Human Brain Project

10 Years Assessment

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Directorate-General for Communications Networks, Content and Technology
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1. Foreword

The Human Brain Project flagship is one of the most groundbreaking research and innovation initiatives undertaken by the EU in the most fascinating and complex area – the human brain.

Between 2013-2023, the HBP flagship brought together more than 500 scientists, engineers and clinicians from all over Europe. They shared a vision of unravelling the mysteries of the human brain through advanced computational methods and cutting-edge technologies. This interdisciplinary collaboration resulted in a paradigm shift in brain research and in ground-breaking developments in neuroscience, computer science, robotics and data management.

The HBP flagship made a remarkable progress in developing new approaches to diagnosing and treating neurological disorders. Its strategy of using some of the world's most powerful supercomputers for advancing neuroinformatics and data-driven research allowed its scientists to produce precise atlases of the brain, multi-scales brain models and simulations, among others.

Thanks to its brain simulation and modelling algorithms, the HBP pioneered early and accurate diagnosis of brain-related conditions and personalized therapeutic strategies for neurodegenerative diseases such as epilepsy. The HBP has also demonstrated significant technological progress in brain-inspired AI and neuromorphic computing as well as in cognitive robotics systems, which are of particularly high relevance for industry.

Finally, the HBP succeeded in developing the unprecedented digital EBRAINS Research Infrastructure. The EBRAINS platform provides researchers with access to high-performance computing resources and advanced analytical tools for sharing and analysing vast amounts of neuroscientific data. By doing so, EBRAINS has democratised brain research, enabling breakthroughs that were previously impossible. It is now used by more than 10 thousand users from more than 1500 research and medical institutes around the world. EBRAINS is now set to be the source of many more groundbreaking discoveries, in close cooperation with the planned European Brain Health Partnership, and the new Virtual Human Twin initiative.

I take the opportunity to warmly thank the independent team of scientific experts, who have put together this report assessing the scientific and technological advancements and impacts of HBP. It highlights the progress achieved and looks ahead to what remains to be explored.

The HBP successes of the past decade affirm that we are on the cusp of a new era in digital neuroscience, one that holds immense promise for science, medicine, engineering and the well-being of citizens across Europe and beyond. As we consider this potential for new discoveries, the importance of continued support and investment in digital brain research becomes ever clearer.

I have no doubt that the next ten years of brain research in Europe will be just as exciting and innovative as the last decade.

Roberto Viola
Director General of DG Connect
European Commission

2. Executive summary

The Future and Emerging Technologies (FET) programme funded by the EU for about 30 years, supported long-term research to create new technologies, especially in multidisciplinary areas. Its mission was to turn Europe's scientific strength into a competitive advantage by supporting projects that could lead to industrial leadership and solve societal challenges. Among its lines of action, the FET Flagships (or simply 'Flagships') were meant to support ambitious long-term, large-scale, multi-disciplinary collaborative research initiatives addressing grand scientific challenges.

In October 2013 the Human Brain Project (HBP) started its adventure as one of the two first FET flagships [(1)] launched by the European Commission. In 2023, the HBP flagship concluded its decade-long journey, marking a successful transformation in research fields to foster a holistic understanding of the brain and the utilization of brain-inspired technologies. By 2023, the HBP flagship had engaged more than 500 international scientists in research and had received EUR 607 million in EU funding. As such, this flagship project stands as one of the largest international, collaborative, and interdisciplinary research projects ever funded by the European Union.

This report focuses on the HBP flagship's key scientific achievements, implementation, and governance model by conducting a comprehensive 10-year assessment of the main project's accomplishments.

The specific objective of the HBP flagship consisted of developing a **federated ICT infrastructure** that would become a research e-infrastructure in the future, helping the neuroscience community collect, analyse, share, integrate and model data about the brain with the aim of understanding better the functioning of the human brain and its diseases. With the above objective in mind, following 10 years of research, the HBP has achieved impressive results and delivered **EBRAINS, an open research digital infrastructure** positioned to have a transformative impact in Europe and beyond. Moreover, the EBRAINS infrastructure continues to empower new applications in brain health and brain derived technologies.

The HBP flagship has established a **new paradigm of digital neuroscience** and a **new interdisciplinary culture of collaboration**. Notable achievements include leading **digital brain atlases**, **advanced brain simulation platforms across scales**, the application of **cognitive modelling and personalized medicine**, as well as remarkable advances in **neuromorphic computing**, **neuro inspired robotics** and **AI**. Considering these achievements, the HBP has catalysed highly interdisciplinary research at scale to enhance our understanding of the brain. The legacy of the HBP flagship can be fundamental in a new phase of neuroscience, which builds upon the new research infrastructure, EBRAINS RI, in a collaborative approach involving many more researchers across the world.

Some of the identified highlights based on scientific results in the HBP are:

- The development of the Multilevel Human Brain Atlas, which is one of the most complete, if not the most complete, highly detailed digital 3D anatomical atlas, available on EBRAINS.

[(1)] Flagships | Shaping Europe's digital future (europa.eu)

- The innovative Virtual Brain simulation engine, which holds great potential for modelling personalised medicine, including in an ongoing clinical trial for epilepsy treatment.
- Within cognitive science, diverse datasets and research tools have been made available on EBRAINS from a broad range of cognitive tasks for use by the wider community (e.g. Human Connectome Project Young Adult fMRI time series, structural and functional connectomes / Julich-Brain Atlas, cytoarchitectonic maps / Generative network model of visual perception that learns invariant object representations through local minimization of prediction errors / Collaborative Brain Wave Analysis Pipeline, and more. [2]
- Research findings based on key cognitive functions used to constrain biologically inspired models of spatial navigation, visuo-motor interactions, and dexterous manipulation were provided.
- Significant advancements in neuromorphic computing were achieved, potentially reshaping future computer designs for energy-efficient machines capable of brain-like learning. In particular, two hardware platforms, SpiNNaker and BrainScaleS, were transformed into open neuromorphic services, thus paving the way for enhanced second-generation systems.
- Significant progress in AI models for applications like computer vision and robotics, offering solutions with fast reaction times and energy efficiency.
- Significant progress in simulation neuroscience, by integrating data across scales, thus revolutionizing our understanding and predictive capability of brain functions. Neuro-inspired AI allowed for the exploitation of scientific results to advance machine-based technologies for AI, including interdisciplinary efforts in studying brain learning rules and to develop more biologically plausible models to enhance robotics, automation, and AI applications.
- In robotics, advancement in embodied cognition by connecting brain models with robotic bodies was pioneered, promoting an understanding of cognition through ‘embodied’ experiments. The Neuro Robotic Platform (NRP)-based innovative experiments, such as multisensory integration and precise movements, fostered research in neuro-derived AI and robotics. A versatile framework for integrating functional models was developed, enhancing research in computational neuroscience and embodied AI, and paving the way for complex cognitive architectures and studies of emergent phenomena.

Throughout the HBP's lifespan, the HBP platforms have evolved into the **EBRAINS Research Infrastructure (RI)**, achieving one of the flagship’s primary goals. The EBRAINS RI has been developed as an integration platform for digital neuroscience and acts as an important research ecosystem developed by HBP. It includes over 1029 datasets, 225 research software applications, 160 interoperable tools and 250 models. It offers a comprehensive framework for advancing brain research, incorporating data services, model services, and a variety of digital libraries and tools, all interactively navigable through the Knowledge Graph / (in 2024: ~70.000 Knowledge Graph Searches and ~1500 - Human Brain Atlas unique users per month).

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[2] Find neuroscience data, models and tools on EBRAINs https://www.ebrains.eu/data/find-data

At the end of the HBP, EBRAINS had approximately 2120 contributors, 8475 returning users and 1491 user institutions and 11 national nodes, to make the scientific results feasible and generate this impact (based on Pioneering Digital Neuroscience, October 2023). This ecosystem enables the combination of tools for complex simulation workflows, as successfully showcased in concrete use cases. EBRAINS marks an unprecedented advancement in neuroscience research, providing regulatory-compliant data access and advanced tools that enhance our understanding of the brain. (details and facts). (3&4)

Overall, these achievements demonstrate how the scientific interest in EBRAINS has grown very considerably, especially during the last years of the flagship fostering international cooperations by partnering projects (international patterning projects were distributed across partners from the UK (~20%), the US (~10%), and others (with 10% together)).
The inclusion of **EBRAINS in the ESFRI Roadmap** ensures sustainable access for researchers to state-of-the-art multi-level resources for modelling, simulation, experimentation, and data analysis. At its core, the physical hardware layer includes **High Performance Computing (HPC) facilities**, further developed within HBP and the associated ICEI project (5). This development makes the EBRAINS Research Infrastructure a one-stop-shop HPC system dedicated exclusively to advance neuroscience research and brain health applications. Furthermore, its inclusion in the Health Data Space Pilot broadens its application field.

While the HBP flagship has prioritized infrastructure development as its main vector of innovation, it has also driven significant advances in **neurotechnology**. Notable progress has been made in areas such as epilepsy, prosthetics, and neuromorphic engineering. The project has produced 35 key exploitable results, bridging the gap between fundamental research and innovation. Twelve of these innovations are protected by patents, with an additional 35 patents filed and awaiting decisions. These innovations are well-positioned to enter the market if effective business development support is provided. As a direct result of HBP's efforts, the number of European neurotechnology companies has further grown, driven by the creation of 12 new start-ups. Both existing HBP private entities, whose inclusion was facilitated through the implementation of Open Calls, and new ventures are at the forefront of addressing significant societal challenges related to demographic changes and their associated health impacts. Through the translation of **innovative solutions into the brain health market**, they contribute directly to European industrial leadership in the neurotechnology sector.

By way of a quantitative overview, the **HBP flagship involved over 500 researchers** from **155 institutions** based across **19 countries**. The HBP generated over **3000 publications**, **92 filed patents** and **12 spin-off companies** and the **EBRAINS digital infrastructure for brain research**.
In terms of education and outreach, the HBP organized over 500 conferences and scientific workshops and impressive number of outreach activities (i.e. 58 publications for non-scientific

(3) D7.9 Enabling digital neuroscience: 10 years of research, co-design development, and collaboration in the Human Brain Project
https://ec.europa.eu/research/participants/documents/downloadPublic?documentIds=080166e5056b73f3&appId=PPGMS

(4) Pioneering Digital Neuroscience: how the 10-year Human Brain Project has transformed brain research
hbp_pioneering_digital_neuroscience.pdf (exo.io)

(5) Interactive Computing E-Infrastructure for the Human Brain Project
https://www.fz-juelich.de/en/ias/jsc/projects/icei

audiences, 80 exhibitions, 181 videos and a large number of followers on HBP-related social media accounts including almost 40,000 followers on ‘X’ and 70,000 followers on LinkedIn). It is important to note that the HBP flagship established 15 Key Performance Indicators (KPIs) to monitor the project’s performance and EBRAINS usage. Specifically, 9 out of the 15 KPIs were over-achieved (> 100%), particularly those related to the number of institutions, in Europe and globally, using EBRAINS and those who contributed data and models to EBRAINS.

In summary, the HBP significantly contributed to advance understanding of the brain and transform the related research fields to allow a more holistic approach and the use of brain-inspired technologies. Developments driven by the HBP have had a **transformative impact on several brain research**, and technology-related fields and showed to have the potential of a transformative impact in brain health.
The scientific results of the project have made an important and influential contribution towards a better understanding of the human brain. Substantial progress was made in bringing neuroscience significantly closer to new clinical and industrial applications. Computational neuroscience took the step towards medical applications through **personalised patient brain models**, which now enable the implementation of **digital twin approaches**. Furthermore, it served as a bridge between brain research and AI, with HBP showcasing the advantages of brain-inspired algorithms, neuromorphic hardware, and neurorobotics.
The basic understanding of the brain has been enriched by the multimodal and multiscale approaches facilitated by the HBP.
Crucially, HBP flagship followed a rigorous programme to ensure the sustainability of its developments: it established the EBRAINS infrastructure as a lasting offering to the scientific community. Moreover, it successfully fostered a new multidisciplinary community in Europe, converging under **the paradigm of** “**digital neuroscience**” (6).

(6) https://direct.mit.edu/imag/article/doi/10.1162/imag_a_00137/120391/The-coming-decade-of-digital-brain-research-A an open community paper with more than 100 authors

3. Introduction

In the early 2000s, a new vision shared by researchers across the world emerged that studying and understanding the human brain, one of the most complex systems ever studied, with billions of elements across spatial and temporal scales, will require a new large-scale collaborative approach. To be successful, this approach needed to include researchers across many fields and novel technologies to model and understand the brain system. Additionally, it should involve harvesting and fusing information of breath-taking complexity. Sparked by this game-changing perspective, the European Union was the first to initiate the flagship Human Brain Project (HBP) in 2013, followed by similar initiatives from the US, Japan, China, and South Korea in subsequent years.

Understanding the human brain implies understanding the principles underlying human cognition, intelligence, and learning. It also involves comprehending the brain's capacity to self-organize, adapt, learn, and heal after injuries or trauma. Importantly, this understanding enables the treatment of brain diseases and dysfunctions, the development of new therapeutic drugs, and the construction of brain-inspired technologies to enhance artificial intelligence. This endeavour spans a wide range of disciplines, from neuroscience to medicine, computer science and AI, complex system science, ethics, and others. Moreover, given its relevance to individuals, society, the economy, and socioeconomics globally, a project like the HBP flagship had to maintain a broad perspective. Efforts to monitor and analyse the impacts of potential and consolidated understanding, and also to engage various stakeholders, including policymakers, mass media, and the general public were central to its success. The intricate nature of these interdisciplinary fields necessitated a new level of mutual understanding, inspiration, collaboration and tool-sharing that was previously unimplemented across and within fields.

Today, with the conclusion of the HBP flagship and various global initiatives in their final stages, along with ongoing research efforts by the international research community, it is widely acknowledged that the human brain is still not fully understood. Understanding the human brain was, in 2013 and remains today, one of the most challenging research questions tackled by humankind.

The following sections of this document provide more details following the assessment of the HBP flagship based on the achievements, implementation, and governance model, from the perspective of experts in the field who observed and evaluated the development of the HBP and its progress over the last 10 years. The assessment also focusses on the overall outcomes of the HBP, the progress made in understanding the human brain, the relevance and impact on society and the economy, and the linked innovations in the field.

