ERA-NET NEURON

STRATEGIC RESEARCH AGENDA

TAKING ON THE CHALLENGES OF NERVOUS SYSTEM DISORDERS

neuron

Network of European Funding for Neuroscience Research

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Robin Ali (University College London, UK), Celso Arango (Universidad Complutense, CIBERSAM, Madrid, Spain), Vania Broccoli (San Raffaele Scientific Institute, Milan, Italy), Francois Berger (University of Grenoble, France), Eero Castren (University of Helsinki, Finland), Joab Chapman (Tel Aviv University, Israel), Monica Di Luca (Milan University, Italy), Martin Dichgans (Ludwig-Maximilian-University Munich, Germany), Isabel Farinas (University of Valencia, Spain), Christophe Mulle (CNRS, Institut Francois Magendie, France), Andreas Meyer-Lindenberg (Central Institute of Mental Health, Mannheim, Germany), Alain Prochiantz (College de France, France), Fabrizio Tagliavini (Instituto Nazionale Neurologico Carlo Besta, Milan, Italy), Wolfgang Wick (University of Heidelberg, Germany), Moussa Youdim (Technion, Haifa, Israel), Ana-Maria Zagrean (Carol Davila University of Medicine and Pharmacy, Bucharest, Romania).

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ACRONYMS

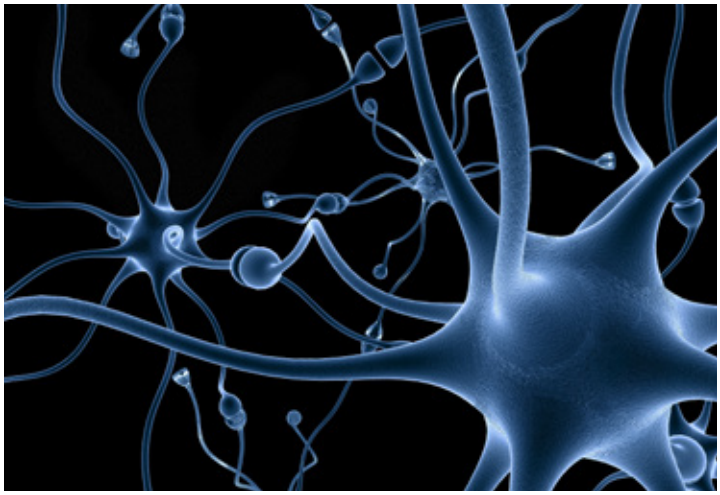
AKA	Suomen Akatemia, Academy of Finland (Finnish NEURON partner)
ANCS-MEdR	Autoritatea Nationala Pentru Cercetare Stiintifica – Ministry of Education and Research (Romanian NEURON partner)
ANR	Agence Nationale de la Recherche (French NEURON partner)
BMBF	Bundesministerium für Bildung und Forschung (German 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
ISCIIII	Instituto de Salud Carlos III (Spanish NEURON partner)
FCT	Fundação para a Ciência e a Tecnologia (Portuguese NEURON partner)
FNR	Fond National de la Recherche (Luxembourgian 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)
INSERM	Institut National de la Santé et de la Recherche Médicale (French NEURON partner)
JPND	EU Joint Programme – Neurodegenerative Disease Research
JTC	Joint Transnational Call for research proposals
LAS	Latvian Academy of Science (Latvian associated NEURON partner)
MINECO	Ministry of Economy and Competitiveness (Spanish NEURON partner)
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
ND	Neurodegenerative diseases
NSD	Nervous system disorders
PPP	Purchasing power parity
PT-DLR	Projektträger im Deutschen Zentrum für Luft- und Raumfahrt (German NEURON partner; NEURON coordinator)
SAB	Scientific Advisory Board
SAS	Slovak Academy of Sciences (Slovakian associated NEURON partner)
SRA	Scientific Research Agenda
SRC	Swedish Research Council (Swedish NEURON partner)
RANNIS	The Icelandic Centre for Research (Icelandic NEURON partner)
UEFISCDI	Executive Agency for Higher Education, Research Development & Innovation Funding (Romanian 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.

