

Feedback from the European Brain Council on the Horizon Europe Work Programme 2021-2022

1. Introduction

The Horizon Europe Health cluster aims at improving the understanding of health and diseases, developing innovative methodological and technological solutions to better manage health and diseases and designing sustainable approaches for the digital transformation and delivery of integrated, person-centered and equitable health and care services. The European Brain Council (EBC) generally welcomes the programme which includes relevant areas that relate to neurological and mental diseases within several calls. However, though the document mentions “non-communicable diseases” and “mental health/illness”, there are very few references to neurological diseases and no further prioritization of brain disorders reflected within the calls. The numbers are clear; in 2010, it was estimated that brain disorders, neurological and mental alike, affected approximately 179 million European citizens and that the costs associated with these conditions were estimated at €800 billion annually (Gustavsson A et al. Cost of disorders of the brain in Europe 2010). In 2016, neurological disorders were the cause of 276 million DALYs & 9 million deaths, with mental disorders adding approximately 8 million deaths annually (GBD 2016 Neurology Collaborators, Estimating the true global burden of mental illness - Lancet Psychiatry 2016 & Mortality in Mental Disorders and Global Disease Burden Implications). Moreover, the consequences of brain-related conditions extend well beyond European healthcare systems and include loss of quality of life, pressure on health and social welfare systems, implications for labour markets with prolonged impairment, great dependency and significantly reduced productivity. In this regard, EBC -together with all its member organisations and societies- are pointing out the importance and the need to have brain research better recognized and supported within the scope of Horizon Europe. This is a key requisite for improving human health and decreasing the overall burden of disease on European citizens. Therefore, we consulted within our wide network of brain researchers, scientists and clinicians and gathered feedback and suggestions for further improving the draft Work Programme below:

2. General feedback

Addressing the full spectrum of brain-related diseases

Brain disorders –both neurological and mental alike- constitute a major factor, alongside cancers and cardiovascular diseases, driving the overall burden of diseases in Europe. The Health Cluster aims to solve the major health-related issues plaguing the European population, yet brain disorders remain low and insufficiently recognized throughout the draft document whilst the majority of brain conditions remain without efficient treatment and none with full cures. Although there are references to mental health/illness and disabilities in some parts of the text (e.g. p. 7), only limited references to neurological disorders are made. Therefore, we suggest using the term “brain disorders”, which covers both neurological and mental conditions, in the topics 1.1, 1.2, 1.3, 1.4, 1.5, 2.5 and 3.3. Moreover, there is only a limited mentioning of sleep and (chronic) pain in relation to specific topics (respectively 1.1 and 3.3). As these represent major factors associated with human health and are strongly related to brain disorders, these terms should be further emphasized throughout the text as well as in the calls and topics.

Importance of collaboration/coordination in the brain research space

Europe-wide collaborations should be stimulated if needed and relevant. We therefore welcome the calls for partnerships in the health research area. To establish fruitful and effective collaboration, we need to better understand the potential for collaboration and interaction, especially with civil society, policy, interest organisations and lay public for the advancement of health and neuroscience. With the project establishing a European Brain Research Area (EBRA), EBC and its member organisations and societies are working towards this important goal with the cluster calls. The aim is to promote cooperation and exchange between brain research projects and to enable or enhance international collaboration and the development of clusters in all areas of brain research involving various stakeholders (academics, clinicians, patients/society, industry, policy ...). In addition, the Shared European Brain Research Agenda (SEBRA), that we are developing is focusing on research opportunities and research and innovation gaps to be addressed in the field and priorities for action in the short and long term and research areas that would benefit most from cross-initiatives cooperation. The EBRA clusters and SEBRA will continue to guide us in the future on how to streamline and better co-ordinate brain research across Europe while fostering global initiatives.

Increased focus on supporting basic research

Although we very much agree on the importance of translational research, we need to be careful not to focus all research priorities solely or exclusively on translation. To effectively perform translational research and because the brain is a very complex matter, we need to stress the value of basic research and keep investing resources into fundamental research. For many brain disorders, the field for translation is not ready yet. The transition to clinical research is often too rapid, which might lead to failure. Therefore, we emphasise the value of hypothesis driven research and related pre-clinical research, definitely with regard to innovation, and we stress the importance of understanding the biological basis of brain diseases.

