ERA-NET NEURON

STRATEGIC RESEARCH AGENDA

Taking on the Challenges of Nervous System Disorders 2021 - 2025

neuron

Network of European Funding for Neuroscience Research

Acknowledgements

The ERA-NET NEURON wishes to thank all the people who were involved in composing this Scientific Research Agenda (SRA). The scientific content of this document was developed by a group of international researchers who covered a broad range of expertise in fundamental neuroscience, neurology, psychiatry, and sensory organs. The joint effort was chaired by Martin Dichgans (Ludwig-Maximilian-University Munich, Germany).

We would like to thank the following members of the ERA-NET NEURON scientific advisory board for their participation

- Stefan Bittner, Johannes Gutenberg-Universität Mainz, Germany
- Paola Bovolenta, Instituto Cajal, CSIC, Madrid, Spain
- Joab Chapman, Tel Aviv University, Israel
- Martin Dichgans, Munich, Germany
- Jean Antoine Girault, INSERM, Paris, France
- Luc Mallet, INSERM, Paris, France
- Fabrizio Tagliavini, Carlo Besta Institute, Milano, Italy
- Ana-Maria Zagrean, Carol Davila University of Medicine and Pharmacy, Bucharest, Romania

and the following experts for their input

- Cristina García Cáceres, Helmholtz Zentrum München, Germany
- Monica Di Luca, European Brain Council
- Ewelina Knapska, Nencki Institute of Experimental Biology, Warsaw, Poland
- Tobias Moser, University Medical Center Göttingen, Germany
- Serge Picaud, Vision Institute, Paris, France
- Jean-Paul Selten, MHeNS School for Mental Health and Neuroscience, The Netherlands

The ERA-NET NEURON is a project supported by the European Commission.

The preparation of the SRA was part of a work package of the ERA-NET NEURON. The work package was led by the French National Institute for Health and Medical Research (INSERM) and the French National Centre for Scientific Research (CNRS). The French team consisted of Etienne Hirsch, Christine Tuffereau, Sarah Joaquim and Alexis Mareschi (INSERM) as well as Bernard Poulain (CNRS). Marlies Dorlöchter, the NEURON Coordinator, Anna Gossen, Hella Lichtenberg and Christina Müller (all from the Project Management Agency DLR-PT, Germany) participated on behalf of the German Ministry of Education and Research (BMBF).

Foreword

The brain is an organ of wondrous complexity, whose mysteries are unravelled year after year by the hard work of generations of researchers and clinicians. Yet, many aspects of its functioning, in both normal and pathological conditions, remain out of our understanding and require to keep on investigating. On the other hand, brain-related diseases affect millions of people in Europe (increasing every year, mainly due to the aging of the population) and impose a societal and economic burden on patients, families and carers, and healthcare systems. In this context, the ERA-NET NEURON network published in 2015 a first issue of the Strategic Research Agenda, whose aim was to outline the research priorities in disease-related neuroscience and to guide the efforts of the neuroscience community. This SRA was intended to serve as a base for joint activities of NEURON partners for the next five to ten years.

However, major developments have occurred since the beginning of NEURON Cofund in 2016, with uneven benefits for each neuroscience field. In accordance with the Scientific Advisory Board recommendations, we hence devised this updated SRA to account for recent scientific, technological and methodological advances in brain-related research, while maintaining the same direction. SAB members and other scientific experts were asked to write additional textboxes, discussing selected topics that showed major advances in the last five years and detailing related challenges and potential solutions to overcome them. From the growing fields of "omics" to the broader approaches investigating the role in brain-diseases of non-neuronal cell types within brain and of other systems, new research questions are thus to be added to NEURON scientific priorities. Meanwhile, development of computer science and new technological tools gave access to new perspectives, such as progresses in brain-machine interfaces and AI-driven data analysis tools, and introduced new methodological questions of real-life data acquisition. Lastly, investigations in more realistic environments reveal more and more how epidemiological effects such as the social environment and well-being are still underestimated in neurological and psychiatric disorders.

This updated issue of the SRA is intended to shape the actions of NEURON in the next five years, both through direct support by means of Joint Transnational Calls (JTCs) and by additional enabling activities. The new developments in brain diseases research discussed in this document highlight the importance for NEURON to give the neuroscience community access to relevant training on these approaches and to strengthen the efforts for standardisation, harmonisation, data sharing and promotion of transdisciplinary work.

Lastly, the update of this SRA point out how sharing of resources is an essential pillar in developing the knowledge and technologies necessary for tackling down brain-related diseases. We thus renew our desire of strengthening our relations with other European organisations toward this common goal, namely with the European Brain Research Area project (EBRA), which NEURON is a member of, with the European Strategy Forum on Research Infrastructure (ESFRI) for methodological and technological aspects, the EU Joint Programme – Neurodegenerative Disease Research (JPND), and the Human Brain Project (HBP).

Contents

Acronyms

AEI	Agencia Estatal de Investigación (Spanish NEURON partner)
AKA	Suomen Akatemia, Academy of Finland (Finnish NEURON partner)
ANR	Agence Nationale de la Recherche (French NEURON partner)
BFN	Brain Foundation Netherlands (Dutch NEURON partner)
BMBF	Bundesministerium für Bildung und Forschung (German NEURON partner)
CIHR	Canadian Institutes of Health Research (Canadian NEURON partner)
CNRS	Centre national de la Recherche Scientifique (French NEURON partner)
CSC	Call Steering Committee
CSO-MOH	Ministry of Health (Israeli NEURON partner)
EPNA	Excellent Paper in Neuroscience Award
ERA-NET	European Research Area Network
EU	European Union
FCT	Fundação para a Ciência e a Tecnologia (Portuguese NEURON partner)
FNRS	Fonds de la Recherche Scientifique (Belgian NEURON partner)
FWF	Fonds zur Förderung der Wissenschaftlichen Forschung (Austrian NEURON partner)
FWO	Fonds Wetenschappelijk Onderzoek – Vlaanderen (Belgian NEURON partner)
FRQS	Fonds de la recherche en santé du Québec (Canadian NEURON partner)
GSRT	General Secretariat for Research and Technology (Greek NEURON partner)
INSERM	Institut National de la Santé et de la Recherche Médicale (French NEURON partner)
ISCIIII	Instituto de Salud Carlos III (Spanish NEURON partner)
JPND	EU Joint Programme – Neurodegenerative Disease Research
JTC	Joint Transnational Call for research proposals
MOH	Ministero della Salute (Italian NEURON partner)
MRC	Medical Research Council (British NEURON partner)
NCBR	Narodowe Centrum Badan i Rozwoju (Polish NEURON partner)
NEURON	Network of European Funding for Neuroscience Research
NWO	Nederlandse Organisatie voor Wetenschappelijk Onderzoek (Dutch NEURON partner)
PT-DLR	Projektträger im Deutschen Zentrum für Luft- und Raumfahrt (German NEURON partner; NEURON coordinator)
RCN	Research Council of Norway (Norwegian NEURON partner)
SAB	Scientific Advisory Board
SAS	Slovak Academy of Sciences (Slovakian NEURON partner)
SNSF	Swiss National Science Foundation (Swiss NEURON partner)
SRA	Scientific Research Agenda
TÜBİTAK	Türkiye Bilimsel ve Teknolojik Araştırma Kurumu (Turkish NEURON partner)
UEFISCDI	Executive Agency for Higher Education, Research Development & Innovation Funding (Romanian NEURON partner)
VIAA	Valsts Izglītības Attīstības Aģentūra (Latvian NEURON partner)

Executive Summary

Brain diseases impose a heavy burden on 380 million patients in Europe, who suffer from significant loss of quality of life during the course of disease. They also strongly impact the patients' families, friends, and carers, who often experience personal tragedies. In addition, the health care systems have to deal with few to no treatment options and ever-rising costs. Therapy and care management of neurological, psychiatric, and sensory organ disorders are still unsatisfactory. Therefore, the main goals of the research projects funded under the umbrella of the ERA-NET NEURON scheme are to give big impetus to novel therapies, to promote the quest for cures and prevention of disease, and to foster our knowledge about normal and pathological brain function.

NEURON is a network of research funding organisations and ministries across Europe, Israel, Canada, and Turkey. It is dedicated to disease-related neuroscience. Joint efforts supporting small to medium scale transnational research consortia have been recognised as key instruments to provide adequate funding to the neuroscience community. Identifying the current but also the upcoming and emerging hot topics in disease-related neuroscience is imperative for the success of NEURON. That is why a group of scientists was invited to compose a research agenda as a framework for the future scientific and strategic focus of NEURON. Within the fields of neurological, psychiatric, sensory organ and peripheral nervous system disorders three main areas were addressed: (i) understanding disease mechanisms, (ii) understanding disease progression, and (iii) interventions. Supporting collaborative transnational research approaches in those areas will contribute to significant improvement in understanding brain diseases thereby reducing the suffering of patients and lowering the burden for the national health care systems.

The NEURON programme is specifically designed to exploit emerging scientific opportunities, overcome barriers to progress, and deliver novel approaches to prevention and intervention. The recommendations outlined in the Strategic Research Agenda address the full spectrum of research and approaches that are required to make a difference in neuroscience. It recognises the important role that other stakeholder groups have in delivering this agenda. The ultimate goal is to provide societal benefit not only in Europe, but also globally. The document provides a framework of opportunities for stakeholders who are willing to conduct joint activities that realign or link national investments. This will achieve increased impact through transnational cooperation. A guiding principle for its delivery will be the annual Joint Transnational Calls for proposals and the fact that the funded research has to be of highest scientific excellence.

Background and Purpose of the Research Strategy

Neurological, psychiatric, and sensory organ diseases are debilitating conditions affecting all age groups from birth to old age. According to estimates, the number of people suffering from these conditions amounts to 380 million people in Europe, and this figure is expected to rise within the next years due to longer life expectancy. Current costs for brain disorders are in the order of almost 800 billion € per year across Europe, highlighting diseases of the nervous and sensory organ system as one of the leading medical and societal challenges. The neurological disorders included in the Global Burden of Disease Study of 2015 caused over 9 million deaths, comprising 17% of global deaths. As measured in Disability Adjusted Life Years (DALYS), neurological and mental disorders accounted for 413.1 million DALYs globally, by far exceeding those from cancer (209.4 million) or cardiovascular diseases (228.9 million, without stroke). Trends are increasing, mostly due to ageing populations (Eur. J. Neuropsychopharm. 2011, 21:718; Lancet Neurol. 2017, 17:877). NEURON is an ERA-NET dedicated to disease-related neuroscience and deals with the entire spectrum of brain and nervous system diseases. The progress achieved through the NEURON activities will thus benefit to hundreds of millions of patients worldwide.