The ERA-NET NEURON is a network of research funding organizations and ministries across Europe, Israel, and Canada. It is dedicated to disease-related neurosciences. Joint efforts supporting small-scale transnational research consortia have been recognized as key instrument 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 recognizes 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 recent 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[1]. Current costs for brain disorders are in the order of almost 800 billion € per annum across Europe, highlighting diseases of the nervous and sensory organ system as one of the leading medical and societal challenges[1]. NEURON is an ERA-NET dedicated to disease related neurosciences and deals with the entire spectrum of brain diseases. The work achieved by NEURON will thus benefit to hundreds of millions of patients in Europe and beyond including Israel and Canada.

1 Gustavsson et al.: Cost of disorders of the brain in Europe 2010, European Neuropsychopharmacology 2011, 21(10):718-779.

NEURON is a collaborative initiative of research funding organizations 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

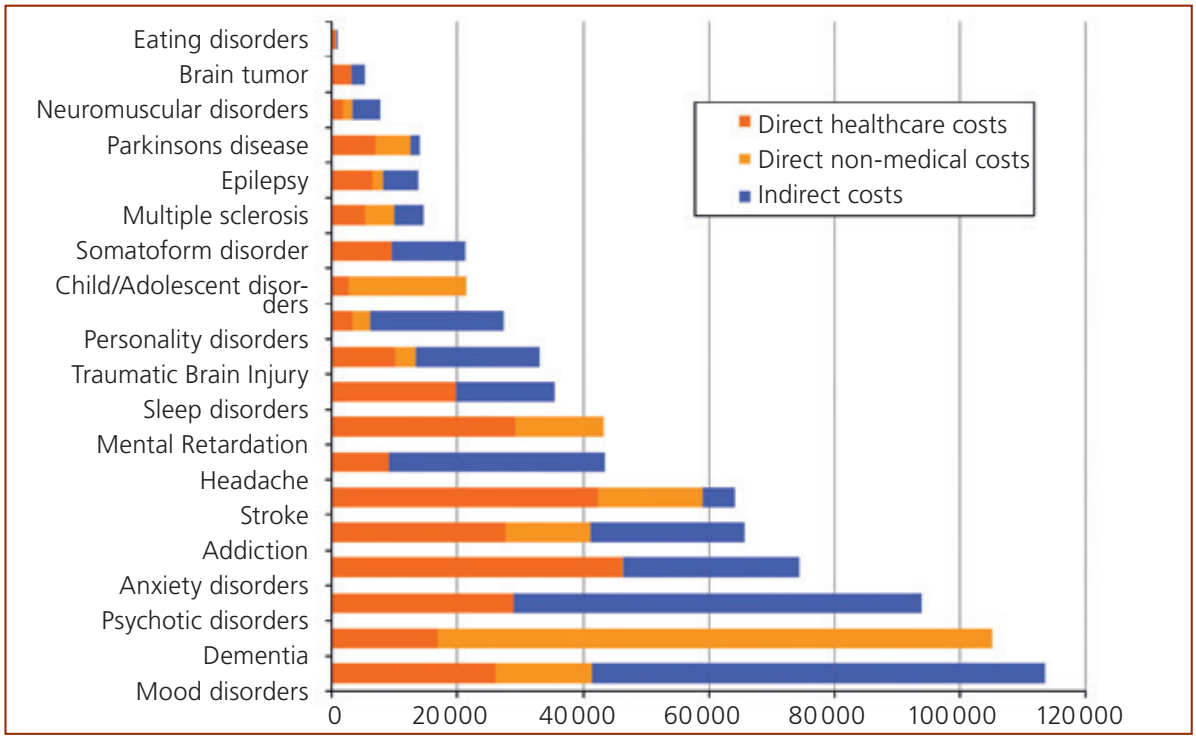


Fig. 1: Total cost by disorder and type of cost (€PPP million, 2010). Taken with permission from ELSEVIER[1].

will serve as a base for joint activities of the funding organizations 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 preclinical and clinical topics in the NEURON agenda.
- Second, a face-to-face discussion was organized during a workshop in Bonn, Germany, on May 13th, 2014.

