The European Brain Research Area

The Shared European Brain Research Agenda

SEBRA

Open consultation

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1. SEBRA

Millions of Europeans are living with brain conditions, mental and neurological alike. To improve their lives and prevent others from being affected, we need to advance the understanding of the healthy and diseased brain, as well as the interaction with the environment. To do so successfully, gaps in currently existing brain research should be identified and priorities for the future should be set.

Brain research has always been a dynamic and evolving field. However, as brain health and brain disorders are an integral part of society and impact society in a large extent, the view on brain research needs to be further broadened. Brain research nowadays must therefore touch upon fields beyond its own biological background and beyond fundamental and translational brain research. Connections should be established with experimental, computational/artificial intelligence and theoretical approaches. Also disciplines like psychology, sociology, education, and philosophy must be comprised. This interdisciplinary approach allows to link neuroscience with empirical and phenomenological sciences, and ultimately transforms brain research towards a more holistic approach.

To address present gaps and priorities in brain research, the involvement of all relevant stakeholders in the brain area is required including basic, translational, and clinical scientists, neurologists, neurosurgeons, psychiatrists, industry, regulators, funders, and policymakers. In addition, the role of people with brain disorders, their families and citizens is of utterly importance and their perspective must be considered during all steps of a research project. Their experiences, needs, views, and quality of life should be considered when performing research. Guidelines, tools, training, and support to enable patient and caregiver involvement in research are critical and should be facilitated. Such collaborations reduce fragmentation in the brain space and contribute to a better understanding of the brain.

To improve the lives of persons with brain conditions and to understand the healthy, interacting, and diseased brain, particular attention should be paid to the use of animal models. Animal models have been and still are utterly important in the understanding of molecular and single neuron basis of brain functions, as well as in the pre-clinical phases of drug discovery pathways. Between 2007 and 2019, animal models were used in 1389 (out of 3874 which is 36%) brain research projects funded by the EC (ref. EBRA mapping report). Animal models in research are also needed for the development of new brain research technologies aiming to produce biomarkers of brain functions and to stimulate the brain or develop therapeutic drugs. The use of animals in this context is strictly regulated by ad hoc EU legislation, which has been revised and updated over the years to prevent misuse and mistreating of the animals used for scientific purposes. Enforcing the 3 Rs (Replace, Reduce and Refine the use of animals) is a guiding principle in the Directive adopted by the EU in 2010 (2010/63/EU), whose aim

was to strengthen legislation and improve animal welfare. The Directive was further amended in 2019, to incorporate additional requirements related to reporting and transparency obligations, as a further step toward the ultimate goal - set by the EC- to replace animal use for scientific purposes with non-animal approaches. The ethical value of this goal is undeniable and fully acknowledged by neuroscientists, who would gladly replace animal models with non-animal approaches granting the same wealth of information. Until that goal is reached, it will be crucial to benefit from all possible tools, methods, and models, including alternative methods.

In addition to animal models, the experimental field of Induced Pluripotent Stem Cells (IPSCs) based research is extremely important and rapidly developing in neurosciences. While seemingly more basic than animal models, human IPSCs can fill some translational gaps by directly using patient's cells. Human iPSCs models have already produce important results for diseases such as Alzheimer's disease (Israel et al. 2012), schizophrenia (Hoffman et al. 2017) and Multiple sclerosis (Nishihara et al. 2022; Perriot et al. 2018). Besides their potential for disease modelling, hiPSCs also hold many promises for cellular therapies for diseases such as Parkinson's disease (Doi et al. 2020).

Importantly, the generation and interoperation of big data sets including clinical data (e.g., from neuroimaging, electrophysiology, novel omics data, etc.), non-clinical real-world data (e.g., from mobile and smart sensors), and novel, validated, analytical tools (e.g., machine learning, artificial intelligence) have to be supported. This allows to stratify patient populations, identify risk factors, qualify biomarkers, predict clinical trajectories, etc

Finally, to improve the positive impact of brain research on society, increased attention must be placed on how brain research is communicated to lay audience and policy makers. The quality of lay scientific communication should be ensured and awareness should be raised about the potential positive or harmful effects scientific claims can have on society and on (political) decision making.