3.1. Evolution of the Project in 10 years

The initial concept of HBP flagship built upon previous European funded projects on brain simulation and neuromorphic computing, such as FACETs (Fast Analog Computing with Emergent Transient States under the 6th Research Framework Program (FP) of the EU), Brain-i-Nets (Novel Brain-Inspired Learning Paradigms for Large-Scale Neuronal Net-works under EU FP-7) and BrainScaleS (Brain-inspired multiscale computation in neuromorphic hybrid systems under EU FP-7) and on the Swiss Blue Brain project. The joint experience and results of these consortia led to formulating the goal of the HBP in the original grant proposal (7) with the aim “to build an integrated ICT infrastructure enabling a global collaborative effort to

(7) Original Grant proposal, The Human Brain Project, ICT-2013.9.9: FET Flagships.

address this grand challenge, and ultimately to emulate the computational capabilities of the brain".
At the beginning of 2014 a debate emerged in the project and in the international neuroscience community that escalated and then culminated in July 2014 in an Open Letter to the European Commission co-signed by several hundred scientists. The signatories requested an evaluation of HBP's governance and scientific approach and called for an independent external steering committee. In reaction to this, a mediation process was solicited by several stakeholders related to HBP flagship and formally set in motion by the HBP's Board of Directors in September 2014. The objectives of the mediation were defined in the Terms of Reference; they included the development of a "proposal for a restructured concerted governance structure and a balanced scientific structure". A committee of 27 members from the EU and beyond, and from inside and outside HBP, were nominated to cover a broad range of expertise in the management of scientific institutions, large-scale research projects and infrastructures and in relevant scientific disciplines. The result was a Mediation report published on March 15th, 2014 [(8)]. The recommendations contained therein were related to both the scientific profile and the overall governance of the project. The key recommendations in respect to governance were tailored to ensure openness and transparency and optimize partnership inside HBP.
Key recommendations in respect to science were the following:

1. define a unique set of concrete and achievable long-term objectives, which could be realized within the projected timeframe;
2. focus on a smaller number of prioritized activities;
3. develop a set of models complementing each other and integrating multiple scales and perspectives, together with the specification, design, implementation and testing of IT platforms enabling and exploiting these models;
4. integrate cognitive and systems neurosciences into HBP;
5. dedicate part of the budget to open calls to integrate new targeted research from outside HBP;
6. clearly and faithfully communicate a sharpened mission statement and objectives of HBP, which is seen as a fundamental responsibility of the consortium.

The HBP consortium responded in full to these recommendations, adapted the governance structure and the lead of the project, installed new necessary bodies, and updated the scientific scope. Importantly, it included the principle of Co-Design projects (i.e., scientists and technologists must collaborate closely to ensure that a scientific instrument's specifications are detailed enough for successful construction) to strengthen the integration of science and technology across domains, and a focus on a fewer clearly defined scientific goals. The newly implemented outreach and communication strategy effectively clarified the objectives of HBP, realigning the public perception with its original transformative goals. This shift was aimed at fostering a deeper understanding of the brain and facilitating advancements in the field.
Despite this, the project continued to be impacted by the initial perturbations, miscommunications, or misunderstandings which occurred during the early HBP phase, and continue to cause a partial polarization in the field.

[(8)] Mediation Report, published 15th March 2014 https://www.fz-juelich.de/en/news/archive/press-release/2015/15-10-30hbp-mediation-concluded

During the phases of the HBP following the mediation process, the HBP reacted continuously to new demands and improved the structure and focus of the project. It reacted with respect to the research focus by combining a bottom-up research approach, oriented on increasing understanding from detailed nerve cells and molecular interactions, with a re-integrated top-down approach including cognitive modelling and AI. The merging of simulations with data-driven methods, and co-simulation to link scales as demonstrated in TVB-NEST [(9)], NRP [(10)], or the personalization of simulation models for clinical investigations, data-driven approaches, and linkage to high-resolution data sources like brain atlases, served to enhance predictive power.
Linking the initially disparate six platforms into an integrated RI-system, alongside technical solutions, seamlessly merged research platforms, enabling intricate, multi-step scientific investigations. Regarding the project organization, the HBP flagship transitioned from centralized decision-making to innovative approaches that integrated diverse viewpoints, evident in both governance and management restructuring, as well as in a number of comprehensive position papers coordinated by the Science and Infrastructure Board (SIB). A key change in the project focus was the previously mentioned re-integration of top-down research, that is research that is driven by behaviour, functions of the brain, and conceptual models, to understand the organization of elements across scales. In particular, this topic concerned the work involved in brain simulation, where moving from many small model systems across different fields to larger data-driven models and simulations was seen as a key path to better integration between the subfields of brain research. The re-integration of top-down processes accounted for the fact that scales of neuroscientific description need to be linked and that different mechanisms and principles are at work on different scales of brain organization. For this, HBP focused on enabling multiscale approaches, the need for more complex concepts, as well as organized efforts for building multidisciplinary collaborations and the appropriate technological instrumentation.

During the second and the last phase of the HBP, in the years 2018-2023, the integration of data-driven and simulation-based research became the key focus towards a transformative impact on the field. During the second phase, the newly introduced 'Co-Design projects' started to produce a clear focus on science and technology and produced many highly impactful publications in the field.

In the last phase, from 2020 to 2023, the project focused on three scientific areas related to network structure and multiscale approaches that were developed. The HBP Showcases represented the final demonstrators of the joint technical developments and instrumentation, such as the atlas, simulation, and artificial neural networks, working collaboratively as a fundamental component of the primary research findings and insights generated by the project. A key element and focus of the HBP flagship was the transformation towards a new area of digital neuroscience. To this end, both the HBP consortium and the European Commission enabled the research in two critical domains. Firstly, an integrated research platform (EBRAINS) [(11)] was developed and secondly, a computing infrastructure that provides new forms of high-performance computing resources (ICEI) [(12)] and new tools that enable

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[(9)] A simulation platform: https://www.humanbrainproject.eu/en/follow-hbp/news/tvb-nest-multiscale-simulation-now-available-on-human-brain-project-collab-platform/
[(10)] Neurorobotics platform: https://neurorobotics.net/
[(11)] An open research infrastructure that gathers data, tools and computing facilities for brain-related research, built with interoperability at the core. https://www.ebrains.eu/
[(12)] Interactive Computing E-Infrastructure for the Human Brain Project https://www.fz-juelich.de/en/ias/jsc/projects/icei

researchers in the field to use simulation platforms, large datasets, and AI-driven analysis tools in a closed loop to match the requirements of the field. With these, the HBP has opened up new pathways between scientific fields, enabling European research to form networks and leverage new synergies between previously disparate scientific approaches.

Given this success, the European Commission has launched in January 2024 the EBRAINS 2.0 project granting €38 million for the further development of services within the EBRAINS research infrastructure until 2026. In the meantime, EBRAINS will continue to develop tools and services to serve the wider research communities in neurosciences, brain medicine, and brain-inspired technologies.

4. Most Relevant Scientific Results and Impact

Given the interdisciplinary character of the HBP and its vast breadth, the assessment of the most relevant scientific results and their impact starts with the overarching Showcases, designed to capitalise on the inter-disciplinary nature of the project. Following the showcases, the report is then structured into the following subtopics: Neuroscience, Cognitive Science, Neuromorphic, Medical Neuroscience, Simulation Neuroscience, Robotics, and Infrastructure developed as part of the HBP.

Six Showcases, delivered in the later phase of the flagship provide examples of tangible results made by the Human Brain Project and its potential for further innovation in the future. These Showcases were further organised as follows: 1 and 2 focused on the virtual ageing brain and the virtual epileptic brain using seizure simulations; 3 and 4 focused on multiscale brain modelling of processes in different states of consciousness and multimodal perception; 5 and 6 focused on modelling motor control and cognitive functions.

- **Showcase 1**, the Virtual Ageing Brain, is a mechanistic model linking changes in structural connectivity and brain function to address the inter-individual variability in decline of cognitive abilities during healthy ageing. At the core of the Virtual Ageing Brain is a dynamical brain network model informed by individual brain imaging data (structural whole-brain connectivity), and a connectivity mask selecting interhemispheric connections is used to define the age-related changes to the structure. It is hoped that this model will support future research that is needed to demonstrate how the Virtual Ageing Brain contributes to our understanding of individual ageing processes. The showcase offers future potential to integrate the theoretical and computational microcircuit, microscale network models with multiscale connectome data, which remains challenging today (Lavanga et al., 2022).

- **Showcase 2** illustrates how improvement in epilepsy surgery is possible with the Virtual Big Brain. Indeed, this showcase demonstrates the potential of digital neuroscience at the individual patient level. It uses models for realistic seizure simulations and estimation of brain parameters, showing how EBRAINS enables personalized multiscale brain simulation for improved outcomes in epilepsy surgery, validated through the EPINOV trial (Naddaf, 2023b). The results of this trial are being expected for the next months. The high-resolution and multiscale brain simulation for epilepsy and the modelling of intervention scenarios, epileptogenic zone estimation is impressive, and it could lead to improvements in clinical outcomes for patients (Jirsa et al., 2023; Wang et al., 2023).

- **Showcase 3** was focussed on brain complexity and consciousness, and includes in its most recent setup a full brain simulation corresponding to different brain states and consciousness levels integrating meso- and micro-cortical mechanisms. This showcase was based on different actions of anaesthetics and compared to the awake condition. The level of synchrony between three species, mouse, monkey and human was compared, and differences identified due to axonal signal propagation between regions associated with brain size differences between the species (Sacha et al., 2024). The implementation was done in The Virtual Brain to yield models where the action on synaptic receptors can be evaluated at the large-scale.

- **Showcase 4** consisted of simulations of object and scene recognition across scales, including a detailed cortical column network, introducing synaptic plasticity and rhythmic oscillations, as well as showing predictive coding at the cellular level based on a cortical column model, and is based on the WhiskEye robot. The models are based in EBRAINS and present a plausible, cognitive architecture that can be learned (Pearson et al., 2021).
- **Showcase 5** has as its primary focus the simulation of in-hand object manipulation performed by an anthropomorphic model, the Shadow Dexterous Hand. This training was carried out in silico. It realised a hierarchical and modular active inference model of the hippocampal – prefrontal circuit that addresses memory guided spatial alternation tasks, by learning and then combining cognitive maps of both physical space and task space (Van de Maele et al., 2023).
- **Showcase 6** demonstrates a closed-loop simulation of advanced cognitive and sensorimotor functions. It focuses on motor control encompassing cerebellar and spinal networks, with parallel fibre plasticity in the cerebellar module and reflex circuitry in the spinal cord. Various levels of model implementation are described from biologically inspired hardware (Bruel et al., 2024).

These showcases are a result of the agile management approach that was pioneered by HBP and can be a blueprint for future large-scale joint research in fast innovating fields. The agile management approach, meticulously fine-tuned by HBP, has provided a much-needed framework for effectively managing and executing complex research endeavors. By embracing agility, HBP has successfully navigated the dynamic landscape of fast-paced innovation and seamlessly integrated diverse research efforts. This groundbreaking strategy not only enables the assimilation of ideas and findings from different disciplines but also fosters a collaborative environment that accelerates progress towards coveted breakthroughs.

Indeed, HBP has pioneered the Virtual Brain multiscale implementations, linking biological realism to stimulated brain activity. The showcases developing biologically informed computer models for motor and cognitive functioning have revealed the complexity of such tasks (Sacha et al., 2024): bridging levels from the microscale in the brain up to behaviour is still in its early phase although significant advances were made. Importantly, information is available to construct large-scale models although simulating such models at the cellular scale represents a huge investment of computational resources and is out of reach for most researchers with no access to such resources.
An alternative approach is to simulate brain activity using population models, which are much less demanding on computational resources. However, such models need to contain enough biological realism to include the relevant biophysical mechanisms necessary to generate brain states, such as membrane conductance and synaptic receptor types (Sacha et al., 2024). The future will learn how these brain models can inform brain changes up to the cognitive and behavioural levels in the individual. To date, however, the HBP has shown the potential for bridging the brain’s scales using digital models that are biologically informed.

4.1. Neuroscience

> **Highlights, Outcomes and Impact**
>
> - Excellent progress in understanding of brain structures and their functions
> - Development of the Multilevel Human Brain Atlas, a highly detailed digital 3D anatomical atlas, that is accessible on the EBRAINS platform
> - A ground-breaking technology, the Virtual Brain simulation engine, which holds great potential for personalized medicine improving clinical outcomes

Neuroscience has played a central role within the Human Brain Project, focusing on the study of the nervous system and brain. The project has made significant contributions to both the understanding of brain structures and their functions, as well as their potential integration. In terms of structure, the project has developed a highly detailed digital 3D anatomical atlas, known as the Multilevel Human Brain Atlas. This atlas is made accessible on the EBRAINS platform, enabling users to navigate through it, utilize it for modelling purposes, and connect it with other resources and atlases. In terms of brain function, the project has made strides in the development of digital technologies that can simulate human brain functions using virtual models.

One key application is the Virtual Brain simulation engine for epilepsy, known as the Virtual Epileptic Patient. This cutting-edge technology is currently undergoing clinical trials, making it the first clinical neuroscience application of its kind. A successful validation of the Virtual Epileptic Patient holds immense potential in facilitating the development of personalized medicine approaches and improving clinical outcomes. Moreover, HBP has advanced and pioneered on many levels the integration of anatomical and functional data through multiscale modelling at the cellular level. This approach shows convincing and converging benefits that warrant further development. By establishing effective links between anatomical and functional information, the project aims to deepen our understanding of the brain and enhance our ability to comprehend its complexities.

The Multilevel Human Brain Atlas is a highly detailed, digital 3D anatomical atlas that serves as a fundamental resource of the Human Brain Project. The atlas is built on the principles of human cytoarchitecture, a microstructural parcellation of the brain. The Multilevel Human Brain Atlas consists of maps of post-mortem brain sections of 20 micrometre thickness stained for cell bodies and digitally imaged. Digital imaging of the stained brain sections combined created a three-dimensional atlas containing cytoarchitectonic maps of cortical areas and subcortical nuclei. Multimodal data on fibre and receptor architecture as well as function is connected to these maps. The cytoarchitectural basis of the Multilevel Human Brain Atlas is also called the Julich Brain Atlas (Amunts et al., 2020). The atlas is probabilistic, based on the brains of multiple individuals, which enables it to account for variations between individual brains.

Currently, the Multilevel Human Brain Atlas contains over 200 probabilistic maps. Moreover, it contains the so-called BigBrain (Amunts et al., 2013), an ultrahigh-resolution reconstruction of an individual brain and microscopical reference space at nearly cellular level that informs, e.g., Showcase 2. The spatial resolution of the BigBrain space is unique, and allows to integrated data from micro to macro, thereby addressing the need to approach the human brain as a multi-scale system. Recently, the atlas was enhanced by the integration of fibre architecture within the human hippocampus, using three-dimensional polarized light imaging (3D-PLI) in post-mortem tissue (Axer & Amunts, 2022). This integration allowed for detailed connectivity information to be combined with cytoarchitecture information. Additionally, brain connectivity data from in-vivo diffusion magnetic resonance imaging (dMRI) of 78 healthy individuals was incorporated, providing comprehensive fibre connectivity coverage across the entire brain. The integration of dMRI data with the Multilevel Human Brain Atlas was optimized based on data from post-mortem hippocampus tissue (Axer & Amunts, 2022), which paves the way for potential integration with other in-vivo brain imaging data in the future. Recent analysis using the Multilevel Human Brain Atlas, in combination with studies on neurotransmitter receptor genes and receptor densities in auditory, somatosensory, visual, and motor systems, has revealed covariation and specific gene expression patterns in functional systems (Zachlod et al., 2022). This combined analysis demonstrates the potential for the atlas to provide new insights into human brain structure and potential brain functioning.

Virtual Brain models have been developed for several applications, including simulations to gain better insight into individual differences in brain ageing, learning, Parkinson's disease, Amyotrophic Lateral Sclerosis, Alzheimer's Disease, depression, and epilepsy. Models are being informed by data from the Multilevel Human Brain Atlas. These Virtual Brain models have demonstrated their potential in early work, subject to continuous improvement with the potential to fully demonstrate their future impact. Standing out is the work on epilepsy, which provides an important showcase for bridging the gap between fundamental research and innovation up to the level of potential novel interventions of the Human Brain Project. Here, virtual brain models have been developed of epilepsy patients who do not respond to medication. The virtual brain model is based on a patient-specific whole brain network model that is constructed from anatomical T1 and diffusion-weighted magnetic resonance imaging (Wang et al., 2023). Each network node is equipped with a mathematical dynamical model to simulate seizure activity. Bayesian inference methods sample and optimize key parameters of the personalized model using functional stereo-electroencephalography recordings of patients' seizures. These key parameters and their personalized model determine the epileptogenic zone networks of the patient. The virtual brain models help to identify the brain areas where seizures emerge and can be considered as a digital twin. In health research, digital twins can be defined as virtual representations of patients that are generated from multimodal patient data, population data, and real-time updates on patient and environmental variables (Venkatesh et al., 2022).