NEURON is a collaborative initiative of research funding organisations and ministries, established to tackle the growing challenges posed by neurological, psychiatric, and sensory organ disorders (for more details and a brief history see Appendix I). NEURON aims to enhance the impact of research by aligning and building upon existing national funding schemes and identifying common goals that would benefit from joint action. This Strategic Research Agenda (SRA) provides a framework for future investment and addresses how European research efforts across Europe and beyond can most effectively be harnessed to improve prevention, diagnosis, and treatment of diseases affecting the brain and nervous system.

Development of the Strategic Research Agenda

Developing a SRA to identify and tackle opportunities and challenges in disease-related neuroscience was one of the main goals of NEURON. The SRA will serve as a base for joint activities of the funding organisations collaborating in NEURON within the next five to ten years. It covers the entire spectrum of brain diseases – as is the mission of this ERA-NET.

The SRA was authored by the international NEURON Scientific Advisory Board (SAB) and a group of additional scientists. Their expertise covered the full range of research into the nervous system and its disorders: neurological, psychiatric, and sensory organ diseases, clinical as well as basic research. The experts participating in the development of the SRA are listed in the acknowledgements.

The conceptual framework of the SRA was built in two steps:

- First, input from the extended SAB was obtained through a structured questionnaire addressing major challenges of research, the major scientific bottlenecks or technological limits, and the relevance of linking pre-clinical and clinical topics in the NEURON agenda.
- Second, a face-to-face discussion was organised during a workshop in Riga, Latvia, on May 14th, 2019.

The main goals of the workshop in Riga were i) to identify existing hurdles in brain and sensory organ research that should be tackled by NEURON and ii) to discuss emerging cutting-edge and future-oriented research areas that could be further developed into joint activities within the framework of NEURON. For each of the research fields a board member gave in a brief summary of the most relevant research questions, followed by a general discussion among all attendees. Basic research was discussed during each session, acknowledging that mechanistic approaches to understand normal as well as pathological function are essential in all fields of disease-related neuroscience. The scientific debate resulted in specific recommendations of research priorities that were summarised in the present SRA document.

This SRA was published on the NEURON web site in May 2020.

A survey is planned to collect input from the greater science community and lay organisations. Researchers will be invited to submit their views online in early 2020. The answers to this survey will also be published on the NEURON web site.

Scientific Priorities

The SRA of the ERA-NET NEURON defines a set of scientific priorities that are directed towards a better understanding and treatment of nervous system disorders taking into account the scientific importance, social impact, and tractability. To achieve lasting impact, there is a need to encourage innovative and multidisciplinary approaches and to foster and extend existing capabilities in basic, clinical, and translational research. Scientific discoveries often emerge from novel technologies, innovative sources, and novel thinking, thus making progress on all these aspects has become a priority. Progress will be dependent upon the promotion of bottom-up approaches supported by more top-down strategic activities. Hence, multi-disciplinary networks including both technically- and disease-oriented researchers from different fields need to be encouraged and recognised if new and effective therapies are to be developed in this area.

Understanding brain and sensory organ diseases critically depends on our mechanistic understanding of the nervous system. The nervous system possesses around one hundred billion neurons connected by millions of kilometres of axons. The numbers of synapses between neurons amounts to something between 10 000 and 100 000 billion. Understanding and treating diseases of the nervous system remains the greatest challenge in the field of health sciences. The assembly of millions of molecular, cellular and tissular components of the nervous system, their dynamic, their plasticity and their physiological properties cannot be reduced to the sum of all the analysable parts. Hence, the major challenge of neurosciences is to analyse and integrate the complexity inherent to the organisation of the nervous system and to understand the neuronal bases of cognitive functions and behaviour while also accounting for brain-body interactions (e.g. the increasingly recognised bidirectional communication with the immune system). This challenge overrules in importance other fields of science because it aims not only to understand fundamental aspects common to any field of biology (genome and heredity, metabolism, compartmentalisation, cellular dynamics, cellular interactions, normal and pathological anatomy, physiology, development, plasticity, ageing) but also the most sophisticated aspects specific to our brain (neural and genetic code, multimodal sensory analysis, memory, behaviour, object recognition and action). This research also tackles what is specific to the human being in its social dimension (e.g. consciousness of our body and our self, thinking, language, symbols, relationship with others, affect).

Below, specific scientific topics and, within these topics, priorities for future research have been identified (summarised in Table 1).

BOX 1. Bi-directional brain-body interactions, including immune system and microbiota

Brain-body interactions are no novelty but a recent wave of new data renewed the interest on this topic and more specifically on the gut-brain axis, i.e. the bidirectional communication system between the gastrointestinal tract and the brain. This is mostly due to the identification of the gut microbiota as a novel key player in this communication and its pervasive effects on all organs and systems of the body, including the brain and the immune system. Profound remodelling of both gut microbiota (i.e. dysbiosis) and immune system associated with age contributes to the onset of age-related diseases, thus associated with immunosenescence and with a chronic, low-grade, systemic activation of the inflammatory system dubbed "inflammaging". The resulting neuro-inflammation (activation of the brain immune system and astrocytes) is an important causal mechanism in cognitive decline leading to higher risk of age-related diseases, including Alzheimer disease and dementia. "Metaflammation", which is a common feature of metabolic diseases such as type 2 diabetes and obesity, can also be considered a specific nutrient-excess-driven form of inflammaging. In addition, gut dysbiosis appears to be involved in other brain pathologies such as (i) major depression; (ii) diseases involving visceral pain perception and hypersensitivity as well as the psychobiology of its cognitive-affective modulation; (iii) the neurobiology of appetite and feeding regulation. Finally, a largely unexplored topic is the role of the gut microbiota in neurodevelopment (autism) and mental health (schizophrenia, bipolar disorders, and other psychiatric diseases).

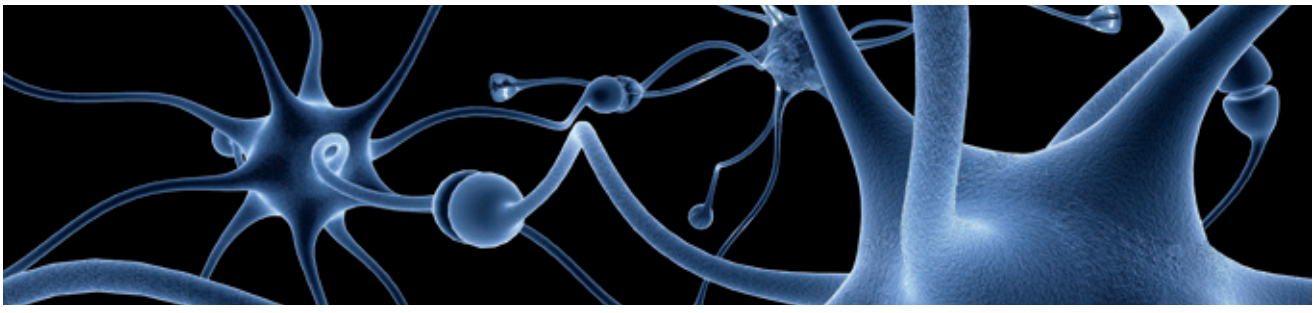
Such cross-talk is based on bidirectional anatomical pathways between brain and gastrointestinal tract, both "top-down" (enteric nervous system and sympathetic and parasympathetic efferent branches of the autonomic nervous system, including the hypothalamo-pituitary-adrenal axis) and "bottom-up" (spinal and vagal afferent nerves). Accordingly, we have to envisage the gut-brain axis within such a complex anatomic neural network, where the gut microbiota, its metabolic products, and more than 20 different peptide hormones secreted by entero-endocrine cells scattered along the gut interact in a very complex circuitry.

Bottlenecks:

- Medicine these days is organised in organ-centred specialities, with only minor interdisciplinarity. This makes it difficult to consider a broader view for neurological and psychiatric diseases, involving knowledge from cardiology, gastroenterology, immunology or endocrinology.
- This topic faces a lack of relevant data and a need to link those data, in order to consider brain diseases in the context of the whole body. This is especially true considering how diet specificities and exposition to contaminants can affect such data.
- Several connections between brain and other systems demonstrate high interspecies differences, leading to strong issues in obtaining adequate animal models.
- Accumulation of knowledge thus raises the need to integrate such a huge amount of data, from both different species and different fields. Adequate methods and structure for data sharing and integration are yet to define.

To overcome these bottlenecks, it is necessary:

- to organise the scientific community, promote interdisciplinarity and encourage data sharing between neurology, psychiatry, cardiology, gastroenterology, immunology, endocrinology, metabolism, etc.;
- to gather more relevant data by the means of multi-systems cohorts and functional mapping of the whole organism and to discuss data sharing methods and structure;
- and to develop non-invasive imaging methods in humans, to deal with interspecies differences.



