronic phase remain largely unknown and need to be studied with suitable experimental approaches to develop effective treatments for the long-term damage after TBI.

Inflammatory processes and cell death mechanisms play an important role in chronic brain damage after trauma. In addition, in the long term TBI appears to lead to changes similar to those in neurodegenerative diseases, e.g., the formation of protein plaques like in Alzheimer's disease or Parkinson's disease. The cerebral vessels may also show changes related to trauma. These changes can impair the regulation of cerebral blood flow and the associated neuronal activities and thus harm energy balance and memory and learning processes in the long term. More basic research is necessary to allow us to prevent the known development of post-traumatic dementia in the future.

The main question in basic research: Which processes are triggered even by a mild TBI that lead to a years-long cascade of sometimes severe brain cell damage, up to and including dementia?

Gaps in clinical research

Despite promising results in animal experiments, to date no drug has been developed that reduces secondary brain damage in the chronic phase, i.e., that has a neuroprotective effect. Mild TBI is a particular challenge: it is still unclear which factors (e.g., genetic predisposition, association with co-medication, accident mechanism, etc.) are associated with a particularly serious course and poor prognosis. Therefore, future research must aim to identify those people who are at risk of a serious course so that they can be referred early on for diagnostic tests and additional therapies. This research need is also relevant in the chronic phase because we need to be able to identify long-term deficits as quickly as possible and minimise them with specialised rehabilitation procedures, for example. Thus, we also need to develop new imaging, diagnostic and rehabilitation methods.

The above research needs are particularly relevant for paediatric TBI patients. The therapeutic application of neuroplasticity in childhood and adolescence is complex: on the one hand, the capabilities from before the accident should be restored and, on the other hand, the prerequisites for normal further development should be fulfilled. If these goals are not achieved, the "established" damage can also have secondary effects on other functional areas that are not directly affected ("growing into the deficit"). Studies on moderate and severe TBI demonstrate better effectiveness and long-term results with early rehabilitation but this aspect has not yet been studied in mild TBI.

Alzheimer's dementia as an example of a degenerative disease

R. Perneczky and A. Flöel (adults)
F. Heinen (children and adolescents)

State of knowledge

Dementia is the main cause of disability and reduced quality of life in old age and affects about 50 million people worldwide (approx. 1.6 million in Germany). This number will increase to over 150 million by 2050 because of the aging of the population, leading to almost insurmountable challenges for health and social systems. About two thirds of dementia cases are due to Alzheimer's disease and, in many patients, cerebrovascular injury (e.g., stroke) worsens the clinical picture. Despite great efforts, disease-modifying treatments are still not available for dementia and the effect of the approved drugs is purely symptomatic and weak. Epidemiological studies have shown that most types of dementia have a multifactorial aetiology, i.e., the individual dementia risk is determined by the interaction of various genetic and lifestyle-related factors, and that other mental illnesses, such as depression, are associated with a higher incidence of dementia in old age.

State of research

Since the early 1990s, we have known from studies of the extremely rare familial variant of the disease that accumulation of amyloid-β fibrils in the brain triggers a cascade of pathological processes that lead to hyperphosphorylation of intracellular tau, neuroinflammation, neurodegeneration and eventually dementia.

Even though the key role of amyloid-β is known, no effective therapies are available yet.

A problem in Alzheimer research, in particular in clinical studies, is that diagnosing Alzheimer's disease on the basis of clinical features is often too inaccurate. Therefore, great efforts have been made to improve biomarker-based diagnostics. In the past two to three years, a lot of progress has been made, in particular in the field of blood markers (amyloid-β, tau, etc.). Amyloid-β pathology also plays an important role in children because the gene for the

precursor protein APP is found on chromosome 21 and, in trisomy 21, leads to cerebral amyloidosis, neurodegeneration and often early-onset dementia.

Gaps in basic research

Despite the clear evidence for the key role of amyloid-β in the disease process, the associated mechanisms of development remain unclear. In addition, we need to clarify how neurodegeneration and other relevant pathomechanisms, such as neuroinflammation, are interrelated.