Importantly, the Multiscale Human Brain Atlas holds promise for further integration with human in-vivo magnetic resonance imaging endeavours developing at even higher field strength, with the breath of existing data available worldwide and developed in parallel to HBP, such as in ABCD (Karcher & Barch, 2021), ENIGMA (Thompson et al., 2020), HCP (Van Essen et al., 2013), and UKBiobank (Sudlow et al., 2015) among others, and with clinical data. Also, the Multiscale Human Brain Atlas can provide the basis on which important plastic changes taking place in the brain can be investigated using longitudinal data to obtain models for development and ageing. Furthermore, the theoretical and computational microcircuit, microscale network models have potential to integrate with multiscale connectome data, which is challenging but an exciting opportunity. The Virtual Brain models successfully predict the evolution of brain activity within the anatomical constraints and can be personalized to describe changes in a participant's brain activity across brain states and potentially across a range of diseases. The models currently lack the capacity to represent functionally meaningful processes such as cognition, and while the prototypes draw inspiration from visual and auditory discrimination tasks, so far, they offer the potential for experimental validation and deeper insights into underlying brain mechanisms.

Taken together, neuroscience in the Human Brain Project has made significant, relevant, and impactful progress towards a common structural brain research reference framework in the EBRAINS infrastructure, based on a highly detailed anatomical core. It has an inbuild potential to improve even further as more data become available. Moreover, the HBP has successfully demonstrated that integrating multiple scales and virtual brain simulations are feasible, add value, and require building new bridges. The virtual brain simulations hold promise for clinical applications. Indeed, these developments have significantly increased the capacity of the neuroscience community to model multiscale neural structure and functions of human brain networks, sustainable for the future in the EBRAINS infrastructure.

4.2. Cognitive Science

One of the main achievements of the HBP was to attempt to fill an important gap in neuroscience: bridging scales to allow understanding of the human brain at all levels, from cellular, microcircuits and system-based mechanisms and architectures, leading to a better understanding of human behaviour, thought and cognition. In turn, this knowledge would drive the potential/industry impact of neuro-inspired event-based AI and robotics. The concept behind this approach was sound, and overarching aim and related objectives were clear. However, the ultimate goal of elucidating human behaviour and cognition through neuroscience was not sufficiently supported within the project particularly in the early stages, although the influence of this work grew towards the latter stages of the HBP.

Highlights, Outcomes and Impact

- Significant advances in our understanding of human cognition and its brain bases, realized in a large number of publications in leading international journals.
- Availability of large, diverse datasets and research tools made available on EBRAINS from a broad range of cognitive tasks for use by wider community.
- Provision of research findings based on key cognitive functions used to constrain biologically inspired models of spatial navigation, visuo-motor interactions, and dexterous manipulation.

Throughout, striking the right balance between scientific research of human brain and behaviour, and implementing this knowledge in the development of neuro-inspired models and building of necessary ICT infrastructure, was always challenging. At the early stages of the project, activities focused on cognition were not well integrated into the HBP despite their emphasis within the project (i.e. the overall project was structured around 12 sub-projects, 4 of which were mainly based on scientific outputs). Furthermore, the abrupt change in the research groups focusing on cognitive processes during the project (2016, following mediation as discussed above) had an impact on the cohesiveness and integration of research on human cognition into the overall project. An early decision was made to restructure the work subsumed under ‘Cognitive Architectures’ meaning it was subsequently scaled back and the relative allocation of resources (budget/personnel) was reduced. Although to some extent this compounded the issue at the time, ultimately however, it provided the opportunity to focus on fewer core cognitive functions in more depth. An ‘open call’ was initiated directly after this restructuring resulting in submissions that were of very high quality and the project was eventually steered around four main topics that captured a broad range of essential cognitive abilities. Thereafter, the HBP consortium demonstrated that they could successfully bridge the gap between neuroscience, cognition and the development of neuro-inspired ITC technology.
At the initial stages of the project, the emphasis was on a selection of key cognitive processes. These included: Perception and Action; Motivation, decision and reward; learning and

memory; space, time and numbers; and multimodal processing. In addition, efforts to characterize cognitive functions unique to the human brain were also conducted using comparative studies. Whilst each of these projects resulted in significant contributions to knowledge in their own right e.g. leading to a Special Issue of 'Neuron' (Dehaene et al., 2015), and these projects leveraged some important collaborations between researchers working on similar issues, efforts at integration into the wider overall goals of the HBP during this early phase of the project were at best, only partial: the projects were not (yet) sufficiently linked with the pipeline of work from brain models (including building of the brain maps and Theoretical Neuroscience) to ICT such as Neurorobotics Platform. Moreover, the scientific investigations relating to cognition and the brain proceeded mainly independently, often without capitalizing on significant advances on connectomics and neurodevelopmental research findings from outside of the HBP. Nevertheless, these activities contributed towards an important legacy of the HBP project, namely the provision of data sets and experimental protocols from behavioural and related neuroimaging (fMRI and EEG) studies of the human brain as well as a considerable contribution to scientific knowledge in terms of journal article publications (i.e. almost 150 under the theme of on 'Understanding Cognition' alone, as sourced on the HBP website). Whilst data sets were likely useful to the wider community the subsequent usage of these contributions by other sections within the HBP consortium was unclear. At the early stages of the project in particular, although the activities conformed to proposed work outlined in the grant, the findings relating to human cognitive functions and underlying neural correlates rarely went beyond the 'state-of-the-art' in that there were no major breakthroughs, mainly as a consequence of failing to capitalise on the rich infrastructure and broad resources available in the project.

The latter phases of the project attempted to rectify this lack of integration by focusing on fewer but core cognitive functions that had a more obvious trajectory within the goals of the overall project, particularly through Co-Design Projects (a good example is CDP4 which focused on visuomotor integration). This focus helped demonstrate a more direct link between the outputs of basic science to the development of technology and as an overall strategy it proved to be much more successful than previous efforts (Bjerke et al., 2018). These functions ranged from states of conscious awareness (Salomon et al., 2016; Storm et al., 2017; Aubinet et al., 2018; Pennartz, 2018; Annen et al., 2019; Martens et al., 2019; Suzuki & Larkum, 2020; Pennartz, 2022), sleep (Capone et al., 2019; Pastorelli et al., 2019) perceptual processes (Gerard-Mercier et al., 2016; Edwards et al., 2017; Spoerer et al., 2017), multisensory processing (Meijer et al., 2017; Meijer et al., 2018; Oude Lohuis et al., 2022), spatial (Chen et al., 2018; Chen et al., 2019), episodic (Prescott et al., 2019) and procedural (Hesseg et al., 2016) memory. Furthermore, the consortium adopted realistic but ambitious proposals to build models that were biologically and behaviourally inspired.

Importantly, during the interim and latter stages of the project a remarkable amount of new and important data, methods, tools, maps and atlases was generated (although the transition of scientific data to EBRAINS was still ongoing by the end of the project). This led to new scientific insights into inter-subject (Zhou et al., 2016) and cross species variability of the brain (from tadpoles, e.g. (Terni et al., 2017), to mice e.g. (Meijer et al., 2017), ferret e.g. (Klaver et al., 2023), non-human primates, e.g. (Yao & Vanduffel, 2022) as well as variability in humans (Amunts et al., 2020; Lavanga et al., 2022). Moreover, there was a demonstrable increase in the influence of these scientific efforts on other developments across the HBP, including multiscale models (i.e. multisensory deep predictive coding model that is neurobiologically inspired), simulations and information for robotic implementations of learning, memory, and multisensory integration in the Neurorobotic platform (Knoll et al., 2016). Beyond these achievements within the HBP the impact of this work was also realised in many scientific publications, including in leading international journals. Examples of successful integration of cognitive models into the project include the applications of predictive coding and analysis of the role of context in processing low-contrast visual information to understand object perception and memory (Showcase 4), and motor-coordination of hand movements for implementation in a robot model (Showcase 5). Other examples, such as visual prosthesis for sight restoration (Chen et al., 2020), have the potential to capitalise on EBRAINS infrastructure in the future to develop technology for future human-specific requirements.

However, either due to missed opportunities available within the overall project or due to limited resources, there still remained some (interesting) scientific investigations that appeared to lie outside the immediate goals of the HBP (or their implementation in modelling or simulations was unclear), even at the late stages of the project. Thus, it was often unclear how the HBP benefitted directly from these 'stand-alone' or fragmented scientific investigations, irrespective of their quality. Some examples include the role of feedback signals on sensory and decision-making processes in the brain; olfactory pathways; personality traits; cognitive decline in age-related disorders including kidney disease; environmental stressors and human brain function; and numerosity and face perception. These research threads were, nevertheless, timely and of interest to the community ensuring their impact on fundamental knowledge through scientific publications (Lee et al., 2023; Martial et al., 2023; Petro et al., 2023) Furthermore, although data curation is ongoing, the future availability of these (and other) respective datasets on EBRAINS will help ensure long-term impact.

4.3. Brain atlases

The human brain is organized across many spatial scales. Brain organisation is being approached by a multitude of studies carried out by different specialized scientific disciplines. However, results coming from all these studies in the end reflect the interaction of one organ, the brain. To address this challenge and to advance our understanding thus means to better integrate our insights into the coherent framework of a multilevel atlas. The HBP has developed a new kind of atlas, a kind of google maps. But for the brain, that goes beyond the interest of a single subcommunity, and addresses the multi-level brain organization in a comprehensive way.

Highlights, Outcomes and Impact

- Taking the lead in developing and providing a new kind of multilevel atlas including brain maps for different species within the same logic and framework, that allow to seamlessly connect the data from the atlas to modelling and simulation, bigdata analytics and other applications
- Developing and realizing a comprehensive tool suite of software including siibra, QUINT and other tools for handling heterogeneous, complex and big data
- Significant progress in mapping the brain at all levels of organisation, with microstructure as a key reference, to enable data integration at both higher scales (e.g., neuroimaging), and lower scales (e.g., high-resolution optical methods, which make the atlas one of the most popular tools of EBRAINS

The rich toolbox and new strategies developed for this multi-scale era of brain research are available on EBRAINS in the form of high-resolution multi-scale atlases of different species – the human brain, the rat brain and, in the last phase of the HBP, also the monkey brain. This is linked to computational models, reproducible workflows and advanced digital tools that can be applied across multiple scales.

The human brain atlas (Amunts et al., 2020) provides different spatial templates, to address to the need of requirements coming from different research questions. While the BigBrain model provides a nearly cellular resolution, two MNI-reference spaces respond to the need of the neuroimaging community, and provide comprehensive maps of fiber tracts (Guevara et al., 2022) and functional parcellations (Thirion et al., 2024). Importantly, all references are interoperable. Moreover, the concept foresees intersubject variability as key feature of brain organization, and provides probabilistic, quantitative maps on brain architecture and function.

The project has delivered the first extensive open access 3D rat brain atlas, the Waxholm Space atlas of the rat brain (Kleven et al., 2023). This atlas has become a fundamental resource in the neuroscience community, facilitating data integration when used in combination with EBRAINS tools for registering 2D and 3D data to atlases. It provides standardization of spatial data from the rat brain and supports a wide range of research, as well as educational and technological applications. Combined with analytical workflows such as QUINT, it offers a robust framework for integrating and analyzing diverse neuroanatomical data (Leergaard & Bjaalie, 2022).

4.4. Neuromorphic

Highlights, Outcomes and Impact

- Pioneering advancement in neuromorphic computing, potentially reshaping future computer designs for energy-efficient machines capable of brain-like learning
- Two hardware platforms, SpiNNaker and BrainScaleS, transformed into open neuromorphic services, paving the way for enhanced second-generation systems
- Significant progress in AI models for applications like computer vision and robotics, offering solutions with fast reaction times and energy efficiency

Achieving simulations of large-scale brain networks up to the cellular resolution, both in space and time, demands the use of supercomputers. However, this requirement comes with a significant need for both time and energy consumption. Today's supercomputers typically require several minutes to simulate just one second of biological time and consume substantial amounts of kilo (KW) or even megawatt (MW) of power. Consequently, research involving processes such as plasticity, learning, and development, which unfold over hours and days of biological time, remain beyond current ICT capabilities.

The HBP has very successfully addressed the efficiency concern, potentially changing the future perception and design of computers. The identified solution relies on Neuromorphic Computing, an interdisciplinary field which involves the development of hardware chips designed to function similarly to biological neural networks. Thanks to this peculiarity, neuromorphic-based systems present key features, typical of the living brains, such as parallelism, low power consumption, adaptability and fault tolerance, making them the perfect candidates to overcome conventional von Neumann computer architectures (Hoefflinger, 2011). Indeed, hardware implementations of neuronal networks offer the potential to conduct simulations within a timeframe comparable to or shorter than biological time, all while consuming low levels of power.

In the original proposal, the HBP aimed to exploit neuromorphic principles to construct more efficient machines able to evolve and learn like the brain, thus overcoming one of the major barriers in the advancement of ICT systems. Indeed, the main focus was on building systems for brain sciences, especially to model brain subsystems and functions. During these 10 years, there was a significant surge in industrial AI, which occurred parallel to the development of the HBP, thus the interest in neuromorphic-based applications shifted more towards AI. Most of the AI work initially started to be carried out by means of GPUs, as at the beginning of the HBP it was not so clear that neuromorphic could support low energy/large scale mainstream AI. By the end of the HBP, a lot more interest in the potential of neuromorphic systems to address some of the issues in mainstream AI was developed. Major identified applications included technical assistance to humans, real-time diagnostics of complex machinery, autonomous navigation, self-repair, and health monitoring.

To achieve its challenging objective, the HBP could rely on some of the major European key players in Neuromorphic Computing, previously involved in a series of projects, such as FACETs, BrainScaleS, Brain-i-nets, ECHORD, SpiNNaker. Moreover, the project benefitted from the expertise of a member of the Science and Infrastructure Advisory Board (SIAB) of the HBP, namely Prof. Giacomo Indiveri from the University of Zurich, who is one of the world's leading scientists in the field. The HBP's work in Neuromorphic Computing specifically capitalized on two of the above cited projects: SpiNNAker [(13)] (Painkras et al., 2013) and BrainScaleS [(14)]. They are quite different but complement each other well in how they work. SpiNNaker was born as a UK funded research project whose goal was to build neuromorphic computing systems based on many core chips with efficient bi-directional links for asynchronous spike-based communication [(15)].

The SpiNNaker platform is a digital system featuring a multiprocessor architecture composed of ARM processors. SpiNNaker achieves real-time performance with an integration time step of 1ms, which suits very well applications in robotics and artificial neural networks. BrainScaleS [(16)] started as an EU-funded research project integrating in vivo experiments with computational analysis to investigate how the brain processes information on multiple spatial and temporal scales, to implement these capabilities in neuromorphic technology. The BrainScaleS system comprises a series of modules, each consisting of a wafer that integrates 448 analog neuromorphic chips alongside a routing system. Within each module, the emulation of 512 neurons and 115,000 synapses takes place, achieving computational speeds 104 times faster than biological time.

