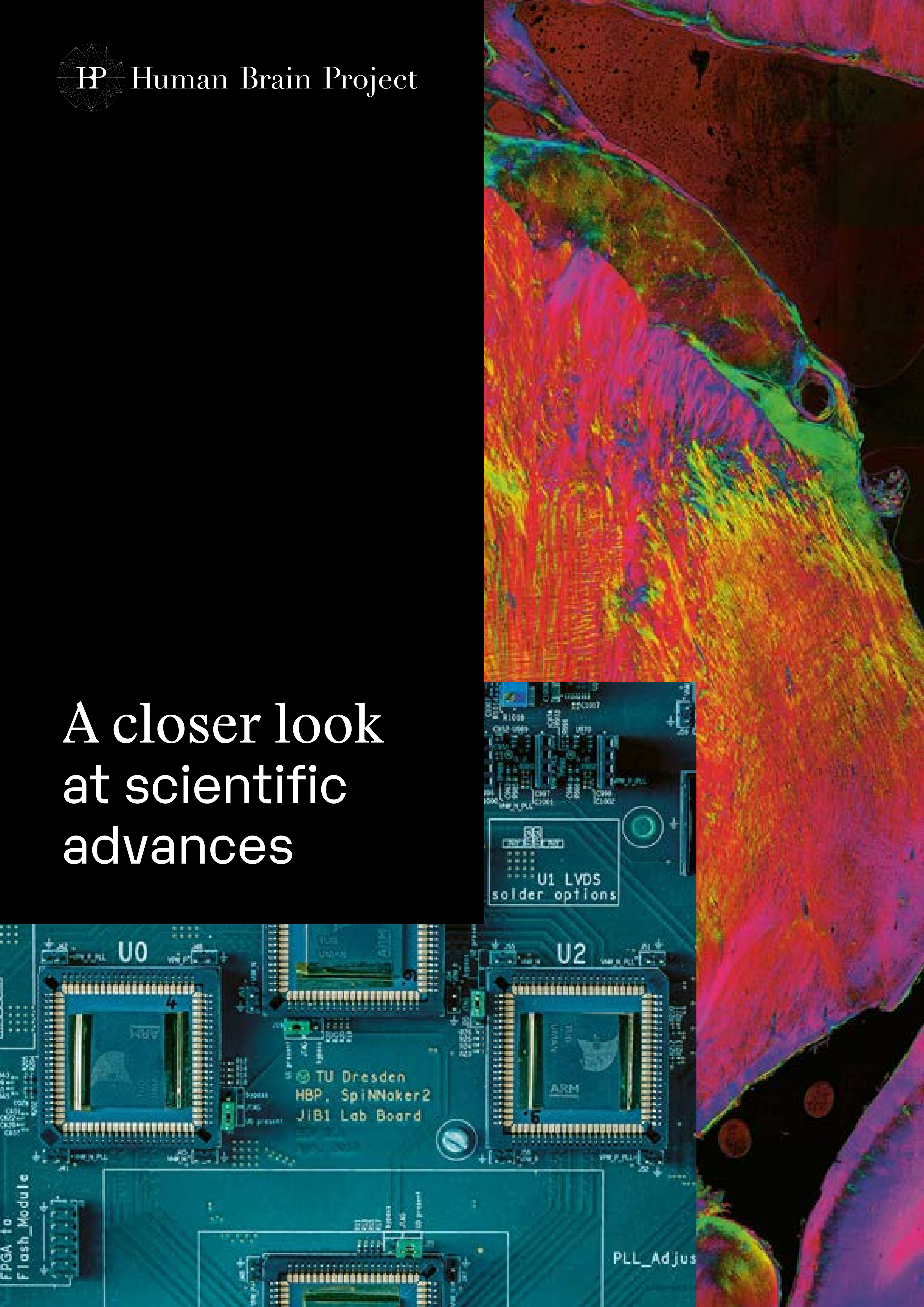
Human Brain Project

A closer look at scientific advances



Human Brain Project

A closer look at scientific advances

Cover Picture 1:
Detail of a human brain section showing the architecture of fibres down to single axons in cortical and subcortical structures, revealed by 3D polarised light imaging. Colours represent 3D fibre orientations highlighting pathways of individual fibres and tracts.

Cover Picture 2:
Closeup of a SpiNNaker2 neuromorphic computing system circuitboard. Neuromorphic computing mimics aspects of information processing in the brain.

Left:
Cytoarchitecture of the human visual cortex and cerebellum.