Topic 1: Understanding Disease Mechanisms (Cell-Based & Animal Models, Comorbidities, and Resilience)

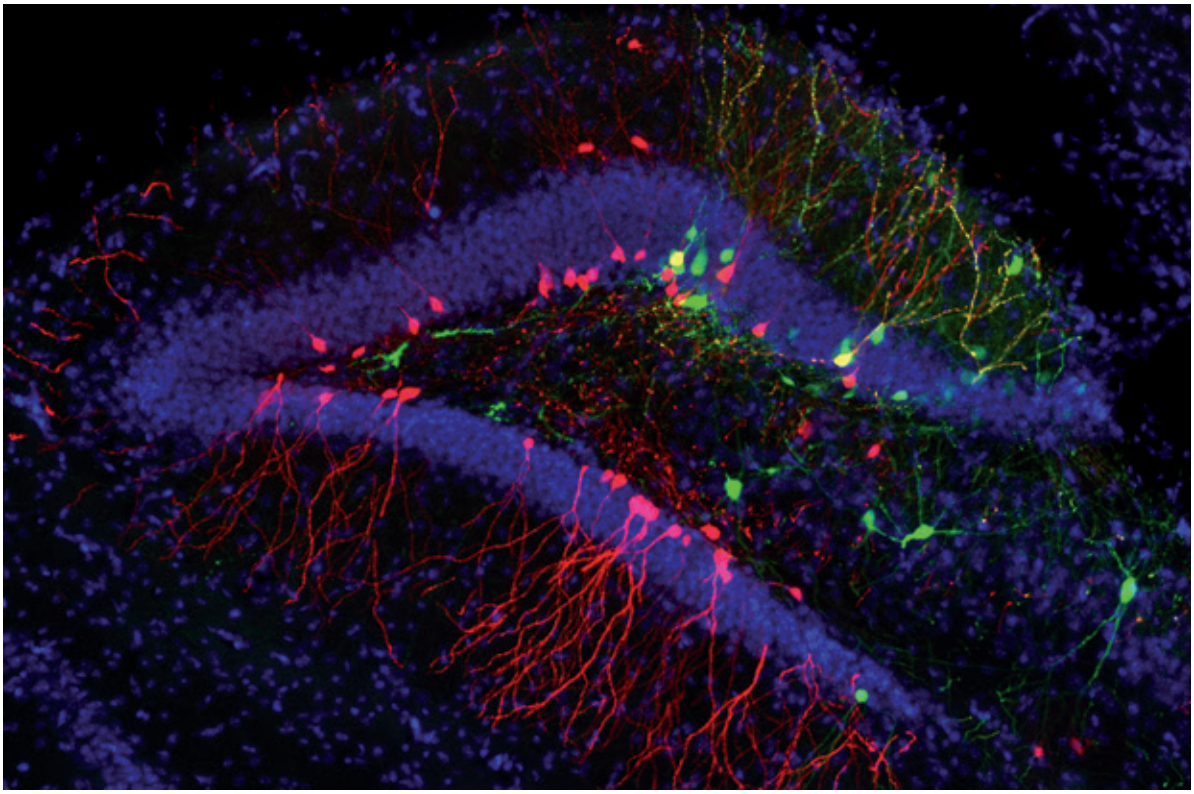
A lasting challenge in basic and clinical neurosciences is our lack of understanding disease mechanisms. Among others the key questions are: what drives nervous system disorders on a fundamental level, what determines people's risks and resilience, and what are the triggering events leading to disease? Priorities are: to uncover genetic, epigenetic, and environmental risk factors for nervous system disorders, to identify the mechanisms underlying co- and multi-morbidity, and to identify 'at-risk' populations for nervous system disorders. Of particular importance is the discovery of modifiable risk factors.

Specifically, there is a need:

- to develop, improve, and validate pre-clinical models for use in experimental studies. These models should be relevant to the diseases under study (construct validity) and account for aspects such as natural history, ageing, and comorbidities.
- to understand the biological basis of nervous system disorders. This may include a broad range of approaches such as systematic accounts of the genetic variability of nervous system disorders, or regional and temporal mapping of the epigenome, transcriptome (including micro RNAs), proteome, and metabolome in patients with nervous system disorders and healthy subjects. The use of state-of-the-art (novel or established) technologies is expected.
- to uncover mechanisms of resilience and compensation. This may involve both experimental (cell- and animal-based models) or human work. Cohort studies on subjects from multiple age strata including the very young and elderly are needed. Deep phenotyping (e.g. clinical, exposure and lifestyle history, neuroimaging, genetic and other) is recognised as a requirement for most studies. The quest for protective factors remains a priority.
- to understand the role of ageing and comorbidity. Research on the molecular, cellular, and synaptic system and functional mechanisms underlying ageing and its interaction with disease-specific mechanisms continue to be important topics. The role of common comorbidities (e.g. vascular, neurodegenerative, and inflammatory) in the manifestation and progression of nervous system disorders should be explored.
- to identify key mechanisms underlying multifactorial disease. The search for shared risk factors (genetic, environmental, other) and shared disease pathways underlying multiple nervous system disorders should be expedited. System approaches to nervous system disorders are gaining weight and should be pursued with even more energy.
- to identify properties unique to the nervous system that could be exploited for novel therapeutic approaches. Examples include the specific architecture of the blood brain barrier, glial cells (microglia, oligodendroglia, astroglia), specific molecular, cellular (e.g. pericytes), and functional (e.g. immune-related) properties of the nervous system, the post-mitotic state of nerve cells, and metabolic factors.
- to leverage novel technologies for tackling disease mechanisms including, for example, the following: optogenetics, tissue clearing/light sheet microscopy, omics-based approaches, neuronal circuits, neuronal networks, induced pluripotent stem cells (iPSCs), ultra-high-field magnetic resonance imaging (MRI). Additional examples include genome editing, single cell sequencing, high-resolution imaging, neuronal reprogramming, and novel immunological techniques. Please note that this list is by no means complete. Progress is expected from the implementation of novel technologies and tools.
- to make use of 'smart' data as well as 'big' data. Exploiting already existing data, combining data from different levels (e.g. genetic, other omics, and imaging) and different sources (e.g. different cellular and animal models or different species), and integrating these data

through advanced computational protocols holds great promise and should be pursued.

- to foster systems approaches to disease including modelling of diseases. To develop a complete and holistic understanding of nervous system disorders research should cover multiple dimensions integrating available genetic, molecular, physiological, and clinical information. This is needed to overcome the limitations of reductionist approaches and to account for the complexity of living systems. In many cases this will employ tools developed by physics and mathematics. Modelling of diseases is an important and potentially powerful area that should be supported.
- to pave the way for approaches to develop personalised medicine. This should involve both an improved account of the specific genetic, epigenetic, and environmental 'make-up' of individuals as well as a detailed characterisation of the responses to exposures to specific pharmacological agents.
- to improve the reproducibility of research findings. This should involve adherence to and continuous development of standards for good scientific practice, efforts to replicate findings in independent datasets, and multicentre studies following standards established for randomised clinical trials.



Labelled hippocampus

BOX 2. "Omics" and "big data" for Neuroscience, Neurology and Psychiatry

Living organisms are composed of trillions of cells, each composed of trillions of molecules in constant interactions. Until recently, biologists mostly focused on a small number of carefully selected cells or molecules, an over-simplistic approach that comes with limitations. During the last decade, technical progress in analytical tools and computer science gave rise to "omics" approaches that aim at the collective characterisation and quantification of large, often exhaustive, pools of biological molecules or cells.

These approaches, applicable to any organ or organism, open exciting new possibilities: (i) they address the complexity of organisms, which cannot be reduced to interactions between selected components; (ii) they allow discovery of important novel components that would be missed otherwise; (iii) they provide the necessary background information for novel hypothesis-driven approaches for understanding mechanisms; iv) the data obtained are well suited to investigations using "systems biology" approaches aiming at understanding the larger picture through identification of components and elucidation of interactions.

Given the complexity of the nervous system, omics offer useful tools and knowledge for other approaches that are becoming indispensable at multiple scales. It is safe to bet that they will tremendously boost progress and lead to many unanticipated discoveries from gene regulation to cognitive neuroscience. Some omics fields in particular are of great interest in the context of brain diseases:

- **Genomics.** Genome sequencing allows the characterisation of variations and mutations associated with increased risk of neurological or psychiatric diseases, or with behavioural traits. Comparison of cells reveals the existence of somatic mutations and clonal effects, whose contribution to brain dysfunction is a novel field of exploration.
- **Transcriptomics & proteomics.** Study of transcribed genes or the entire protein landscape in specific cells and comparison between subjects or experimental conditions sheds light on cellular regulations and responses.
- **Epigenomics.** Characterisation of the epigenome and 3-dimensional structure of chromatin opens a new way to understand developmental events and traces of environmental aggressions, revealing how early alterations can explain increased risk for mental health many years later.
- **Single-cell transcriptomics.** Single-cell transcriptomics provide an unprecedented tool for exploring the diversity of cell types in the brain and their modifications between species and in disease conditions, and recently developed spatially resolved transcriptomic techniques even open the possibility to link anatomical organisation and molecular profiling.
- **Connectomics** is a major challenge specific to neuroscience. Elucidating the organisation and function of the nervous systems requires extensive knowledge of their wiring. The full connectome of the fruit fly (250 000 neurons) is currently being elucidated and bigger brains such as from the mouse (about 75 million neurons) are being investigated. High resolution connectome of the human brain (close to 86 billion neurons) is still out of reach, but rapid progress in brain imaging techniques is bringing invaluable medium-scale information about long distance connections and provides a powerful framework for understanding function and dysfunction.
- **Phenomics** is also specific to neuroscience. As the collection of data on behaviour and functional brain imaging grows, progresses in this field are achieved thanks to close interactions between neurologists and psychologists.

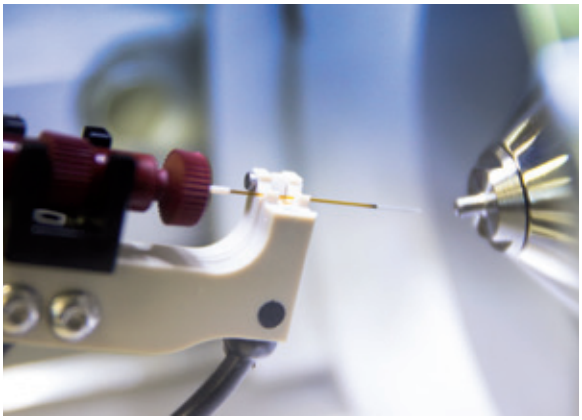
The major bottleneck of omics approaches is the huge quantity and complexity of data generated, which require large efforts to harmonise, store and analyse. To solve this issue, efforts should be focused on key elements:

- Progress requires improvement and standardisation of methodology and technology of data acquisition, to allow for more sharing of harmonised and detailed data.
- Powerful bioinformatics tools are required for analysis, which is only possible to develop thanks to progress in data collection techniques, storage capacity and processing speed and the rapidly evolving machine learning and artificial intelligence techniques, which themselves can be inspired by advances in neuroscience.

It is thus essential to promote close interactions between biologists, chemists, physicists, engineers, mathematicians and computer scientists, developing a transdisciplinary network.