Even if both Spinnaker and BrainScaleS existed before the HBP, having undergone their original design and development in other projects, the HBP played a crucial role in supporting the significant software activities needed to transform these pre-existing hardware platforms into open neuromorphic services. This involved the construction of software stacks for both machines and the development of the PyNN language (Davison et al., 2009), which was utilized for both Spinnaker and BrainScaleS. Then, the primary achievement of the HBP in neuromorphic computing lies in the conversion of these systems into services. Additionally, the HBP supported the development of second-generation for both platforms, resulting in the emergence of Spinnaker2 and BrainScaleS2, which was also integrated into EBRAINS (Billaudelle et al., 2020), towards the end of the project.

While these second-generation systems did not feature prominently in the immediate results of HBP, they hold significant promise for future developments, thanks to their unique combination of versatility and speed in emulating spiking networks. Notably, SpiNNaker2 is

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(13) https://www.humanbrainproject.eu/en/collaborate-hbp/innovation-industry/technology-catalogue/spinnaker/
(14) https://www.humanbrainproject.eu/en/science-development/focus-areas/neuromorphic-computing/
(15) https://apt.cs.manchester.ac.uk/projects/SpiNNaker/
(16) https://brainscales.kip.uni-heidelberg.de/index.html

being commercialized through the Technical University of Dresden spin-off company SpiNNcloud Systems GmbH [17] thanks to national grants and industry support from prominent companies like BMW and Infineon, with whom it collaborates on pilot projects to investigate the exploitation of neuromorphic computing in their respective business sectors. BrainScaleS2, on the other hand, contributed to advancements in learning operations and expanded the system's functionality, including dendritic branch modelling. These enhancements would not have been feasible in the initial release of the systems.

Along with Intel's Loihi technology [18], these are the only large-scale neuromorphic systems in operation today anywhere in the world, but Spinnaker and BrainScaleS remained the only publicly available, openly accessible neuromorphic systems worldwide, rendering them highly unique. Among them, Spinnaker stood out as the largest neuromorphic computing platform in terms of its capacity to handle biological-scale computations (at least until April 2024). Notwithstanding, it is important to underline that Intel has not focused on brain modelling, which was, instead, the main objective of the HBP in neuromorphic development.

Within the HBP, there existed a synergistic cooperation among various groups to attempt the implementation of cortical microcircuits, originally developed by Julich. Different groups were pursuing various types of implementations: some on supercomputers, some on neuromorphic platforms, and others on GPUs. Their aim was to achieve biological real-time processing. Spinnaker was the first to achieve important results (Rhodes et al., 2020), albeit based on older technology. Subsequently, all the other groups achieved similar results but using much more recent technology. Both Spinnaker and BrainScaleS possessed the capability to seamlessly integrate software to support new learning rules (Bellec et al., 2020; Cramer et al., 2020; Stöckl & Maass, 2021). A notable example is the eProp algorithm (Rostami et al., 2022). eProp is an algorithm that effectively implements graded descent learning, achieving a biologically realistic management of time. In terms of applications, thanks to HBP's outcomes in neuromorphic computing, advancements have been made in impactful AI models for computer vision (Göltz et al., 2021; Zenke et al., 2021), quantum tomography (Czischek et al., 2022; Klassert et al., 2022), robotics, industry, and autonomous systems, where fast reaction times, low latency and energy efficiency are essential (Yik et al., 2023).

The HBP strongly encouraged and supported the collaboration between theoreticians, modelers, hardware, and software developers to significantly improve both Spinnaker and BrainScaleS. Being part of the HBP significantly facilitated the process of finding individuals with similar interests and ideas. In this regard, it presented a remarkable opportunity for all the teams involved in advancing neuromorphic technology.

[17] https://spinncloud.com/

[18] https://www.intel.com/content/www/us/en/research/neuromorphic-computing.html

4.5. Medical Neuroscience

Highlights, Outcomes and Impact

- The Virtual Brain models showcase bridging the gap between fundamental digital brain research and innovation up to the level of a clinical trial in epilepsy patients
- The potential for detailed brain maps to aid personal treatment of brain diseases
- The importance of digital platforms for sharing data across borders to advance science for brain health

Today, almost one in three people globally will develop a neurological disorder at some point in their lifetime (Feigin et al., 2020). Moreover, the Global Burden of Diseases, Injuries, and Risk Factors Study (GBD) 2019 shows that mental disorders remain among the top ten leading causes of burden worldwide, with no evidence of global reduction in the burden since 1990. The total European (in 2010) costs of brain disorders was 798 billion Euro's (Olesen et al., 2012). Indeed, it was recently stated in a WHO Position paper (2022) that optimizing brain health improves mental and physical health and creates positive social and economic impacts, all of which contribute to greater well-being and help advance society.

The Human Brain Project approached this challenge of understanding the functioning of the human brain and its diseases by studying the brain at multiple levels (in parallel) while trying to bind these levels together because, in the words of director of the HBP, Katrin Amunts, "Research on the brain requires an understanding of the multilevel and multiscale of the brain" (Naddaf, 2023a).

In medical neuroscience, the focus of the Human Brain Project has been on personalized health and diseases of the human brain. In the first years of the Human Brain Project, efforts went into building an international platform for sharing clinical data, the Medical Informatic Platform (MIP). The Medical Informatics Platform (MIP) was developed to provide a cloud based, federated, open-source service for advanced analytics for diagnosis and research in clinical neuroscience. The early development and wide aim of the MIP exposed multiple challenges that needed to be overcome, including ensuring secure data-sharing of multicentre clinical data internationally while taking GDPR regulations into account. The federated aspect of the MIP is laudable since it potentially allows data to stay locally and moves around software for analysing the data across nodes. However, the use of the MIP has remained limited. More recent efforts for data sharing, such as the Human Intracerebral EEG Platform (HIP) and EBRAINS Health Data Cloud started at a smaller scale and are more targeted to specific projects, which seems to work better. Importantly, in recent years, the focus was more on developing digital brain models to improving brain health, such as in epilepsy and major depressive disorder, and for a good reason.

The aim of better understanding the functioning of the human brain and its diseases remains as relevant today as it was at the start of the Human Brain Project, despite the significant contributions made toward this goal. Indeed, substantial progress has been made in the Human Brain Project in developing digital models to better understand the functioning of the human brain and its diseases; the future will learn how it will lead to improvement for clinical medicine to optimise brain health.

A particular highlight was the work on epilepsy, which provides an important showcase for bridging the gap between fundamental research and innovation up to the level of potential novel interventions of the Human Brain Project. Here, virtual brain models have been developed of epilepsy patients who do not respond to medication. Currently, a clinical trial using the virtual brain models is ongoing in an expected 356-patients with the aim to provide surgeons with a precise tool to help individual surgery decisions and improve outcomes (Human Brain Project Task Force for Science Communication, 2023; Wang et al., 2023). Indeed, with improvement of predictive power of personalized virtual brains models, and with further testing in clinical trials, virtual brains may inform clinical practice in the near future (Jirsa et al., 2023). This work is impressive and can be considered as an example of the potential of digital twins to medical neuroscience and personalised medicine.

The potential of including novel microstructural maps of the human brain in future research in the field of psychiatry was shown in a study on major depressive disorders. Subregions of the frontal poles of 73 depressed patients and 73 healthy individuals were compared using structural magnetic resonance imaging (Bludau et al, 2017). This was combined with cytoarchitectonic maps of the human frontal pole showing two distinct areas within the frontal pole, and by statistical learning algorithms it was found that the left medial frontal pole has the most discriminative morphological and genetic features of the frontal pole subregions. Including cytoarchitectonically specific maps (Julich-Brain Atlas) in the current analytic framework allowed for assessing the spatial arrangement and the degree of volume loss in the frontal pole in depressive patients. Indeed, these microstructural maps and the JuGex tools on EBRAINS allow for a more specific assessment of regional atrophy than is possible by macro-anatomical definitions (Bludau et al., 2016) and to identify differential functional involvements and genetic profiles of brain areas (Bludau et al., 2018). Recently, unrelated to the Human Brain Project, the utility was demonstrated of the first objective brain-based biomarkers in the management of personalized deep-brain stimulation of the subcallosal cingulate for symptom relief for treatment-resistant depression (Alagapan et al., 2023). Detailed brain maps such as developed in the Human Brain Project may hold the potential to aid such personalized treatment of severe psychiatric disorders in the future.

Research and clinical advancements in personalized medicine require large-scale data sharing to ensure progress. The Human Brain Project aimed to provide services for advanced analytics for diagnosis and research in clinical neuroscience to ensure that clinical data could be shared in a GDPR compliant manner. This has led to the development of three platforms offering services on an international scale within a GDPR-compliant, cloud-based, trusted research environment (TRE): The Medical Informatics Platform (MIP), the Human Intracerebral EEG Platform (HIP), and more recently the EBRAINS HealthDataCloud (EHDC).

Services for advanced analytics for diagnosis and research in clinical neuroscience are highly needed by science and medicine. However, building such services has not been an easy task. With a personalized clinical medicine scope, focusing on the individual, such platforms are rather complex to implement, and overall progress has been slow. Currently, the MIP includes a federated network of multiple distinct European centres and hosts several disease-related models in the fields of epilepsy, stroke, dementia, traumatic brain injury and mental health [19]. The HIP is smaller, focused on a specific kind of data and clinical trial, and more centralized, making it easier to operate after compliance for data sharing is provided. At present, the HIP platform provides access to multiple European centres and hosts Intracerebral EEG (IEEG) patient datasets. IEEG data is a valuable and limited resource, and its integration has the potential to drive significant progress in the fields of epilepsy and brain research [20].

A third and even more recent endeavour is the EBRAINS HealthDataCloud (EHDC). The EHDC is being developed by a mixture of existing Human Brain Project (HBP)/EBRAINS infrastructure partners and leading health data service providers that have recently joined the HBP. The HealthDataCloud aims to provide EBRAINS services for sensitive data. The

[19] https://www.ebrains.eu/tools/medical-informatics-platform

[20] https://www.ebrains.eu/tools/human-intracerebral-eeg-platform

EBRAINS HealthDataCloud is a federated research data ecosystem of interoperable nodes including a central node deployed at EBRAINS RI and an expandable set of satellite nodes deployed at hospitals, research institutes and computing centres [21]. The EHDC seems to include a mixture of a federation of nodes with a central server and has a much larger and broader scope on brain health, promising an approach for sharing data that is potentially powerful, provided security and GDPR compliance remain safeguarded. Services provided by these EBRAINS platforms have the potential to bring benefits for society, by enhancing neuroscience research and, in this way indirectly in the medium to long term, to an improvement of healthcare services related to brain diseases. A valuable contribution towards the enhancement of the research and innovation capacity of the partners involved has been provided so far. The future will learn how the full usability and uptake of these platforms by the community is ensured, especially by the medical community at large. Finally, the new EBRAINS 2.0 project is building on the efforts of the HBP in the field of Medical Neuroscience, and developing a network of European hospitals, together with the European Academy for Neurology, to gather unique and high-quality neuroimaging data of patients.

4.6. Simulation Neuroscience

HBP researchers were among the first to understand that, in order to develop accurate and comprehensive brain simulations, it is fundamental to investigate the dynamics and organization of brain networks across these diverse scales (D’Angelo & Jirsa, 2022). In the original HBP proposal, the Brain Simulation Platform had the goal of integrating data in multi-level models, starting from the mouse up to the human brain. By utilizing supercomputing technology, the platform aimed to simulate and visualize the models’ behaviour. Validation against biological experiment results would have identified data gaps, ensuring continuous improvement in model accuracy throughout the project.

Highlights, Outcomes and Impact

- Significant progress in brain simulation by integrating data across scales, thus revolutionizing our understanding and predictive capability of brain functions
- Personalised modeling, especially in epilepsy treatment and clinical trials
- High-resolution data and modeling techniques to drive modern neuroscience towards personalized diagnostics and therapy, marking a significant advancement in medical approaches

Now, after a decade of dedicated effort, HBP researchers have advanced brain simulation by simultaneously exploring multiple scales. This breakthrough enables them to study the brain in ways never before possible.

The brain simulation activities have been probably one of the most successful of the entire project, both in terms of results, dissemination, and impact. Many of the developments started as the activities of a few partners and focussed on so many different problems that an integrative view was very difficult to appreciate. Notwithstanding, thanks to the significant effort done within the last phase of the HBP, most of modelling results are now part of EBRAINS, the

[21] https://www.healthdatacloud.eu/

HBP centralized platform intended to accommodate all the diverse models and results and now available for the entire scientific community (Schirner et al., 2023).

Over the years, brain simulation methods developed in the HBP have expanded in both range and predictive capability. Starting from the early development of The Virtual Brain (TVB) simulation engine (Ritter et al., 2013; Woodman et al., 2014; Sanz-Leon et al., 2015)al., 2014), a lot of improvements have been made in epilepsy treatment, where the prediction of seizures and the outcomes of surgical procedures can now be achieved through brain models personalized to the individual patient data (Jirsa et al., 2017; Makhalova et al., 2022)2). Thus, thanks to the HBP, a novel connection between brain simulation and clinical practice has begun to be possible, with personalised modelling emerging as an unforeseen but pivotal advancement in computational modelling and simulation. Significant strides have been made, notably with the integration of digital twin technology into medical practice thanks to HBP's implementation of personalized modelling through TVB. This innovative approach is currently undergoing testing in the EPINOV clinical trial for epilepsy, running in France and involving 13 hospitals (Wang et al., 2023).

By capitalising on those results, HBP researchers have started utilizing multi-scale simulations to study other pathologies than epilepsy (Jirsa et al., 2023), such as Parkinson's disease (Meier et al., 2022), where simulation of the DBS therapy could help clinicians further optimize the treatment. Importantly, as a platform for whole-brain modelling, TVB is now integrated with high-resolution atlas data and high-resolution neural network modelling using NEST in Co-Simulation frameworks (Goldman et al., 2023; van Keulen et al., 2023).

Many other key achievements are worth mentioning: experimental and computational studies to study how the morphological properties and dendritic structure of neurons influence their behaviour and impact phenomena at higher levels of brain organization, including consciousness (Goriounova et al., 2018; Gidon et al., 2020); investigating the role of neuronal networks in perception (Filipchuk et al., 2022); unravelling the structure and function dynamics in cortical microcircuits of the cerebellum (De Schepper et al., 2022); application of modelling techniques in HBP to better understand and/or classify the evolution of different pathologies or physiological states such as ALS (Polverino et al., 2022), Multiple Sclerosis (Sorrentino et al., 2022), Alzheimer's (Triebkorn et al., 2022), treatment-resistant depression (An et al., 2022), and brain ageing (Escrichs et al., 2022).

The HBP has facilitated the progress of researchers in enhancing diverse computational brain modelling and simulation strategies, partly through their integration with EBRAINS, pioneering the development of innovative multi-scale models. The links between anatomical and functional data using multiscale modelling at the cellular level seem to show converging benefits that deserve further development. Such modelling and simulation strategies will not only enhance research outcomes but also serve as a fundamental principle driving modern neuroscience, where Digital Twins of the individual brain will serve to improve personalized diagnostics and therapy (Amunts et al., 2022). Thanks to these results, the HBP has pioneered a truly personalised medical approach.

