NeurotechEU
The European University of Brain and Technology

Description of the Alliance: NeurotechEU is the European University of Brain and Technology (www.theneurotech.eu), founded in 2020 under the European Universities Initiative. NeurotechEU aims to establish a trans-European network of excellence in the field of brain and technology to increase Europe's competitiveness in education, research, and innovation. By bringing together leading European universities and associated partners, NeurotechEU creates a unique educational environment where the next generation of researchers, professionals, and citizens can cooperate and work across different European and global cultures.

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D2.1 Scientific Challenges in Neurotechnology

Executive summary

This document outlines pressing scientific challenges in the evolving field of neurotechnology that are currently of high relevance to the research community. The challenges reflect key areas in which the research community sees significant potential for advancement and innovation. For each dimension within NeurotechEU, a dedicated discussion group was established, which collaboratively identified and analysed the most pressing scientific challenges. Later, these scientific challenges were organised into the five content spaces of NeurotechEU. In total, 18 scientific challenges were defined along the five content spaces. With this document, and following versions, NeurotechEU will focus on using its network and resources to actively address these challenges. This will include creating targeted educational programs, facilitating cross-disciplinary collaborations, and driving research initiatives.

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Introduction

1.1 Purpose of this document

This document aims to outline pressing scientific challenges in the evolving field of neurotechnology that are currently of high relevance to the research community. It provides a structured analysis of these challenges, each categorised according to the dimensions of NeurotechEU. These challenges reflect key areas in which the research community sees significant potential for advancement and innovation, as well as areas that pose notable difficulties or limitations in currently available methodologies and technologies.

To ensure this document remains current and impactful, it will undergo regular updates incorporating recent advances addressing existing challenges. Each update will not only highlight the latest developments in neurotechnology but will also delve into the broader implications of these scientific challenges for the field.

In future updates, NeurotechEU will focus on using its network and resources to actively address these challenges. This will include creating targeted educational programs, facilitating cross-disciplinary collaborations, and driving research initiatives. In this way, NeurotechEU aims to be a strong, adaptable academic community that is well equipped to tackle the ongoing and future challenges in neurotechnology, thus contributing to the advancement of the field and the development of innovative solutions.

1.2 Development of the Scientific Challenges

For each dimension within NeurotechEU a dedicated discussion group was established, bringing together researchers from various institutions within the alliance. These groups met online to collaboratively identify and analyse the most pressing challenges in neurotechnology, each group focusing on issues specific to its expertise and dimension. These discussions aimed to provide a comprehensive understanding of the critical scientific and technical obstacles in the field, which will ultimately guide NeurotechEU's research and educational programs.

During the meetings, the researchers were guided by key questions designed to frame each challenge within a broader context. These questions included:

- **What is the scientific challenge in Neurotechnology?** This encouraged researchers to clearly define the problem within their area of expertise and NeurotechEU dimension, ensuring that the challenge was written in a way that highlighted its importance and impact.
- **Why is this particular challenge relevant?** This question led to conversations about why the challenge is important in the respective field of neurotechnology, focusing on its role in advancing science, driving innovation, and opening up new practical applications, and also taking societal impact into account.
- **What is the current status of the challenge?** Researchers examined the existing approaches, ongoing research, and recent advancements related to the challenge, providing information about where the field currently stands in terms of solutions or understanding.
- **How can NeurotechEU contribute to addressing the challenge?** This question focused on identifying potential actions for NeurotechEU to make a meaningful impact, whether through collaborative research, curriculum development, resource sharing or community-building efforts.

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Following these discussions, challenges were organised into appropriate content spaces (Fig. 1) to strategically focus resources on areas with the greatest need and potential impact.

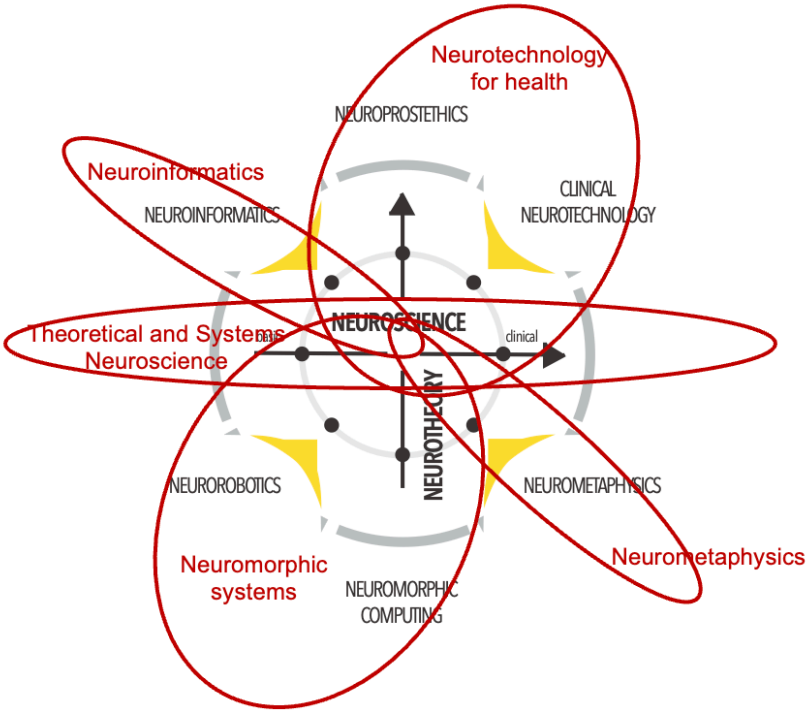

Figure 1: Content spaces of NeurotechEU. Due to thematic and content-related similarities, certain dimensions are grouped into content spaces.