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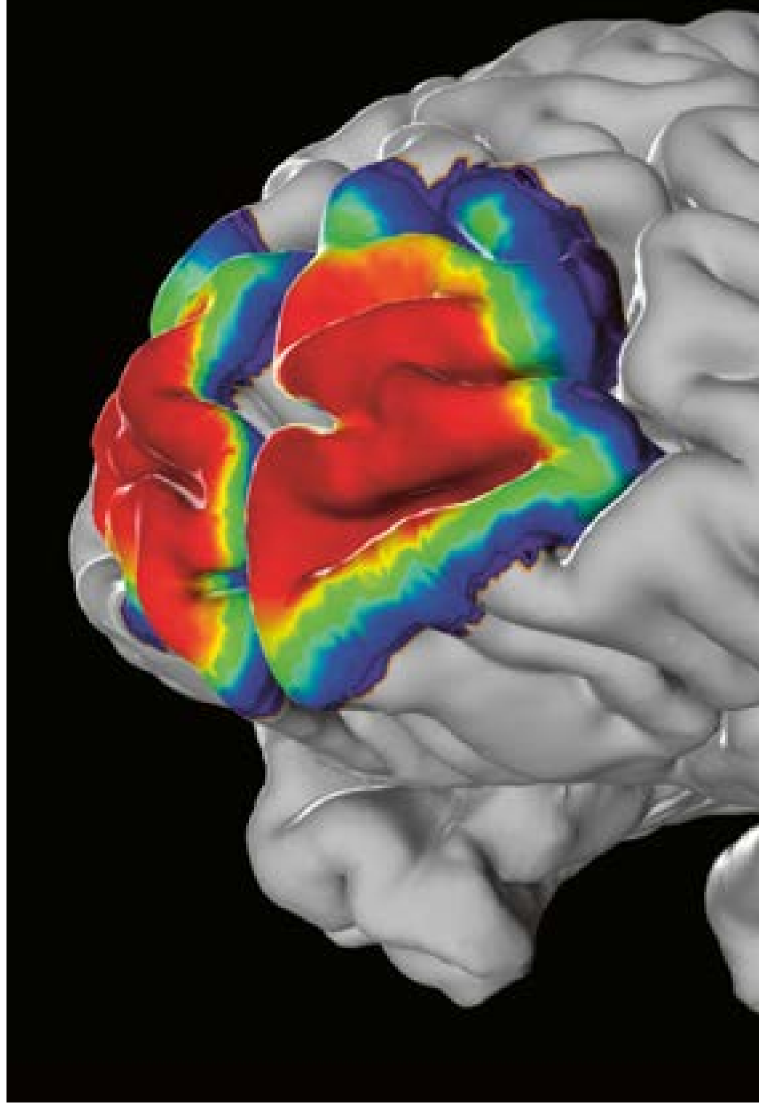
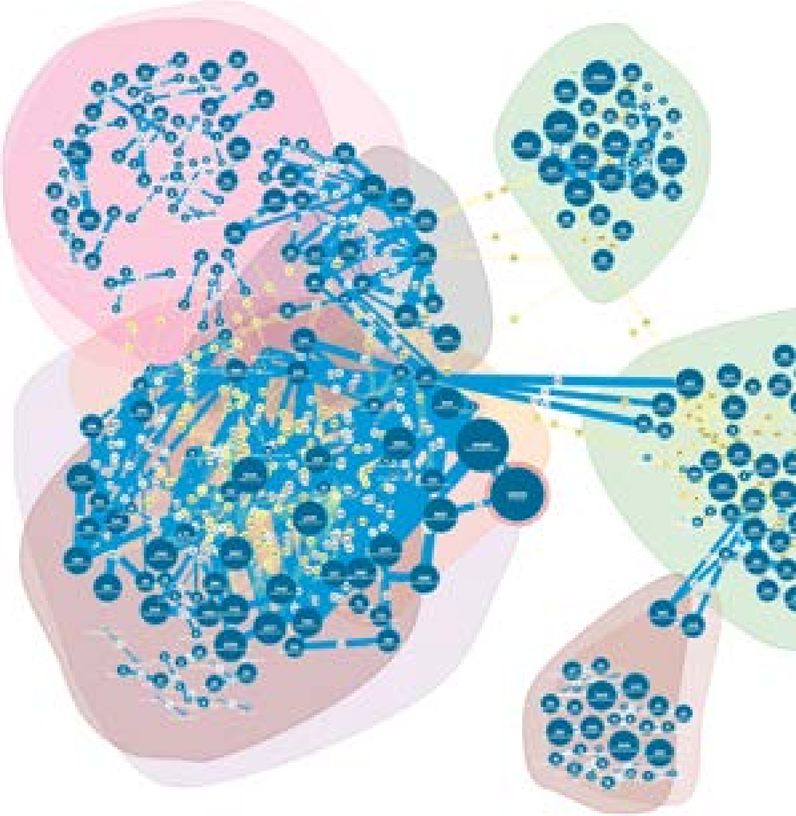


14 The HBP has developed an atlas of the human brain with unprecedented detail.



68 “Those who are preparing for the future will build data sharing into the research process.” Jan Bjaalie

Human Brain Project

500+

Researchers

607 M

Euro*

10

Years**

2,500+

Publications

19

Countries

150+

Institutions

1

Infrastructure for
brain research

EBRAINS

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* including partner contributions
** 2013–23

Brain research at the interface of computing and technology

> “The Human Brain Project, one of three European Flagship projects, is now in its final phase. It has been an inspiring journey that brought us here!”

Since its inception in 2013 as a European Future and Emerging Technologies (FET) Flagship, the Human Brain Project (HBP) has pioneered a new paradigm for brain research at the interface of computing and technology.

In order to better understand how function, but also dysfunction and brain disease, emerge from an organ as complex as the human brain, we have worked together in a systematic and highly collaborative way. The project has developed new digital research technologies for the community, ultimately, resulting in the ESFRI-listed research infrastructure EBRAINS. Every development in EBRAINS has been driven by the questions and needs of the research community.

Today, we see that this approach has been highly successful. The powerful digital toolset for brain research developed within the HBP, together with curated data, models and atlases as well as fruitful collaborations have led to excellent results. Research teams across Europe enabled by these new tools have gained deep new insights into the brain, established novel approaches for the diagnosis and therapy of brain diseases and developed technological innovations inspired by the brain.

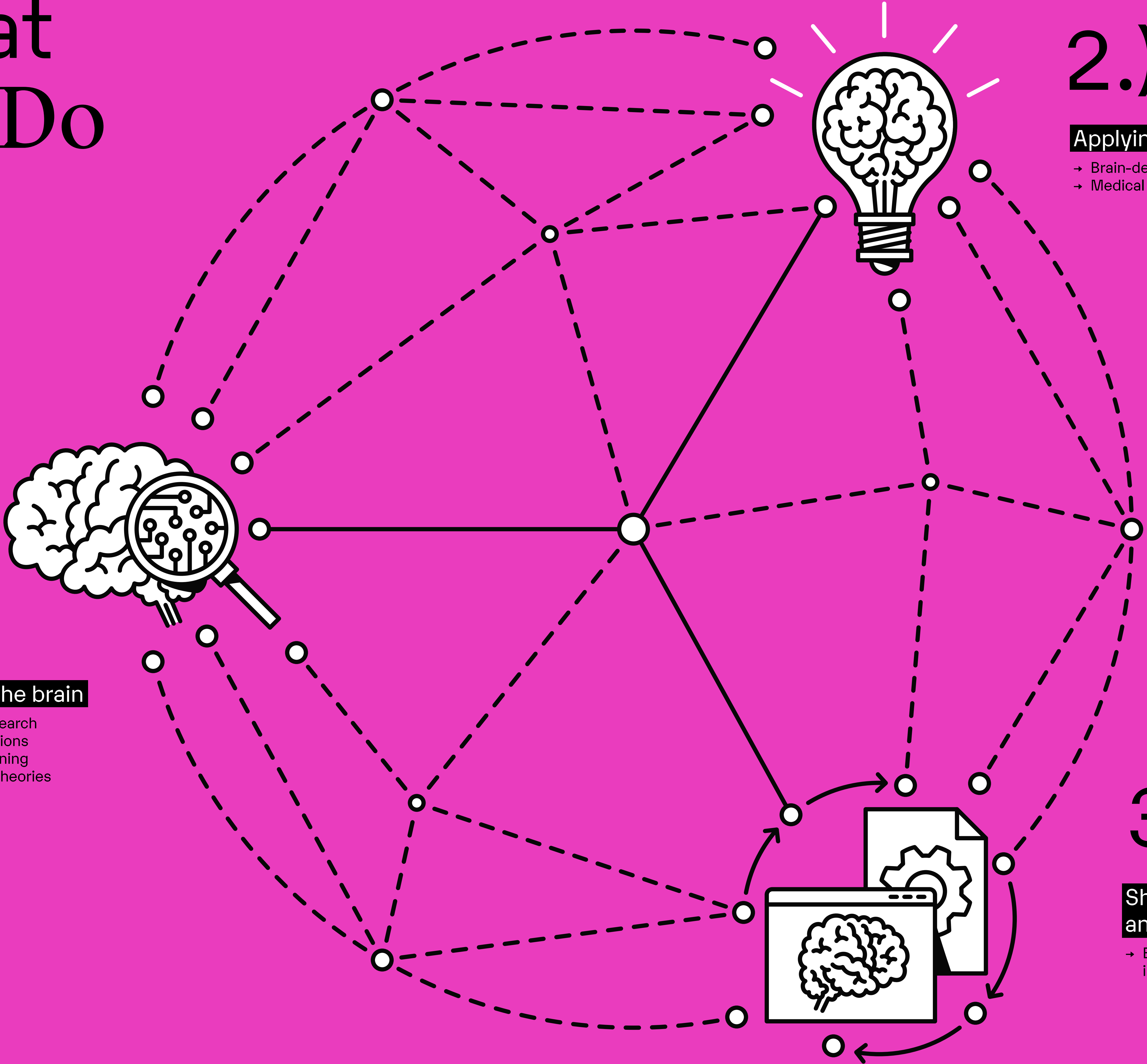
Over the course of our project, computing and digitalisation have permanently changed the way brain research is carried out – a transformation that has been breathtaking in its pace, scale and impact. Supercomputers, big data analytics, simulation, robots and AI have all become new additions to the “toolbox” of modern neuroscience. In turn, learning from the brain is also changing these technologies – from neuro-inspired AI and computing to cognitive robotics. The HBP has been a driver of these developments in both directions.