Gaps in clinical research

Despite numerous strategies, a cure is not yet in sight. We need a comprehensive strategy for preventing dementia.

The development of disease-modifying treatments also still focusses on eliminating amyloid-β. To date, all clinical studies have failed because of a lack of efficacy or poor tolerability, but there is currently hope that an effective passive immunisation strategy will be approved. However, at best, this approach will enable only an effective slowing down of the disease processes, not a cure. Therefore, a great need for better drugs will remain that also prevent accumulation of tau or counteract neuroinflammation, for example, and that can be used in both children and adults. In addition, more research is needed that focuses on non-drug approaches that enable comprehensive, resource-saving prevention of dementia.

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Depression in children and adults

G. Schulte-Körne (children and adolescents)
P. Falkai (adults)
G. Gerlinger

State of knowledge

Every year, 27.8% of adults in Germany (17.8 million inhabitants) meet the criteria for a mental illness and 7.7% (4.9 million) the criteria for unipolar depression (1). In children and adolescents, the prevalence is 5.4% (2). The incidence is increasing in adolescent girls. After anxiety disorders, depression is the second most common mental illness; noteworthy here is that the presence of an anxiety disorder often precedes a depressive illness so an anxiety disorder can be viewed as a risk factor or precursor illness. Depression is defined by illness episodes in which mood and drive deteriorate to significantly lower levels than beforehand for at least 14 days. As a general rule, people have depression for months or years before it is recognised and only about a third of cases receive guideline-based treatment.

It takes two years for depression to be identified in adolescents. Only 12.5 percent receive adequate treatment.

The approximately 2-year delay in treatment of depression in adolescents is very long. Only 12.5% of children and adolescents are in child and adolescent psychiatric or child and adolescent psychotherapeutic treatment (3). Depression has a high recurrence rate in children and adolescents, and primary school children with depression have an increased risk of having another period of depression (4). In children and adolescents, family-related, psychoeducational and psychotherapeutic treatment approaches are the mainstay of therapy and longitudinal studies on treatment course, in particular inpatient treatment, are lacking.

The treatment options for adults have been well studied and range from low-threshold interventions (e.g., digital health applications) for mild episodes and purely psychotherapeutic treatment recommendations to combined treatment with pharmacotherapy and psychotherapy or neurostimulation approaches for severe episodes of the disease (5). About 50% of those treated in adulthood respond very well to the evidence-based treatment options and have no difficulty in again leading a life without significant impairments. The other half of those affected live well with disease-related limitations, but about 10% of all patients develop a chronic disease course. Such a course is characterized

by relevant impairments in concentration and reduced vitality and mood that do not respond to the usual psychotherapeutic or pharmacotherapeutic treatment options and are associated with significant limitations in work and private life. Unfortunately, new treatment options such as esketamine and non-invasive brain stimulation (NIBS) have done little to change the situation. With almost half a million people affected in Germany, the topic of difficult-to-treat or chronic depression represents a very large, unmet medical need. Even though some novel treatment approaches such as NIBS, vagus nerve stimulation and rapid-acting antidepressants (RAADs) have been introduced into therapy at specialised centres in recent years, they only help some patients and are not yet widely available in clinical care. Furthermore, because no biomarkers are generally available for managing therapy in the field of depression treatment, the choice of an effective therapy is determined purely on the basis of the clinical impression, a fact that also contributes to the latency in treatment response.

In line with its high prevalence rate and the severe impairments it causes, depression is one of the main drivers of the increasing number of work absences due to illness and the growing rate of inability to work because of mental illness (6). It contributes significantly to the 44.4 billion euros (13% of the total costs) in direct costs related to mental illness in Germany (7).

State of research

The cause of depression is related to an interaction of genetic and environmental risk factors. The heritability, i.e., the proportion of disease caused by genetic factors, is estimated to be 50% to 60% and follows a complex genetic model. This means that many common gene variants (single nucleotide polymorphisms, SNPs) interact, each with only small individual effects, and together and through their interactions increase the genetic risk and ultimately cause it to cross the threshold for disease. This genetic risk interacts both with environmental risk factors that affect the stress axis (such as experiences of mobbing and chronic stressors at work and in everyday life) and with early stressful life events, such as early traumatisation through physical, sexual or psychological violence, which can have long-term functional consequences for limbic brain structures. Important is that none of the genetic changes alone, but also no individual environmental event, determines a later depression; on the contrary, the risk factors are cumulative and probabilistic.