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2. Scientific Challenges in Neurotechnology

2.1. Theoretical and Systems Neuroscience

2.1.1 Lack of Biomarkers and Experimental Disease Models

While research in neurotechnology has made great advances in recent years, several challenges remain. One major challenge in clinical neuroscience (psychiatry, neurology) is the availability of biomarkers and experimental disease models. Biomarkers at different levels of analysis (e.g. molecular, brain structural, brain functional, behavioural) are needed to support diagnosis, to make prognoses concerning disease progression, to optimise therapeutic interventions and to predict treatment responses. They are frequently studied in experimental disease models but may also be useful as surrogate endpoints in clinical trials. There is currently a general lack of well-validated biomarkers in relation to neuropsychiatric disorders. As Pratt and Hall 2018 point out: “For conditions such as cancer and diabetes, the discovery and development of biomarkers has had a large impact on management and treatment [1]. However, the development of biomarkers for psychiatric conditions has lagged behind that of other areas of medicine, with no biomarkers currently in routine use for the major psychiatric disorders.”

This situation adversely impacts clinicians’ ability to make accurate diagnoses and complicates drug development, where there is a high attrition rate of new compounds in Phase II and III clinical trials [2] Appropriate biomarkers and experimental model systems are therefore needed to facilitate the early discrimination between compounds that are likely to succeed or fail later [3]. However, there is dissatisfaction in academia and industry with regards to existing experimental models and biomarkers. As Kola and Landis argue, there is a “need to develop experimental medicine paradigms that are more predictive of outcomes and to carry out such proof-of-concept clinical trials much earlier in development" [4]. Moreover, within the field of antipsychotic drug development, Javitt et al recently argued that “a major limitation to glutamate-targeted treatment development is the lack of appropriate biomarkers to evaluate this effect in early-stage clinical trials to confirm target engagement” [5].

There are various reasons why the development of valid biomarkers is challenging. These include the clinical heterogeneity of diagnostic groups, failures to translate experimental models across species, and others. This challenge has significant societal impact, due to the personal and economic harm experienced by sufferers of neuropsychiatric conditions as well as their family carers.

Overall, this leaves a situation where advances in neurotechnology in relation to biomarker and model development are greatly needed. ‘Neurotechnology’ can be understood here within a broad, intermediate phenotype framework whereby novel biomarkers are considered useful at various levels of analysis, from molecular genetics via cellular and circuitry levels all the way to neurocognitive and behavioural assessments. A helpful framework in this regard may be the NIMH Research Domain Criteria (RDoC) units of analysis. Inbuilt into this framework is the necessity of interdisciplinary collaborations. There is also considerable scope for connections between academia and industry, especially with regards to development of novel compounds. Accordingly, key researchers and potential partners are academic researchers in NeurotechEU from different disciplines (neuroscience, psychology, psychiatry, neurology) as well as suitable industry partners. Given the complexity of working with multi-level biomarker data, multivariate and AI-supported data analytic approaches will be of importance in this context.

2.1.2 Complexity of Neurodegenerative Diseases

Neurodegenerative diseases affect the central nervous system, with a range of pathological hallmarks occurring, including inflammation, the loss of neurons and dysfunction of the neuronal network. Diseases such as Alzheimer's, Parkinson's and Multiple Sclerosis (MS) represent a widespread neurodegenerative disease spectrum that affects millions of people worldwide. Several potential factors, such as gender and genetics that may favour these diseases have been discussed in recent years, but the causes of the diseases remain unknown [6]. There are studies that consider an EBV-infection to be the main cause due to a higher risk of infected people developing MS [7]. Nonetheless, the remaining lack of clarity regarding these diseases poses a major challenge for preclinical and clinical research. During recent years, various contradictory approaches in MS research to the pathophysiology of this disease have been considered [8]. The involvement of various cell types in this disease process has been discussed, but the question of which cell type is primarily contributing to the pathophysiology still needs to be answered [9-11]. In addition to the investigation of the complex disease mechanisms, the heterogenous clinical pattern of MS also represents a significant challenge for clinicians. The disease is characterised by various symptoms ranging from spasticity to visual sensorial impairment, and the occurrence of different disease courses has made it known as a disease with a thousand faces [6]. The disease course differs in terms of relapses and progression of the disease, with the relapsing remitting type being characterized by complete remission or partially residual deficits between the relapses, and the secondary progressive MS, the most frequent progressive form, starts with a relapsing phase followed by disease progression after about 20 years [6, 12, 13]. Since there is no cure for the disease, the treatment of MS aims to directly affect relapses and to modify the disease course to reduce disease activity and thereby sustain the patients' quality of life [14]. B-cell-depleting drugs are of particular importance in the treatment of MS, such as the humanised monoclonal antibody Ocrelizumab, which showed positive effects on patients suffering from primary progressive MS, a disease course which is characterized by an initial disease progression [15, 16]. There are currently ongoing trials investigating the potential of new treatments for MS such as CAR T cell therapy. The application of CAR T cells has already been successful in the treatment of other diseases such as blood cancer. The ability to effectively penetrate into brain tissue and the efficient B cell depletion represents a promising approach of treatment of MS patients [17].