1.1. Future brain research priorities

1.1.1. Understand the healthy brain

To understand the healthy brain, different aspects need to be considered: Its development, maintenance, and function. Especially developmental neuroscience still represents a challenge because abnormal brain development contributes to a wide range of psychiatric and neurological diseases. Understanding the biological processes that underpin healthy brain development is therefore of critical importance. For example, how does a gene translate at the level of protein and how does a protein translate at the level of the system? In this context, a particular focus on stem cells is required. This also includes the understanding of the development of the brain throughout its

lifetime and more concretely in the different age groups (< 1 year, children, adolescents, adults, elderly). Such understanding will allow to correct or mitigate defects at each stage during brain development and so reduce the burden of brain disorders in society.

1. **Understand the foetal brain** Brain health and brain disorders can be triggered before birth, during the pregnancy. A healthy prenatal environment is therefore of utter importance for healthy brain development and adverse prenatal exposures have been found to increase the risk for brain disorders. Therefore, efforts need to be put into the understanding of the foetal brain and its development throughout pregnancy using for example advanced foetal magnetic resonance imaging (De Asis-Cruz et al., 2021).
2. **Understand the ageing brain** With the increasing life expectancy of European citizens, the understanding of healthy ageing as well as age-related brain disorders must continue. Therefore, it is necessary to increase the number of brain research studies in the elderly (> 65 years old).
3. **Harmonize animal studies across species up to complex human findings** To understand the human condition, both humans and animals should be studied. However, the vertical approach – from animal to human models – should not be systematically used as the only approach to understand the human brain. The human brain structure and function differs from the mouse brain. Therefore, a more horizontal interspecies approach to study the brain is suggested.
4. **Develop the theoretical including mathematical, and conceptual level of neuroscience** To accelerate the understanding of the healthy brain, there is a need to consider the contribution from humanities and social sciences (philosophy, sociology, economics, …). Conceptual and theoretical models need to be developed to explain brain functions including the social and societal frame. Such models should be based on computational neuroscience and brain simulation. This accelerates the development of clear hypotheses and expectations motivating targeted data collection and analysis.

1.1.2. Unravel the interacting brain

The brain does not stand alone but is embedded in an internal environment - the body - and an external environment – the outside world (e.g., geographically, socially). As the brain structure and function depend on interactions with these environments, all aspects of these complex brain-environment interactions should be examined. Future research should thus consider the impact of the environment (e.g., political, economic, social, technological, cultural and climate factors) on the brain. This should happen in an integrative manner and in relation to the bodily interactions. In addition, it is also necessary to broaden our approach from studying the neuron and network of neurons to understanding the impact of other cells of the body and, the external environment on the brain.

Finally, the translation between basic and clinical neuroscience, and from animal to human research are relevant and ambitious goals requiring multiscale analysis as well.

The following specific priorities have been identified:

1. **Understand the phenotypic and endophenotypic expression of (molecular) pathologies across scales** We need a clear understanding of how molecular processes act at the level of specific neurons to affect information processing at the level of circuits, and finally how these circuit level processes are integrated within neural systems to control the behaviour and cognition of the whole animal in both normal and pathological situations. To appreciate the complexity of the system, we need bridges between different research fields in order to understand how the brain integrates its activity with that of other systems including the immune system, metabolism and vascularization, and with the environment. Only by understanding how these levels interact will we be able to develop a clear understanding of how neuronal processes control behaviour and physiology and thereby define the strategies to tackle important societal challenges of brain disorders both in development and in adulthood.

2. **Understand networks between different brain compartments** Structural and functional networks and interactions between brain compartments must be assessed. Brain compartments do not only include neurons and non-neuronal cells (e.g., like astrocytes, microglia), but also the immune system, body fluids (e.g., blood, cerebrospinal fluid, etc) as well as the entire network of cellular and compartmental features of the brain and their interactions (molecules, sub-cellular structures, non-neuronal and neuronal cells, immune system, „body fluids “). Research across those levels must be promoted.