On the neurobiological level, the main feature is disturbed synaptic plasticity in limbic brain structures, probably particularly in the hippocampus. Several pathophysiological mechanisms converge on this terminal pathway: low-grade neuroinflammation with increased pro-inflammatory and reduced anti-inflammatory cytokines and other signalling pathways, altered secretion of neurotrophic factors and an increase in excitatory neurotoxicity, with an imbalance in glutamatergic NMDA/AMPA-mediated neurotransmission, to name just a few. This disturbed synaptic plasticity underlies a dysconnectivity of limbic-prefrontal circuits. This is reflected on the one hand in altered functional connectivity, which can be assessed by fMRI, and on the other hand in disturbed white matter integrity, as can be seen in DTI and related imaging methods.

Pharmacological and other therapeutic methods result in a rapid adaptive change in activation, e.g., in the amygdala and other parts of the limbic system, which also indicates that a fine structural change in limbic circuit function, e.g., through the emergence of new nerve cells and their networking, underlies depressive disorders. Accordingly, a possible common mechanism of action of antidepressants, but also of psychotherapy, is restoration of neuronal plasticity in prefrontal limbic control circuits.

Gaps in basic research

Depression has complex neurobiological causes that still need more detailed scientific evaluation.

The results of research to date show that the different types of depression represent very heterogeneous diseases with completely different developmental pathways that may then converge on a common pathway, at least in part. The differentiation of this heterogeneity and the attribution of specific pathomechanisms to an individual in the sense of precision medicine represent a large translation gap in affective disorders. Currently, some aspects (cellular function, micro and macro circuits) can be examined in humans only indirectly or not at all so there is an urgent need for new experimental translational methods to identify pathophysiological mechanisms in the living human organism – with the help of scalable biomarkers – and, based on the findings, to suggest suitable treatments.

In this context, artificial intelligence approaches are also promising for studying genetics, epigenetics, transcriptomics, metabolomics and proteomics in large studies on longitudinally phenotyped cohorts and linking them to multimodal imaging data, digital phenotyping and physiological measurements. This work will allow new pathomechanisms to be identified and then treated in a targeted way and early on. The fact that such an approach can be successful is demonstrated by examples such as the contribution of the FKPB5 gene to depressive disorders: here, based on the understanding of the gene x environment interaction, research achieved a pathophysiological understanding from the risk gene to the epigenomic regulatory mechanisms.

Gaps in clinical research

Clinical research must find (bio) markers to enable better treatment of subgroups.

Little research has been performed on whether and how early diagnosis and treatment of precursor diseases such as anxiety disorders in childhood and adolescence can prevent depression in adulthood. On the other hand, hardly any data are available to explain the observed association between depression and neurodegenerative dementia, such as Alzheimer's dementia, and how a transition can be prevented. Specific therapies that consider comorbidities such as anxiety disorders or addictions are lacking. In general, we can expect that the understanding of disease mechanisms with different effects during disease development will allow (bio)markers to be identified for disease subgroups, for which mechanism-based, new therapeutic approaches will then have to be developed and evaluated in clinical studies. As an example, first approaches are testing immunomodulatory therapies based on different immunological biomarkers which could be used specifically in patients with depression.

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5q-linked spinal muscular atrophy as an example of a rare disease

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State of knowledge

5qSMA is a rare disease and type 1 of the disease, which has a severe course, is the most common genetic cause of death.

Rare (or orphan) diseases are defined as diseases that occur in less than 1 in 2000 people. Nevertheless, in Germany about 4 million people are affected by rare diseases. 5q-linked spinal muscular atrophy (5qSMA), which has an incidence of approx. 1 in 7,500 live births in Germany and a carrier frequency of 1 in 50, is the most common genetic cause of death in childhood. Manifestations can vary greatly: from an onset in the neonatal phase (significant muscle weakness, respiratory and bulbar disorders) to one in old age (e.g., with mild muscle weakness in the pelvic girdle area). Depending on the complex clinical symptoms of those affected, time-intensive, multi-professional care is required that places a heavy burden on families. This care uses enormous human, organisational and last but not least, economic resources of families and the health care system.