In our final phase, we are focusing our research on three main topics: neural networks that we study across different spatial and temporal scales, their significance for consciousness and its disorders and the development of artificial neural networks and neurorobotics. We are strongly supporting open science and continue to build tools, connect workflows and advance EBRAINS technologies that enable sophisticated multi-scale investigations into the brain’s complexity.

In this booklet, we provide both an overview and a deeper look into some of our newest results – most of them from 2022. I hope you enjoy reading these pages.

Katrin Amunts
Scientific Director of the
Human Brain Project

What We Do



1.)

Studying the brain

- → Empirical research
- → Brain simulations
- → Machine learning
- → Models and theories

2.)

Applying the knowledge

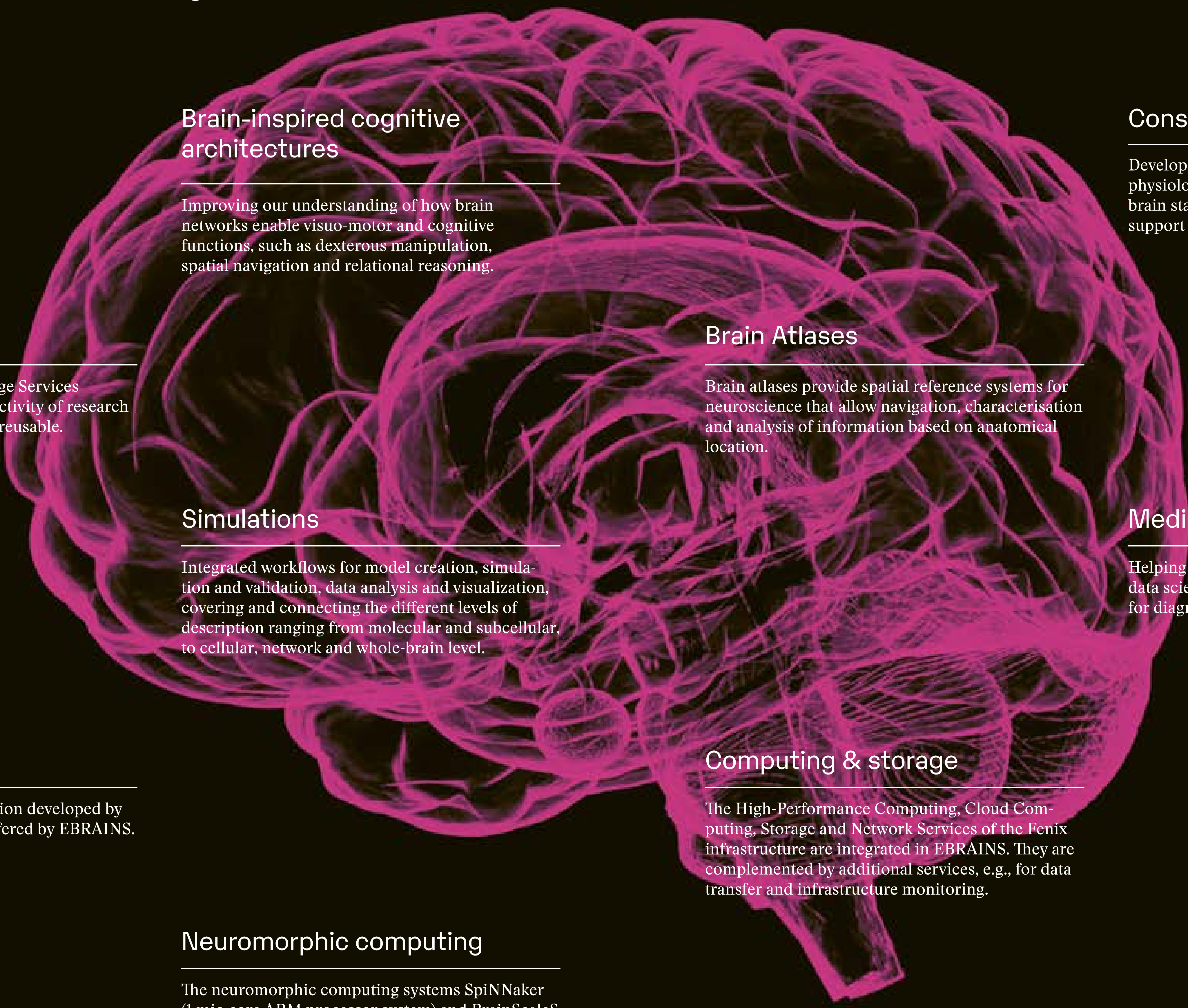
- → Brain-derived technologies
- → Medical applications

3.)