Similarly, for Alzheimer's disease, Amyotrophic Lateral Sclerosis (ALS) and Parkinson's disease, there are subgroups of patients that exhibit different rates of neurodegenerative decline, and different treatments will likely be required for these different subgroups. As a range of experimental models are available to study these complex diseases, matching a specific disease model to a specific subgroup of patients might pave the way for identifying the most appropriate treatment regimens.

It would be erroneous to assume that the difficulties posed by neurodegenerative diseases are the sole obstacles to be overcome in neuroscience. The complexity of diseases, like psychiatric disorders, represents a significant challenge for researchers as well. Given the high prevalence of mental diseases such as depression worldwide, there is also a pressing need to identify novel approaches that can enhance the understanding of this medical field. As previously stated, one potential avenue for investigation would be the identification of suitable biomarkers for the improvement of diagnosis.

NeurotechEU could address these challenges by forming research collaborations. Since the NeurotechEU project includes high-ranking scientists who conduct research in the field of neurodegeneration and

psychiatric disorders collaborations would strengthen the scientific progression and the development of innovative research approaches.

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2.2 Neuromorphic Systems

Neuromorphic systems represent a new and rapidly developing field, showing significant promise for advancing our understanding and applications in neurotechnology. As this area continues to evolve, we are committed to expanding this section to reflect the latest advancements and emerging research directions.

2.2.1 Young Neuromorphs Community

We have begun collaborating with the *Young Neuromorphs Community*—a network of early-career researchers and innovators dedicated to the advancement of neuromorphic systems. This community will not only contribute insights and expertise but also take an active role in co-organizing events and workshops focused on neuromorphic systems. These events will provide a platform for sharing knowledge, fostering interdisciplinary collaboration, and promoting innovation within this growing field.

Looking ahead, we aim to further integrate the *Young Neuromorphs* into other content spaces within NeurotechEU. By broadening their involvement across various research domains, we hope to foster a vibrant, interconnected community that drives progress in neurotechnology and enriches the educational and collaborative initiatives within our alliance.

2.2.2 Design Effective Neuro-inspired Computing Architectures in a few concrete use cases

The spiking neural networks as a theoretical computing model have been studied for a while, as well as their hardware implementations, but they still are at the early research prototypes validated on basic benchmarks, not real use cases. Using DVS cameras or spiking cochlea would enable end-to-end event processing of natural data in some real-world use cases. Some more work is needed in computer-aided design tools, including AutoML and open prototyping platforms.

2.2.3 Scalability

Scalability, the ability of a system to grow efficiently without losing performance, is a critical challenge in neuromorphic computing. As these systems expand, energy consumption increases, making it difficult to maintain efficiency [18], and posing significant material and design challenges [19]. To address this challenge, it is essential to develop energy-efficient architectures and design scalable communication networks and algorithms. Additionally, fostering collaboration between material scientists, engineers and neuroscientists will advance the search for solutions to scalability.

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2.3 Neuroinformatics

Advancements in neurotechnology and large pools of open data have revolutionised neuroscience– rapidly moving it towards an open, large-scale, data-sharing community. To fully embrace the potential of open science, neuroscience must adopt standards, methods and tools that support a FAIR (Findable, Accessible, Interoperable, and Reusable) scientific model [20, 21]. While clear steps have been taken in the form of data-sharing mandates from funders and FAIR neuroscience research infrastructures such as EBRAINS, key gaps remain in developing practical tools and infrastructures that are commonly accepted and widely adopted within neuroscience. We previously reported on the challenges that advancements in neurotechnology and big data present to the neuroscience community-at-large [22]. In that report we identified five categories of challenges caused by neurotechnological advancements and big data and proposed a roadmap for how the neuroscience community should address those challenges. Herein, we present three challenges caused by neurotechnological advancement specific to the field of neuroinformatics, the subdomain of neuroscience that combines neuroscience and informatics to: (i) develop tools and databases for the management and sharing of neuroscience data across all scales of analysis; (ii) develop computational models of the nervous system and neural processes; and (iii) develop tools for analysing and modelling neuroscience data.

The current state-of-the-art and a potential roadmap for how the NeurotechEU community can solve these challenges through its efforts in education and research.