The main goals of the workshop in Bonn 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 in disease related neuroscience. The scientific debate resulted in specific recommendations of research priorities that were summarized in the present SRA document.

This SRA is published on the NEURON web site on January 19th, 2015.

A survey is planned to collect input from the greater science community. Researchers will be invited to submit their views online in early 2015. The results 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 (NSD) 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 recognized 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 kilometers 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 organization of the nervous system and to understand the neuronal bases of cognitive functions and behaviour. 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, compartmentalization, and 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. conscientiousness 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 (summarized in Table 1):

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 the disease mechanisms. Among others the key questions are: what drives NSD 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 NSD, to identify the mechanisms underlying co- and multi-morbidity, and to identify 'at-risk' populations for NSD. An important issue 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 NSD. This may include a broad range of approaches such as systematic accounts of the genetic variability of NSD, or regional and temporal mapping of the transcriptome, proteome, and epigenome in patients with NSD 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 recognized as a requirement for most studies. The quest for protective factors remains a priority.

- to understand the role of aging and comorbidity. Research on the molecular, cellular, and synaptic system and functional mechanisms underlying aging 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 NSD should be explored.
- to identify key mechanisms underlying multifactorial disease. The search for shared risk factors and shared disease pathways underlying multiple NSD should be expedited. Systems approaches to NSD 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, specific molecular, cellular, and functional 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, omics-based approaches, neuronal circuits, neuronal networks, induced pluripotent stem (iPS) cells, molecular and ultra-high-field MRI. Additional examples include genome editing, single cell deep-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 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 NSD 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 personalized medicine. This should involve both an improved account of the specific genetic, epigenetic, and environmental 'make-up' of individuals as well as a detailed characterization of the responses to exposures to specific pharmacological agents.

TOPIC 2: UNDERSTANDING DISEASE PROGRESSION (PATHOLOGY, DIAGNOSIS, BIOMARKERS, STRATIFICATION)

Current clinical assessment tools lack sufficient accuracy to capture the surmised complexity of NSD 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.

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 harmonized terminology.

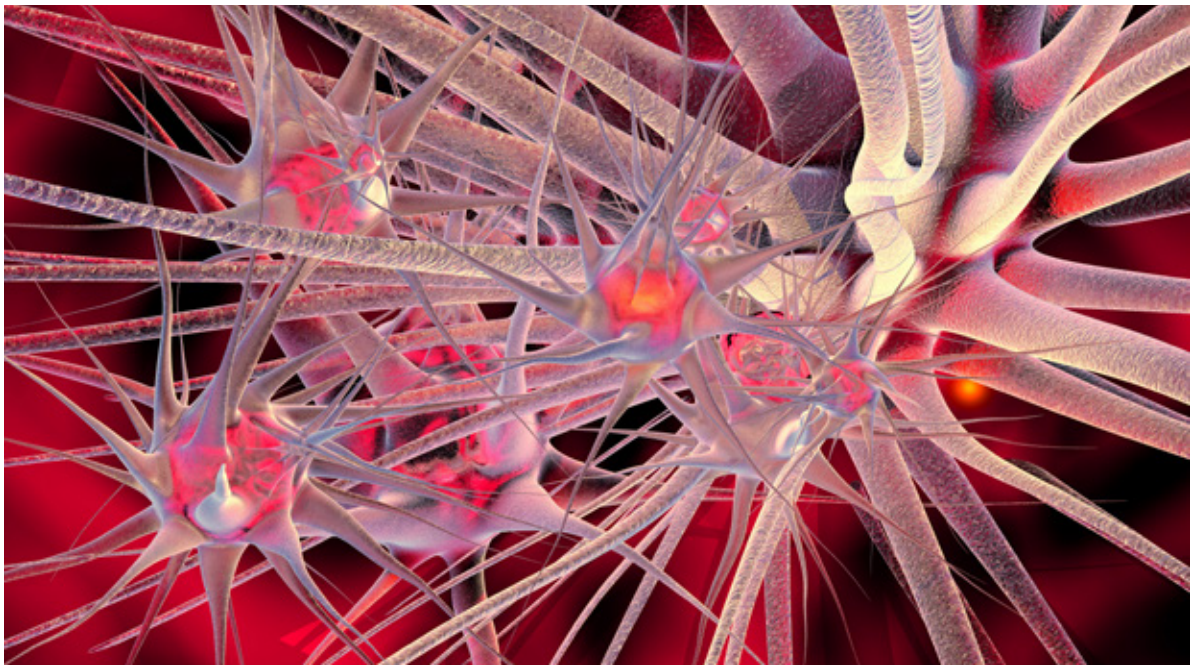
- to identify markers for disease prediction, early diagnosis, and progression. Ideally, these markers should be easy and rapid to obtain (e.g. blood, olfactory epithelium, or neuroimaging). They should be accurate, have a high sensitivity and specificity, and be suited for use in the target population of greatest interest. These issues need to be addressed by future studies.
- to identify markers predicting therapeutic response. This will usually require access to data from randomized controlled trials. Alternative approaches are 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 them manifesting during early childhood, adolescence and/or later). A better understanding of 'phases 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.