3. **Understand the development, maintenance, and function of the brain through interaction with its internal environment** As the environment in which the brain is embedded is everchanging, an understanding is needed of how the brain develops in such a dynamic environment, how the brain compartments interact with this environment, and how brain plasticity developed and maintained. This does not only include the external environment but specifically the internal environment of the brain in the body (e.g., brain-gut connection).

4. **Cognitive, affective, and social neuroscience** A better understanding of the role of the brain in complex cognitive functions is required. Memory, consciousness, emotions (e.g., stress, anxiety, happiness), empathy, compassion, actions, language and communication, are all complex functions allowing humans and animals to interact with each other and with their broader external environment (e.g., emotional responses play an important role during brain disorder

interventions). Therefore, more brain research studies investigating interactions between the brain, the body and its external environment are required. Those studies should also consider individual differences in emotional, cognitive, and social functions, as well as interactions between nature and nurture.

1.1.3. Fix the diseased brain

To understand and cure the diseased brain, there is first of all a clear need to improve the capacity to translate ground-breaking discoveries into basic neuroscience to the clinical settings. Furthermore, a better and complete understanding of disease mechanisms is crucial. The creation of a translational awareness supported and fostered in all research centres where basic and applied/clinical researchers work together and interact with the goal of potential clinical application will be instrumental and should be encouraged.

In addition, we need to gain better insights in the development and progression of brain diseases, improve the prediction of brain disorders, identify appropriate treatments, understand the impact of neurorehabilitation, uncover protective and preventive factors (including genetic, epigenetic, environmental, and social factors for brain disorders), as well as compensation mechanisms. To address these disease priorities, investments are particularly fundamental in the field of personalised and precision medicine.

1. **Development, reappraisal, and validation of brain disease models** A better characterization of existing models of disease development is necessary. Also, more advanced models and patient specific pre-clinical models should be developed, evaluated, and validated. To allow for this, novel technologies (e.g., digital models), and advanced methodologies (organoids, iPSC, simulations) must be used and preclinical trial networks should be implemented. Reproducible statistically powered translational studies/confirmative studies should also be performed allowing for providing information for preventive, diagnostic, treatment, and rehabilitation strategies. Such information needs to be in line with regulatory aspects to speed up the transformation in clinical settings.

2. **Need for large longitudinal based studies** There is a need for well characterized phenotyped and genotyped longitudinal patient cohorts that can be used for different types of studies. This allows gaining better insight into the development and progression of brain diseases. Specifically in clinical trial programmes, the target population must be stratified and described precisely. The studied population should include gender issues, ethnicity and geographical origin, the socioeconomics and all ages of life including very young children and very old people. This practice increases the translation capacity of brain research.