State of research

Today, quality of life is significantly better thanks to improved care and three available drug treatments.

Research on 5qSMA is a success story and shows paradigmatically how consistent basic research over a period of 20 years can lead to successful treatments.

The *SMN1* gene, and to a lesser extent the *SMN2* gene, is required for the production of a sufficient amount of survival motor neuron (SMN) protein. Biallelic mutations in the *SMN1* gene result in a lack of SMN protein, particularly in alpha motoneurons; however, SMN protein also plays a fundamental role in other organs. Today, its known functions are regulation of cell homeostasis, biogenesis of ribonucleoproteins, mRNA trafficking, local translation, cytoskeletal dynamics, endocytosis and autophagy.

Clinical research focusses on long-term courses and evaluations of organ involvement. For example, the role of the heart and its possible clinical pathology has not been sufficiently well studied. However, this knowledge is

important to determine whether any cardiological follow-up examinations may be necessary in the course of the disease.

Since 2017, nusinersen (Spinraza®, EMA approval on July 1, 2017) has been available for the treatment of all clinical subtypes by intrathecal administration according to a defined scheme. Since 2020, one-time intravenous administration of onasemnogene abeparvovec (Zolgensma®, EMA approval on May 1, 2020) is available for type 1 SMA or SMA with up to 3 SMN2 copies. Risdiplam (Evrysdi®), a small molecule, is approved in the USA (FDA approval in August 2020) and in Europe (EMA approval in March 2021) for all SMA subtypes from the age of 2 months. Nusinersen and risdiplam aim to upregulate the *SMN2* gene to compensate for the absence of the *SMN1* gene; onasemnogene abeparvovec, a synthesised transgene, replaces the natural *SMN1* gene.

Gaps in basic research

We still do not fully understand the pathophysiology of 5qSMA. Some modifiers are known but they do not explain all the clinical phenomena. To further improve our understanding of the interrelationships, the following research is required:

- SMN-independent signalling pathways must be investigated to enable us to counteract SMA pathology.
- The contribution of novel emerging phenotypes (neuronal and systemic) after recovery in patients with SMA and in animal models must be determined.
- Key functions and roles of the SMN protein at different time points during development and/or in different tissues and organs must be characterised.
- Additional biomarkers that determine the success of treatments that restore SMN in SMA must be identified and those that have already been detected must be further described.
- New and improved preclinical animal models of SMA must be developed.
- The effects of combining different therapeutic approaches must be studied.

Gaps in clinical research

Despite the encouraging developments in the treatment of 5qSMA, important questions about the symptoms and basis of the disease and translational aspects remain unanswered. Working on these questions is the important task in the coming years.

The ever-improving care, including new medications, are changing the clinical picture and the lives of those affected and their families. Most patients see substantial improvements in life expectancy and quality of life, which is an important positive effect. Nevertheless, adverse effects must be estimated that are not yet fully known or understood. If drugs for rare diseases, so-called orphan drugs, have a positive effect on the course of the disease they are approved relatively quickly and, at that time, not all adverse effects are known or completely understood. Therefore, even after approval it is very important to record long-term treatment data in industry-independent registers and to work on important new questions in a learning system.

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Stroke in children and adults

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State of knowledge

Stroke is preventable and treatable – but the potential often remains untapped. Strokes can affect all age groups. They occur suddenly (approx. 260,000 per year in Germany), often repeatedly or also insidiously over many years. Strokes are the leading cause of permanent disabilities, the second leading cause of dementia and the second leading cause of death. Diseases of the cerebral blood vessels are one of the most common diagnoses in German nursing homes. Currently, they cause annual costs of approx. 8 billion euros. However, these costs do not reflect the psychological and social consequences for patients and their caregiving relatives. As a result of the demographic trend, these burdens will increase further in the coming decades unless we act now.