Topic 2: Understanding Disease Progression (Pathology, Diagnosis, Biomarkers, Stratification)

Current clinical assessment tools lack sufficient accuracy to capture the surmised complexity of nervous system disorders thus necessitating more detailed, mechanistically driven disease classifications. In addition, there is a great demand to identify the earliest disease stages and to develop sensitive and specific disease markers for use in clinical practice. The identification of prognostic markers and of markers for monitoring of disease progression and of treatment response represents another important avenue of research that is of great medical interest. The refinement of disease classifications and the discovery of novel biomarkers continue to be driven by technological advances in omics-based techniques, immunology, imaging, biochemistry, and computational protocols.



Miniaturisation of research devices

To make progress in this area there is a need:

- to improve and to develop biologically-driven disease classifications. Disease classifications should be globally applicable, suited for use in clinical practice, build on clearly defined standards (diagnostic assessments, procedures etc.), and should use a harmonised terminology.
- to identify markers for disease prediction, early diagnosis, and progression. Ideally, these markers should be easy and rapid to obtain (e.g. blood, olfactory epithelium, or neuroimaging). They should be accurate, have a high sensitivity and specificity, and be suited for use in the target population of greatest interest. These issues need to be addressed by future studies.
- to overcome the disparity of information for specific populations. For instance, there is a relative lack of genetic information on nervous system disorders in non-Caucasian populations.
- to identify markers predicting therapeutic response. This will usually require access to data from randomised controlled trials. However, there are novel in silico approaches such as Mendelian Randomisation that are increasingly recognised as being highly informative. Alternative approaches include small but targeted studies on interventions showing large effect sizes.
- to understand diseases from a lifespan perspective. Many disorders root in events developing throughout the lifespan (beginning even before birth and then manifesting during early childhood, adolescence and/or later). A better understanding of 'periods of vulnerability' and triggering events is required for a full account of disease pathogenesis and for developing preventive strategies.
- to leverage novel methods for prognostic modelling. Future studies should make use of continuous developments in epidemiology, biostatistics, and modelling also exploiting the emerging power of artificial intelligence (AI).

BOX 3. Artificial intelligence in brain research: use in mining of heterogeneous data, automatic analysis of images (MRI, histology, EEG, etc.)

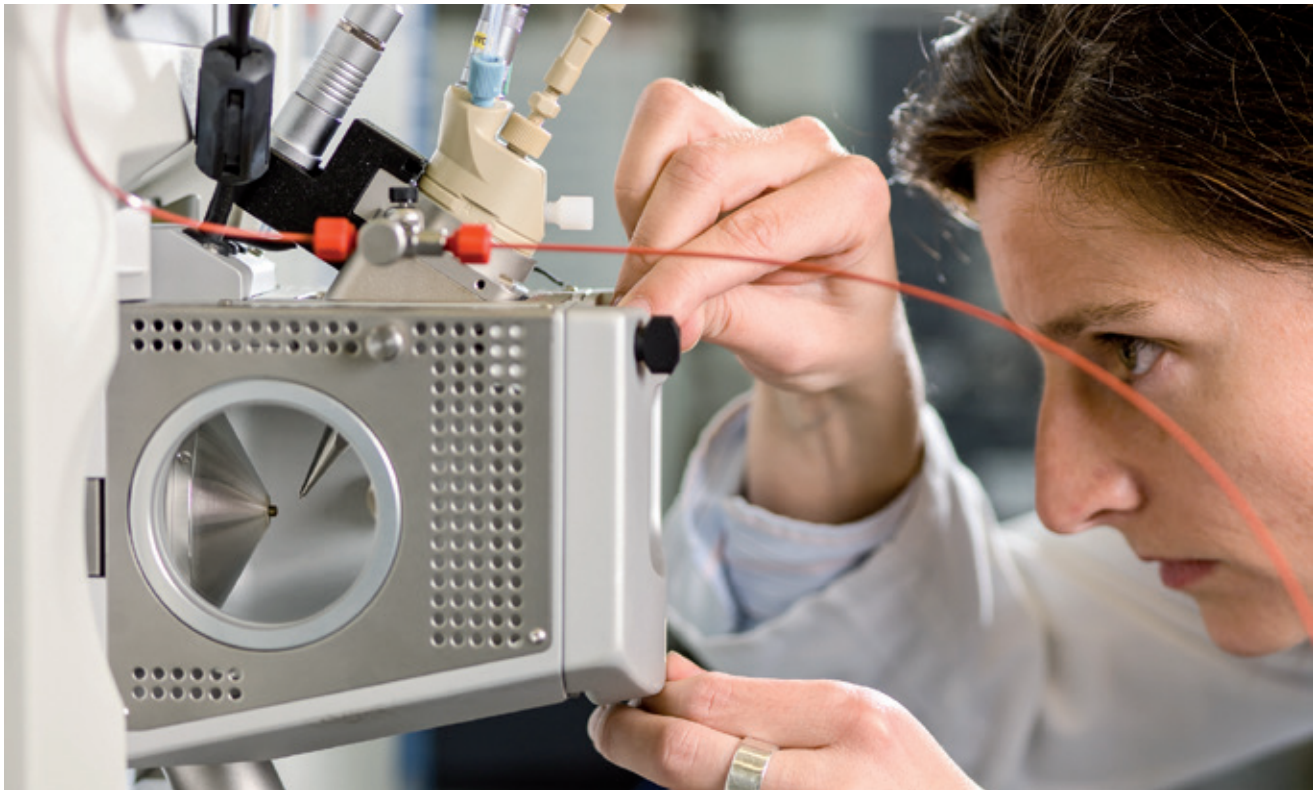
Recent work suggests that AI can provide methods to automatically analyse neural data in order to make advances in important issues in neuroscience, both in fundamental and applied research. However, these methods can rarely be used out of the shelf in neuroscience for several reasons.

First and foremost, they need to adapt to the specificity of neural data. In particular, the most successful AI tools are usually trained on billions of examples, such a wealth of data that is rare in biomedical research. Therefore, AI methods need to be adapted to neural data that is sparser. These data will also often come from different sources and will therefore be more heterogeneous than a fully curated dataset. This heterogeneity will be another important obstacle to overcome.

Finally, recent work has shown that an important control is to show when and how these methods will be better than standard tools (e.g. linear regression) to analyse neural data.

Emphasis on the following areas would best advance research progress:

- Using AI tools to analyse large amounts of images, e.g. for 3D reconstruction in anatomy.
- Prediction of phenotype and disease, based on genome, brain scan, images, or any relevant neural data.
- Connecting the brain and its environment: predicting responses of sensory areas measured with fMRI, imaging or electrophysiology, from the presented stimulus; or conversely, predicting motor actions or decision outcome, based on neural recordings. This includes designing novel AI-inspired methods to solve these problems.
- Using our knowledge in neuroscience to design novel algorithms that will allow to improve substantially current AI algorithms in learning tasks.



Researcher's instrumental fine tuning

Topic 3: Interventions (Prevention and Treatment)

Translating novel discoveries from basic research into effective therapies remains one of the prime missions of NEURON. The value of existing pre-clinical (in-vivo and in-vitro) models is disputed as in many cases the expected breakthrough has not yet been achieved. Drug-development programmes have been impeded by a lack of appropriate disease models, difficulties in prioritising interventions, lack of standardised procedures to conduct experimental studies, lack of suitable surrogate markers for interventions, and various other challenges. Progress in this area requires resolving these issues and adopting a more systematic approach that promotes bi-directional translations between clinical and experimental studies and that involves multiple disciplines including industry. Re-purposing of drugs left by industry in the pre-competitive domain represents another opportunity.

In particular, effort is needed:

- to validate already existing disease models (cell-based and model organisms) for interventions. This should include cross-validation of molecular (profiling), biochemical, histopathological, imaging, and behavioural outcomes while accounting for principal differences in anatomy (e.g. grey to white matter ratio), life span, metabolism, and complexity between organisms (e.g. neuropsychology).
- to optimise or to develop novel disease models (cell-based and model organisms) for use in drug development and toxicity testing. Human iPSCs and stem cell based approaches offer the promise of establishing high-throughput (neuronal and non-neuronal) cell screens representative of specific genetic backgrounds. Aside from broadening the basis for therapeutic testing the generation of novel human disease models (tissue engineering) and animal models holds promise for targeted mechanistic studies. Rodent models remain the backbone for pre-clinical testing but alternative models (e.g. Drosophila, Zebrafish) should also be further developed and used.
- to optimise selection criteria and stratification of patients for clinical studies. There is great demand to 'enrich' clinical studies and enhance the chance of showing clinical efficacy. Stratification could be based on endo-phenotypes, biomarkers, age, sex, genetic (e.g. polygenic risk scores) or environmental risk profiles, and/or clinical endpoints.
- to identify the optimal time window to assess treatment efficacy, an issue that may have contributed to the low success rate of previous early-phase clinical trials. Efforts should be directed to early interventions and prevention. This goes hand-in-hand with the discovery of accurate and highly sensitive and specific disease markers (see Topic 2). Some treatments may have negative side effects when given too early or too late – an issue that requires further studies and personalised therapeutic approaches.
- to strengthen investigation of compensatory mechanisms, including neuronal plasticity as a basis for novel treatment approaches. This includes research on stem cells as well as on factors promoting the sprouting of axons and synaptic plasticity. Compensatory mechanisms may also be seen on the cognitive level and the underlying mechanisms should be studied in more detail.
- to validate strategies of neuronal regeneration and neuronal circuit reconstitution in adult diseased brains through cell replacement or pharmacological approaches.
- to promote the development of preventive strategies. This may include innovative strategies to implement already established therapies with proven efficacy but poor implementation in the public.
- to make use of drug repurposing. Drugs left by the industry in the pre-competitive domain should be considered for testing in future experimental studies. The selection of appropriate targets should be informed by validated strategies of target selection and make use of currently available databases.

BOX 4. Novel technologies for tackling disease mechanisms

Until the early 19th century, the nervous system was a "black box" whose organisation and functioning remained mainly unknown. Since then, technological progress allowed for major advances in unravelling brain function. Yet, due to the exceptional complexity of the nervous system, more questions have emerged, from molecular interactions within and between cells to the anatomical organisation of neuronal circuits and their dynamic interactions.