TOPIC 3: INTERVENTIONS (PREVENTION AND TREATMENT)

Translating novel discoveries from basic research into effective therapies remains one of the prime missions of the ERA-NET 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 e.g. a lack of appropriate disease models, difficulties in prioritizing interventions, lack of standardized 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 behavioral 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 optimize or to develop disease models (cell-based and model organisms) for use in drug development and toxicity testing. iPS 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 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 optimize 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 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 personalized 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.

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 the ERA-NET NEURON has identified the following specific challenges realizing that this list is by no means exhaustive:

NEUROLOGICAL DISEASES

Driven by an advanced mechanistic understanding and a number of ground-braking discoveries, treatment options in many neurological diseases like stroke, Parkinson's disease, multiple sclerosis, 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 discernable 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 emphasizing the need for a systems approach and for considering disease-crossing mechanisms. Genetics continues to play a major role in neurological research with an impact on disease classifications, mechanistic understanding, risk prediction, and targeted treatment. Neuroimmunology is another expanding field that continues to reveal an ever growing array of novel targets of which many 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 recognized 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. 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 reorganization after spinal cord injury represents another relevant area of research where improving therapeutic options remains a challenge.

PSYCHIATRIC DISORDERS

More than any other disease group psychiatric disorders are associated with enormous burden, as well as indirect costs due to – in part – loss of working capacity. Mood disorders, psychotic disorders, anxiety 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, 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 personalized treatment as well as prevention. Mental disorders frequently start in childhood and – in parts – relate to abnormal brain development early in life. In fact, most psychiatric disorders are nowadays conceptualized 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 100 common and multiple rare variants robustly associated with psychiatric conditions. Analyzing these variants – understanding the mechanisms by which they induce disease – represents one 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 recognized 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 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.