3. **Development of research on the nosography of brain disease** Especially, the common classification of mental disorders should be revisited in light of the common symptoms seen in different mental disorders. Therefore, omics and other biomarkers (clinical features, neuroimaging, EEG) for different brain diseases and disorders occurring at specific developmental ages should be identified, characterized, and validated and its contribution to diagnostics, prognosis and prediction of treatment outcomes should be investigated. In this perspective, also the ethical development of specific and effective biomarkers and treatments in relation to sex/gender (including non-binary), socio-cultural and ethno-racial differences need to be reflected on and considered.
4. **Understanding the blood-brain barrier** Increasing insight into the pathophysiology of brain diseases —be they metabolic, inflammatory, traumatic, immunological, or neurodegenerative— has led to the development of many promising therapeutic agents that could have a tremendous impact on disease processes. The brain, however, is well protected against the entry of many reagents by the blood-brain barrier, which does not allow the passage of large molecules, including antibodies. This is particularly important as monoclonal antibodies that can be tailored to target many relevant dysfunctional molecules have been highly effective in a large variety of systemic disease classes. The biggest challenge in the design of new neurotherapeutics is to enable them to attain an even distribution within the brain inside the blood brain barrier.
5. **Understanding the effectiveness of treatment strategies** Several treatment options for brain disorders exist, from pharmacological treatments to non-pharmacological approaches (e.g., lifestyle and diet) and brain computer interface-based strategies. However, a better understanding is needed on the effectiveness of all those different strategies (alone or in combination with other treatments). For example, despite effective pharmacological treatments, more than 50% of patients with epilepsy still develop abnormal neurobiological and neurophysiological processes underpinning motor and cognitive impairments. In addition, the novel techniques of DNA- and RNA-based interventions (ref. RNA-based Covid Vaccinations) should be explored. This will fundamentally change how we interact with the brain in health and disease.
6. **Performance of effective prevention studies** Studies on effective interventions, including effects of diet and lifestyle, to prevent and delay the progression of dementia (e.g., cognitive, and behavioural impairment), stroke and other cerebrovascular disorders, mental and neurodevelopmental disorders, behavioural disorders, rare diseases over lifetime and epilepsy should be performed. In addition, it is required to focus on early stages of diseases and to move the intervention window from full blown pathologies to asymptomatic or early-stage patients, and

from repair to prevention. Such shift is mainly critical for neurodegenerative and other chronic brain disorders.

7. **Identify and investigate common disease factors** We need to identify and investigate factors, (e.g., symptoms and predictors) which are transversally manifested in several brain disorders. The role of those transversal factors common to several disorders should be defined. Both the pathogenetic level and the putative interaction of these factors with the environment should be addressed. For example, sleep plays an important role in brain disorders throughout the lifetime, acts as a modulator of brain development and alterations of the physiological structure of sleep can interact with specific mechanisms underlying neurodegenerative disorders (i.e., accumulation of pathological proteins). Also, behavioural changes, often observed in neurological and psychiatric disorders, deserve more attention. Finally, effects of cultural context including social factors as common factor of brain disorders need to be addressed. For example, social media usage/addiction on brain and cognitive development should be studied.

8. **Understand sensory organ diseases from a brain perspective** Due to the fragmentation in the scientific and medical world (neurology, psychiatry, ophthalmology, and Ear Nose Throat - ENT), sensory organ diseases have often received little attention in brain research. Therefore, a particular focus needs to be put on understanding sensory organ diseases from a brain perspective (ref. SRA NEURON).

1.2. Enabling actions

To ensure that the priorities can be addressed by the brain research community, the conditions for carrying out brain research should improve. Implementing the enabling actions listed below allows excellent brain research as well as the exploitation of the research results. Novel tools to advance the understanding of unknown basic brain functions will be developed and the generation of novel therapeutic approaches will result in a reduced burden of brain disorders in Europe and worldwide.

1.2.1. Create a multiscale, including translational, environment on the work floor.

Excessive fragmentation in the Brain Research Area limits its full potential. The brain research landscape consists of silos of basic researchers, clinical researchers, neurologists, psychiatrists, neurosurgeons, Ear Nose and Throat (ENT) specialists, ophthalmologists, etc. Collaboration between all these “silos” is required and a change in “spirit” or culture in the brain research community needs to be implemented. Especially the gap between basic and clinical researchers must be closed. In addition, cooperation with other experts (e.g., engineers, computational scientists) and stakeholders (e.g., health care professionals, patients, and their representatives) should be encouraged. The following actions will pave the way to improvement:

1. **The creation of dedicated translational structures and teams** Brain research teams should consist of basic AND clinical researchers. Such teams should be sustainable in the long term (i.e., 5-20 years) instead of only being functional for the short duration of a project (3-5 years).

2. **Interdisciplinary education and training** for current and future generations of basic, preclinical, and clinical brain researchers.

3. **Set up of specific multidisciplinary programs** e.g., dedicated funding; infrastructure (e.g., innovation hubs) for clinicians and scientists' programs at national and EU level.