Such complexity leads to a large range of nervous system disorders, representing a substantial proportion of the pathologies that affect our modern society, the large majority of which have no or poor treatments. Finding effective treatments is an urgent need that can only rely on a better understanding of the disease and its causes using, improving or developing state of the art technologies. Namely, genome editing approaches have allowed generating animal models that better mimic human diseases but their cellular and molecular dissection requires different and constantly evolving technologies. The following approaches are likely to foster significant progress:

- **Tissue clearing** with light sheet microscopy has revolutionised the study of the central nervous system organisation in animal models. Human brain clearing would also be a unique tool for correlating and validating 3D data from MRI and diffusion tensor imaging, with consequent improvement of disease diagnosis. Yet, if different tissue-clearing procedures (iDISCO, CUBIC-L, CLARITY etc.) allow to visualise increasingly larger pieces of tissues and to address human central nervous system organisation, a number of obstacles need still to be solved. Among them are the scalability of the clearing methods and the development of light-sheet microscopes with longer working distances and a larger field of view.
- **Optogenetics** has become a powerful strategy to control neuronal function with an exquisite temporal and spatial resolution. The combination of cell type-specific genetic manipulations with in vivo fibre optics allows to investigate specific brain circuits controlling a given cognitive function or behaviour and to target specific neuronal subpopulations for stimulation or inhibition with potential therapeutic applications. At the cellular level, optogenetics can also be applied to manipulate single neuron firing, its gene expression, protein-protein interaction or enzyme activation, and these photo-switches can be exploited to ask fundamental questions of intracellular signalling and its impact on intercellular communication in the brain.
- **Molecular and ultra high field magnetic resonance imaging** (MRI) are powerful non-invasive approaches to obtain maps of the brain activity with high spatial and/or spectral resolution, better signal-to-noise ratio, and unique image contrast. They provide meaningful information on neuroanatomy, brain activity, perfusion, vascular anatomy, diffusion, neurochemistry, and metabolic rates. Application and improvement of these techniques can open up completely new avenues in the understanding of biological processes.
- **Lipid imaging.** Neuronal physiology heavily relies on membranes of which lipids are, by far, the most abundant components. A number of common and rare neurological diseases involve lipid alterations, which can now be monitored thanks to novel probes based on photo-reactive and photo-crosslinking moieties that can be activated in a sequential manner. Additional strategies based on lipophilic short toxin peptides offer promises for future advances in this field.
- **Induced pluripotent stem cells** (iPSCs) are the result of epigenetic reprogramming of somatic cells and represent an opportunity to model both hereditary and acquired human diseases almost with individual specificity. Genome editing strategies have further fostered the use of iPSCs to investigate a definite mutation in human cellular models and isogenic lines. Growth of iPSCs in two-dimensional monolayers has however important limitations, including variability and reproducibility. Current efforts are directed to obtain more sophisticated cultures to better mimic brain diseases.

While these new technologies open many perspectives to investigate brain-related diseases, they are still to be improved and new approaches may develop in the coming years which the neuroscience community need to pay attention. There is a key challenge of closing the gap between basic research in neuroscience and technological developments of engineering. Several solutions can overcome this bottleneck:

- The links between neuroscientists, biologists, physicists and chemists need to be reinforced, and the creation of multidisciplinary research teams must be encouraged, together with the reconciliation of academic research and engineering.
- Neurotechnological infrastructures are to be developed, dedicated to facilities and resources useful for the whole neuroscience community such as instrumentation centres.

Training of basic researchers and clinicians to the use of these new tools and methods should be promoted to ensure best usage of the available technologies and homogenised data.

Specific Priorities and Challenges

Aside from the above-mentioned general priorities and topics there are specific challenges to individual diseases and disease categories. The expert panel of NEURON has identified the following specific challenges realising that this list is by no means exhaustive:

Neurological Diseases

Driven by an advanced mechanistic understanding and a number of ground-breaking discoveries, treatment options in many neurological diseases like stroke, multiple sclerosis, Parkinson's disease, and epilepsy have greatly improved. Yet, progress in other areas such as dementia is still lagging behind. This, in part, relates to a reductionist view of disease processes. Neurological conditions have traditionally been separated into mechanistically distinct families, including vascular, neurodegenerative, and inflammatory conditions. Underlying this classification is the assumption that disease manifestations relate in a categorical fashion to a discernible mechanism. As a result, research efforts have been focused in large on single mechanistic groups. Recent insights have revealed a more complex interrelation between (neuro-)vascular, neurodegenerative, and (neuro)inflammatory mechanisms emphasising the need for a systems approach and for considering disease-cross mechanisms. Genetics continues to play a major role in neurological research with an impact on disease classifications, mechanistic understanding, assessment of causal relationship with risk factors through Mendelian randomisation, drug development, and risk prediction. Indeed, genetics is paving the way towards personalised medicine. Neuroimmunology is another expanding field that continues to reveal an ever growing array of novel targets many of which hold promise for the development of novel interventions. The biology of the brain vasculature and the mechanisms underlying stroke are increasingly well understood, but – until now – translation of neuroprotective strategies into the clinic has been without success. A recognised component of both, multiple sclerosis and stroke, is secondary neurodegeneration, which significantly contributes to the long-term consequences of these and other brain injuries and thus represents an important target for research. Tissue engineering by use of human inducible pluripotent stem cells (iPSCs) in combination with CRISPR/Cas9 mediated genome editing holds great potential with respect to both studying disease mechanisms and drug screens. The molecular, pharmacological, and electrophysiological disturbances underlying disorders of specific brain circuits remain another avenue to study diseases. Deep brain stimulation has become an established therapy for a growing number of diseases. Neuronal and glial repair as well as cell reprogramming and renewal are research fields that hold great promise for curing neurological diseases. Understanding the mechanisms of recovery, repair, and functional reorganisation after spinal cord injury represents another relevant area of research where improving therapeutic options remains a challenge.

A labelled neuron

BOX 5. Research on non-neuronal cells: astrocytes, pericytes, oligodendrocytes, microglia and other immune cells

The human brain contains billions of cells with extensive molecular, morphological and functional diversity. Both non-neuronal and neuronal cells are in an intimate and coordinated association forming intricate and dynamic circuits exquisitely designed to perform specific functions. Over the last decades, brain research has focused on deciphering neuronal networks thus permitting an inquiry into brain functions at unprecedented levels of detail and sophistication. Here, we argue for the necessity to also put the spotlights on non-neuronal cells and their interactions with neurons. Glial cells including astrocytes, tanycytes, oligodendrocytes and microglia are very dynamic and have the capacity to chemically and physically influence the connectivity and plasticity of neuronal circuits required for normal brain functions. Indeed, impairments on the non-neuronal compartments have been linked with neuronal dysfunction and ultimately to the development of neurological diseases. Recent advances in biology, optics, genetics and pharmacology have resulted in the emergence of novel and highly sophisticated approaches for studying beyond neuronal circuits and exploring neuronal-glial interactions and their involvement in the development of brain diseases. This expanding knowledge will help to redefine our understanding of regulation of brain functions and potential pharmacological interventions for treating brain diseases.

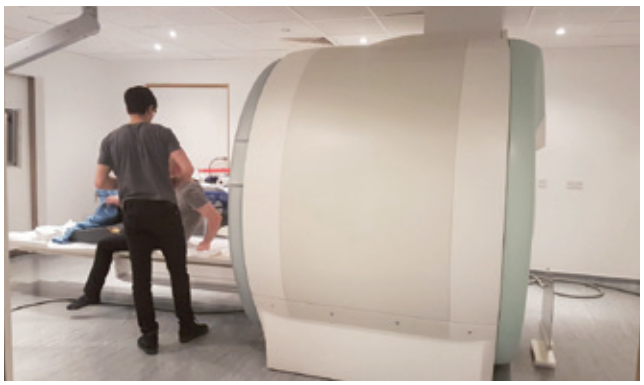
New advances in neuroscience that will help to solve current unanswered questions:

- Large-scale single-nucleus RNA sequencing studies of the human brain to determine the molecular composition of non-neuronal brain cells.
- High-resolution Hi-Plex imaging to assess the three-dimensional interface between non-neuronal and neuronal cells.
- Human stem cell-derived brain organoids containing non-neuronal and neuronal cells to model glia-neuron interaction.
- Patient-specific disease modelling in the dish can be achieved with induced pluripotent stem cells (iPSCs) reprogrammed from patient's cells into both non-neuronal and neuronal cell types.
- Identification of disease-causing variants with high specificity for non-neuronal cells. Such studies may support a causal role for non-neuronal cells in pathogenesis of brain diseases in human.

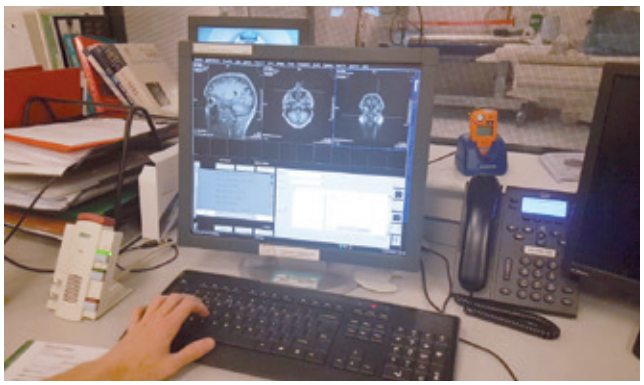
Bottlenecks:

- Lack of adequate animal models to replicate human diseases and pathologies as well as for testing therapies.
- Limitations on studying the brain as an organoid in a "dish".
- Poor communication and coordination in the definition of common objectives between basic and clinical researchers.
- Integration of the large amount of "omics" data necessary for the understanding of the brain cell biology and physiology by scientists to tackle concrete problems.
- Need for a consensual systematic classification of non-neuronal cells based on their morphology, physiology and gene expression (akin to what is being done for neurons now).

Most of these bottlenecks could be solved by developing multidisciplinarity in brain research. The classification of non-neuronal cells needs to be improved and the properties of these cells better understood. Finally, it is essential that non-neuronal cells, as critical elements of the neuronal networks, are not set aside in the developing connectomics investigations.