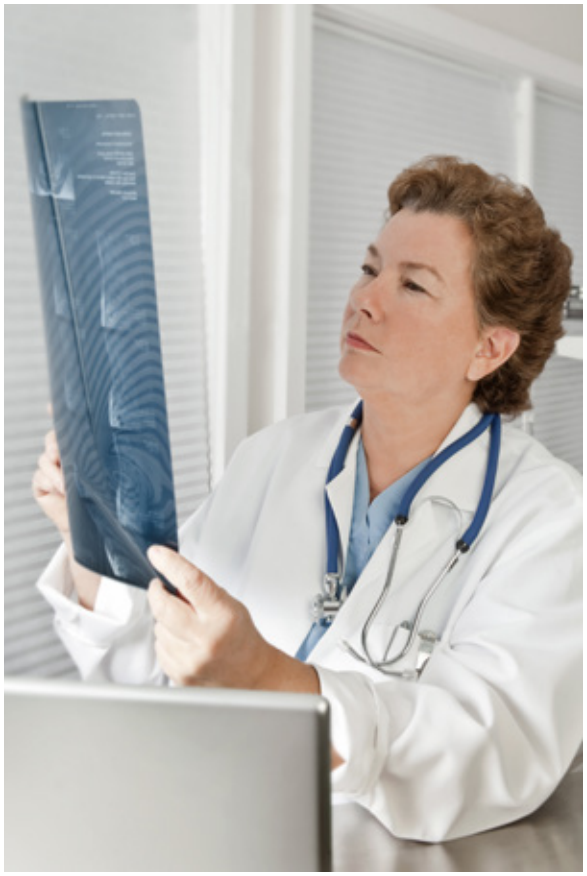
SENSORY ORGAN DISEASES AND PERIPHERAL NERVOUS SYSTEM DISORDERS

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, strabism 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 recognized as the 'window into the brain'. There is great potential for cross-fertilization 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. Finally, another important area is the autonomic nervous system. Future studies should make use of novel animal models and recent technological advances such as optogenetics, and computational approaches.

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 in focused workshops:

- Understanding the role of aging, comorbidity, and multifactorial aspects of disorders;
- Developing novel technologies for tackling disease mechanisms including data analysis, disease modelling *in vivo*, *in vitro*, and *in silico*;
- Identifying properties unique to the nervous system that could be exploited for novel therapeutic approaches;
- Uncovering mechanisms of resilience and compensation;



- Identifying biomarkers for diagnosis, progression, treatment response, side effects of treatment for stratification of disorders and personalized medicine;
- Understanding diseases from a lifespan perspective;
- Unravelling the mechanisms of mental disorders;
- Identifying disease-crossing mechanisms in stroke and dementia;
- Building knowledge about sensory organ disorders.

THE FOLLOWING DISEASES ARE INCLUDED IN THE RESEARCH AGENDA

- Diseases of the central nervous system,
- Diseases of the peripheral nervous system,
- Diseases of the neuromuscular junction,
- Diseases of the autonomic nervous 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 (ND) are not excluded from the research agenda. However, it should be recognized that these diseases are covered by the ‚Joint Programme – Neurodegenerative Disease Research' (JPND) with its specific Research Strategy published in 2012 (http://www.neurodegenerationresearch.eu).

NEURON Funding Measures: Research Consortia and Joint Transnational Calls for Proposals

The NEURON joint funding programme is targeted to support small scale transnational consortia of up to five 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. They share methodology, infrastructure, materials, skills and expertise. Inclusion of studies in humans is not a requirement but strongly encouraged.

Phase III clinical trials as well as large scale omics studies requiring large budgets are usually outside the range of activities supported by the ERA-NET NEURON.

Enabling Activities

In addition to direct support of research groups by means of JTCs, the ERA-NET NEURON should seek to improve the conditions for carrying out research in a more indirect way.

EARLY-CAREER SCIENTISTS

To overcome deficits in the quality of clinical as well as fundamental biomedical research, focused training activities are required at all levels of the academic education and early career stages. Those activities could include exchange programmes for early-career scientists, international summer/winter schools, or 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 research and patient data, standardization and harmonization efforts have to be made in order to enable optimal use of valuable information. A policy of open-access data should be 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 the pharmaceutical industry would stimulate the development of therapies for brain diseases, many of which still lack effective treatments. It is one example for the need of a closer partnership between academia and the industry in terms of material, data, and knowledge exchange.

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 aging 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 personalized medicine	Identify: ■ Causes of disease, ■ Non-modifiable & modifiable risk factors, ■ Factors involved in resilience, ■ 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, ■ Prognostic modeling, ■ Early treatment, ■ Predicting therapeutic response.
Promoting Interventions	■ validate already existing disease models (cell-based and model organisms) for interventions ■ optimize or develop disease models for use in drug development and toxicity testing ■ optimize 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: ■ Novel preventive strategies, ■ Innovative therapeutic approaches, ■ Novel delivery systems for pharmacological and non-pharmacological approaches, ■ Optimized use of already available drugs.