4.7. Neuro-inspired AI

Highlights, Outcomes and Impact

- Exploitation of neuroscientific results to advance machine-based methodologies for AI
- Interdisciplinary efforts in studying brain learning rules to develop more biologically plausible models
- Development of biologically plausible models to enhance robotics, automation, and AI applications

The lack of mention of 'AI' (Artificial Intelligence) in the original proposal of the HBP signifies the evolving nature of scientific developments in the field over the last ten years. Initially focused on computational neuroscience, the project later incorporated AI with the goal of exploiting neuro-inspired learning mechanisms to improve machine-based methodologies and techniques. This progression and evolution highlight the pivotal role of neuroscience as a means of translating brain research into tangible outcomes capable of driving the advancement of AI (Verzelli et al., 2024).

Indeed, when the HBP was proposed as an EU FET Flagship back in 2012, it demonstrated a strong interdisciplinary nature, where boundaries between different fields blurred and new approaches could emerge. It is worth highlighting that two of the HBP's initial goals were (i) Theory to identify mathematical principles underlying the relationships between different levels of brain organization and their role in the brain's ability to acquire, represent, and store information; (ii) ICT platforms as an integrated system offering services to neuroscientists, clinical researchers, and technology developers that accelerate the pace of their research. Given the above, the project clearly was in the perfect position to advance AI-based approaches, thanks to its strong interdisciplinary nature and focus on both computational modelling and ICT.

From its inception, the HBP put a lot of effort into studying the brain's learning rules at different scales to be further exploited for machine-based applications (Amunts et al., 2024). All neuronal/neural networks, whether found in living organisms or created artificially, rely on plasticity processes for learning. While neuroscientists have collected a wealth of data on plasticity, even within the HBP, a comprehensive theoretical framework to tie it all together was lacking. On the other hand, deep learning techniques in artificial neural networks could be systematically developed, but they often involve elements that do not mirror biological processes. In the last phase, HBP researchers worked towards bridging this gap. The work aimed at addressing the intricacies of brain complexity at both temporal and spatial scales, to unravel the influence of various properties of brain networks (e.g., plasticity, topology, modularity) on resultant behaviour (Schirner et al., 2023). Indeed, most of the activities involved the development of brain-inspired models and learning rules to be more biologically plausible, with the final aim of advancing innovative applications in robotics, automation, and AI.

In this regard, the modelling approach combined brain-inspired architectural principles with parameters derived from biological learning. Modular design allowed a single module to serve multiple architectures. Outcome architectures were expanded to include higher-level cognitive functions and embodied in robots for tasks like navigation and manipulation. Some of the key achievements of these activities include: biologically plausible hierarchical memory models such as the BrainProp algorithm for attentional feedback (Pozzi et al., 2020); the development of recurrent neural networks trained with a biologically plausible learning rule to solve multistep visual routine tasks (Kroner et al., 2020); hierarchical visual processing (Kroner et al., 2020); visual relational reasoning (Thompson et al., 2022); models for spatial planning and navigation (Muhle-Karbe et al., 2023; Stöckl et al., 2024); compositional inference, i.e., “assemble” knowledge from different sources (Nelli et al., 2023; Max et al., 2024).

In parallel, HBP researchers investigated the impact of attention, synaptic tags, feedback connections, and neuromodulators on learning. Their focus was on combining the development of biologically plausible learning rules within neural networks with the ability to learn and adapt similarly to the human brain. Some of the main outcomes encompass: the biologically plausible implementation of natural-gradient-based plasticity for spiking neurons (Kreutzer et al., 2020); the investigation of how task-dependent top-down signals can reshape the functional mapping of sensory processing networks at the micro and mesoscopic levels (Wybo et al., 2023); the emergence of predictive coding through synaptic plasticity in hierarchical cortical areas (Dora et al., 2021).

It is important to notice that, due to the highly inter- and multi-disciplinarity of the topics entailed in these activities, interactions among partners were often significantly more challenging than in other activities. This led to the formation of small sub-groups of institutions and scientists, each undertaking different experiments and parallel studies simultaneously. Indeed, HBP activities in this area appears quite fragmented, without a clear coherence and a small direct impact on the broad range of potential applications foreseen in the original proposal (cf. ‘Neuromorphic’ and ‘Neurorobotic’s sections). As of today, few of the developments have been integrated in the EBRAINS platform or tested in relevant environments. Nevertheless, the results obtained achieved relevance among both neuroscientists and computer scientists, and many of them were published in high-impact journals, denoting the scientific quality and impact of the research performed.

4.8. Robotics

Modern AI developments, such as large language models and image recognition systems, can nowadays replicate cognitive functions previously thought to be exclusive to biological brains. However, these models lack bodily experience and environmental interaction. Similarly, typical computer models of the brain used by neuroscientists, even if complex and useful, may not fully capture the richness of real-life cognition, which involves the interaction of mind, brain, body, and environment. Indeed, behaviours, ranging from the simplest reflexive actions to the most intricate cognitive processes, are shaped through the continuous interplay between an organism and its environment. The brain orchestrates these behaviours

Highlights, Outcomes and Impact

- Pioneering advancement in embodied cognition by connecting brain models with robotic bodies, promoting understanding of cognition through 'embodied' experiments.
- Neuro Robotic Platform (NRP)-based innovative experiments, such as multisensory integration and precise movements, fostering research in neuro-derived AI and robotics.
- A versatile framework for integrating functional models, enhancing research in computational neuroscience and embodied AI, and paving the way for complex cognitive architectures and emergent phenomena studies.

through the coordinated activation of neuronal assemblies, dynamically adapted depending on the task.

To the HBP, it was clear that to emulate brains and behaviours, embodiment was not only necessary but fundamental (Prescott & Wilson, 2023). To this end, the HBP community has pioneered new scientific tools that allow connecting brain models with robotic bodies to study processes of 'embodied cognition' thanks to a framework named Neuro Robotic Platform (NRP), designed from the early phases of the HBP. The goal of NRP was indeed to provide an experimental setting to test the capabilities of the developed brain-derived models, to be further exploited also in the industrial context. The idea was to provide the EU research community with robots equipped with 'human-like' brains, capable of better cognition (Schirner et al., 2023). To this end, the HBP scientists started designing several neurorobotic solutions, allowing them to perform fully simulated experiments (virtual brain and virtual robot) and hybrid experiments (either a physical or virtual robot connected to a simulated or neuromorphic brain) in a fully closed-loop fashion.

Some of the key achievements include: multisensory information integration, such as the MultiPredNet based on predictive coding and able to integrate visual and tactile information (Pearson et al., 2021); object manipulation with high degree of dexterity, provided by AngoraPy (Anthropomorphic Goal-Driven Responsive Agents in Python) which enables neuroscientists to build and train neural network models with a brain-derived architecture in ecologically valid settings using reinforcement learning and goal-driven modelling (Weidler et al., 2023); precise movements and coordination through a neuro-derived AI system (e.g., interaction between an artificial neural network mimicking the cerebellum and a robotic arm (Abadía et al., 2021; Antonietti et al., 2022); cobotics (i.e., robots designed for direct interaction with humans in a shared space) simulations developed using EBRAINS in which robots learn to interact with humans in a safer way, to allow humans to better 'trust' collaborating with robots – well demonstrated in Showcase 6 (Feldotto et al., 2022; Stolpe & Morel, 2023); integration of The Virtual Brain large-scale as well as NEST simulations into the NRP; generation of synthetic data as input for Machine Learning experiments; integration with major HBP neuromorphic technologies such as SpiNNAker and BrainScaleS.

Thanks to its modular architecture, open-source nature, and comprehensive online documentation, the NRP offers computational neuroscience and embodied AI communities a versatile framework for seamlessly integrating multiple functional models. Notably, the NRP enables each model to operate and communicate at different frequencies within the simulation time domain, mirroring the diverse neuronal activities observed in the brain's anatomical areas and thus providing robots with brain-derived skills. This unique capability would support the future development of complex cognitive architectures with diverse components, facilitating the in-depth study of emergent phenomena. Furthermore, the NRP's use of container technology ensures its adaptability and readiness for integrating new simulation software, AI systems, or brain models without concerns about dependency conflicts.

Despite these results, however, the integration of the activities of the NRP with the outcomes from activities related to brain modelling (i.e. 'The human multiscale brain connectome and its variability') and neuroscience (i.e. 'Networks underlying brain cognition and consciousness') has been only partially addressed by the consortium. The robotic application has been around since the project's beginning (cf. HBP proposal), so a focus on more integrative work was the aim during the final years. Notwithstanding this aim, a strategic view of the research as a whole, and the outcomes across the possible (many) robotic applications, was not successfully addressed. At the end of the project only a few examples (e.g., Showcases 5 and 6) were provided. Furthermore, the relationships of the activities with respect to EBRAINS are still not clear, thus limiting the impact of the platform for real-world applications.

4.9. Integration platform for digital neuroscience (EBRAINS)

The research ecosystem developed by the Human Brain Project, subsequently referred to as EBRAINS, is a crucial component of the digital neuroscience field. With approximately 160 tools integrated, and an average Technology Readiness Level (TRL) of 7, the EBRAINS ecosystem provides a robust framework for advancing brain research. The successful integration of a diverse portfolio of tools alone constitutes an important milestone for the advancement of digital neuroscience.

The adoption of the platform has successfully advanced through the HBP. By September 2023, the EBRAINS community boasted 8475 users from around 1500 institutions, fostering a collaborative environment for further exploration of the brain. This number has increased after the end of the HBP to more than 10.000.

Highlights, Outcomes and Impact

- EBRAINS integrates 160 interoperable tools facilitating its access to a community of approximately 8500 users from around 1500 institutions around the world (as of Sept 2023).
- Initially developed at HBP, the integrated High Performance Computing infrastructure is being further developed in the ongoing ICEI project. Potential health applications are exploited in sequel projects eBRAIN-Health, TEF-Health and AI-MIND.
- FAIR data services, and open software facilities crystallize the platform's commitment to open science encouraging the development of complex collaborative breakthrough approaches for digital neuroscience.

Among its facilities EBRAINS includes the Knowledge Graph, an impressive metadata management system that enables data annotation and curation. This ensures effective management of the data, software and models integrated on the platform, which can be navigated interactively.

EBRAINS currently includes the following [22] :

- Comprehensive human, macaque, and rat brain atlases;
- Numerous datasets for experimentation and analysis;
- Modelling, Simulation and Computing Platform.
- Validation and Inference Services;
- Health Research Platforms.

The capability of working with sensitive data is mainly achieved through the delivered Health Research Platforms. Here the HBP has successfully paid special attention to achieve GDPR-compliance and cover all the regulatory requirements for handling sensitive data. It is worth mentioning that the “Human Data Gateway” service (inside the Sensitive Data stack of EBRAINS Services) is assumed by the Health Data Cloud (HDC) platform, which is part of

[22] https://www.ebrains.eu/

Health Research Platforms together with the MIP and the HIP (see Medical Neuroscience section above).
Modelling services offer a variety of simulation software tools for multi-level brain modelling. These tools are enabling the developed virtual models of neurological conditions like epilepsy, dementia, and cognitive processes associated with perception and memory. They provide integrated access to the data required for implementing model workflows of unprecedent complexity (see Showcases section). Overall, the EBRAINS platform provides researchers with a comprehensive ecosystem for conducting the most advanced brain research, with robust data and model services that support the construction of intricate workflows.
The EBRAINS platform integrates a range of modern digital toolkits and libraries crucial for modelling and simulation in digital neuroscience. These tools are meticulously designed to address various aspects and scales of brain function and structure, empowering researchers to conduct detailed and ground-breaking studies.

Among the comprehensive collection of 160 tools, some are particularly noteworthy due to their pivotal importance and strategic position within the EBRAINS ecosystem:

1. **Knowledge Graph:** a metadata management system developed to find and share software, models and data. It includes functions for search, editing, query building, statistics and APIs, and manages 1064 data sets, 4 metadata models, 225 pieces of software and 18 webservices from 2195 contributors.

2. **OpenMINDS:** The Open **M**etadata **I**nitiative for **N**euroscience **D**ata **S**tructures is a community-driven metadata framework for neuroscience graph databases that was empowered by HBP and EBRAINS. The openMINDS metadata models are adopted by the EBRAINS Knowledge Graph, the EBRAINS Atlas Service, and The Virtual Brain (TVB). It is currently in the process of being adopted by the Japan Brain/MINDS project. [23]

3. **EBRAINS Curation Workflow:** The curation workflow ensures that metadata is accurately entered into the Knowledge Graph according to the OpenMINDS framework. It organizes data properly and makes it accessible in a standardized and interoperable format with a Data Descriptor. Additionally, it links data to relevant analytical tools.

4. **Siibra toolsuite:** this software has been developed for interacting with brain atlases and is including a siibra-explorer, an interactive 3D atlas viewer and a dedicated programmatic Python client. It is tightly integrated with the EBRAINS Knowledge Graph [24], allowing the seamless querying of semantically and spatially anchored datasets for the exploration of the regions of the human, rat, mouse and monkey brains at microscopic detail, as well as the discovery of related multimodal data features. siibra-python is offering an easy and well-structured way to include maps, reference templates, region definitions and linked datasets into reproducible programmatic workflows.

(23) https://brainminds.jp/en/

(24) https://kg.ebrains.eu/

5. **The Virtual Brain (TVB):** TVB (Ritter *et al.*, 2013) is a crucial component within the EBRAINS platform serving as a powerful tool for whole-brain simulation. Its purpose is to integrate empirical data into personalized brain network models, offering a comprehensive approach to understanding brain function. TVB is specifically designed to construct, run, and integrate neural mass models, enabling researchers to study the dynamics of large neuron populations. The TVB is emerging as being potentially pivotal in neurological studies, including those on brain ageing, disease progression in neurological disorders, and the effects of neurosurgical interventions. A strong indication of its success is the integration of the TVB into several public-funded projects, highlighting its significance within the scientific community and the suitability to unleash the potential of digital neuroscience already today.

6. **NEST:** The purpose of NEST (Gewaltig & Diesmann, 2007) is to facilitate the simulation of large-scale neuronal networks, with a particular emphasis on spiking neurons, in order to better understand the dynamics of the brain. NEST offers efficient and scalable solutions that can be implemented in high-performance computing (HPC) environments, making it an ideal tool for conducting large and complex simulations. Its ability to run simulations on HPC facilities has been recognized as one of its most notable features (Tikidji-Hamburyan *et al.*, 2017). NEST is commonly used in research studies that investigate brain connectivity, learning processes, and the emergence of neural patterns. It serves as a valuable resource for studying and analysing these neuroscientific phenomena.

7. **Neuron:** NEURON (Carnevale, 2007) is used for biophysically detailed neuronal modelling, enabling researchers to simulate neurons and networks with anatomical realism. It is one of the two tools most commonly used for cellular level simulations, although it can also be used for network-level simulations. The tool NEURON seamlessly integrates with various hardware platforms, allowing for simulations that range from single cells to large networks.

8. **Arbor:** Arbor (Abi Akar *et al.*, 2019) is an outcome of the HBP to enable high-performance simulation of multicompartment spiking neural networks, offering detailed insights into neuronal computation at the cellular level. It is specifically designed to excel in performance and scalability, making it suitable for extensive models that demand intensive computational resources. Arbor is particularly valuable for researchers studying complex brain functions that require integrating large datasets or high-resolution models.

The EBRAINS ecosystem promotes the combination of tools for complex simulation tasks within simulation workflows. Examples have been showcased to demonstrate the infrastructure's utility and flexibility (see Showcases). The data repository hosts multi-scale data, supported by FAIR data services, demonstrating the platform's commitment to open science. Additionally, the development of a neuromorphic energy-efficient ecosystem, featuring innovative algorithms and chips, represents a significant step towards sustainable scientific research.