MRT scanning preparation



MRT scanning observations

Psychiatric Disorders

Psychiatric disorders are associated with an enormous disease burden, as well as indirect/societal costs due – in part – to loss of working capacity. Mood disorders, psychotic disorders, anxiety disorders, stress-related disorders, addiction, and personality disorders are among the most pressing health issues, while the underlying mechanisms are far from being understood. There is growing appreciation that categorical disease entities, as currently defined in contemporary disease classification systems, are biologically heterogeneous and show considerable pathogenetic overlap as well as comorbidity. Systems neuroscience have largely replaced traditional neurochemical theories while treatment options have not yet sufficiently advanced. In a ten-year perspective it is expected that the diagnosis of mental illness is replaced by a circuit-based account. Mechanistic understanding shall move from the disease itself towards an understanding of illness risk, thereby enabling pre-emptive and personalised treatment as well as prevention. Mental disorders frequently start in childhood and – in parts – relate

BOX 6. Naturalistic neurosciences and community based clinical studies

There are limitations on the current clinical studies as experiments are often not evaluated in the real-life conditions. Not only does this apply to pre-clinical studies, where experimental animals are not studied in conditions reproducing their natural environment, but also to clinical trials as most clinical or physiological readouts of the studies in neurology and psychiatry are evaluated in controlled specialised clinics. The results might differ from those obtained over time at home, at work, or in other natural surroundings, the naturalistic "normal" environment. Naturalistic neuroscience emerged recently in an attempt to conduct research in more real-life conditions while keeping control of key aspects to ensure reproducibility.

Problems are to be solved regarding the use of real-life data in brain-related diseases:

- Too few laboratories are developing naturalistic approaches for animal studies, which require profound adaptations of animal facilities, laboratories and experimental designs, even though it is more in accordance with ethical guidelines.
- Naturalistic neuroscience goes hand in hand with advances of portable electronic devices and data acquisition capabilities, and thus need improvements in the computational expertise and resources.
- There are major bottlenecks in the collection of data, including the data acquisition tools, the integration with regular medical outcome measures, standardisation, and validation.
- There are many psychological and procedural barriers regarding data ownership including a lack of traceability and transparency of clinical research directions, data security issues and concern over comparison of patient outcomes with other centres.

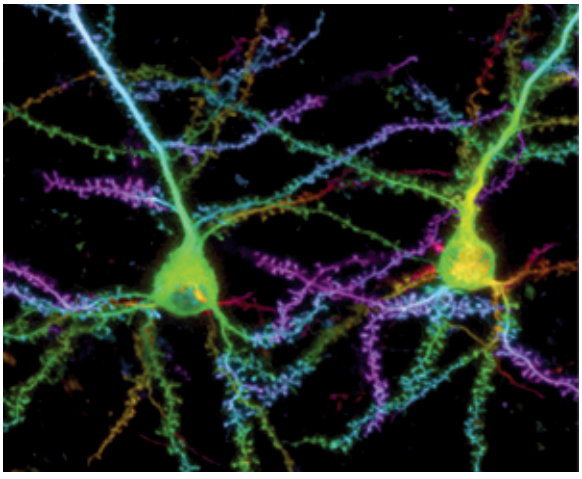
Propositions to solve these issues:

- Development of more automated experimental procedures for animal studies would be most beneficial, especially in behavioural experiments. Continuous recording of a group of animals, tracking each individual without the presence of the experimenter, allows both, to reduce stress and to investigate the behaviour of individuals within a social group on larger time scales.
- In the field of standard clinical data, many issues have been successfully addressed as part of large international databases sponsored either by national societies or pharma companies. There are distinct advantages for even larger and more diverse platforms to link clinical, imaging, biochemical, genetic, molecular, statistical, social and public health, and cost data with meaningful naturalistic data. Targeted sponsorship of such projects by multinational neuroscience support agencies is a distinct window of opportunity.
- It is important to develop data acquisition tools, and to define ground rules for the data collection and software.
- In order to enable analysis of joint data and best use of joint resources and infrastructure, central facilities should be developed to ensure continuity and protection of data, to provide a platform of data analysis and statistics, and to provide training of post-docs and fellowships for physicians and scientists. All participants should be provided with a fair opportunity to analyse their own data.
- Relations should be strengthened with government agencies, pharmaceutical companies, and other industry for their support and their anonymised controlled access to invaluable information for policy formation.
- Data should be validated by correlation to all types of relevant measures including formal diagnoses, disease course, genetic, clinical laboratory data, imaging, and social measures.

to abnormal brain development early in life. In fact, most psychiatric disorders are nowadays conceptualised as neurodevelopmental disorders. Hence, understanding the role of aberrant brain development remains one of the major challenges in the field. Genetic studies have revealed more than 300 common and multiple rare variants robustly associated with psychiatric conditions. Analysing these variants, many of which are located in regulatory regions of the human genome, and understanding the mechanisms by which they induce disease represents a promising approach to deepen our understanding of these conditions. Combining the power of advanced neuroimaging (both structural and functional) with genetics remains another promising research field for psychiatric research. There is an increasingly recognised role of computational neuroscience for linking genetic abnormalities and the molecular and cellular defects with diseased behaviour and psychiatric disorders. The development of preclinical models and refinement of their construct validity remains another challenge in the field of psychiatric disorders. Optogenetic and other emerging technologies such as ultra-high-field MR imaging and positron emission tomography (PET) enable the dissection of neuronal circuits relevant to the understanding of mental health. As seen in neurological diseases, identifying new targets for prevention and treatment and avoiding off-target effects remain a top priority.

Sensory Organ Diseases and Peripheral Nervous System Disorders

Sensory organ diseases cover a broad range of often debilitating conditions including but not limited to disorders of the eye and adnexa (retinopathies, glaucoma, cataracts, strabismus etc.), ear (in particular inner ear and vestibulocochlear nerve), and cutaneous (skin) organs. Research on sensory organ systems has become in many cases a blueprint for aspects relevant to the nervous system in general. Thus, for example, the retina including its vascular supply is now recognised as the 'window into the brain'. There is great potential for cross-fertilisation with neurovascular and neurodegenerative research as well as for the development of restorative approaches and prosthetics. The sensory system seems particularly amenable to gene- and cell-based therapeutic approaches, both of which represent promising areas of research. Identifying the critical period for functional deficits, cellular death, and for therapeutic interventions remains a key challenge in this area of nervous and sensory system disorders. Reinforcement of synaptic connectivity and neuronal circuits has emerged as major theme relevant to the development of novel therapeutic approaches. Integration of transplanted neuronal cells into neuronal circuits can now be studied in increasingly high detail both morphologically and functionally. A large number of genetic defects have been linked to sensory organ diseases with major implications for disease classification and mechanistic studies. Understanding the biology of pain and developing novel analgesic strategies remain top priorities in the field. There is a need for integration of information from different sensory organs to improve the function of prostheses. Finally, another important area is the autonomic nervous system, with new major developments on body-brain interactions revealed new questions to be investigated. Future studies should make use of novel animal models and recent technological advances such as optogenetics, and computational approaches.



Neurons labelled with different fluorescent probes

BOX 7. Brain machine interfaces, including uses for handicap compensation

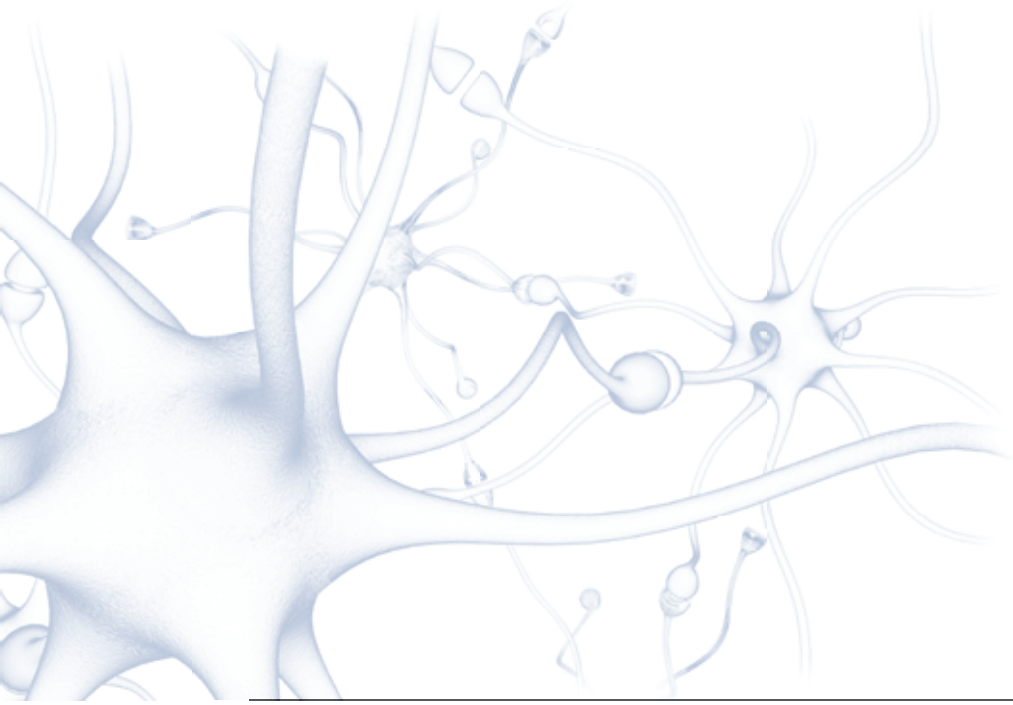
Diseases of the brain and nervous system can result in major disabilities including cognitive impairment and loss of locomotion or sensory function. Progress in cerebral activity recording methods and computer calculation since the late 1980s allowed researchers to investigate the use of recording or artificial stimulation of remaining neural circuits to restore some functional performances, opening the field of brain-machine interfaces (BMI). In 2015, a European consortium called "The Future of Brain/Neural Computer Interaction: Horizon 2020" outlined five major application axes to develop in the near future: replacement, restoration, enhancement, supplementation and improvement of natural central nervous system output (on cognitive, motor or sensory levels).

However, except for audition or deep brain stimulation in Parkinson's disease, these approaches are poised by either progressive loss of efficacy in electrical stimulation or too low resolution. The same is true for reading neuronal activity to control external devices for limb movement. Therefore, the field is facing the great challenge to improve these brain machine interfaces by the development of innovative materials, new device architectures, and discrete actuators or captors buried in the tissue. There is a need for developing new tissue/electrode interfaces with long-term stability for close interactions. Alternative approaches are also providing very promising avenues for either distant activation or distant measurements such as optogenetic therapy, optical imaging, and ultrasound technologies. However, these alternative technologies require more sensitive sensors or actuators with the corresponding precise stimulators and recorders. Finally, testing in good animal models recapitulating all the constraints of human patients is required to speed up clinical applications.