Challenges

1. Implementation of the FAIR Guiding Principles by neuroscience researchers, software tool developers and infrastructure providers. Specifically, which standard or best practice should be adopted, how to implement the standard, and how/where to publish data for reuse
2. Integration of heterogeneous neuroscience data across scales (from genes to behaviour) and interoperability between research infrastructures
3. Large-scale data analysis

Relevance

Widespread adoption of The FAIR Guiding Principles for Scientific Data Management and Stewardship (an effort to make scientific outputs Findable, Accessible, Interoperable, and Reusable by both humans and machines) by funding agencies will expedite neuroscience's transition from a 'cottage industry' to a more open science, global community [23]. This development will be particularly challenging for the neuroinformatics community due to neuroscience's large number of subdisciplines, techniques, data types and model systems, as well as the fact that neuroscience has not had a long-standing tradition of open data. It is important to note that the FAIR Guiding Principles are only a general framework that requires each domain to develop and adopt its own standards, best practices and methods. Neuroscience will have to establish a common community definition of what entails FAIR neuroscience, which will be challenging due to its vast subdomains and the techniques employed in them. The task will be made more challenging due to the fact that the standards landscape in neuroscience is filled with competing, incomplete and overlapping standards/best practices, making it difficult for researchers, tool developers and infrastructure providers to know which standard or best practice to select.

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For neuroscience to become FAIR, it requires that the neuroinformatics community develops and maintains the necessary infrastructures in the form of web-accessible repositories for neuroscientists to publish data, code and workflows. It also requires a means to identify, define and support community-relevant standards both for data and metadata. Moreover, a domain as diverse as neuroscience benefits from centralised information hubs to make it easier for researchers to find FAIR data, tools and services on FAIR practices. Finally, neuroscientists will need training in how to share FAIR, including good data management practices in the lab, how to organize their data, use standards and to find tools that are available to assist them, since this is not traditionally taught in neuroscience training programs [24]. In addition to FAIR repositories for data and code, the neuroinformatics community will also need to develop software tools that import/export data using community standards and index their repositories in metadata aggregators such as the INCF KnowledgeSpace and the Neuroscience Information Framework InterLex.

Data standardisation is an essential element of FAIR and plays a pivotal role in data integration and facilitates infrastructure interoperability and large-scale data analysis. In terms of data integration, FAIR data standardisation converts data into a standard format that both humans and machines can read and understand. It is essential for preserving data quality and ensuring that data is usable and accessible. FAIR data standardisation is also important in infrastructure interoperability in that it enables different systems to share and efficiently use data, as well as makes it easier to process, analyse and store data in repositories.

The importance of the FAIR Guiding Principles in neuroinformatics cannot be overstated. The adoption of these best practices and tools that support FAIR, such as the move away from proprietary data formats and toward open-source alternatives including Python or the drive to standardise electrophysiological, calcium, or molecular imaging analysis pipelines is critical to accelerating scientific discovery as it can expand collaboration, reduce errors and maximise reuse of data, code and tools. Of equal importance, in the age of machine learning and artificial intelligence, data should be published with integration in mind, so they can be interpreted in new ways and leveraged to extract new knowledge. For this to happen, neuroscience as a discipline needs to adhere to the FAIR data principles, ensuring that the results of science are Findable, Accessible, Interoperable and Reusable, to both humans *and* machines.

Current state-of-the-art

Organizations like FAIRsharing and the International Neuroinformatics Coordinating Facility have taken leading roles in efforts to make it easier for neuroscience researchers, tool developers and infrastructure providers to find and select the appropriate (meta)data standards for their use cases. FAIRsharing provides a global registry of (meta)data standards, best practices, policy documents and databases covering many scientific disciplines. It provides users with links to documentation and provides an indication of the readiness level of the (meta)data standards, best practices, policy documents, and databases indexed. Conversely, the FAIR Roadmap developed by the International Neuroinformatics Coordinating Facility is specific for neuroscience. It provides the neuroscience community with a portfolio of (meta)data standards and best practices with links to software tools and infrastructure implementing the standards. It also provides users with detailed information about the use cases covered by each standard with links to implementation tutorials. All (meta)data standards and best practices indexed in the INCF FAIR roadmap are vetted by an expert panel and the neuroscience community-at-large and re-

evaluated every two years to ensure they are still maintained and provide information on any additional use cases covered.

Towards establishing common formats to achieve interoperability between systems and data formats, several efforts have been launched. For instance, the Brain Imaging Data Structure (BIDS) standard has been proposed as a common framework for organizing and sharing neuroimaging data. Other standards, such as the OpenEEG format have been developed to promote interoperability among electroencephalography (EEG) systems and the Neurodata Without Borders (NWB) format have been developed to provide a common standard to share, archive, use and build analysis tools for neurophysiology data. While these examples are promising, the adoption of common standards in neurotechnology and big data research has been slow, and the development of new standards can be time-consuming and resource intensive. As such, it is crucial that stakeholders work collaboratively to establish common standards that are widely adopted and facilitate the integration of diverse data sources.

Roadmap for NeurotechEU

The NeurotechEU community is positioned to help lead the transition to making neuroscience more open, FAIR, and citable through its efforts with education, research collaborations, and infrastructure. Specifically, NeurotechEU should aim to:

1. Mandate training on FAIR data management practices as a core component of its Joint-Masters Programme and provide educational opportunities to apply this knowledge (i.e. data challenges in which students use open data for analyses)
2. Develop FAIR data management training modules and tutorials for practicing research professionals (doctoral students, postdocs, and investigators) and publish on Campus+
3. Provide support for members of the NeurotechEU community to join community standardisation efforts
4. Promote the use of community standards and the adoption of their respective tools and infrastructures by NeurotechEU investigators
5. Provide an index of community standards on Campus+ complete with information about appropriate use cases, links to tutorials, and index of supporting tools and infrastructure
6. Work to achieve systems interoperability between major research infrastructures at partner institutions

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2.4 Neurotechnology for Health

Clinical Neurotechnology describes the bridge between neuroscience, technology and clinical practice. This dimension explores the possibilities of bringing technologies from experimental settings to real world applications. We identified the main application areas of technologies within clinical neurotechnology as (i) Clinical Research, (ii) Diagnostics, and (iii) Treatment. We described each application area and discussed scientific challenges in each.