MULTIDISCIPLINARY RESEARCH COLLABORATION

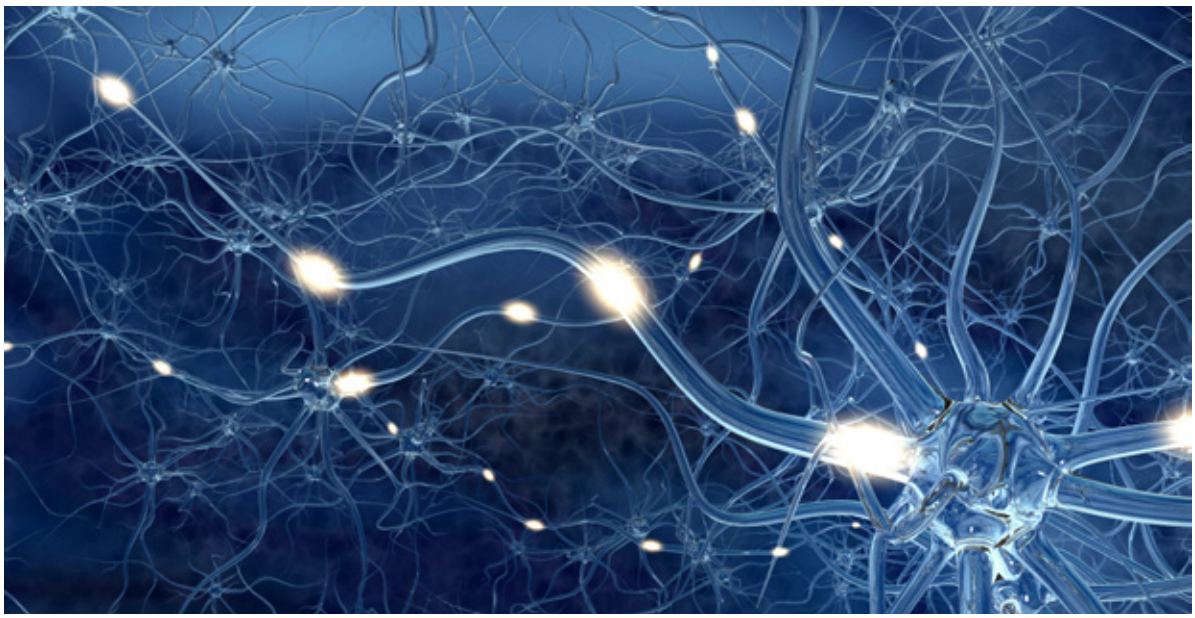
To unravel the complex nervous system and its diseases, the traditional division into academic disciplines needs to be overcome. Promoting collaboration between fundamental and clinical scientists, combining expertise from the biomedical sciences and e.g. engineering provides a powerful environment for 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. The ERA-NET NEURON should contribute in all its activities to tearing down conceptual barriers.

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 Programme by the European Commission, Horizon2020, is of major importance as it is the largest European source 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 initiative ROAMER (Roadmap for Mental Health Research in Europe) provides information about priorities specific to research into psychiatric diseases and conceptual frameworks how to tackle them. The European Strategy Forum on Research Infrastructures (ESFRI) may enable the use of platforms and other infrastructural support.



Appendix: The ERA-NET NEURON

HISTORY

Since 2007, 24 ministries and funding organizations from 18 countries across Europe, Israel and Canada 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 organizations 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 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), Iceland (RANNIS), Israel (CSO-MOH), Italy (MOH), Latvia (LAS), Luxemburg (FNR), Poland (NCBR), Portugal (FCT), Romania (ANCS-MEdR, UEFISCDI), Slovakia (SAS), Spain (ISCIII, MINECO), Sweden (SRC), 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 joint calls for proposals 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 and 2013), Cerebrovascular Disorders (2011), Neuroinflammation (2014), and Neurodevelopmental Disorders (2015).

An award was designed as a form of support and encouragement for early-career researchers. NEURON partner organizations issue this award annually to recognize 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.

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

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German Aerospace Center (DLR)
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Health Research
Heinrich-Konen-Str. 1
53227 Bonn
Germany
Internet: http://www.neuron-eranet.eu/en/38.php
E-Mail: info@neuron-eranet.net

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51580 Reichshof-Nosbach
www.sku-l.de

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