Emphasis on the following areas would best advance research progress:

- Development of new biocompatible materials for brain-machine interfaces.
- New interface designs for stable recording and stimulation of neuronal circuits.
- Production of discrete actuators and captors for reading and writing neuronal activity.
- Distant activation and stimulation by optical and ultrasound technologies in the brain such as optogenetic therapy.
- New sensors and actuators for optical and ultrasound technologies.
- Evaluation on large animal models to speed up the transfer toward clinical applications.

Finally, on a methodological level, interdisciplinarity is obviously a key factor to foster more efficient and rapid technological advances in BMI.



Options for Future Joint NEURON Activities

The following research areas and questions in the field of neurological, psychiatric, and sensory organ diseases can be putative topics for further exploration:

- **Unravelling the mechanisms of neuropathic pain.** Chronic pain of neurological origin affects up to 10% of the general population [1] but the multiple causes and underlying mechanisms identified lead to difficult treatment decisions, hence the need to encourage research on this topic.
- **Uncovering the mechanisms of cerebrovascular disease and investigate novel therapeutic concepts.** These diseases are among the most life-threatening neurological events (stroke alone was considered second cause of deaths by WHO [2]) and are at high risk to cause severe long-term disabilities. Thus, it represents a heavy burden that need to be addressed by the neuroscience research community.
- **Developing innovative recording and stimulation strategies for neuroprostheses and other brain-machine interfaces.** Progress in both neurosciences and computer science allowed for the development of brain-machine interfaces, particularly interesting for individuals with sensory or motor disabilities. Technological needs shall be answered (notably stimulators and recorders precision) for these solutions to be more beneficial for patients suffering from sensory organs and nervous system diseases and deficiencies.
- **Understanding the role of endogenous and environmental alterations during brain development in mental disorders in the teenager or young adult.** The early part of life has strong implications for the individual's mental health. It is thus particularly important to tackle mental disorders to encourage investigation of the role of alterations in the brain development occurring before and after birth.
- **Investigating the use of human iPSC-based and organoids models of the human brain to understand neurological and psychiatric disorders.** New modelling technologies have emerged, broadening the basis for therapeutic testing for brain-related diseases. If these methods have already proved themselves useful, technological and organisational limitations are yet to be addressed to impact their influence in brain research.
- **Performing cross-disease analysis of pathways related to mental and neurological disorders.** Recent investigations have identified commonalities in both neurological and psychiatric disorders (e.g. neuroinflammatory mechanisms, altered energy functions, …). Research needs to be fostered to build knowledge on these mechanisms and their role in brain-related diseases.
- **Identifying the specificities and role in pathology of chromatin regulation and epigenetic modifications in brain cells.** Epigenetic mechanisms play an important role in both maturation and plasticity of neurons, being consequently strongly involved in brain-related disorders, and represent a basis for the development of personalised medicine.

1 Colloca et al. Neuropathic pain. Nature Reviews Disease Primers 2017;3:17002.

2 Global Health Estimates 2016: Deaths by Cause, Age, Sex, by Country and by Region, 2000-2016. World Health Organization 2018.

BOX 8. Social stress, social connectedness, social status, influence on neurological and psychiatric disorders

Epidemiological evidence indicates that persons lower in the hierarchy are more likely to be affected by a wide range of diseases. Key factors include a subjective sense of control over one's life (autonomy) and the opportunity for social participation. This is also true for many mental (e.g., depression, anxiety, addiction, schizophrenia) and neurological disorders (e.g., cerebral infarction, dementia), with social connectedness acting as a buffer.

Policy makers can play a positive role in both prevention and intervention, provided that they are supported by high-quality information. Challenges are (i) lack of research that examines the impact of societal changes (e.g., migration from Eastern Europe to Western Europe, migration from developing countries, increasing socio-economic inequality, social media) on social connectedness, (ii) lack of trials that attempt to increase connectedness and (iii) limited knowledge about biological mechanisms underlying vulnerability for and resilience against social stress.

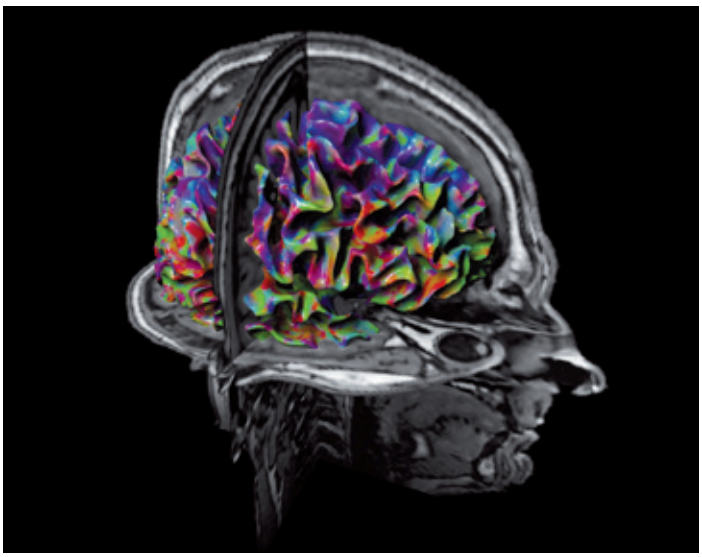
Emphasis on the following areas would best advance knowledge:

- Longitudinal studies measuring the impact of social changes (see above) on social status, social connectedness, brain functioning and the incidence of disease.
- Long-term experiments that examine the consequences of policy on social status, social connectedness, brain functioning and the incidence of disease.
- The development of new instruments to measure social defeat, social exclusion, social connectedness.
- The development of new animal models that reflect the complexity of social life.
- Research into mechanisms whereby low status increases the risk for disease, in both animals and humans through e.g. sustained hypercortisolism or sensitisation of mesolimbic dopamine system.

The following diseases are excluded from the research agenda

- Diseases not involving the nervous system,
- Diseases primarily affecting other organs or systems.

Neurodegenerative Diseases are not strictly excluded from the research agenda. However, it should be recognised that these diseases are covered by the 'Joint Programme – Neurodegenerative Disease Research' (JPND) with its specific Research Strategy published in 2012 and updated in 2019 (https://www.neurodegenerationresearch.eu/initiatives/the-2018-jpnd-research-and-innovation-strategy/)

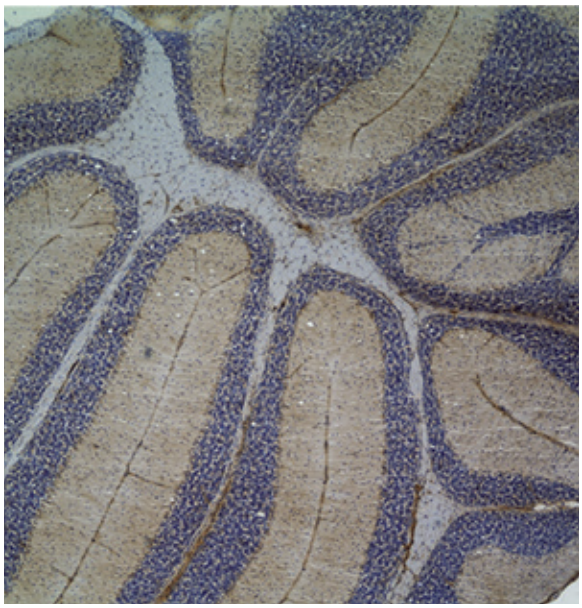


Brain image

NEURON Funding Measures: Research Consortia

The NEURON joint funding scheme is targeted to support small to medium scale transnational consortia consisting of up to six research groups from at least three participating countries. Consortia are encouraged to include basic scientists and clinicians across disciplines, in order to reinforce translational multidisciplinary research. The consortia should share technology, infrastructure, materials, skills and expertise and promote mobility of researchers. Inclusion of studies in humans is not a requirement but strongly encouraged.

Establishing new large cohorts, conducting phase III clinical trials as well as large scale omics studies are usually outside the range of activities supported by the NEURON.



Microscopic analysis of a brain section

Enabling Activities

In addition to direct support of research groups by means of JTCs, NEURON should seek to improve the conditions for carrying out research in a more indirect way. This could involve supporting the development of enabling technologies amongst other measures.

Early-Career Researchers

To overcome deficits in the quality of clinical as well as fundamental biomedical research, focused training activities are required at all levels of academic education and career stages. Those activities could include exchange programmes for early-career researchers, international summer/winter schools, workshops, and programmes promoting bench-to-bedside research. The latter should be directed towards early-career clinicians and experimental neuroscientists to learn from each other and obtain skills needed for the specific challenges in the respective environment. Better integration of scientists at the early stages of their careers into established research groups could be promoted by creating contact platforms.

Data Sharing, Material, and Infrastructure

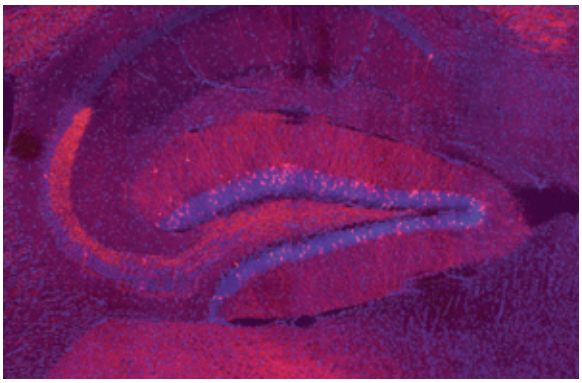
With growing amounts of available data (epidemiological, clinical, omics, imaging etc.) efforts for standardisation and harmonisation gain importance in order to enable optimal use of scientific information. NEURON should continue implementing a policy of data sharing and making data openly accessible as a prerequisite for funding in the NEURON framework. Likewise, sharing high end infrastructure, biomaterials, and other resources is desirable and will improve research success and efficiency.

Partnership with Industry

Testing new therapeutic applications for known, but differently-used compounds considerably reduces the time frame and decreases the costs of drug development. Drug repurposing is thus an important strategy to rapidly translate research findings into clinical trials. Promoting this research field by paving collaboration with pharmaceutical industry (big pharma) may stimulate the development of therapies for brain diseases, many of which still lack effective treatments. Collaboration with small or medium sized enterprises is similarly important and may help pushing new therapeutic concepts towards clinical applications. It is one example for the need of a closer partnership between academia and the industry in terms of material, data, and knowledge exchange.