Sharing data, tools and resources

- → Building the open, digital infrastructure EBRAINS

Focus areas of the Human Brain Project



Data & knowledge

The EBRAINS Data and Knowledge Services increase the efficiency and productivity of research by making data discoverable and reusable.

Neurorobotics

The service for embodied simulation developed by the Human Brain Project, now offered by EBRAINS.

Brain-inspired cognitive architectures

Improving our understanding of how brain networks enable visuo-motor and cognitive functions, such as dexterous manipulation, spatial navigation and relational reasoning.

Simulations

Integrated workflows for model creation, simulation and validation, data analysis and visualization, covering and connecting the different levels of description ranging from molecular and subcellular, to cellular, network and whole-brain level.

Neuromorphic computing

The neuromorphic computing systems SpiNNaker (1 mio core ARM processor system) and BrainScaleS (physical analog neuromorphic system) are available through EBRAINS.

Connectivity & dysconnectivity

Developing personalised network models and relevant clinical applications to better understand brain behaviour.

Brain Atlases

Brain atlases provide spatial reference systems for neuroscience that allow navigation, characterisation and analysis of information based on anatomical location.

Computing & storage

The High-Performance Computing, Cloud Computing, Storage and Network Services of the Fenix infrastructure are integrated in EBRAINS. They are complemented by additional services, e.g., for data transfer and infrastructure monitoring.

Consciousness & cognition

Developing a multi-scale understanding of physiological, drug-induced and pathological brain states and determining how they can support consciousness and cognition.

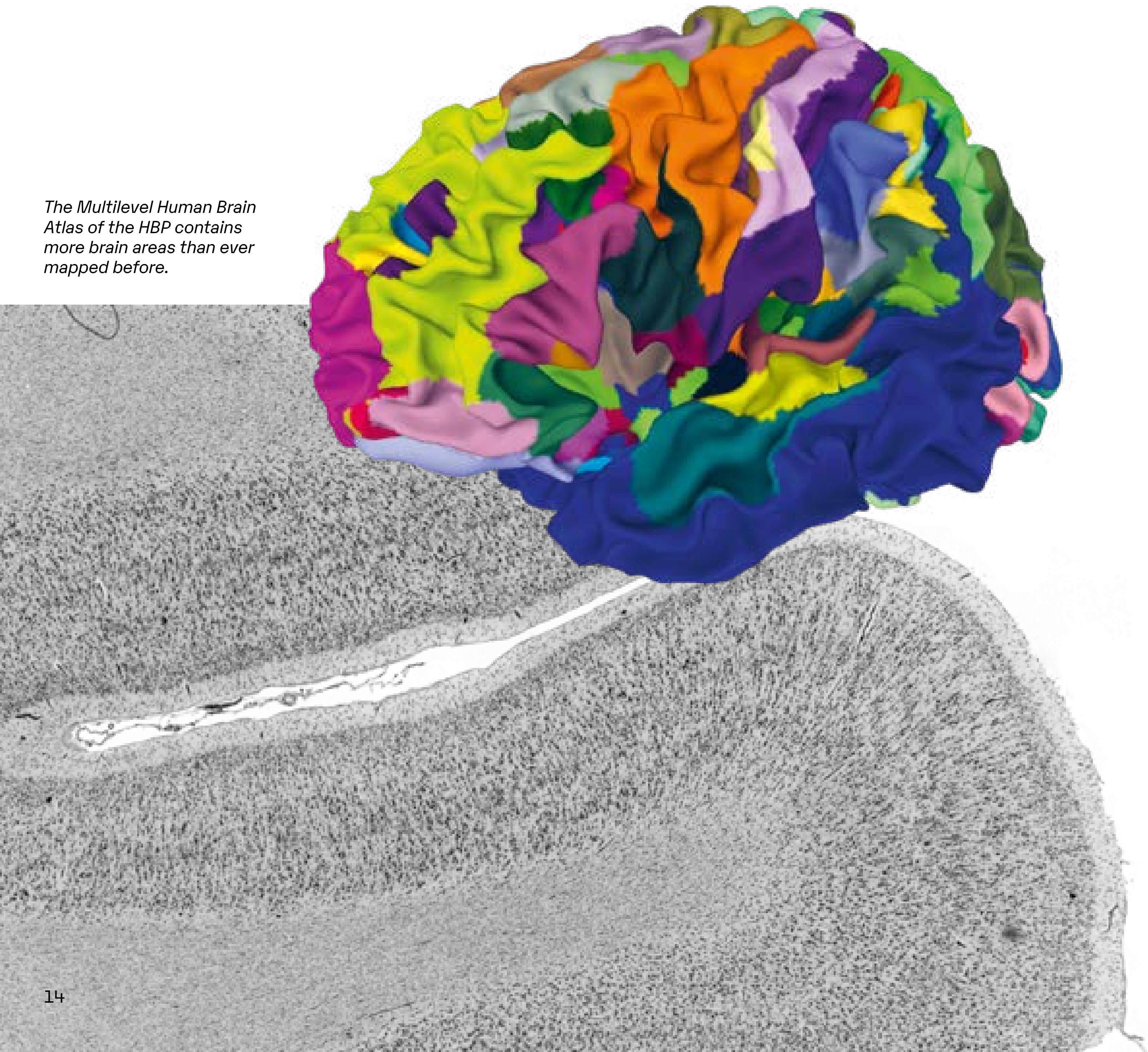
Medical data analysis

Helping clinicians, clinical scientists and clinical data scientists who aim to adopt advanced analytics for diagnosis and research in clinics.

Brain section being imaged with polarised light to visualise fibre tracts.