In Germany, about 260,000 strokes occur in adults compared with only 300 to 500 cases in children and adolescents. Therefore, the state of research in the very young age group is not ideal.

Stroke is not only a disease of adults; even though it is much rarer, with only 300 to 500 cases per year, it can occur in young age groups, from neonates to adolescents. Two-thirds of paediatric stroke patients have residual motor impairments, and post-stroke epilepsy is also common. Special attention must be paid to the effects of stroke on cognition, behaviour and well-being because these aspects play a decisive role in how this age group copes with life and in their success in life. Because of the large impact of stroke on the affected children and their families, long-term, interdisciplinary, multi-professional biopsychosocial care is needed that focuses on the child and the characteristics of their development in everyday life.

State of research

The introduction of systemic thrombolysis and mechanical thrombectomy in people with ischemic stroke has resulted in marked improvements in clinical outcome after stroke. The nationwide availability of stroke units and the introduction of new drugs to treat atrial fibrillation, one of several causes of stroke, mark further milestones in stroke treatment and the prevention of stroke events.

Findings from basic research and in particular from genetics have made a significant contribution to our understanding of the disease and the development of new treatment approaches.

Accordingly, in the past few decades various molecular mechanisms have been identified that drive cell death in nerve cells after a stroke. However, this knowledge from basic science has mostly yet to be successfully translated into everyday clinical practice. Thus, the large number of positive preclinical studies has not yet led to new, innovative therapies that protect the brain tissue damaged by a stroke (neuroprotective agents). Consequently, even after many decades of stroke research the problem persists that recanalizing therapies are the only available effective treatment options that can rescue damaged brain tissue and thus positively influence neurological recovery in the long term.

In stroke, the advances and positive experiences in adults cannot simply be transferred to young people.

Although at least the above-mentioned evidence-based treatment options are available for strokes in adults and nationwide care has been successfully established at stroke units and neurovascular networks, the treatment of children and adolescents with acute stroke is still suboptimal and comparable care structures are not available throughout the country. The treatments established in adults can only be used in children as off-label treatments, with limited experience and limited evidence, and their specific efficacy and risks in children and adolescents need to be understood and critically reflected on. Randomised, prospective clinical studies, in particular on acute treatment, are not usually feasible in children because of the small number of cases and often delayed diagnosis. The broad, dynamic experiences from adult neurology and their positive developments cannot simply be transferred to paediatric patients because of the specific features of the developing brain in children and the fundamentally different aetiology of strokes in children.

Gaps in basic research

Basic research is facing the great challenge of translating these findings into everyday clinical practice. Therefore, funding is required for cutting-edge research at universities that, besides research on new molecular mechanisms, aims at the targeted translation of existing basic scientific knowledge.

Some of the mechanisms that lead to delayed cell damage and fatal cell death after a stroke are quite well understood. Such mechanisms include the so-called excitotoxic effect of the synaptic messenger substance glutamate on the main hubs in the brain, the glutamatergic synapses. However, research is urgently needed on how an undersupply of energy directly influences glutamatergic synapses, which are affected very early on in the ischemic cascade.

Still almost completely unexplored, for example, are the causes of the variations in vulnerability of different brain areas to a disruption of the energy supply. In addition, it remains unclear why cellular disturbances due to an energy deficit are sometimes partially or completely reversible but sometimes result in permanent damage. A key role may be played by delayed inflammatory processes, which are still largely not understood and only develop after the acute stroke phase.

In future studies and research projects, a new approach to damage mechanisms will afford new insights into pathomechanisms: whereas research to date has focused mainly on nerve cells, a system-oriented analysis of all involved compartments that includes neuronal cells (pre- and postsynaptic), glial cells (astrocytes, microglial cells) and the extracellular space will point the way ahead. This holistic understanding of the basic pathomechanisms is urgently needed for development of better therapeutic strategies for treating stroke-induced brain damage.

In childhood stroke, the complex pathomechanisms are not yet fully understood. Therefore, research on this topic must focus on genetic, immunological and endogenous risk factors.