4.10. Education and Outreach

Highlights, Outcomes and Impact

- Establishment of a coordinated HBP website and other social media outlets with large following (over 70,000)
- Online courses and teaching on topics in Neuroscience publicly available with almost 200 instructional videos
- Large number of early career researchers supported through HBP.
- Over 500 conferences and workshops organised and 80 exhibitions

Throughout the duration of the HBP project there have been a number of excellent examples of efforts towards Education and Public Outreach. Initial efforts were mainly focussed on training workshops targeted at existing members and students within the project. For example, education workshops on data mining at earlier stages of the project were necessary for the later development of EBRAINS. Furthermore, these were mainly organised locally, with a focus on small audiences. The impact of educational or outreach activities was not measured at the initial stages, therefore it was not clear how effective these were at serving the HBP community's needs. However, as the project developed these programmes became more efficient and were geared towards a pan-European organisation, targeting more diverse audiences both within (e.g. theoretical neuroscientists to computational modelling) and outside the HBP. This was successfully achieved via the development of targeted websites and through social media. The establishment of the HBP website included dedicated pages to education and outreach and acted as a central resource for information about upcoming events (either in person or online) as well as a repository for educational tools. Towards the later stages of the project, public outreach became useful for disseminating the specific results and achievements of the HBP project.

Some particular examples of excellence in these endeavours are worth highlighting. For example, the HBP organised a large number of training events and educational events (over 90 in total). These ranged from hands-on workshops (over 50) which were focussed at specific skill acquisition (e.g. Theoretical Neuroscience – EITN) or increasing awareness of the project itself (e.g. HBP summits). Overall, the educational programme of the HBP hosted over 5,000 participants. These 'in-person' events were supported by the establishment of a co-ordinated HBP Education website which significantly enhanced impact on teaching and learning of the human brain, from neuroscience to ICT platforms [(25)]. At of the end of the project, the website attracted more than 15,000 visitors. The online courses and teaching material organised and disseminated by HBP online were exemplary, with contributions from leading researchers from across Europe explaining advances in science and technology and specific achievements of the HBP. Moreover, these educational video resources were made widely available via a public E-library on the HBP website.

Over the years the HBP supported the training and mentoring of a large number of early career researchers (PhD students and post-doctoral researchers) across a number of partner sites. Such training was particularly effective at improving the skills of early career researchers in neuroscience in areas such as IT tools and programming (as evidenced through satisfaction surveys). The large number of followers on the HBP LinkedIn page (~ 70,000 followers) is testament to support for research careers. Both mobility and diversity were important aspects of the quality of this training. For example, members from over 21 European countries were

[(25)] https://www.humanbrainproject.eu/en/education-training-career involved in some educational events and the proportion of participants across genders approached equality towards the end of the project. The HBP Education Committee Program also supported teaching of cognitive neuroscience in schools. This effort may support future generations of European neuroscientists but also, hopefully, help to address gender imbalances in neuroscience that was an intractable issue throughout the 10 years of the HBP (but certainly not unique to the HBP).

Beyond the formal structuring of Education and Public Outreach activities, other educational opportunities occurred within specific activities of the HBP. There were some particularly noteworthy activities including the community workshops and hackathons that were designed to support community involvement in e.g. cortical and hippocampus modelling. In addition, the HBP facilitated public engagement and consultation on potential ethical, social and philosophical implications of the research activities within the project (via actions such as Foresight Lab and EuropeSay) thus ensuring wide stakeholder involvement in complex but topical issues such as consciousness and the use of AI in neuroscience.

5. EBRAINS Research Infrastructure: present and future impact

One of the main goals of the HBP was the creation of an ICT infrastructure for the advancement of brain research. This goal has been achieved through the implementation of the EBRAINS Research Infrastructure, which is conceptualized as an ecosystem of integrated tools, services and resources. It serves as a comprehensive ecosystem encompassing various tools and data, empowering researchers to construct intricate workflows. Special emphasis was placed on compatibility and interoperability addressing the interdependencies between tools and services integrated in the ecosystem (see Integration Platform section above), which was realized through the effective employment of standards and profuse documentation. This is an important achievement within the HBP given the heterogeneity of partners involved in the flagship and a direct result of its EU added value. In this context the HBP has effectively developed a long-lasting structure based on previous disaggregated research efforts in Europe. Given the presence of the Research Infrastructure in different successive projects, it can be positively stated the HBP has successfully integrated efforts and resources beyond their duration.

By offering a plethora of sophisticated tools, the EBRAINS Research Infrastructure has managed to ensure that researchers have a sustainable access to state-of-the-art multi-level resources for modelling, simulation, experimentation and data analysis. The infrastructure enhances neuroscientific research in depth and accelerates discoveries by enabling more accurate and comprehensive studies of the brain than ever before. Of particular interest is the integration of a high-performance computing infrastructure, as well as compute and storage resources that specifically address the needs of agile and highly innovative research by the project ICEI [(26)] that is closely linked to the HBP (see below). This research often involves closed-loop interactions between the researcher and the tools provided by the EBRAINS RI.

The EBRAINS RI has managed to become therefore a one-stop-shop (OSS) high performance computing (HPC) system exclusively dedicated to neuroscience research, which constitutes a paradigm change of paramount relevance for the development of digital neuroscience and brain health applications. In today’s fast-paced digital landscape, leveraging the potential of HPC services becomes a breakthrough for addressing complex problems as the ones posed by the understanding of the brain.

With the advent of the EBRAINS RI, neuroscience and brain research have the potential not just of becoming efficient but also fuelled by the speed and agility of HPC. From servers to databases, storage to software, and everything in between, the EBRAINS RI may redefine, if adequately scaling, for which further public support will be needed, how computing resources are harnessed for complex modelling and analytical endeavours. It has the potential to become a game-changer for EU neuroscience research and neurotechnology. To facilitate access to the complete ecosystem, an interface to the service catalogue has been implemented based on the Knowledge Graph, which constitutes an additional cornerstone in the interoperability of the different parts. Its development has been realized paying special attention to usability aspects, whose required future improvement are of fundamental importance for the spread adoption within the neuroscientific research community. In this context, the EBRAINS 2.0 project for the further development of services should specially focus on usability and scalability of the tools. Although EBRAINS has made significant improvements in facilitating access to information and data through the Knowledge Graph, there are still challenges that need to be addressed. One of these challenges is enhancing the platform's commercial viability and user-

[(26)] https://www.fz-juelich.de/en/ias/jsc/projects/icei friendliness. As EBRAINS transitions from cost-free early adoption programs to models that require private investment, it is important to strategically demonstrate the value of the infrastructure to potential users and investors who rely on it as a technology backend for their businesses.

The value of EBRAINS as a Research Infrastructure for a broad community outside the neuroscience one is being realized in further public funded endeavours. The Health Data Space Pilot project is a two-year long European project that will build a pilot version of the European Health Data Space (EHDS) infrastructure for the secondary use of health data, which will serve research, innovation, policy making and regulatory purposes. The project will connect data platforms in a network infrastructure and develop services supporting the user journey for research projects using health data from various EU Member States.
EBRAINS partners in the Health Data Space Pilot consortium and contributes as a data platform and IT infrastructure provider. It further supports the project by providing IT security, metadata catalogues, data quality and interoperability. The inclusion of precisely these components demonstrate as well which parts of the Research Infrastructure are the best recognized ones among the general community. Furthermore, the inclusion is of strategic importance for the adoption of the data management principles defined and implemented during the HBP in a broader clinical context. The health domain is lacking data management frameworks as those offered by the Health Data Cloud and therefore a perfect playground for ensuring its future sustainability.
The RI aims to offer federated services related to distributed data structures, an objective that would have remained elusive without the crucial contribution of the HBP. The offered services are enabled by the four-layered EBRAINS Architecture formed by the Front end, the EBRAINS Services itself, a Platform Middleware, and the Infrastructure Hardware (see Fig 1).

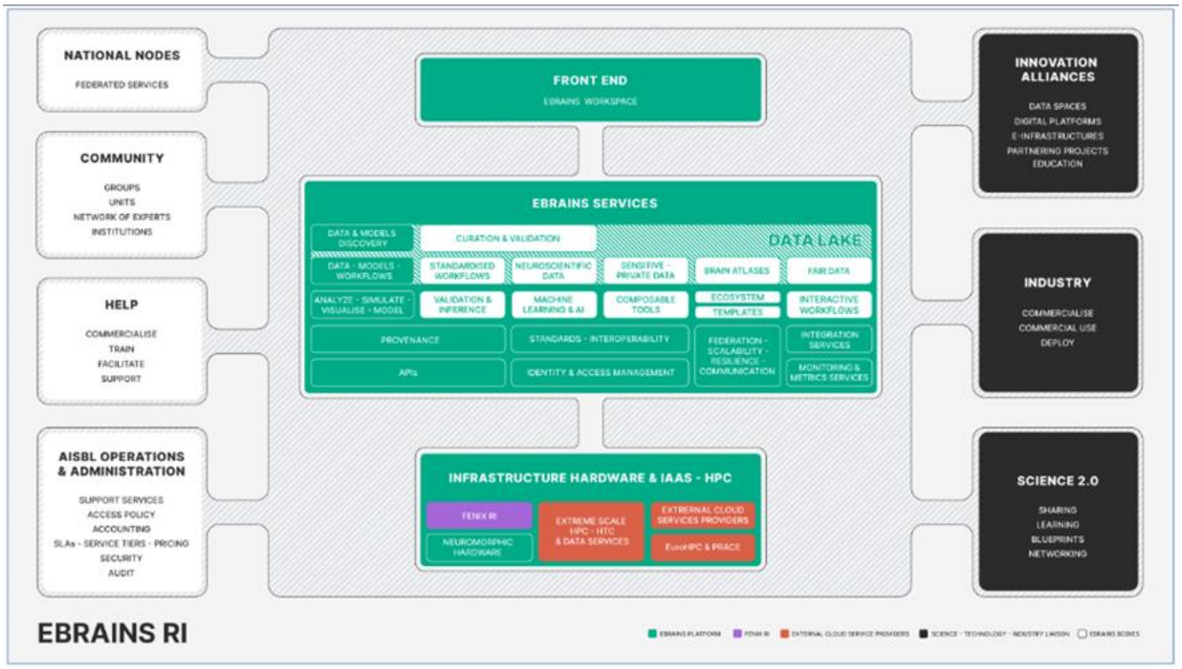

Figure 1 – OVERVIEW OF THE EBRAINS RESEARCH INFRASTRUCTURE

(*Source:* HBP DELIVERABLE D5.7)

The EBRAINS physical core layer constitutes one important aspect of the overall infrastructure for becoming a central part in the future development of digital neuroscience: it operates in a multi-site High-Performance Computing environment. The infrastructure has been partially furthered within the ICEI project, which together with the HBP co-funded its development and implementation. Hence, the ICEI project, a coordinated action of the five leading supercomputing centres in Europe, located in France, Germany, Italy, Spain, and Switzerland, concretely aimed to develop a set of federated services in line with their respective national programs and service portfolios. Its implementation constituted a coherent interface between national programs and the HBP one.

The ICEI focused on realizing important components of the Fenix Research Infrastructure, which constitutes one of the key components of the EBRAINS Hardware Infrastructure *(see Figure 1)*. The Fenix RI aims to provide scalable computing and data services in a federated manner, primarily catering to the computing infrastructure needs of the neuroscience community. Under the HBP third phase, the Fenix RI, along with novel neuromorphic computing services, was integrated into the joint infrastructure layer of EBRAINS. As part of the ICEI project, the supercomputing centres offered cloud-like services that are aligned with the work cultures of scientific computing and data science. This includes the development of interactive supercomputing capabilities on their cutting-edge extreme computing and data systems, and key features including scalable compute resources, a federated data infrastructure, and interactive computer services to provide access to the federated data infrastructure, as well as to scalable compute resources. In combination with integration into the EBRAINS ecosystem, these activities have pioneered the use of high-performance computing and will likely have a transformative impact in digital brain science.

Enabling the employment of the infrastructure for concrete usages is critical for the fruitful deployment of the infrastructure. With its broader usage in mind, different deployment types have been implemented for development, contribution and usage of the different tools and services, from which Standardised workflows, and VM-hosted services are the most remarkable ones. The profuse usage of standard tools as achieved in the EBRAINS RI, e.g. Common Workflow Language (CWL), Spack, is crucial for its sustainable further development. The implemented solution for the deployment of packages distributed responsibilities in a meaningful way and its incremental deployment strategy has demonstrated to be a successful one over the HBP life.

With the increasing relevance of cybersecurity threats, part of the HBP effort has been dedicated to development of a protection facility for the future Research Infrastructure. EBRAINS has succeeded in developing its own cybersecurity framework, formally defining the roles, relations, and responsibilities of the Information Security Officer (ISO) and the CyberSecurity Incident Response Team. Their responsibilities and concrete function assignments are being refined and adapted to a quick changing-threat landscape. The right choice of structures, procedures and roles will become an important milestone contributing to the sustainability of the RI. This might be a critical point in designing the overall cybersecurity policy of EBRAINS as it will also have to consider the regulatory constraints within the Health sector. This aspect requires continuous development and effort assignment given the future expected importance of EBRAINS as a central research facility.

In conclusion, the EBRAINS represents an unprecedented development in neuroscience research infrastructure, providing advanced tools and services that can enhance our understanding of the brain. As the platform evolves, it holds the potential to not only advance scientific knowledge but also revolutionize the treatment of neurological and mental disorders worldwide, while also promoting the implementation of preventive and personalized medicine. Thus, in the long-term the potential impact is very promising. However, to sustain the momentum of innovation and ensure that the EU remains at the forefront of technological advancements in brain research and beyond, it is crucial that these initiatives continue in the future. In that context, the launch in January 2024 of the EBRAINS 2.0 project for the further development of services within the EBRAINS research infrastructure until 2026 is welcome.

6. Innovation Impact

The HBP has selected the infrastructure aspect at its core and focused on the EBRAINS services as its major vector of innovation. Important advances within the HBP have been made with the creation of a powerful Research Infrastructure as described in the former section. It is worth further underscoring some innovative neurotechnology like the significant advances in the field of prosthetics, which present several examples among project outcomes (see Sec. below). A unique achievement of the HBP at an international level has been the advance in neuromorphic engineering and chips. Novel tempo-spatial ultra-high-resolution neuroimaging, which are important for furthering brain research, have not been fully developed within the HBP but some innovations in PET and microscope imaging are along these lines. Innovations like neurodata-driven serious gaming for rehabilitation and closed-loop neurotechnologies integrated with AI are setting new benchmarks in the field but were underrepresented within project outcomes.

6.1. Impact and Support of H2020 Goals

The HBP flagship has significantly advanced Europe's position in the global neurotechnology innovation landscape. Among the many achievements, the Innovation Radar [(27)] activity identified 35 key exploitable results from the consortium. Here it is worth highlighting the importance of the business development activities that support the innovations to successfully reach the market in the future. While, notably, 7 of these 35 results have a clear potential to develop into sustainable businesses, 15 of them require an improvement to the business model to make a path into the market.