FEATURE

Mapping at multiple scales – the most detailed atlas of the human brain



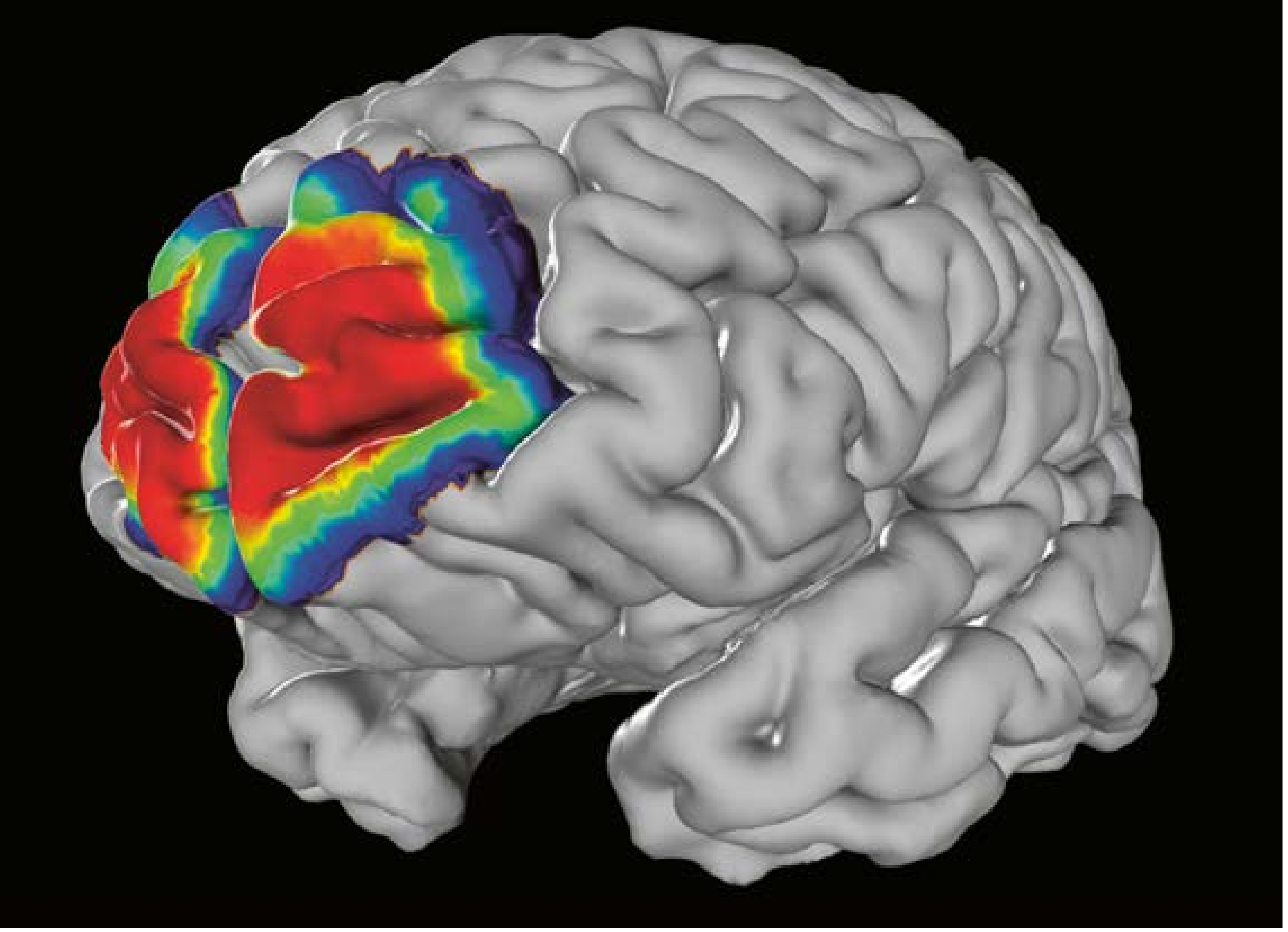
The Multilevel Human Brain Atlas of the HBP contains more brain areas than ever mapped before.

Brain sections of 20-μm thickness were stained for cell bodies before digital imaging.

> The Human Brain Project has developed an atlas of the human brain with unprecedented detail and has made it freely available for everyone to browse online on the EBRAINS platform.

The human brain atlas can be compared to Google maps – for the brain instead of planet Earth. Just like Google maps, anyone can access the brain atlas using a simple web browser. Whereas an atlas of the world includes political, topographical or traffic information, the atlas of the human brain displays microstructure, connectivity and function. Zooming into the brain atlas, you can see cells instead of cities, and zooming out, you can see the borders of brain areas instead of countries.

When clicking on the name of a country in Google maps, or on an area in the brain atlas, a sidebar with additional information about the region pops up, and you can go beyond just looking at the maps and information. The brain atlas allows you to extract the underlying data to run an analysis or to put them into a simulation.



Probabilistic map of the frontal pole area Fp1 in the Multilevel Human Brain Atlas.

Like its counterpart, the brain atlas is dynamic, allowing continuous addition of new information. Via the Human Brain Project's EBRAINS infrastructure, research groups from all over the world can integrate their own data into the living atlas, enabling the scientific community to work collaboratively on decoding the human brain.

Drawing borders

Brain mapping has a hundred-year tradition; yet, the concept of the HBP's atlas is fundamentally new. Not just because of its digital and three-dimensional nature, but because it accounts for inter-subject variation. This is a crucial difference when comparing mapping the brain to mapping the world: while there is only one planet Earth, there are about eight billion human brains on it – and they are all slightly different. The question is: how different? And what do these differences mean for function?

HBP researchers from Forschungszentrum Jülich and the Heinrich-Heine University Düsseldorf in Germany have stained the cell bodies of thousands of ultra-thin brain sections produced from 23 post mortem brains, digitised them and analysed their cytoarchitecture – the distribution, density and morphology of cells (Amunts et al. 2020). This microstructure of the brain reveals its parcellation into clearly distinguishable areas.

The team digitally reconstructed the mapped areas in a three-dimensional space and superimposed the maps of ten different brains for each area to generate probabilistic maps that show exactly how much the localization and size of an area varies from one individual to another.

The Julich Brain Atlas, which forms the centrepiece of the HBP's Multilevel Human Brain Atlas, already contains more than 200 such probabilistic maps – including dozens of previously unmapped areas – and new ones are continuously added. Some of the most recent examples include maps of the insula, a large region that supports the integration of many functions including interoceptive, sensorimotor, cognitive and social-emotional processing (Quabs et al. 2022) and new areas of the anterior prefrontal cortex, a region that plays a major role in cognitive functions (Bruno et al. 2022).

Combining modalities

To understand a system as complex as the human brain, researchers need to combine insights from different levels of organisation. The HBP's atlas enables just that – by supporting the integration of data from different scales and modalities into one common reference space. Modalities already integrated into the atlas include functional data generated by cognitive scientists from the French National Institute for Research in Digital Science and Technology (Inria) (Dadi et al. 2020) and density measurements of neurotransmitter receptors produced by researchers from Forschungszentrum Jülich (Palomero, Kedo et al., 2020).