Gaps in clinical research

The special challenges include cerebral haemorrhages, which have a particularly unfavourable prognosis (half of those affected die within the first year), diseases of the small cerebral blood vessels (approx. 25% of strokes) and other vascular diseases that primarily affect the brain and for which no effective treatments are available yet. Also unsolved is the problem of secondary damage to nerve cells after a stroke, e.g., due to inflammatory processes. This issue is actually made worse by the currently available recanalisation treatments because the restoration of blood flow can enhance the inflammatory response in the affected brain. Some progress has been made and treatment options are within reach. The same is true for new approaches to promote post-stroke functional recovery by electrical stimulation and the development of new drugs to prevent cerebrovascular diseases.

Unacceptable: In children and adolescents, the interval from a stroke until treatment is 23 hours on average. A good prognosis requires an intervention within the first 6 hours.

The same is true in children and adolescents: time is brain. For stroke in childhood, the main priority must be to reduce the hitherto unacceptable delay in provision of care (according to the literature, the mean time from stroke to treatment is 23 hours).

The development of (telemedicine) neurovascular care networks for paediatric stroke, analogous to the situation in neurology, could allow every child to receive optimal personalised acute treatment. The presence of multidisciplinary expertise in these care networks is a prerequisite for the complex aetiological confirmation of diagnosis and for establishing the individual risk profile and associated individual relapse prevention. In particular in the case of arteriopathies such as focal cerebral arteriopathy, a frequent cause of strokes in children, the benefit of immunosuppressive therapy must be evaluated in clinical studies.

Cerebral haemorrhage is the most common cause of stroke in children. It requires special kinds of treatment.

Brain health over the human lifespan: from prevention to rehabilitation

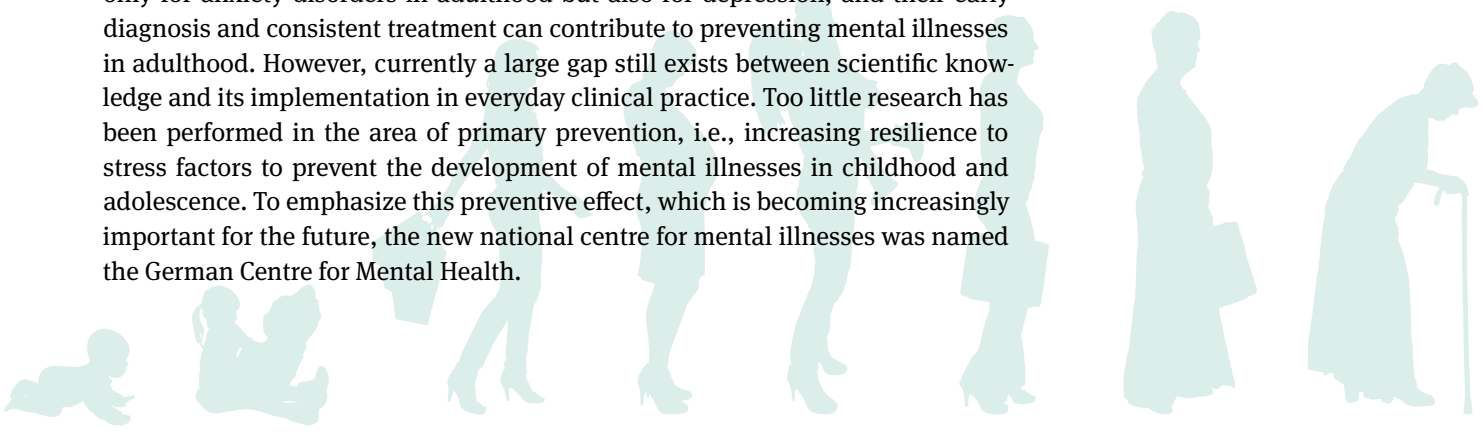
T. Mokrusch
J. Deckert

Brain diseases or impairments in brain health due to stroke, traumatic brain injury, multiple sclerosis, Parkinson's disease, the degenerative processes of dementia, schizophrenia, depression, anxiety disorders, etc., have a high global burden of disease. Therefore, they represent a high burden for those affected and the community. From 1990 to 2017, the number of life years with a brain disease increased by 52.9% (1). Mental illnesses are the second most common reason for inability to work and account for 10% of work absences due to illness and, at a rate of 40%, are the most common reason for early retirement (2, 3).