2.4.1 Neurotechnology in Clinical Research

Neurotechnology is redefining clinical research, opening new paths for understanding, diagnosing and treating brain disorders. There are various evolving technologies within neurotechnology which still hold a high potential to be integrated in research [25].

One of the key benefits of neurotechnologies in clinical research is their ability to address neurological and psychiatric conditions, which represent some of the most urgent challenges in modern medicine. Disorders such as Alzheimer's, Parkinson's, schizophrenia and depression are marked by biological and clinical complexity that requires highly sophisticated research tools to understand them.

Innovations in technology are providing deeper insights into brain function and neural connectivity, allowing researchers to explore the complexities of the brain. Advanced neuroimaging techniques and neural mapping tools allow for more precise measurements of brain activity and connectivity patterns. This opens the way for earlier and more accurate diagnoses of neurological and psychiatric conditions, as well as the development of personalized treatments that target specific areas of the brain.

Technologies designed to interface with the nervous system, such as brain-computer interfaces (BCI), high spatial resolution MRI, and digital twin technology, are new tools to study the brain in real time and with incredible details. These technologies allow researchers to monitor neural activity, intervene through direct stimulation, and simulate brain dynamics in virtual environments, offering new perspectives on addressing diseases that were once nearly impossible to study or treat effectively.

Examples

A major unsolved challenge in Brain-Computer Interfaces (BCI) is achieving high-resolution, real-time decoding of complex thoughts or intentions in a non-invasive manner [26]. Current non-invasive BCIs, such as those using EEG, provide low-resolution signals and are limited to detecting general brain states or basic motor commands. This restricts their use for more elaborated tasks, like controlling advanced prosthetics or decoding abstract thoughts. Invasive BCIs, while more precise, come with significant risks such as infection and device degradation. Developing a non-invasive solution that offers both precision and long-term reliability remains an important challenge in BCI research. A potential solution to improve non-invasive BCIs could involve high-density EEG arrays combined with personalized machine learning algorithms [27]. The dense arrays would capture more detailed brain activity, while advanced algorithms would be trained to recognize each individual's unique neural patterns, improving the accuracy of thought decoding. This approach could allow real-time interpretation of more complex brain signals without the need for invasive implants, bridging the gap between non-invasive simplicity and high-resolution precision.

2.4.2 Neurotechnology in Clinical Diagnostics

Neurotechnology is an integral part of clinical diagnosis, to the extent that it is difficult to envision a world without its use in neurological assessments. Established neurotechnologies such as electroencephalography (EEG), positron emission tomography (PET), computed tomography (CT), magnetic resonance imaging (MRI), and magnetoencephalography (MEG) are standard tools in diagnosing a wide range of neurological conditions. Given the significant impact of these technologies, a challenge for future research lies in fostering the development of new, emerging neurotechnologies. As neuroscience advances, new diagnostic tools will be essential to deepen our understanding of complex neurological disorders and to enhance personalized medicine. However, the road from bringing an emerging technology from the lab into clinical practice can be long and winding. Possible challenges on the way could be integrating new technologies in existing clinical workflows, the cost and accessibility of new technologies, regulatory approval and the acceptance and trust of doctors and patients towards neurotechnologies.

Examples

Magnetic Resonance Imaging (MRI) is useful for medical and research purposes, but its ability to capture small details in the brain is still limited by its spatial resolution. This is particularly problematic in techniques like functional MRI (fMRI), where the relatively large voxel sizes obscure fine brain structures. Even with advanced 7 Tesla MRI machines, these issues persist, limiting the mapping of brain activity and early diagnosis of conditions like neurodegenerative diseases that involve small-scale brain abnormalities. Current MRI technologies cannot capture these details effectively. A potential solution would be to use 14 Tesla MRI. This ultra-high field MRI promises significantly higher spatial resolution, allowing for clearer visualization of tiny brain structures and more precise mapping of neural activity [28]. The 14T machine could overcome the limitations of previous systems, offering improved diagnostics for conditions like Alzheimer's disease at much earlier stages.

Wearable neurotechnologies, particularly non-invasive wearable sensing technologies have made significant advances in recent years, particularly in their ability to continuously, in real-time, monitor physiological parameters such as brain activity (e.g., EEG), heart rate variability, rest-wake activity, and even stress levels [29]. This is vital for detecting subtle changes that could signify the onset of neurological or psychological conditions, such as epilepsy, Alzheimer's or mood disorders. Early detection has the potential to lead to timely interventions and improved patient outcomes.