Combining different modalities demonstrates that brain areas are more than just a system of structural parcellation: they have a physiological meaning as functional units of the brain that are distinct from one another on several levels. This is exemplified by a recent study showing how microstructural differences of brain areas correlate with distinct functions in visual-spatial orientation and associative memory (Stenger et al. 2022).

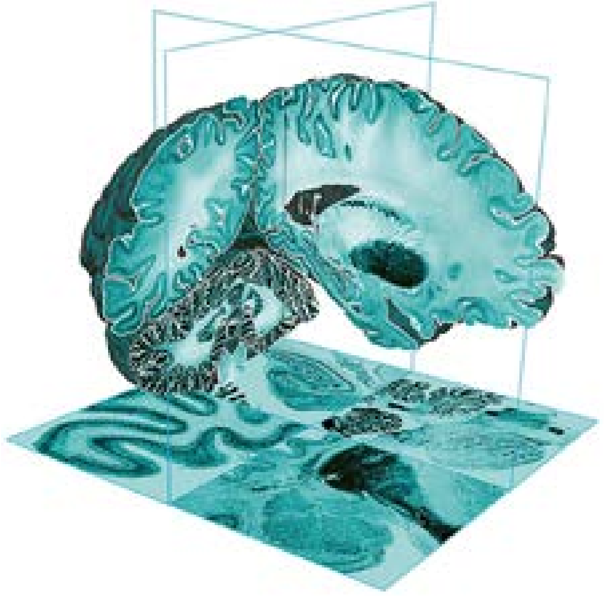
HBP researchers have also recently combined the analyses of the cytoarchitecture, the distribution of neurotransmitter receptors and the transcription of neurotransmitter receptor genes to uncover basic principles about the organisation of functional units of the brain (Zachlod et al. 2022). Each cytoarchitectonic area has a distinct pattern of receptor architecture and gene expression; however, a simple "mosaic" of brain areas does not explain how specific areas work together in an organised fashion, each playing a distinct role, resulting in cognitive functions. The researchers studied 15 cytoarchitectonic areas within the visual, auditory, somatosensory and motor systems and found that receptor distributions and gene expression change gradually along structural hierarchies within each functional system. In other words, they revealed that the changes occur in a systematic way in parallel with an increasing complexity of information processing.

Tracing connections

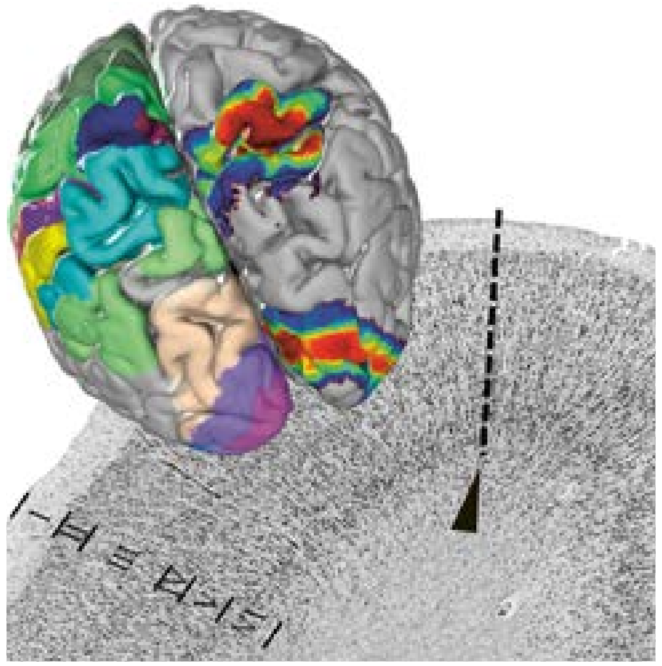
But how do distant parts of the brain work in concert to give rise to complex human perception and behaviour? To understand this, there is no getting around examining how individual cells and entire brain regions are connected with each other. To this end, the atlas includes connectivity data generated by HBP researchers from NeuroSpin in France in collaboration with a team at the University of Concepción in Chile (Guevara et al. 2017). The researchers have modelled fibre tracts at millimetre resolution based on diffusion MRI data from 78 healthy individuals. To study nerve fibres in post-mortem brains at very high resolution, researchers at Forschungszentrum Jülich have developed a technique called three-dimensional polarised light imaging (3D-PLI).

In order to bridge connectivity data from several spatial scales, HBP researchers from NeuroSpin, Jülich and the University of Florence have recently imaged one and the same tissue block from the human hippocampus using several different methods: anatomical and diffusion magnetic resonance imaging (aMRI and dMRI) 3D-PLI and two-photon fluorescence microscopy, respectively (Axer & Amunts 2022).

By integrating the resulting data from the different



The BigBrain is a 3D reconstruction of an individual human brain stained for cell bodies at ultra-high, near-cellular, resolution, released in June 2013 by a team of researchers from the Montreal Neurological Institute and Forschungszentrum Jülich.



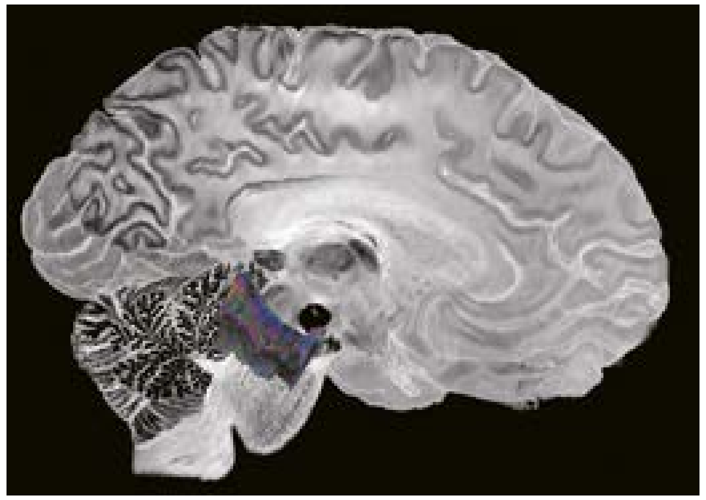
The Julich Brain Atlas includes probabilistic area maps as well as maximum probability maps and shows cytoarchitecture at high resolution.

spatial scales into one common reference space within the atlas, the teams have provided crucial insights into the microstructural characteristics of complex fibre bundles.