In the Federal Republic of Germany (1,942 hospitals with 498,718 beds, 1,142 preventive and rehabilitation facilities with 164,266 beds), payers spend 91.3 billion euros every year on hospital treatments and the total expenses for health care services amount to 390.6 billion euros, 36.5 billion of which are for rehabilitation and participation services (figures for 2017 from the Federal Ministry of Health and the Federal Working Group on Rehabilitation).

From prevention to rehabilitation

The benefit of using preventive measures to avoid neurological and psychiatric diseases is beyond debate. Prevention is not only important for individual health but also has clear economic benefits (4). One hereby distinguishes between primary, secondary and tertiary prevention and in primary prevention, between general, selective and indicated prevention (5). In the field of mental illness, there are differentiated concepts for the prevention of subsequent diseases and relapses, in particular for secondary and tertiary prevention. Thus, mental illnesses in childhood and adolescence, such as anxiety disorders, are precursor diseases not only for anxiety disorders in adulthood but also for depression, and their early diagnosis and consistent treatment can contribute to preventing mental illnesses in adulthood. However, currently a large gap still exists between scientific knowledge and its implementation in everyday clinical practice. Too little research has been performed in the area of primary prevention, i.e., increasing resilience to stress factors to prevent the development of mental illnesses in childhood and adolescence. To emphasize this preventive effect, which is becoming increasingly important for the future, the new national centre for mental illnesses was named the German Centre for Mental Health.



The same is true for rehabilitation, also with respect to both individual and national economic health. Every euro invested in rehabilitation saves the state three to five euros in overall national economic costs, including the financing of absences from work, pension payments and costs for lifelong follow-up care (6, 7).

A look at the plans of other member states of the European Brain Council shows that rehabilitation is understood on the European level as a major contributor to the health of the entire population and is integrated into the overall planning (8, 9).

The example of neurorehabilitation research illustrates the momentum developing in the field of rehabilitation of brain diseases. This research has been performed for three decades and has been increasing, as is reflected in the number of publications. In the past 30 years, the number of publications in PubMed (search term "neurorehabilitation") has increased from 88 to 5166 per year. During this period, research in the field of neurological rehabilitation has yielded a large number of new diagnostic methods and therapeutic procedures. These results were mainly achieved through close professional contact between research groups in the fields of basic science and acute treatment.

One example of the clinical and technical development of innovative treatment approaches in neurorehabilitation is the use of robotics. This term refers to therapy devices that support lost movements with the help of intelligent, electronically controlled mechanisms and that can also bring the patient back. Just as pioneering are the therapeutic developments in the field of virtual reality: not only can they be used to practice motor skills, but cognitive deficits are also increasingly becoming the focus of therapeutic successes.

In the field of mental illness, rehabilitation measures are firmly established for schizophrenic illnesses, with a complex system of options depending on the impairment and needs of those affected, e.g., they also include employment possibilities on the third labour market, which enable participation of those affected (10). Compared with the situation in schizophrenia, in the field of affective disorders rehabilitation is much less differentiated, despite the high prevalence of these disorders, the associated long periods of inability to work and the high rate of early retirement. Therefore, there is a considerable need for research in this field.

In the meantime, three scientific professional associations and patient organisations have been established in this field: the German Society for Neurorehabilitation (DGNR) as a professional association of doctors, the German Society for Neurotraumatology and Clinical Neurorehabilitation (DGNKN) as an association of doctors and therapists and the Federal Association of NeuroRehabilitation (BNR) as the umbrella organization of service providers.

In the field of mental illness, the German Society for Social Psychiatry (DGSP), the Federal Working Group for the Rehabilitation of Mentally Ill People (BAG RPK) and the German Association for Clinical Psychotherapy, Prevention and Psychosomatic Rehabilitation (DGPPR) have become involved.