Addressing the scope of the various topics

As we have witnessed in the more recent years, the current work programme also includes topics that generally are very broad by nature. This means that the programme is inclusive which we consider to be positive, but it also opens up for a larger number of submissions. As a consequence, there is likely to be an increased number of rejections and the need for reviewers will continue to grow. We recommend that the scope of the various topics is reviewed and further adjusted and narrowed where needed.

3. Specific comments

Introduction

On p. 6, we propose to also include “scientific (research) societies” next to the other stakeholders mentioned: research organizations, researchers from academic institutions, research organisations, small and medium enterprises, and large companies, as well as citizens and patients, patients associations, providers of health and care services and regulatory instances.

Destination 1

On p. 7 we suggest adding neurological disabilities to the listed conditions as follows: “... to chronic health conditions, physical, mental and neurological disabilities, or age-related impairments”.

Topic 1.1 Prevention of obesity through the life course

We confirm the importance of this topic as it is very important for maintaining a healthy brain. Prevention of obesity will also mean prevention of brain disorders. The gut-brain interaction between

the brain and other parts and mechanisms in the body (e.g., organs) has often been ignored or underrecognized. With the discovery of microbiota in the gut and their role in communication between the brain and the digestive system, the interaction between obesity and brain disorders (especially psychiatric and neurodegenerative diseases) needs to be further investigated. Therefore, an increased focus on brain disorders is needed in this topic and again should not only be restricted to addressing the connection between mental health and overweight but include brain health in general (both neurological and mental alike).

Topic 1.2: Towards a molecular and neurological understanding of mental health and mental illness for the benefit of citizens and patients

As mentioned above, we would not restrict the wording to mental health and mental illness and therefore suggest to broaden the scope of the topic to include a reference to neurological disease and to change the wording to “Towards a molecular and neurological understanding of mental health/illness and neurological disorders...” This is especially relevant where there are strong linkages in biomarker development between psychiatric and other neurological diseases.

Topic 1.4: The Silver Deal

We acknowledge the importance of neurodegenerative diseases such as dementia, but would suggest to further extend the scope of Topic 1.4 in order to address the full spectrum of brain-related diseases in the elderly population. As such, we recommend including expected outcomes aimed at addressing the impact of other chronic neurological diseases such as epilepsy, stroke and post-concussion syndrome*.

Topic 1.6: AI tools to predict the risk for chronic diseases

Early detection is for many brain-related diseases crucial as this enables more effective healthcare interventions to be made at an earlier stage in the disease pathway, thus further optimizing outcomes and slowing down the progression of certain diseases. The development and deployment of AI provides tremendous opportunities for enhancing the early detection of many non-communicable diseases. In light of the increasing societal burden of brain-related conditions, we propose to extend the scope of Topic 1.6 and add additional outcomes aimed at specifically supporting the development of innovative AI tools and solutions for enhancing the early detection and diagnosis of both mental and neurological conditions.

* see annex for more information on stroke and concussion

Amongst other issues, these outcomes should aim at providing large longitudinal population-based studies integrating different types of data (i.e., genetics, biomarkers, and clinical aspects) as these play a key role in enhancing the understanding of the development of certain brain-related diseases. Moreover, strong synergies should be put in place with the research-related components of the European Commission's White Paper on Artificial Intelligence ([EBC feedback on the White Paper](#)). Finally, we also propose a broadening of the expected outcomes to include 'better trial stratification' and 'more precision-oriented therapies that are better linked to the stage of the disease'.

Destination 3

We propose to expand the 'Expected Impacts' to include a reference to chronic disease and treatment resistant disease as follows: "Health care providers are able to tackle diseases (infectious diseases, including poverty-related and neglected diseases, chronic disease and treatment-resistant disease, non-communicable and rare diseases) and reduce the disease burden on ...".

Topic 3.1: Comparative effectiveness research for healthcare interventions in areas of high public health need

Regarding reference to the databases, we support the fact that sustainability is considered. For the health care related calls we would suggest to make it stronger as we regard it as a must that European investments are made lasting for further utilization. In the scope of this topic reference is made to elderly and paediatric population as examples for whom healthcare is challenging, but we suggest to also include patients with chronic diseases and comorbidities.