Advancing brain medicine

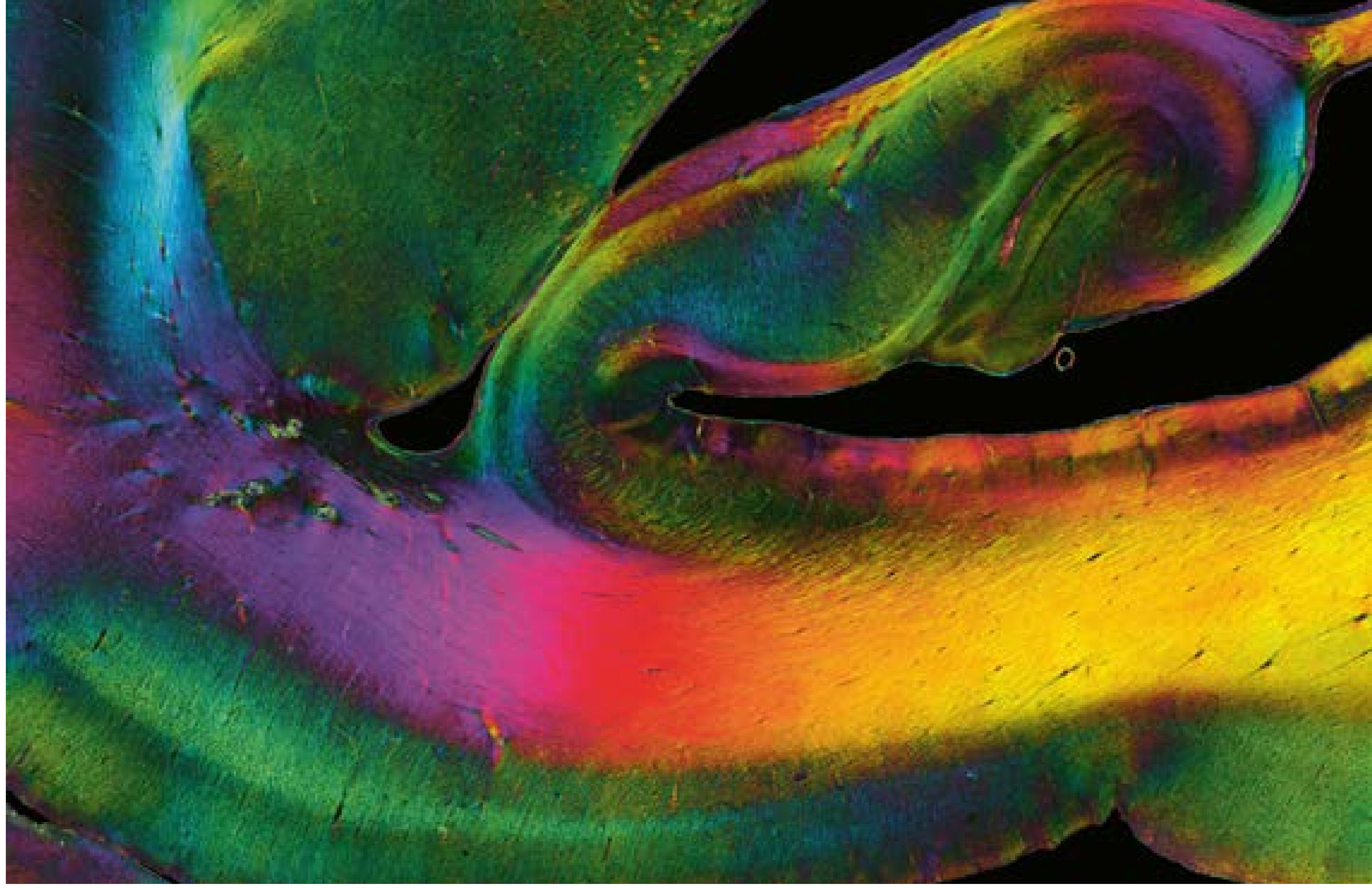
The HBP's atlas not only empowers researchers to study the healthy brain but has also become an important tool for better understanding brain disorders. Recently, researchers from Jülich, Düsseldorf and the Ernst von Bergmann Klinikum in Potsdam, Germany, have used the atlas to show in detail that in Parkinson's disease the volumes of certain brain regions decrease over time in a specific pattern that is associated with clinical symptoms and largely coincides with the pattern described in Braak's famous staging theory (Pieperhoff et al. 2022).

The atlas also contributes to directly improving medical treatments. For example, clinical researchers from Aix-Marseille University in France, are using the high-precision data of the atlas to optimise surgery of patients with epilepsy who don't respond to pharmacological intervention. The researchers have developed personalised brain models to identify the areas where seizures emerge in a patient's brain. A 400-patient clinical trial is currently ongoing with the aim of providing surgeons with a precise tool to help individual surgery decisions and improve outcomes (Wang et al. 2023). The HBP's Multilevel Human Brain Atlas serves to enhance the accuracy of the method.



The connectivity information of the hippocampus is integrated into the atlas.

Preparation of a human donor brain at -50 °C prior to polarised light imaging.



Fibre architecture within the human hippocampus. Colours represent 3D fibre orientations highlighting pathways of individual fibres and tracts.

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→ Guevara M, Román C, Houenou J, Duclap D, Poupon C, Mangin JF, Guevara P (2017). Reproducibility of superficial white matter tracts using diffusion-weighted imaging tractography. *NeuroImage* 147:703-725. doi: 10.1016/j.neuroimage.2016.11.066

→ Palomero-Gallagher N, Kedo O, Mohlberg H, Zilles K, Amunts K (2020). Multimodal mapping and analysis of the cyto- and receptorarchitecture of the human hippocampus. *Brain Struct. Funct.* 225(3):881-907. doi: 10.1007/s00429-019-02022-4