Despite these positive developments, to date this topic has not been firmly anchored in the health and social policy regulatory framework and the losses caused by friction between the different cost bearers have not been overcome. In this respect, there is a need not only for research but also for health policy action.

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Shaping the future: e-health, digitalisation, telemedicine

T. Mokrusch
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The areas with a great need for research and therefore also a need for financial support include electronic health, which has the potential to improve documentation and data exchange in prevention, inpatient acute treatment, rehabilitation and outpatient follow-up care.

Although digital elements in the care structures of the German healthcare landscape have been prepared and implemented under the term e-health for three decades, they still lag behind those of other European countries and were also near the bottom in an international comparison (1).

Nevertheless, this politically desired development is perceived mainly positively by the general public and was also accelerated by the corona pandemic. It has currently reached a further step in its development with the Digital Care and Caregiving Modernization Act (DVPMG). As a result of the DVPMG, which came into force on 3.6.2021, and the Future Hospital Act (KHZG) a fund will be established for the future of hospitals that provides 4.3 billion euros for digitisation, cybersecurity and emergency care. Projects at university hospitals can be funded with up to 10 percent of the funding volume of the respective state. However, the use of these funds for research on brain health is not provided for in this setting.

E-health is strategically divided into:

- General organisational applications with data protection and data exchange (e.g., electronic health card, electronic patient records, hospital information systems)
- Specific telemedicine applications (e.g., digital health applications and video treatment)
- Types of online health communication (e.g., video consultation sessions with doctors and psychologists, speech therapists, occupational therapists and physiotherapists).

E-health applications are fundamentally important in all stages of the human lifespan. Brain health determines our life from the day we are born and requires preventive measures, acute interventions and subsequent rehabilitation with lifelong follow-up care.

The pandemic has caused a sharp increase in the psychological burden on the population, as well as in the use of video treatments and digital health applications and the associated possibilities for reimbursement. At the same time, internet companies such as Google and Amazon have intensified their activities in the field of electronic health care in the form of both online psychotherapy services and semi-automated, treatment-based drug options,

including sales and shipping. Extensive studies are required in these areas to differentiate between meaningful, guideline-based therapies and uncontrolled, possibly externally controlled self-therapy measures.

Examples of topics with a need for research funding are:

- Telemedicine care in the acute stage and during rehabilitation (2, 3, 4)
- Further development of treatment programs for neurorehabilitation and psychotherapy that use virtual and augmented reality (5, 6)
- Development and evaluation of e-health interventions for specific user groups (e.g., children and adolescents with mental illness) that have been underrepresented so far in telemedicine care
- Development of long-term solutions for online options for mental disorders and illnesses that go beyond simple counselling (feasibility and effectiveness studies of professional psychotherapy sessions)
- Establishment of a stroke programme as a decision support system for doctors and therapists in the entire care chain (stroke unit/ITS – early neurological rehabilitation/weaning – neurorehabilitation – follow-up care) is conceivable and desirable, analogous to the IBM programme “Watson for Oncology” (7)
- Development of a weaning centres register, which includes the quality of the facility, processes and results, as an interface between neurological intensive care and early rehabilitation
- Development of a platform within the telematics infrastructure (TI) with an integrative user interface for the current components, such as digital health applications, video treatment platforms, communication in the medical sector, electronic patient records and electronic case records, e-appointment services, etc.
- Evaluation of the “combined care” of online therapy and personal treatment in clinical practice to achieve the optimal balance and effectiveness
- Outcome studies within the phase model and long-term studies with a duration of over 10 years

E-health is well on the way to becoming more strongly established in politics, business and the general population than before the pandemic. Digital agencies, forums and centres that were established nationwide either privately or by government ministries want to or should encourage digitalisation in the health care system by cross-linking themed research by universities, non-university institutions and industry (Health Innovation Hub at the BMG, Future Laboratory for Health in Society for Scientific Data Processing in Göttingen, Centre for Digital Innovations Lower Saxony, and many others). Interest in the therapeutic use of electronic media is also increasing among patients and doctors in private practice and reached its highest level in 2020 because of the pandemic so that meanwhile more than half of the doctors in private practice now offer video consultations (8).

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The German Brain Plan Agenda 2030

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