2.4.3 Neurotechnology in Clinical Treatment

Neurotechnology has already been applied in clinical treatment, particularly through applications such as Deep Brain Stimulation (DBS) and cortical interfaces. DBS, which involves the implantation of electrodes to modulate neural circuits, has proven highly effective in treating movement disorders such as Parkinson's disease and dystonia, as well as psychiatric conditions such as obsessive-compulsive disorder. Cortical interfaces, or brain-computer interfaces (BCIs), have enabled direct communication between the brain and external devices, offering life-changing solutions for patients with paralysis or neurodegenerative diseases by restoring motor control or communication abilities. However, the full potential of neurotechnology in clinical practice remains largely untapped, as different types of neurotechnologies face distinct challenges such as invasiveness, scalability, and regulatory approval and are therefore still primarily experimental [30].

Examples

Adaptive deep brain stimulation is a promising neurotechnology for clinical treatment, of movement disorders like Parkinson's but practical implementation remains a significant challenge. Several factors, including the technological complexity and limited data on long term stability of the approach, make it difficult to put this technology into clinical practice [31].

Many neurological disorders, including epilepsy, Parkinson's disease and MS present highly variable symptoms and progression patterns across patients, making it difficult to predict how an individual will respond to treatments. This variability complicates clinical decision-making, often leading to prolonged trial-and-error phases where patients undergo multiple treatments before finding one that works. Additionally, the dynamic nature of these disorders, with symptoms that can change over time, makes it challenging to continuously adapt treatments in real-time.

A potential solution involves using digital twin technology to create a virtual replica of a patient's brain, integrating real-time neuroimaging, electrophysiological data, and behavioural metrics. These digital twins would simulate disease progression and responses to various treatments, allowing clinicians to test different interventions—such as medications, deep brain stimulation, or surgery—in a personalized, risk-free environment. By continuously updating the model with new data, the digital twin would adapt to changes in the patient's condition, providing real-time feedback and enabling more accurate, personalized treatment plans for a wide range of neurological disorders.

Integration of non-invasive wearable sensors into personalized treatment is a critical and complex challenge in neurotechnology. One of the primary hurdles is the creation of an effective closed-loop system that seamlessly facilitates real-time sensing and feedback. Such a system would continuously monitor physiological and neurological data, analyse it in real time, and provide personalized therapeutic interventions based on the individual's current state. Achieving this would require intensive signal processing and accuracy, advanced algorithms to interpret the data in real-time, timely feedback mechanisms, adaptation to individual variability, and conscious implementation of ethical practices [32].

2.4.4 Artefact mitigation in neural decoding

Neural decoding is the neuroscience field that focuses on analysing neural activity to get useful information to interact with neuroprosthetic devices. In this regard, neural decoding can be based on processing neural activity from different neural sources. Neural decoding is based on different paradigms depending on the neural source and technology used to register the neural activity (i.e. EEG, EMG, EOG).

In recent years there have been relevant advances in this field, e.g. deep learning techniques are being applied to increase decoding performances [33], or EEG activity is being decoded for commanding lower-limb exoskeletons [34]. However, this field faces a great challenge, which is to discriminate the information associated with the neural event object of study from other neural activity caused by external stimuli or inner mental processes. These commonly named artefacts can contaminate the decoded information, leading to poor decoding results that cannot be used to interact with neuroprosthetics devices.

Neurotech EU could address this challenge, as there are research groups within Neurotech EU that have the scientific background requited to develop new algorithms that could mitigate the impact of artifacts in neural decoding.

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2.4.5 Neural stimulation

Neural stimulation focuses on activating/inhibiting brain areas in order to provide a temporal or permanent change in neural structures and the brain processes associated with them. Non-invasive and invasive techniques have been developed for brain stimulation [35, 36].

Although it has be demonstrated as a successful technique in the case of some affections, such as depression or Parkinson, its efficacy is still controversial in other applications. Therefore, more clinical trials have to be performed. In addition, spatial resolution in the case of non-implanted devices is poor and it is hard to reach inner brain zones outside cortex. New external stimulation devices should therefore be developed in order to achieve higher spatial resolution and reach inner brain zones. In addition, implanted devices should be miniaturized as much as possible and develop biological power supply systems.

NeurotechEU could address this challenge, as there are members who are clinical centres so they could be in charge of clinical trials, additionally, there are partners with experience in non-invasive neurostimulation techniques.

2.4.6 Neuroprosthetics for cognitive disorders

Neuroprosthetics have been mainly focused on sensory and motor disorders. However, their application to cognitive functions is not clear. Indeed, there are only few studies that suggest they could be useful for some cognitive and memory deficits [37]. In this regard, neuroprosthetic systems that affect neural oscillations and trigger neuroplasticity related to cognitive disorders should be developed, especially considering cognitive problems related to elder people.

NeurotechEU could address this challenge by designing neurostimulation strategies focusing on brain areas related to specific cognitive issues and testing them in clinical centres.

While it is clear that further development of neurotechnologies will certainly advance our understanding, diagnosis and treatment of several neurodegenerative diseases, their implementation within society will be dependent on available economic resources. There is, thus, an aspect of equity that we need to take into account within this field of development, as we do not wish to aim for efficacious clinical solutions which are only available to those who can afford them. NeurotechEU can be transparent about this issue and raise awareness within the EU about this aspect.