Topic 3.2: Building a European innovation platform for the repurposing of medicinal products

Developing new innovative treatments for improving the lives of people living with mental or neurological conditions is often very challenging. Factors that hinder the pace of innovation in this field include, amongst other issues, the overall complexity of the brain as well as the limited understanding of brain functioning and the pathophysiology of many brain disorders (despite advances in brain research). Furthermore, failure rates in drug development in neuroscience are in many cases higher than in other areas. Repurposing of medicinal products holds the potential to provide new therapeutic options for patients living with a brain condition. As such, the repurposing model that is to be elaborated as part of Topic 3.2 should particularly focus on repurposing medicines and driving innovation in the brain research space. Moreover, programmes and actions that are to be launched as part of this topic should utilize information from genetics as this has proven to be highly informative in prioritizing drug targets and identifying indications for drug repurposing and

repositioning e.g. through Mendelian Randomisation approaches and Phenome-Wide Association Studies.

Topic 3.4: Pre-clinical development of the next generation immunotherapies

This is an important and rapidly expanding field. Improved immunotherapeutic agents, particularly personalized to specific disorders are urgently required to shorten management and hasten recovery while preventing chronic neurodisability.

Destination 4

Topic 4.3: Personalised medicine and infectious diseases: understanding the individual host response to viruses (e.g., SARS-CoV-2)

An urgent priority is to understand short, mid-, and long-term effects of SARS-CoV-2 in the nervous system, brain and on cognition ([Lessons learned from COVID-19](#)). There are still many open questions, such as possible long-term association with neurodegenerative diseases, access of drugs to the brain tissue, direct action on respiratory centers, thrombotic effects, encephalopathies by the virus, etc. Although SARS-CoV-2 is the obvious virus of the day, common pathogens such as cytomegalovirus, herpes simplex virus should not be neglected both in terms of detection, management /treatment and prognosis stratification techniques.

Destination 5

Topic 5.2: Next generation advanced therapies to treat frequent and serious medical conditions with unmet needs;

The topic on advanced therapies is of great interest, however we feel it is very focused on some specific tools therefore excluding other gene and cell therapy approaches. Therefore, we suggest to add to “...pluripotent stem cells, gene editing or RNA...” the following on p. 66 “... or where introduction of a gene (such as gene therapy with chemogenetics) corrects cellular function.”

Topic 5.9: Innovative tools for use and re-use of health data (in particular electronic health records and/or patient registries)

We strongly support the use of existing data (bases) for modeling (diagnosis, prevention, therapy prognosis, care...) and would even suggest to emphasize this in other related calls of Destination 5. On another note, we propose adding text on ability for patient engagement and patient contribution to self-care through tools such as patient portals to enrich/ re-use data.

4. Conclusion

The Horizon Europe Work Programme for 2021-2022 holds the promise of becoming a robust tool for accelerating brain research and advancing the understanding of the human brain, which is crucial for ultimately reducing the disease burden imposed by brain disorders on European society. We therefore sincerely hope that the proposed recommendations will be taken into consideration as these are paramount for improving the health and well-being of EU citizens and developing effective solutions that could have a real and meaningful impact on patients affected by brain-related diseases. Whenever needed, we remain committed to support the EU in further improving the Work Programme and offer to again mobilize our network of scientists and experts in order to provide further input and expertise as regards the content and scope of the health-related topics.

ANNEXES



**Response of the European Stroke Organisation to the
Horizon Europe consultation document:
Cluster 1 Health 2021-22**

These comments are submitted by the Executive Committee and Trials Network Committee of the European Stroke Organisation (ESO), and the ESO Trials Alliance.

Specific Comments:

ESO warmly welcomes the Horizon Europe Work Programme, which includes the highly relevant areas of stroke and vascular dementia within several calls, which cause significant health challenges across the EU and globally. We would like to request some clarifications and raise some concerns, as follows:

1. **We request that the available budget be clarified.** We note that no budgetary details are provided. Specifically we emphasise that sufficient budgets must be available for academic-led randomised clinical trials testing new treatments for stroke and vascular dementia. This is essential to conduct these trials to the standards required by Good Clinical Practice and those of national and international regulatory bodies.