In terms of intellectual property, 12 patents were granted to innovations generated within the HBP (see complete Table in the Appendix). These include some in the US, highlighting a strategic focus to patent innovations outside the EU, where models and methods typically are not so easily patentable. It is difficult to compare project outcomes of different brain initiatives in terms of patents given the lack of data from other projects. This is a successful demonstration of transparency in HBP reporting. In summary, HBP has been instrumental in helping to boost European industrial leadership, enhancing competitiveness, job creation, and addressing societal challenges.

To link the achievements of the HBP to the technological advancements in the field of neurotechnology, an approach from the UNESCO Neurotechnology [(28)] expert group (Hain et al 2023) was utilized (refer to the clustering analysis results in the Appendix). The analysis identifies the following as most relevant (number of patents is given in brackets): Multimodal Neuromodulation (535 patents), Neuromorphic Computing (366 patents), Seizure Prediction (190 patents), Brain-Computer Interfaces (146 patents), Medical Image Analysis Technologies, Limb Rehabilitation, Tinnitus Neurotechnology, Sleep Optimization, Assistive Exoskeletons, and Neuroimaging comprising different neurosensing modalities. Among these relevant areas, Seizure Prediction and Neuroimaging/Neurosensing were the ones most actively generating patents in the HBP (refer to Figure 2 below). The HBP consortium lists 92 filed patents applied in 15 countries. Approximately 35 of these patents are still awaiting decision and might increase the total number of patents directly generated from project works in the future.

[(27)] Innovation Radar > Discover great EU-funded innovations (europa.eu)
[(28)] https://unesdoc.unesco.org/ark:/48223/pf0000386137

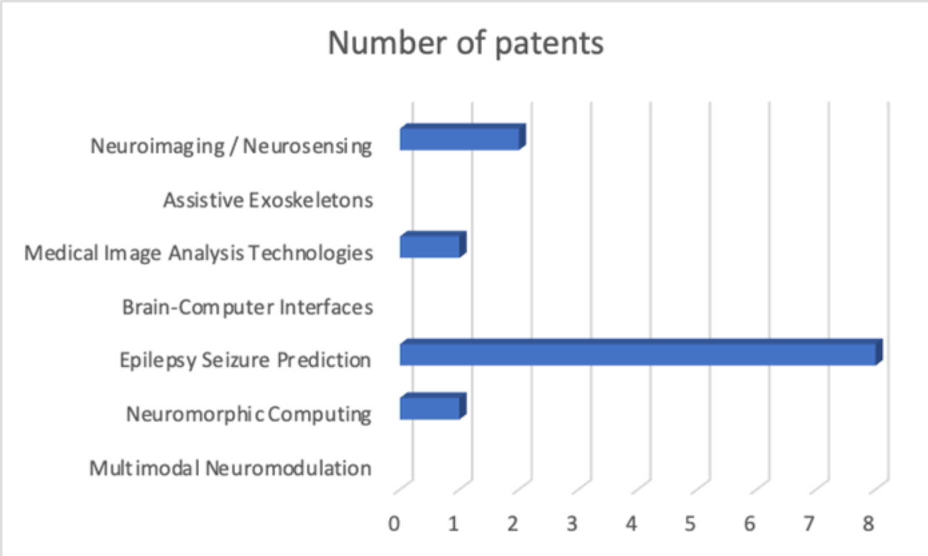

Figure 2 – Number of active patents generated within HBP in the different key innovation areas
Source: HBP reports

An important factor in promoting innovation is the implementation of open software licensing policies. By encouraging wider access to software tools created under the HBP, opportunities for collaboration were increased, potentially speeding up the adoption of new technologies in the medium term. While open-source licenses and permissive commercial licensing terms can enhance collaboration, they may hinder commercial acceptance if not implemented correctly. Due to the challenge of creating sustainable business models from open software licenses, more attention, effort, and funding need to be directed towards this area in the future. Additionally, the lack of uniformity in software licenses has complicated the establishment of a consistent commercialization strategy for the entire ecosystem surrounding EBRAINS, which serves as the central integration platform for the various technologies developed within HBP (see Sec. EBRAINS as Integration Platform).
With respect to the upcoming societal challenges, the Human Brain Project (HBP) implementation was relevant to attain the 2030 Agenda for Sustainable Development in issues related to health, demographic change, and well-being, whose importance is accentuated by an increasing prevalence of mental and neurological disorders. The HBP flagship outcomes are naturally linked to brain health issues, and especially those related to an increase in the ageing population, which have precise associated brain health problems. Increase of well-being has been successfully addressed through the activities on mental health.

6.2. Relevance of Technology Project outputs

HBP most relevant project outputs can be grouped under the aforementioned areas of key innovation relevance as following:

- **Epilepsy technologies** (seizure prediction)
    - Multi-scale brain simulation models
- **Neuromorphic Computing**
    - Neuromorphic computing semiconductors
    - Spiking neural network AI algorithms

- **Medical Image Analysis Technologies**
    - Brain atlases and navigation
    - Health data cloud
    - Fenix Research Infrastructure
    - Ceph storage that combine HPC and cloud systems
- **Rehabilitation and Assistive Technologies**
    - Visual prosthesis
    - Spinal cord rehabilitation
    - Neurorobotics Platform
- **Neuroimaging and Neurosensing Technologies**
    - Molecular modelling for drug discovery
    - Consciousness probing technology

Although some outputs of the project overlapped in the domains of Multimodal Neuromodulation and Brain-Computer Interfaces, advancements were confined specifically to Deep Brain Stimulation and Neuromodulation in Disorders of Consciousness. These clinical applications, with the notable exception of the highly developed epilepsy technologies, were not a primary focus within the flagship activities. This limitation likely stems from the Human Brain Project's (HBP) predominant orientation towards basic research (see Sec. Most Relevant Scientific Results and Impact), which prioritized fundamental neuroscience questions. Hence, the industrial engagement in the HBP was modest, with only 8 small and medium-sized enterprises (SMEs) out of 155 partners, representing 5%—a proportion consistent with other large-scale research projects historically. Despite these challenges and lack of strategic focus on innovation, the HBP has catalysed its impact in this aspect as well, with 20 companies introducing products to the market, including 12 start-ups founded on research from the project (see complete Table in the Appendix). In this context the implementation of Open Calls has been a successful strategy to increase the amount of direct private involvement but not sufficient for the efficient translation of scientific advances into broad innovation opportunities. Taking as reference the amount of neurotechnology companies grounded in the HBP partner countries (see Figure 3), we can derive a further performance indicator. The number of companies in the countries represented within HBP accounts for a total of 249, i.e. a share of 25.85% of the neurotech world companies. Thus, the growth factor in the number of European neurotechnology companies directly resulting from the start-up creation within HBP is of 4.8%. Both the existing HBP and the new ventures are at the forefront of addressing significant societal challenges through the translation of innovative solutions into the market and a direct contribution to the European industrial leadership in the neurotechnology economic sector. We comment on the most significant ones in the following paragraphs.

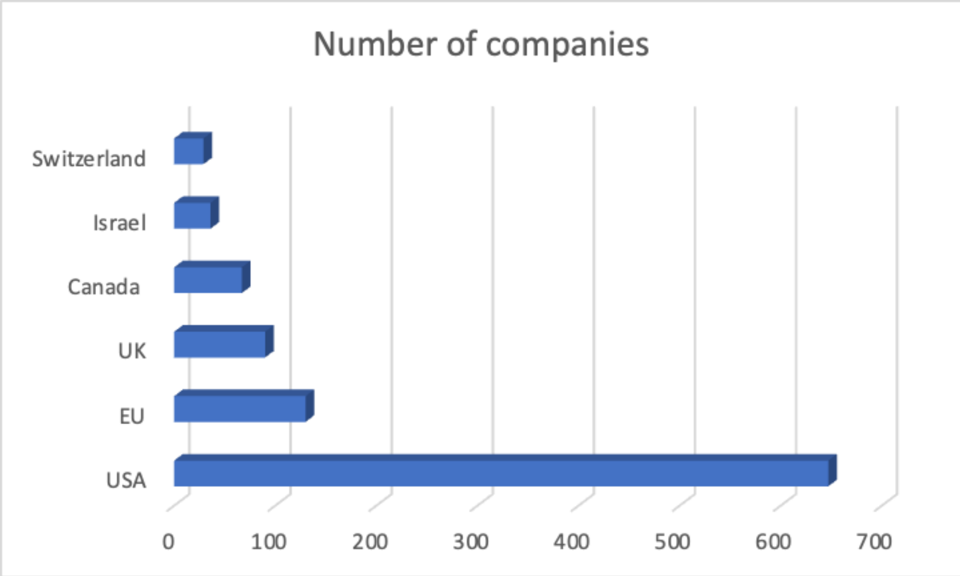

Figure 3 – Number of Neurotechnology companies in the top countries with EU aggregated data

Source: data from NeuroTech Interactive Charts https://www.neurotech.com/charts

The Virtual Brain has transitioned into a significant entrepreneurial venture with the establishment of **VB-Tech SAS** (Virtual Brain Technologies). Its mission is to establish the virtual brain as a new standard of care for neurological and neurodegenerative diseases. VB-Tech benefits from an international team that includes researchers, engineers, and clinicians who have played a pivotal role in developing The Virtual Brain (TVB) technology and are committed to its future advancement. Among its strategic partners, VB-Tech collaborates with the SATT (Société d'Accélération du Transfert de Technologies), a key investor and technology transfer entity that supports the start-up. Additionally, VB-Tech is poised to accelerate the development of its clinical functionalities and applications through partnerships with EBRAINS. The company also works closely with the APHM (Assistance Publique – Hôpitaux de Marseille), a major clinical partner that provides crucial insights and testing environments for medical applications. Further support comes from Codebox and Codemart, technology firms that have been integral to the development of the TVB technology, offering software solutions and technical expertise. This transition not only highlights the commercial potential of brain simulation research but also paves the way for transformative impacts in the treatment of brain disorders.

ONWARD Medical, a spin-off from EPFL (École Polytechnique Fédérale de Lausanne), is at the forefront of medical technology, dedicated to commercializing advanced spinal cord stimulation therapies resulting in part from HBP-supported science. ONWARD aims to transform the lives of people with spinal cord injuries by enabling movement, function, and independence through its proprietary ARC Therapy™. This targeted, programmed approach to spinal cord stimulation not only holds the potential to restore basic motor functions but also explores additional health benefits such as improved bladder control, sexual function, and blood pressure regulation. This is a market with an increasing number of market players such as Boston Scientific Corporation (US), Abbott (US), Nevro Corp. (US), Medtronic (Ireland), Stimwave LLC (US), Nuvectra (US), Beijing PINS Medical Co., Ltd (China), Cirtec Medical (US), NeuroSigma, Inc. (US), Synapse Biomedical Inc. Most competitors in this space, such as Medtronic and Boston Scientific, offer broader medical device portfolios but do not specialize exclusively in spinal cord injury solutions. These companies typically focus on a wide range of stimulation devices that treat everything from chronic pain to cardiac issues, which might dilute their focus on innovations specifically tailored to spinal cord injuries. Therefore, we can augur a very promising market uptake of technologies commercialized by ONWARD Medical.

Phosphoenix is a trailblazing MedTech start-up originating from the Netherlands Institute for Neuroscience (NIN) work supported by the HBP, with a focused mission to restore functional and life-enhancing vision to individuals who are blind due to non-functional retinas or optic nerves. Phosphoenix has developed an innovative visual prosthesis that bypasses traditional visual pathways by interfacing directly with the brain. This technology represents a significant advancement in vision restoration. At the core of Phosphoenix's technology is a sophisticated system where the user wears a pair of glasses equipped with a camera. This camera captures live video feeds that are processed in real-time by a pocket processor using advanced AI techniques. The processed data are then converted into electrical stimulation instructions that are communicated to a brain implant. This implant delivers tiny electrical pulses directly to the visual cortex, inducing the perception of phosphenes—dots of light that the brain interprets as visual information, much like viewing a constellation of stars in the night sky. By generating multiple phosphenes, Phosphoenix's device allows for the creation of interpretable images, potentially providing a pathway towards new form of vision for individuals who have lost their sight. This direct brain interface exemplifies an interesting use of neural and AI technologies to offer a tangible improvement in quality of life, marking a significant step forward in medical technology and neuroprosthetics.

One of the most active and successful fields within HBP has been that of Neuromorphic computing. Neuromorphic computing is reshaping technology by emulating the neural structure of the human brain, achieving unprecedented efficiency and computational power. Central to this innovation is neuromorphic chips, which allow for high-speed, parallel data processing while consuming less energy, making them ideal for mobile and edge computing. The neuromorphic technology is noted for its scalability and fault tolerance, vital for applications in unpredictable environments such as remote sensing and autonomous vehicles.

In this context it is remarkable the spin-off of HBP results into the company **SpiNNcloud System GmbH**. The company has already received public funding among others from the EIC Accelerator program and the German government. As neuromorphic technology advances, the company is moving from cost-free early adoption programs to models driven by private investment, promoting robust industrial engagement and ensuring commercial viability. This strategic shift is crucial as it fosters a sustainable ecosystem that not only supports the continued development of neuromorphic technologies but also integrates them into mainstream applications more effectively. The focus on leveraging private investments and already existing strategic industrial collaborations with Intel by the TU Graz, and with BMW and Infineon by SpiNNcloud Systems is essential for validating the practical utility of neuromorphic technologies. In this context it is advisable for the company to start transitioning from free-cost early adoption programs to sustainable business models.

An important innovation stemming from the Human Brain Project (HBP) is the technology for probing consciousness, which has proven instrumental in accurately diagnosing coma patients. This technology has been developed into a commercial venture by the spin-off company, **Intrinsic Powers, Inc.,** originating from the University of Milan and the University of Wisconsin. Based in the US, Intrinsic Powers, Inc. focuses on developing a device designed for clinical use to assess the presence of consciousness in patients. This advancement is backed up by a secure IP position (see patent Table above). It represents a significant leap forward in medical technology, offering neurologists new tools for precise assessments of consciousness in critical care scenarios, thus enhancing patient care and decision-making processes.

There are missing data on the commercial potential of the EBRAINS technological platform, whose exact assessment would require knowing among others the exact number of users external to the consortium. There are some figures for this estimation provided by the HBP (see Sec. EBRAINS as Integration Platform), but they might present some bias as they do not stratify one-time login users and institutions. However, even a relatively lower number of external users than the one currently provided would constitute a high rate for a relative recently created platform and demonstrate a great long-term impact potential. Its future expansion is supported by the listing of EBRAINS on the ESFRI Roadmap for Research Infrastructures, its membership in the European Open Science Cloud and the participation of EBRAINS in the European Health Data Space Pilot.

7. EU added-value

The European Union's position in the global landscape in brain research and related technologies reveals a mix of challenges and opportunities. The Human Brain Project has successfully contributed to addressing these challenges. However, the EU still lags behind the United States in several key innovation metrics, such as the overall investment in brain initiatives and the number of patents per capita. Data from the UK ICO [(29)] and the UNESCO [(30)] that analyse the neurotechnology field [(31)] help establish the annual investment in the respective International Brain projects (see Figure 4).