2.5 Neurometaphysics

Five challenges have been identified to be particularly acute in the field of neuroethics and neurolaw. These problems seem not only to be discussed particularly intensively at the moment but will also shape the field for years to come. Due to their relevance these challenges should be address with particular attention by NeurotechEU.

2.5.1 Brain Predictions

For a long time, attempts have been made to make predictions about future conditions or developments on the basis of brain data. The term brain data includes, for example, MRI or PET images, but also data generated by EEG or MEG. Future conditions and developments can be understood as the development of pathological conditions, for example, but also non-disease-related characteristics such as character traits of an individual. The use of AI-based methods of data analysis has made brain predictions much more powerful and it can be assumed that this area will continue to develop rapidly.

While early prediction of disease is undoubtedly helpful, especially when effective therapeutic interventions are available, such predictions can also raise *serious ethical questions [38].* A primary issue lies in *epistemic uncertainty* in cases of early predictions, disease interception, and the current practice of subgroup analyses, or borderline cases, which can lead to 'false positives.' Take, for example, the interesting case of comatose patients. Of course, PET images, fMRI strategies, etc., have proven incredibly useful in reassessing the vital prognosis of certain patients. However, detecting minimal cortical activity can generate significant epistemic uncertainties regarding the state of consciousness of those patients (whether they are in vegetative or in a minimally conscious state), leading to false hopes and expectations, which could be devastating for their families or the medical staff.
A second ethical issue relates to the *clinical relevance* of predictions and the therapeutic interventions to be adopted. The facilitation of detection via AI techniques can for instance encourage relentless detections to the detriment of patients, which could be harmful if we consider that these techniques (such as scans, etc.) are intrusive.

In general, one can ask who should be allowed to make or demand such predictions and for what purposes they may be used.

Apart from medium and long-term predictions based on brain data, there are indications that such methods can also be used for short-term predictions. Potential applications range from computer games to surveillance at the workplace or in schools. Apparently, this also raises numerous ethical questions. Against this background, the concept of predictive privacy is now being discussed intensively.

2.5.2 Brain Manipulation

In a way, the manipulation of brain states is complementary to analyzing brain data. In recent years, various *non-invasive* methods have been developed, in particular transcranial magnetic stimulation (TMS). Through refined technology on the one hand and the combination with better prediction methods on the other, this technology will presumably continue to develop strongly and conquer numerous fields of application [39]. Again, the use of TMS and similar procedures could be used to treat diseases, and this could bring significant benefits for patients.

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However, even in these non-invasive cases, it is important to carefully investigate any unknown side-effects to avoid iatrogenic harm, potential psychological harm to the patient and their family, and to ensure the patient's privacy and integrity are respected.

More invasive brain manipulation methods, such as AI technology implants (BCI), fall under the category of "biological enhancement" and present even more serious challenges related to privacy and integrity. Initiatives such as the Neurorights Foundation argue that a new understanding of fundamental rights is needed to meet these challenges.

2.5.3 Brain Organoids

In addition to the analysis and manipulation of brain states, there is another area that raises a number of ethical questions. This is the creation and further refinement of brain organoids, an area of research that is expected to make significant advances in the coming years. In research, brain organoids derived from (mainly induced) pluripotent stem cells serve as three-dimensional in vitro models for the study of early neurodevelopment and brain disorders. As such, organoid technology has the potential to provide opportunities to the study of neurodevelopment and brain disorders in areas that have been previously inaccessible to research. This includes questions concerning the interaction between genes and the environment. Although, as new model systems, brain organoids still face methodological challenges. Yet, in the medium term, they are expected to reduce the amount of animal testing within the Three R — Reduce, Refine, Replace — framework. In the clinical context, in particular, the creation of brain organoids generated from stem cells of individual patients creates opportunities for personalized treatment approaches and toxicology testing [40]. However, the possibility to therapeutically transplant brain organoids, for example, after injury or stroke, also raises significant ethical concerns: First, because of the risks of affecting brain function and behaviour in ways that are difficult to predict and, second, because of the restricted reversibility of these invasive interventions [41]. These are issues that have also been raised in regard to the creation of human/non-human or intra-specific chimeras whose implications regarding subsequent alterations of brain function are yet to be explored [42].

From an ethical point of view, brain organoids raise significant questions that, for example, concern the informed consent standards of donated cells or tissue. Other challenges relate to the commercialisation of the technology, which raises the issue of a fair distribution of benefits of innovation. Here again, it is important that privacy and integrity issues are further explored to minimise potential harm that could result from a breach of personal information and to increase the net benefits that patients can derive from technological advances [43].

In this context, there has been considerable international debate in recent years about whether and to what extent brain organoids deserve protection in their own right [44]. While current regulatory frameworks treat brain organoids as equivalent to stem cell and biospecimen research, this might change as they display signs that justify assumptions about conscious states or the capacity for suffering [45-47]. While such considerations have implications, for example, for the patentability of brain organoids [48], attempts to closely monitor progress face considerable methodological challenges which make it difficult to evaluate the need for further protection [49, 50].
Hence, evaluations of how to deal with the epistemic and normative uncertainty of the rapidly advancing technology will be an important task for the years to come.