4. **The creation of permanent positions and career tracks for senior clinician scientists / medical scientists / computational (AI) scientists and specialized clinical experts.**

5. **The removal of legal constraints and increased flexibility for inner EU and international education** at all stages of professional life (i.e., master student, PhD, postdoc, established researcher, professor).

6. **Support for multi-stakeholder associations** to bring together the relevant key players in the brain space (including the patients).

1.2.2. Encourage smart data sharing.

There is a wealth of existing data in brain research. This huge amount of data should be exploited to ensure relevant use, intelligent interpretation, and smart application. Use of existing datasets and sharing of existing and new pre-clinical and clinical (e.g., from neuroimaging, electrophysiology, novel omics, behavioural data, etc.) data should be a priority. Acquisition and storage of new data should follow standardized rules and best practice examples. They should be available in open access mode.

1. **Inclusion of real-world data in datasets** Data sets should include biomarkers, stratification of patients and real-world data (RWD) including non-clinical RWD (e.g., quality of life data from mobile and smart sensors). The collection of RWD in addition to other types of data is important for the development of accurate brain health and disease models, for the development of novel interventions like prevention, to allow early detection, to evaluate disease progression and treatment efficacy as well as the ongoing management of brain disorders (including both mental health and neurological disorders).

    a. **Use of wearables and sensors** To accelerate the detection of early symptoms and evaluate disease progression and treatment efficacy under real life conditions, wearables and sensors need to be used. However, attention need to be paid to the safety of those technologies

and especially to the protection of data and privacy (e.g., collection, storage and sharing of location and personal – health - information).

b. **Patient relevant outcomes (PRO's)** When performing brain research, not only disease outcomes should be considered but also personalised neurorehabilitation and effects of interventions on quality of life of patients and/or other PRO's like social inclusion, return to work, etc. Ideally, standard sets of patients reported/relevant outcome measures would be developed. The individual preferences, needs and goals of patients need to be prioritised.

2. **Standardisation and harmonisation** An effort should be made at European level to harmonize existing data, protocols, and procedures. This should include a regular updating of the guidelines for clinical trials by the EMA as the guidelines for Parkinson or schizophrenia, for example, are almost 10 years old[1][2]. Scales, questionnaires, and approaches need standardisation to allow comparability of datasets. Finally, such harmonization and standardisation need to allow for integration of specific data into regulatory and reimbursement processes.

3. **The development of open multiscale infrastructures and platforms** Efforts are needed to continue in further developing open multiscale infrastructures and platforms. One example of a necessary platform is a European-wide proof-of-concept trial and preclinical trial data-sharing platform and related technology development platform. In addition, the inclusion of regional and national research infrastructures (e.g., EBRAINS national nodes) as partners in the EU programmes should also be reinforced.

4. **Sound analysis and interpretation of big data sets** Existing analytical tools should be updated, and novel ones should be developed. In this context, special attention needs to be paid to the validation of AI algorithms to predict the risk for and progression of chronic diseases. Appropriate IT-infrastructures should be developed, and competent personnel needs to be hired.

1.2.3. Develop new technologies and innovation

Brain research has been characterised by significant progress over the past years. Breakthroughs in the understanding of the brain are imminent, and recent advances offered by enabling tools such as artificial intelligence (AI), biomarkers and big data will further benefit neuroscience and accelerate

[1] https://www.ema.europa.eu/en/documents/scientific-guideline/guideline-clinical-investigation-medicinal-products-treatment-parkinsons-disease_en-0.pdf

[2] https://www.ema.europa.eu/en/documents/scientific-guideline/guideline-clinical-investigation-medicinal-products-including-depot-preparations-treatment_en.pdf

the discovery of innovative therapeutic solutions for unmet needs (Chen et al., 2020; Markram et al., 2013).