Multidisciplinary Research Collaboration

To unravel the complexity of the nervous system and its diseases, the traditional division into academic disciplines needs to be overcome. Promoting collaboration between fundamental and clinical scientists, combining expertise from the biomedical sciences and e.g. engineering provides a powerful environment for novel ideas and approaches. Findings about common pathways show that the classification into neurological and psychiatric diseases is artificial. Hence, strengthening the links between neurologists and psychiatrists will improve the conceptual basis of understanding brain diseases. NEURON as a network should contribute in all its activities to tearing down conceptual barriers.



Labelled hippocampus

Capacity Building

Being globally well-networked is inevitable for successful research performance in neuroscience since it enables collaboration, exchange of expertise, and access to collaborative funding schemes. For countries with small neuroscience communities, success rates in European funding programmes are unsatisfactory. Mutual benefit could be achieved by finding ways to facilitate networking activities with already well-linked research groups and to encourage research groups from these countries to participate in NEURON activities.

Interaction with European Initiatives

Mutual knowledge about the goals and activities of other existing initiatives will enable fruitful discussions and interactions of the involved stakeholders. Concerted actions may be needed to respond to the societal challenge of brain disorders. Among these initiatives, the Framework Programmes by the European Commission, Horizon 2020 and Horizon Europe are of major importance as they are the largest European sources of research funding. In the 'EU Joint Programme – Neurodegenerative Disease Research (JPND)' EU member states focus their efforts and investments on a selected group of brain diseases. The Human Brain Project (HBP) aims to advance knowledge in the fields of neuroscience, computing, and brain-related medicine through a collaborative ICT-based scientific research infrastructure. Coordinated by the European Brain Council (EBC), JPND, HBP, and NEURON collaborate in an EU-supported project to promote a European Brain Research Area (EBRA). The European Strategy Forum on Research Infrastructures (ESFRI) may enable the use of platforms and other infrastructural support.

Subject/Topic	Priorities	Outcomes
Understanding Disease Mechanisms	• Develop, improve, and validate pre-clinical models for use in experimental studies, • Understand the biological basis of nervous system disorders, • Uncover mechanisms of resilience and compensation, • Understand the role of ageing and comorbidity, • Identify key mechanisms underlying multifactorial disease, • Identify properties unique to the nervous system that could be exploited for novel therapeutic approaches, • Leverage novel technologies for tackling disease mechanisms including, for example, the following: optogenetics, -omics based approaches, neuronal circuits, neuronal networks, induced pluripotent stem cells, molecular and ultra-high-field MRI, • Make use of 'smart' data as well as 'big' data (e.g. derived from -omics approaches), • Foster systems approaches to disease including modeling of diseases, • Pave the ground for approaches to personalised medicine.	Identify: • Causes of disease, • Factors involved in resilience, • Non-modifiable & modifiable risk factors, • Triggering events, • Novel targets for interventions.
Understanding Disease Progression	• Improve and develop biologically-driven disease classifications, • Identify markers for disease prediction, early diagnosis, and progression, • Identify markers predicting therapeutic response, • Understand diseases from a lifespan perspective, • Leverage novel methods for prognostic modeling.	Enable: • Risk prediction, • Early diagnosis, • Predicting therapeutic response, • Early treatment, • Prognostic modeling.
Promoting Interventions	• Validate already existing disease models (cell-based and model organisms) for interventions, • Optimise or develop disease models for use in drug development and toxicity testing, • Optimise selection and stratification of patients for clinical studies: could be based on endo-phenotypes, biomarkers, genetic or environmental risk profiles and/or clinical endpoints thus providing a greater chance of showing efficacy, • Identify the optimal time window to assess treatment efficacy, an issue that may have contributed to the low success rate of previous early-phase clinical trials, • Strengthen investigation of compensatory mechanisms, including neuronal plasticity, as a basis for novel treatment approaches, • Promote the development of preventive strategies, • Make use of drug repurposing.	Facilitate: • Innovative therapeutic approaches, • Novel delivery systems for pharmacological and non-pharmacological approaches, • Novel preventive strategies, • Optimised use of already available drugs.

Table 1: Topics summarised

Appendix I: The ERA-NET NEURON

History

Since 2007, ministries and funding organisations from countries across Europe and globally have joined forces in the "Network of European Funding for Neuroscience Research" NEURON. This initiative was launched under the 6th Framework Programme of the European Commission as an ERA-NET – a platform to coordinate collaborative action between funding bodies and foster a European Research Area (ERA). The participating partner organisations are major stakeholders and provide considerable funding for disease-related neuroscience in their countries. They agree that excellent research is a prerequisite to overcome the societal burden of brain diseases and that such research requires promotion and investment in an internationally concerted action. NEURON partners support research that is directed at a better understanding of brain and nervous system diseases and their progression in order to pave the way for new or improved routes for diagnosis and therapy.

NEURON Partners

Austria (FWF), Belgium (Flanders, FWO, Wallonia, FNRS), Canada (CIHR, Québec, FRQS), Finland (AKA), France (ANR, INSERM, CNRS), Germany (PT-DLR/BMBF), Greece (GSRT), Israel (CSO-MOH), Italy (MOH), Latvia (VIAA), The Netherlands (BFN, NWO), Norway (RCN), Poland (NCBR), Portugal (FCT), Romania (UEFISCDI), Slovakia (SAS), Spain (ISCIII, AEI), Switzerland (SNSF), Turkey (TÜBİTAK), United Kingdom (MRC).

Selected Activities

One of the core activities of NEURON is funding of translational research in the diverse fields of disease-related neuroscience. Annual JTCs attract excellent research groups from the participating NEURON countries. So far, the following research areas were addressed: Neurodegeneration (2008), Method and Technology Development (2009 and 2012), Mental Disorders (2010, 2013 and 2018), Cerebrovascular Disorders (2011), Neuroinflammation (2014), Neurodevelopmental Disorders (2015); Neuroethics/ELSA in Neuroscience (2015, 2017 and 2020), External insults to the nervous system (2016), Synaptic dysfunction (2017), Biomarkers (2019), and Sensory Disorders (2020).

An award was designed as a form of support and encouragement for early-career researchers. NEURON partner organisations issue this award annually to recognise the most remarkable and outstanding scientific publications by early-career researchers in the field of disease related neurosciences (Excellent Paper in Neuroscience Award EPNA).

Intense consultation with the neuroscience community ensures effective support of relevant scientific questions. Renowned international scientists are invited to regular workshops and symposia to discuss the latest research developments in specific areas, or barriers and hurdles and ways to overcome those. A permanent Scientific Advisory Board is central to the research funding strategy of NEURON.

NEURON follows in its activities the principles of Responsible Research Innovation. This approach focuses on patient engagement in the processes of the calls for research proposals, the promotion of easier access to scientific results, and the take up of gender and ethics issues. Thematic workshops and training opportunities are offered to promote formal and informal science methodology aimed at improving reproducible output.

Educational video clips about brain research and neurological and psychiatric disorders are designed to inform the general public about the work of NEURON. To address a larger audience the video clips are in addition posted on YouTube. These clips and regular newsletters are part of the NEURON outreach activities.

For more details, see
http://www.neuron-eranet.eu/index.php

Imprint

Published by ERA-NET NEURON
German Aerospace Center (DLR)
Project Management Agency in DLR
Health Research
Heinrich-Konen-Str. 1
53227 Bonn
Germany

Internet: http://www.neuron-eranet.eu/en/38.php
E-Mail: info@neuron-eranet.net

May 2020

Layout
sku:l communication
Michaela Richter
51674 Wiehl
www.sku-l.de

Edited by
DLR-PT Project Management Agency,
Health Research

Photo Credits

Title:
AdobeStock_169698038 | Adobe-Stock_289516045 | AdobeStock_144205619 | Shutterstock_129508265 | Neurosphere, ChromISyn consortium, Eloisa Herrera, Instituto de Neurociencias, Universidad Miguel Hernández, Campus de San Juan, Sant Joan d'Alacant, Alicante, Spain | CA1, ChromISyn consortium, Angel Barco, Instituto de Neurociencias, Universidad Miguel Hernández, Campus de San Juan, Sant Joan d'Alacant, Alicante, Spain | Rat cortical neuron, AxonRepair consortium, Andrew Kaplan, Alyson Fournier, The Neuro (Montreal Neurological Institute-Hospital), McGill University, Montreal, Canada | MRT scanning observations, BIOAX-TBI consortium, Karl Zimmerman, Imperial College London, UK | Hippocampus, ImprVision consortium, Benedikt Berninger, Johannes Gutenberg University Mainz &Focus Program Translational Neuroscience, Germany | Labelled neurons, SynPathy consortium, Olivier Thoumine, University of Bordeaux, France | Researcher's instrumental fine tuning, SILENCE consortium, Ralph Schlapbach & Bernd Roschitzki, ETH Zurich, Switzerland | Blood-brain barrier of the CNS, MICRO-MET consortium, Ari Waisman, Johannes Gutenberg University Mainz, Germany

Content:
Page 3, 10, 14, 22: © Shutterstock_129508265
Page 7: © Fotolia_134931825
Page 12: Hippocampus, ImprVision consortium, Benedikt Berninger, Johannes Gutenberg University Mainz &Focus Program Translational Neuroscience, Germany
Page 14: Miniaturisation of research devices, SILENCE consortium, Ralph Schlapbach & Bernd Roschitzki, ETH Zurich, Switzerland
Page 15: Researcher's instrumental fine tuning, SILENCE consortium, Ralph Schlapbach & Bernd Roschitzki, ETH Zurich, Switzerland
Page 18: A labelled neuron, SynPathy consortium, Nils Brose, MPI Goettingen, Germany
Page 19: left: MRT scanning preparation; right: MRT scanning observations, BIOAX-TBI consortium, Karl Zimmerman, Imperial College London, UK
Page 21: Neurons labelled with different fluorescent probes, SynPathy consortium, Olivier Thoumine, University of Bordeaux, France
Page 24: Brain image, SCI-NET consortium, Alexander Leemans, University Medical Center Utrecht, The Netherlands
Page 25: Microscopic analysis of a brain section, MS-NANOMED consortium, Pere Santamaria, University of Calgary, Alberta, Canada
Page 26: Labelled Hippocampus, ChromISyn consortium, Angel Barco, Universidad Miguel Hernández de Elche, Alicante, Spain

www.neuron-eranet.eu