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2.5.4 Brain Patents

The last challenge we highlight is dealing with brain patents [51]. The technological developments addressed in the first three challenges are reflected in an increasing number of patents relating to technologies related to the brain. Whether there should be restrictions on patentability is also currently being discussed. Similar discussions have already been held under the heading 'patentability of living things.'

2.5.5 A new Legal Concept of Consciousness

The interaction, in the field of neurotechnology, between, in one hand, invasive brain machine interfaces implanted in the brain or non-invasive wearables brain machine interfaces and, in the other hand, physics, electronics, signal processing, computer science & machine learning, leads to the need to focus on a new European instrument : the Artificial Intelligence Act (Regulation (EU) 2024/1689 of the European Parliament and of the Council of 13 June 2024 laying down harmonised rules on artificial intelligence and amending Regulations (EC) No 300/2008, (EU) No 167/2013, (EU) No 168/2013, (EU) 2018/858, (EU) 2018/1139 and (EU) 2019/2144 and Directives 2014/90/EU, (EU) 2016/797 and (EU) 2020/1828).

In the AI Act, it is possible to find broad definitions of AI system which covers the use of computer science and machine learning in the context of neurotechnology : "AI system is a machine-based system designed to operate with varying levels of autonomy and that may exhibit adaptiveness after deployment and that, for explicit or implicit objectives, infers, from the input it receives, how to generate outputs such as predictions, content, recommendations, or decisions that can influence physical or virtual environments".

The main approach of the AI Act is centred on product safety, precisely on artificial intelligence system safety, but this approach is supplemented by other levels of concern, such as the protection of the fundamental rights of humans confronted with this system.

Concern for the protection of fundamental rights in the AI Act has led to the introduction of a new prohibition of unacceptably risky AIS.

In particular a new legal concept arises in article 5 of the AI Act: consciousness: « Article 5 Prohibited AI Practices
1. The following AI practices shall be prohibited: (a) the placing on the market, the putting into service or the use of an AI system that deploys subliminal techniques beyond a person's consciousness or purposefully manipulative or deceptive techniques, with the objective, or the effect of materially distorting the behaviour of a person or a group of persons by appreciably impairing their ability to make an informed decision, thereby causing them to take a decision that they would not have otherwise taken in a manner that causes or is reasonably likely to cause that person, another person or group of persons significant harm; ».

Recital 29 of the AI Act gives some precisions on this article : "Such AI systems deploy subliminal components such as audio, image, video stimuli that persons cannot perceive, as those stimuli are beyond human perception, or other manipulative or deceptive techniques that subvert or impair person's autonomy, decision-making or free choice in ways that people are not consciously aware of those techniques or, where they are aware of them, can still be deceived or are not able to control or resist

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them. This could be facilitated, for example, by machine-brain interfaces or virtual reality as they allow for a higher degree of control of what stimuli are presented to persons, insofar as they may materially distort their behaviour in a significantly harmful manner".

The recital 29 of the AI Act states also that: "The prohibitions of manipulative and exploitative practices in this Regulation should not affect lawful practices in the context of medical treatment such as psychological treatment of a mental disease or physical rehabilitation, when those practices are carried out in accordance with the applicable law and medical standards, for example explicit consent of the individuals or their legal representatives".

However, due to the heavy penalties attached to the article 5 by the AI Act, these legal clarifications are not enough, since the concept of consciousness is the subject of intense debate not only in neuroscience [52-59], but also in philosophy: Charlotte Gauvry' works on borderline consciousness [60, 61]

This article 5 of the AI Act and the heavy penalties attached to this rule raise many questions concerning the consecration of a legal concept of consciousness, while the notion of consciousness is highly debated in neuroscience, medicine and philosophy alike. It could be interesting to carry out an interdisciplinary study of this notion of consciousness.

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Conclusion

Given the expansive and complex nature of neurotechnology, we convened experts from diverse specialisations to collaboratively identify scientific challenges across the eight dimensions, which were subsequently organised within the NeurotechEU content spaces. The gathering of the results revealed that each field is confronted with substantial difficulties ranging from the lack of biomarkers for diagnostics to the ethical and epistemic concerns of brain predictions. To address these scientific challenges and to achieve progress in the fields of neurotechnology, the subsequent phase of the process requires a detailed analysis of these issues, with the objective of identifying all existing innovations and developing solutions through a collaborative approach. Therefore, actionable plans such as incorporating suitable training in the education of the next generation at an early stage of their development and establishing a strong scientific network and research collaborations should be considered. This urgent need to work on the progression in each content space also arises from the social responsibility of NeurotechEU. For instance, the application of neurotechnologies in a clinical context has the potential to enhance disease diagnosis, therapy and, subsequently, the quality of life for patients. However, associated fields like neuroethics should not be neglected since it is essential to monitor technological developments in particular artificial intelligence and safeguard the interests of society. For that reason, the social impact of neurotechnologies needs to be considered in the next steps. To inform society about the advantages and progress of technologies, it is crucial to disseminate the knowledge of the expert groups in a generally understandable way to the public.

In conclusion, it can be stated that the aforementioned work provides an optimal foundation for intensive collaboration in each content space of neurotechnology by all partners. Nevertheless, by addressing the identified scientific challenges, a sustainable effect should be achieved for the future in the form of lasting impact and optimisations, not just in the form of short-term changes.

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