We emphasise that, to avoid statistical under-powering, **large sample sizes** required to generate new robust clinical trial evidence are frequently needed, often in the range of 1,000-4,000 patients^{7,8}. We also note the high costs associated with conduct of clinical trials, including **institutional overhead payments (20-30%), staff salaries, data management centre costs, monitoring costs, legal and insurance, drug purchase and logistics, regulatory fees, patient expenses, and site payments.**

We recommend that the budget range for such trials deliberately is set widely, **in the range €3-20 million**, depending on the size and scope of trial proposals. By comparison, this budget range is the norm for similar trials funded by the industry sector and by the US National Institutes of Health.

For information, the EU-funded WAKE-UP clinical trial in acute stroke treatment cost approximately €11.6 million. WAKE-UP recruited approximately 1,300 patients and demonstrated a 60% improved likelihood of excellent outcome in stroke patients treated with 'clot-busting' thrombolysis when the time of onset was unknown. This successful EU-funded trial, published in the New England Journal of Medicine, resulted in changes to global clinical guidelines and practice⁶.

2. We request **clarification on the duration of funding** allowed. Usually EU awards are of 3-5 year duration. However, large European multi-centre trials

involving many centres may take 18-24 months to set up, after funding is received. This is due to the requirement to submit and approve regulatory, ethical, insurance, and contract documents across multiple countries and centres. Stroke trials may then require several years of patient recruitment and follow-up. This is **especially true of trials of secondary prevention and vascular dementia**, where the effect of the intervention may become apparent after 3-5 years follow-up. Longer award durations, or a mechanism to provide for award extensions (ideally costed extensions) are required to address these longer-term priorities.

This point is relevant for several Calls (eg. Topic 1.4, The Silver Deal; Topic 3.1 Comparative Effectiveness research for healthcare interventions in areas of high public health need; Topic 5.3, Optimising effectiveness of existing prescription drugs, with Biomarkers, for major diseases [excluding cancer]).

3. We note the CSA 3.3 placeholder for and EU wide Clinical Trials Network – public health emergencies. No details are yet available. As cardiovascular disease is the leading cause of death globally and in Europe, stroke is the leading cause of acquired disability, and dementia (including vascular dementia) a major cause of morbidity in older adults, **we recommend that stroke and vascular dementia are included in the definition of public health emergencies and not excluded for eligibility for this Clinical Trials Network Call.**
4. We request that **programmes on repurposing of medicinal products** should explicitly **include utilizing information from genetics**, which has proven to be highly informative in prioritizing drug targets and identifying indications for drug repurposing and repositioning e.g. through Mendelian Randomisation approaches and Phenome-Wide Association Studies.

The point is relevant for several calls (e.g. Topic 3.2, Building a European innovation platform for the repurposing of medicinal products; Topic 3.6 Development of effective therapies for rare diseases with an unmet medical need).

Context:

1.1 Importance of stroke and cerebrovascular disease:

The World Health Organisation and Global Burden of Disease Study have identified that cardiovascular diseases are the leading cause of death worldwide, accounting for an estimated 17.7 million deaths in 2015¹. Of these, stroke is the second leading cause of global death, and a major cause of disability. **In Europe**, the Burden of

Stroke in Europe report by ESO and the patient organisation Stroke Alliance for Europe (SAFE) confirmed that **stroke is a leading cause of death and disability**. Due to ageing populations, the absolute numbers of people in Europe affected by stroke is **projected to increase by 30% by 2035**. Direct healthcare costs of stroke in Europe were €20 billion in 2015, with a further €25 billion in indirect costs. Stroke and vascular disease of the brain are **also major contributors to cognitive decline and dementia**^{1,2}, both major public health challenges across EU states, with associated very high healthcare costs related to provision of community and long-term care.

ESO and SAFE have identified improved acute treatment, prevention, and recovery as areas for therapeutic strategic focus to improve stroke outcome. In stroke survivors, recurrent stroke and coronary artery events are important contributors to death and disability, occurring in 25-30% of stroke survivors by 5 years, despite use of guideline-based therapies³⁻⁵. **New clinical trials** of interventions to prevent these recurrent events (**secondary prevention**) **are needed**. Emergency treatments may have major benefits to limit brain injury in acute stroke caused by artery occlusion (ischaemic stroke) or rupture (haemorrhagic stroke). **Trials of new emergency treatments are urgently required**. Many patients, regardless of their acute treatment, are confronted with major disabilities. Little high-quality data from clinical trials is available to guide treatments for stroke recovery, which is a priority for people living with stroke. **New clinical trials of interventions to improve stroke recovery are needed**.