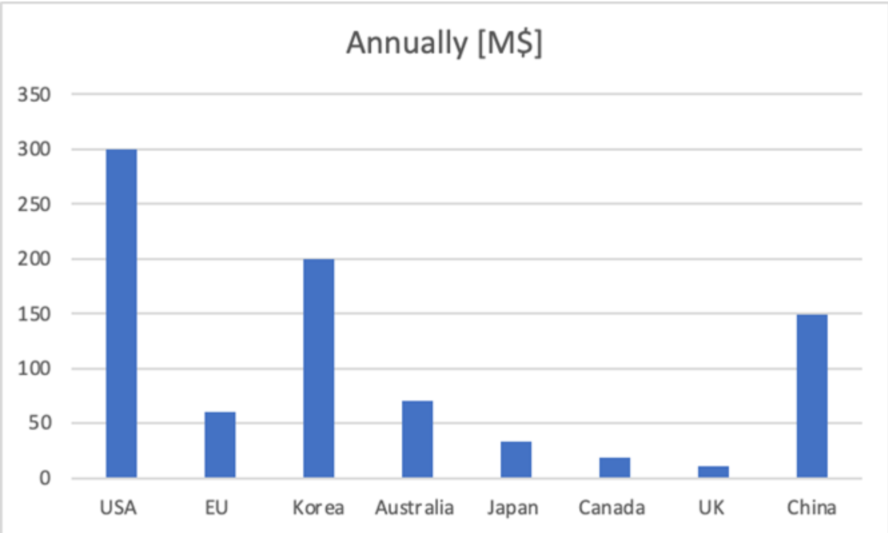

Figure 4 – Annual average public investment in the international Brain Projects in M$.
Source: Data from the UK ICO[31] and UNESCO Neurotechnology expert group[32] reports

The disparity in investment levels and patent generation indicates a more conservative but also decentralized approach in the EU towards funding cutting-edge neuroscientific research and securing intellectual property rights, especially in the neurotechnology sector. Recognizing these gaps, the EU public funding has been pivotal in strengthening the EU's efforts to close them, and the HBP Flagship, instrumental in sustaining the competitiveness of the fields of neuroscience and neurotechnology in the EU. The HBP Flagship has constituted a strategic push not only aiming to elevate the EU's standing in these high-tech sectors but also to stimulate economic growth and technological leadership in neurotechnology, a critical area of future societal relevance. The more central position of basic neuroscience within the HBP may make the innovation fruits of such an investment flourish in years to come.

As several international brain initiatives progress, it is important for the EU to maintain its competitive edge by continuing to fund digital brain technologies which are clearly needed and require intensive funding to become actual breakthroughs. These facts are especially relevant taking into account the special focus of the US Brain initiative on Neurotechnologies, which

(29) https://ico.org.uk/media/about-the-ico/research-and-reports/ico-tech-futures-neurotechnology-0-1.pdf#407d9760c6f192e4b2d0178cb1f05bf0

(30) https://unesdoc.unesco.org/ark:/48223/pf0000386137

(31) Here neurotechnology has to be understood in its broadest sense. As defined by the OECD it includes “devices and procedures that are used to access, investigate, assess, manipulate, and emulate the structure and function of neural systems” (OECD 2019) https://www.oecd.org/en/topics/sub-issues/emerging-technologies.html

targets as its immediate goal to accelerate the development and application of innovative technologies (Hain et al 2023 UNESCO report [32].

Neuroscience is a highly diverse and multidisciplinary field that is experiencing rapid progress in methodological advances, facing new challenges in handling large research data, and witnessing an increasing prominence of team science. It increasingly requires digital research software solutions that can work together, facilitate data sharing for reproducible work, and drive integrative efforts. Overcoming the challenges inherent in this goal calls for a high degree of sophistication. The HBP made several strategic decisions early on to position itself as a driving force in these developments. Among these decisions were the strengthening of communication and European networks across disciplines, the development and provision of dedicated research infrastructure, an effective outreach and communication strategy, and building a deeply connected multidisciplinary community. Crucially, the HBP utilized its 10-year duration to tackle the challenges associated with brain complexity and interdisciplinarity in ways that would reshape the field while maintaining the multidisciplinary character of the Flagship.

The Co-design approach developed by the HBP served as a central element in achieving its ambitious goals. The strong emphasis on integrating a highly interdisciplinary approach, embraced by a large number of groups, made the HBP unique in the international neuroscience landscape. Notably, the intense focus on digital neuroscience was a hallmark of HBP. Particularly, through EBRAINS, HBP established a sustainable Research Infrastructure that offered solutions to key problems in the field. Another distinctive strategy of the HBP was its investment in creating lasting impact through infrastructure and data curation, forming a closed-loop interaction with simulation and AI/ML-driven methods. This strategic direction mirrored breakthroughs seen in fields like particle physics with facilities such as CERN and fusion experiments like ITER. While the core principle of requiring large-scale developments and significant time and investment for breakthroughs remained consistent, the challenges addressed by the HBP were fundamentally distinct due to the vast complexity of the human brain and the extensive heterogeneity in the associated research fields.

Achieving an understanding of the human brain and its cognitive processes necessitated not only the construction of infrastructure but also a continuous re-evaluation of goals, and fostering connections between fields to identify potential pathways. This demanded agile and adaptive project management and research goal orientation. In this context, the HBP was a pioneer in large-scale agile research and in developing a connected management structure that swiftly and effectively balanced top-down management for steering and agile processes at the research group level. This dynamic approach enabled rapid adaptation and the exploration of innovative new pathways. A key takeaway was the recognition of the importance of constant adaptation in the management structure, openness to external research through programs like open calls and vouchers, and significant flexibility in adjusting the research agenda and redefining goals. While still perceived externally by some as lacking focus, consistency, and structure, this flexibility truly enabled the project to respond promptly to demands and the rapid pace of innovation inherent in fields like neuroscience, AI, ML, and related areas.

Most significantly, HBP nurtured a new generation of researchers capable of bridging interconnected fields, laying the groundwork for a long-lasting impact that harnesses the full potential in digital neuroscience. In its final project phases, the HBP exhibited high efficiency, showcasing a pioneering research approach suitable for fields sharing rapid innovation and extreme interdisciplinarity. The project yielded numerous outcomes such as demonstrators and impactful publications, generating insights with exceptional visibility and influence.

[32] https://unesdoc.unesco.org/ark:/48223/pf0000386137

Furthermore, the HBP promoted digital neuroscience across multiple European countries, transforming it into a fully European project with hubs in various states that had long been deeply involved. The project also led to a plethora of successful and impactful research initiatives across Europe.

8. Conclusions

Understanding the human brain, in all its structural and functional complexity, was a formidable challenge for humankind in 2013, at the start of the HBP, and it remains so today. The approaches that can be taken to study the brain are varied, but to successfully unravel its mysteries and elucidate the mechanisms and principles used to support cognition, action and thought necessarily involves coordination and collaboration between multiple disciplines from neuroscience to engineering. Without such an approach, although important knowledge would still be gained, the depths of discovery and a holistic understanding of the brain at multiple scales and operations would continue to remain elusive. Such an undertaking required a new paradigm of digital neuroscience and a new interdisciplinary culture of collaboration.

The HBP took on this challenge, from its inception, and undertook a major endeavour to study the biology of the brain and model its functions by utilizing and developing brain-inspired technologies. Consequently, the HBP has made a significant contribution to our understanding of the fundamental structures and mechanisms of the brain over the past 10 years. Moreover, the project has led to a new level of mutual understanding, inspiration, and tool-sharing that was previously unimplemented across and within fields.

The main legacy of the HBP is its influence on generating a new phase of neuroscience, enriched by the multimodal and multiscale approaches to the study of the brain. Moreover, the HBP will continue to influence neuroscience within Europe largely due to the contributions it has made to fundamental knowledge (e.g. over 3000 publications including 2250 journal articles and 124 theses) but also in the RI of EBRAINS.

EBRAINS is a crucial component of the digital neuroscience field, enabling the transition into a new era, supported by approximately 160 integrated tools, many datasets, next-generation brain atlasing, simulation platforms and AI-based analysis of big data. This RI is on the ESFRI roadmap to become a strategic RI for Europe, and through national nodes will enlarge the network to ensure its long-term success. The European Commission has granted €38 million for the further development of services within the EBRAINS research infrastructure until 2026. EBRAINS RI, together with the vision for Digital Brain research (articulated in Amunts et al. 2024, a joint position paper of over 100 researchers from within and outside the HBP), play a key role in the strategic research agenda for the future European Partnership for Brain Health and scientific vision. Consequently, EBRAINS will continue to develop tools and services to serve the wider research communities in neurosciences, brain medicine, and brain-inspired technologies.

Importantly the FET flagship model, because of its scale, facilitated collaboration and synergies across a large number of fields, resulting in advancements in Neuroscience, Cognitive Science, Neuromorphic Computing, Medical Neuroscience, Simulation Neuroscience, Robotics, and Research Infrastructure. This would not have been possible in smaller-scale projects which tend to be driven by one or two main disciplines. Furthermore, the flagship instrument itself offered sufficient agility to quickly address the challenges that the HBP faced, both internally and externally, at the initial stages. As a result, the HBP flagship rapidly redefined its objectives and introduced a major shift in both governance as well as scientific direction. Again, the flagship instrument offered sufficient scale to allow for a flexible restructuring from within the consortium which led, ultimately, to a new multidisciplinary community in Europe, converging under the paradigm of "digital neuroscience".

9. Appendix

9.1. Evaluation methodology

Scope

Ten years after its start in October 2013, the EC invited a Panel of high-level independent experts, to undertake an evaluation of the Human Brain Project Flagship. The scope of this evaluation is i) primarily the Human Brain Project Flagship achievements, and ii) its implementation and governance model. The evaluation covered the operational period from October 2013 to its end in October 2023. More specifically the evaluation assessed the success of the HBP against the specific objectives of the HBP and the general objectives of the FET Flagship instrument.

Evaluation panel methodology

A panel of 5 external and independent experts was appointed by the Commission's Director-General for Communications Networks, Content & Technology to carry out the 10- year evaluation of the GF. The panel worked by consensus.
These experts have the relevant expertise and experience from various academic institutions and from the private sector. They also participated in the periodic HBP monitoring and evaluations, either in part or in total, during the 10 years of the lifetime of the project.
The panel was assisted by officials of the EC.
The methodology, based on Panel's expertise and judgements, was informed by a range of evidence and data including:

- Final consolidated report of the HBP achievements, including HBP brochures;
- Relevant policy documents;
- Reports on research activities, including periodic activity reports of the HBP;
- Periodic review reports by the relevant Commission services and the HBP;
- Interviews with relevant stakeholders within the HBP consortium (e.g. Katrin Amunts, Jan Bjaalie, Steve Furber);
- The ex-post H2020 evaluation report sections dedicated to the HBP.

9.2. Neurotechnology Key Innovation Areas

The report herein has utilized the Key Innovation Areas as reported by the UNESCO in its 2023 report. The Neurotechnology Key Innovation Areas resulted from a clustering approach of the keywords appearing in the Neurotechnology patents: The result of the clustering approach is depicted in the following Figure.

Figure 5 – Neurotechnology key topics as identified in the UNESCO Neurotechnology expert group report [(33)] in Figure 16

Source: authors' own compilation on data from European Patent Office's Worldwide Patent Statistical Database (PATSTAT) (2000-2020)

(33) https://unesdoc.unesco.org/ark:/48223/pf0000386137

9.3. Table of Patents linked to HBP

HBP result	IPR owner	Application title	Patent No.
Neural data visualisation	URJC	Method, apparatus and computer program product for rendering a 2D non-photorealistic image for visualization of neural data	ES201530522 (07.10.2016)
Light-sheet microscopy	CNR -U. FIRENZE	System and method for measuring the focus state of an optical instrument	US 11237375 (01.02.2022)
TVB Epilepsy	AMU-CNRS- AP-HM-INSERM	A method of modulating epileptogenicity in a patient's brain	US 11191476 (22.08.2019)
TVB Epilepsy	AMU-CNRS- AP-HM-INSERM	A method of modulating epileptogenicity in a patient's brain	JP 7132555 (30.08.2022)
TVB Epilepsy	AMU-CNRS- AP-HM-INSERM	A method of modulating epileptogenicity in a patient's brain	EP3484355
TVB-Personalised in-silico approach	AMU-CNRS- AP-HM-INSERM	Method for identifying a surgically operable target zone in an epileptic patient's brain	EP3977483A1
Qbeast	75% BSC, 25% UPC (Technical University of Catalonia)	Distributed Indexes	US 11474988 (23.12.2021)
Qbeast	75% BSC, 25% UPC (Technical University of Catalonia)	Distributed Indexes	EP 3861464 (20.07.2023)
Spinal cord rehabilitation	EPFL	A SENSORY INFORMATION COMPLIANT SPINAL CORD STIMULATION SYSTEM FOR THE REHABILITATION OF MOTOR FUNCTIONS	EP3558448B1
Individual Brain Charting	CEA, INRIA	Computer-implemented method of building a database of pulse sequences for magnetic resonance imaging, and a method of performing magnetic resonance imaging using such a database	US 10976395 (13.04.2023)
Perturbational complexity index for detecting consciousness	UMIL, WISC	METHOD AND APPARATUS FOR ASSESSING ELECTROCORTICAL	US 8457731
SpiNNaker2	COGNISCIENCE LIMITED (UMAN spin-off)	On Chip Router	EP4144049

9.4. Table of Companies involved in the HBP

Nature	Company	Tool	Country	Institution
Start-up	VB-Tech	Virtual Epileptic Patient (VEP)	FR	Aix-Marseille Université
Start-up	Indoc Research Europe	Health Data Cloud (HDC)	DE	Charité University Medicine Berlin
Start-up	SpiNNcloud Systems	SpiNNaker 2	DE	Technische Universität Dresden, University of Manchester
Start-up	Nanomatch	Unicore (key user only)	DE	Forschungszentrum Jülich
Start-up	Clepio Biotech	Ligh Sheet Microscopy	IT	University of Florence
Start-up	Qbeast	Qbeast Universal Storage Engine (key user only)	ES	Barcelona Supercomputing Center
Start-up	Onward Medical	Spinal neuro-prostheses to overcome paralysis	CH	École polytechnique fédérale de Lausanne
Start-up	Phosphoenix	Neuroprosthesis for the blind	NL	Netherlands Institute for Neuroscience
Start-up	Bettering our Worlds	Animus	UK	University of Sheffield
Start-up	Bitbrain	Bitbrain & SBC memory (Sparse Binary Coincidence) on SpiNNaker	UK	University of Manchester
Start-up	Orbit	Embrace (responsible Research & Innovation)	UK	De Montfort University
Start-up	Intrinsic Powers	Perturbational Complexity Index (PCI)	USA	University of Milan, U. Wisconsin
SME	Inglobe Technologies	GROW - General-purpose Robot for Object retrieval in Warehouses	IT	Inglobe Technologies
SME	AI2Life	GROW - General-purpose Robot for Object retrieval in Warehouses	IT	AI2Life
SME	ROBOTNIK AUTOMATION SLL	PROMEN-AID - Proactive Memory iN AI for Development	ES	ROBOTNIK AUTOMATION SLL
SME	Biomax Informatics AG	NEURO-CONNECT - Knowledge management solution for multimodal brain atlas and connectome integration	DE	Biomax Informatics AG
SME	Alpine Intuition	CESPAR - Closed-loop exoskeleton simulation for personalized assistive rehabilitation within HBP NRP	CH	Alpine Intuition
SME	Autonomyo	CESPAR - Closed-loop exoskeleton simulation for personalized assistive rehabilitation within HBP NRP	CH	Autonomyo
SME	Bit&Brain Technologies SL	Neuro-robin - Closed loop upper limb neurorobot simulator	ES	Bit&Brain Technologies SL
SME	GEM Imaging SA – ONCOVISION	LB2020 - LIVING BRAIN	ES	GEM Imaging SA – ONCOVISION

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