1. **Novel technologies** New technologies can accelerate brain research and the development of new therapies, as well as improve quality of life. This includes nanotechnology for drug delivery, digital therapeutics and techniques (e.g., the use of virtual reality in psychotherapy), wearables/sensors and neuroprosthetics/robotics. The same strict standards and regulation as for pharmacological treatment should be used to evaluate the efficacy of such novel technologies. This requires dedicated funding to perform randomised control trials of technologies. In addition, current and existing technologies (e.g., neuroimaging, brain stimulation) must be validated. This will accelerate the field of translational neuroscience and allow for personalized monitoring of responses to individualized treatments and neurorehabilitation. In general, also the efficacy of validated existing and novel technologies (e.g., helping patients to treat and manage their disease) needs to be ensured.
2. **Telemonitoring/telemedicine** Due to the Covid-19 pandemic, the digital transformation of healthcare accelerated, and a reconfiguration of care pathways occurred (e.g., home care, online consultation). For example, the use of telemedicine[3] approaches for diagnosis, monitoring and interventions accelerated which also facilitated the collection of more real-world data including those from caregivers and families of young people. However, the impact of telemonitoring/telemedicine on the patient, the gaps and best practices still need further assessment and understanding. In addition, electronic Health[4] and mobile Health approaches need to be developed under an ethical framework considering the potential harmful effects these novel approaches can have on an individual and on the society. Therefore, outcomes, user satisfaction, friendliness, autonomy, and implications of those novel approaches need to be measured and compared with traditional care.
3. **Value of innovation** Socio-economic, cost and quality of life data of novel approaches for the management and treatment of brain disorders need to be generated. These approaches should be compared with current best practice intervention and studies should include questions around reimbursement and implementation in the healthcare system. Importantly, we need to keep in mind that value of innovation may be disadvantageous from an economic point of view in terms of

[3] Telemedicine is the use of telecommunication and information technology to provide clinical health care from a distance.

[4] The WHO defines eHealth as the cost-effective and secure use of information and communications technologies in support of health and health-related fields, including health-care services, health surveillance, health literature, and health education, knowledge and research.

direct costs and still have a huge value in terms of indirect costs (often difficult to quantify) and for people's lives.

4. **Get industry back** Industry has left most of neuroscience research particularly in neurodegenerative diseases but also in others. Therefore, funding programs need to be developed to get industry/biotech back. Those funding programs and opportunities should not be restricted to Europe but should also be developed globally and allow for collaboration with US/Canada, Asia, Australia etc. Moreover, scientists need to be trained on how to approach and talk to industry/biotech partners/investors (e.g., be aware of their priorities), on how to create a business plan, be informed about intellectual properties/rights, etc.

1.2.4. Overcome regulatory, administrative, and legislative hurdles/limitations.

Currently, brain research is faced with several regulatory, administrative, and legislative hurdles which slows down discoveries and breakthroughs in the field.

1. **Enhancement of the engagement between brain researchers and regulators** The access to regulators should be facilitated and researchers need to increase their knowledge on the regulatory rules. In this perspective, several aspects of brain research should be considered: From animal – also primates - experimentation to data sharing and ethics to biobanking / human post-mortem studies to clinical trials. On the other hand, regulators need to be made aware of the regulatory struggles and administrative burden for researchers (e.g., the ethical approval of work in laboratory rodents).
2. **The creation of common data rules on the use of complex human and patient data** across the member states in Europe, data sharing with industry, Small and Medium Enterprises (SME's) and between different EU and non-EU countries. In particular in the field of technology and innovation (e.g., web-based ICT platform for telemonitoring assistance) there is an urgent problem related to national regulations and legal barriers about treatment of data and platforms of sensitive patient data. It is very important to consider both national and European laws when developing/using/taking up study results, new technologies, therapies, for brain research and clinical applications. We need to ensure that EU-member states allow for data sharing. Harmonisation of the legislative pathway is needed.
3. **The development of a clear scientific discovery-to-market pathway** This will accelerate the regulatory process. Such engagement will also allow to develop new methodologies through which evidence can be collected, validated, and integrated into regulatory and reimbursement processes. This will allow innovations to reach the patients and citizens who need them.

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