About the European Stroke Organisation (ESO):

The European Stroke Organisation is a pan-European society of stroke researchers and physicians, national and regional stroke societies and lay organisations that was founded in December 2007. The ESO is an NGO comprised of individual and organisational members. The aim of the ESO is to reduce the burden of stroke by changing the way that stroke is viewed and treated. This can only be achieved by professional and public education, and by making institutional changes. ESO serves as the voice of stroke in Europe, harmonising stroke management across the whole of Europe and taking action to reduce the burden of stroke regionally and globally.

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“WHITE PAPER”

The Sports-Related Concussion in Europe (SoRCE) Consortium

The intensity and speed of modern sports put athletes at high risk for sustaining a sports-related concussion (SRC). SRCs is a traumatic brain injury characterized by transient neurological symptoms, and pose an increasingly recognized health problem in view of the large number of Europeans participating in sports every day. While most recover within days from an SRC, an estimated 15-30% of those who sustained an SRC experience prolonged recovery or develop devastating chronic symptoms. Children and women seem to have worse outcome following SRC. Further, repeated SRCs, which often occur over the career of an athlete, lead to an increased risk for life-long disabilities including an increased risk for dementia and mental health problems⁵.

Soccer is Europe’s most popular sport with an estimated 55 million male and 7 million female players. The estimated incidence of SRC in European soccer is ca 1.38 per 1000 hours of game play indicating a large number of concussed soccer players annually. A recent epidemiological study in Scotland found an increased risk for dementia in former professional soccer players. A growing body of research suggests an association between exposure to repeated head impacts (e.g., heading the ball in soccer) and alterations in brain structure and function in soccer players of all levels and across all age groups.



Contact sports such as rugby, American football, and ice hockey have an even higher incidence of SRCs per hour of play time. To date, there are no objective measures for early diagnosis or prognosis and the diagnosis of SRC is based on subjective symptoms reported by the athlete. Moreover, it is impossible to predict who will have an uneventful recovery and who will develop long-lasting symptoms. Most importantly, current therapeutic options are solely based on symptomatic treatment (e.g. pain medication for headache). No treatment is available to improve long-term outcome.

Aim of the consortium

There is a huge unmet need for prevention, diagnosis and treatment of the short- and long-term consequences of sports-related concussion (SRC) in Europe. While participation in sport has vast health benefits, there must be increased focus on the risks of SRCs to optimize the safety of the athlete.

GLOBAL AIM: To prevent, diagnose and treat the short- and long-term consequences of sports-related concussion (SRC) in Europe

In this European-wide consortium, consisting of key international leaders across a variety of competences, we outline a comprehensive approach to the problems of SRC. We will study SRC from the molecular level in the experimental setting, across diagnosis to the treatment

and rehabilitation phase in the concussed athlete. Specifically, we use state-of the art digital technology, develop clinically-relevant experimental SRC models adhering to the 3R principle, use novel Imaging techniques and create large databases for tissue, fluid and epidemiological analyses. By bringing in industrial partners, insurance companies, sports physicians and major European sports clubs, we establish a potential for not only advancing the knowledge of SRC but also creating possibilities for the development of innovative diagnostics and therapies as well as establishing solid guidelines for European athletes. Importantly, we also create platforms for the education of the athletes and his/her legal guardian and for sports leaders as well as laymen dispersing knowledge and management protocols across European countries.

Research methodology

Using state-of-the-art epidemiological, biomarker, genetic, experimental and imaging methods, we explore SRC from “bench to pitch”. We create platform for education and the creation of refined management guidelines and we team with industrial partners for improved detection, prediction, monitoring and management of SRC.

Summary

The SoRCE consortium, created and led by four highly experienced clinicians and researchers in the field of brain injury, consists of a wide range of experts across Europe and has an unprecedented approach to the understanding, management and treatment of SRC. This unique research effort addresses numerous topics of key importance for the future brain health of athletes participating in sports, ultimately improving the outcome of all athletes following SRC in Europe.

Consortium led by Peter Vajkoczy



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