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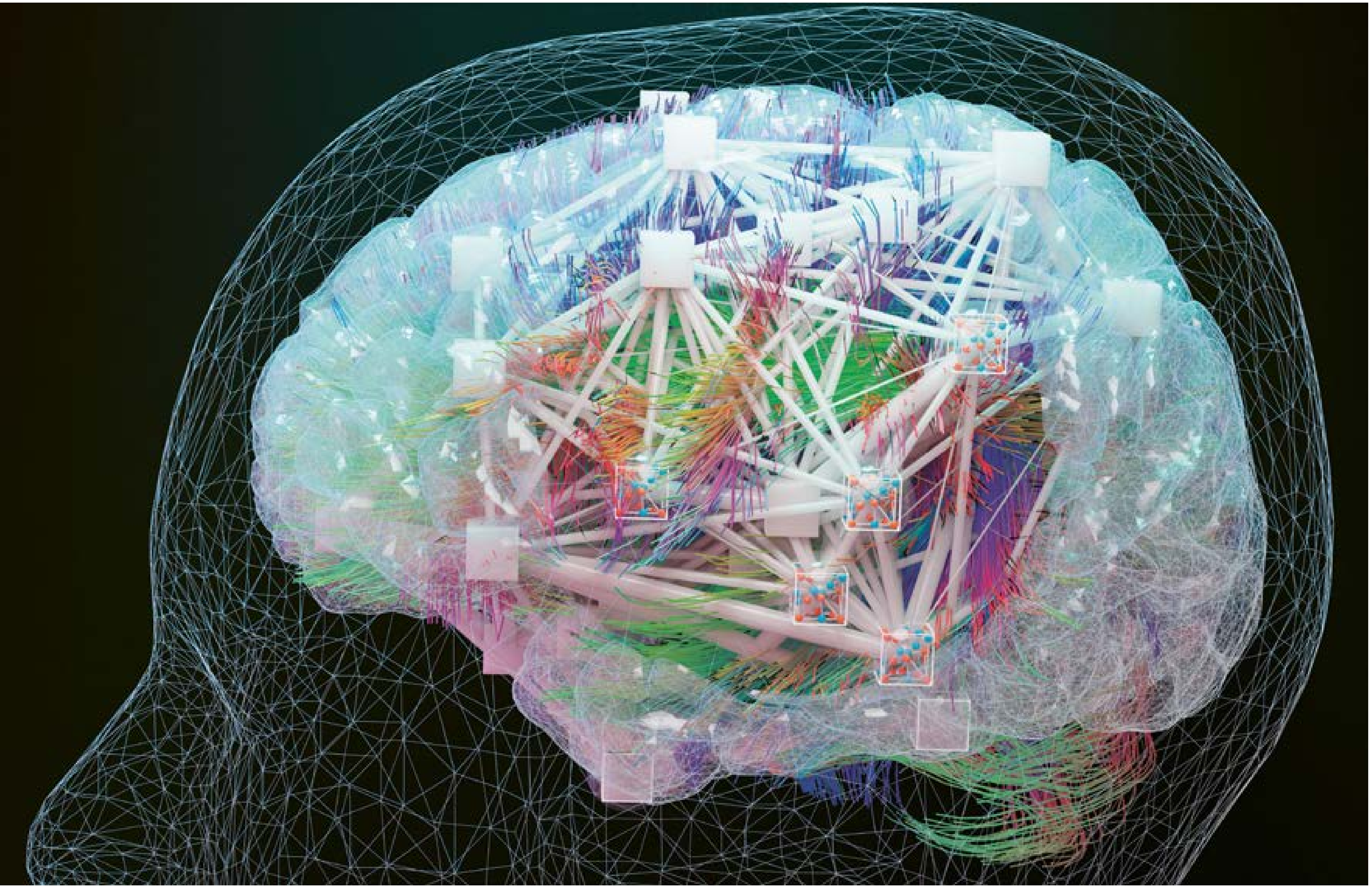
Taking brain simulation to the next level – the multi-scale approach

HBP researchers are simulating the brain with virtual models, an approach which is yielding novel insights into the organ's function. These advanced technologies have enabled powerful new approaches in clinical neuroscience. Now, HBP scientists are modelling multiple scales at the same time.



Different layers of a personalised brain network model.

Simulation is a powerful tool to better understand and predict how complex systems behave and evolve. This is particularly true when looking at the human brain. Within the HBP, researchers integrate neuroscience data into models and simulate the brain on different scales. By linking experiment and theory in this way they have shed new light on brain function and have opened the door for novel clinical applications. Now, HBP researchers have taken simulation to the next level – or rather to multiple levels at once.

All scientific phenomena are observed at defined scales, and brain activity is no different. However, if you focus on one scale, the trade-off is that you either miss the whole picture of what's happening in the brain, or you lose key details at smaller scales. Many questions can only be understood by looking at several layers of brain activity at the same time – with a so-called "multi-scale" approach, which had long been considered out of reach.

Over the years, the HBP has empowered researchers to push forward and scale up different approaches of computational brain modelling and simulation, representing brain mechanisms from the smallest level to the whole brain. In the final phase of the project, different simulation engines on the EBRAINS research infrastructure are being interlinked to enable multi-scale simulation with connected platforms. The collaborative environment, computing power and digital tools of the HBP are now advanced enough to enable researchers to construct the first multi-scale models, allowing them to study the brain in unprecedented ways.

The range and predictive power of the HBP's simulation approaches have increased in recent years, and personalised brain modeling has become a new approach for understanding and treating debilitating neurological diseases. This includes advances in the treatment of epilepsy: seizures and the effects of surgical intervention can now be predicted by simulating virtual brain models that are based on measurements of the individual patient's brain.

The roots of this progress reach all the way back to the early stages of the HBP, when a team from Aix-Marseille University began to adapt "The Virtual Brain" simulation engine for epilepsy – the first clinical

Patient-specific brain imaging data are combined with computational models to locate the epileptic zone.

application of the technology. The team wanted to develop a tool to improve the success rates of epilepsy surgeries, which are the main therapy option for millions of people with the drug-resistant form of the disease.

Since then, much has happened: the proof-of-concept studies in clinics in collaboration with epilepsy doctors were a success; a long-term clinical trial has been funded by the French state and is currently running in thirteen hospitals; industry partner Dassault Systèmes came on board; “The Virtual Epileptic Patient” has become an open platform on the HBP’s EBRAINS infrastructure (Schirner et al. 2022), and the team from Marseille has founded the VB-Tech spin-off for commercialisation (see p. 55). In 2023, the team presented the detailed novel methodology that is applied in the clinical trial (Wang et al. 2023).

While The Virtual Brain is currently being adapted to address additional diseases, the team in Marseille is using the extensive neuroscience resources on EBRAINS to push the model’s predictive power to new limits: The team is making major steps towards bringing high-resolution anatomical data from the HBP’s human brain atlas into the simulation framework. Their latest release of The Virtual Brain is now fully integrated with the digital atlas tool siibra, which facilitates the incorporation of brain region features from different sources into the computational models. This was only made possible through the tight linkage of services on EBRAINS and the close collaboration of teams in the HBP community.

HBP researchers have already applied multi-scale simulations to target Parkinson’s disease (Meier et al. 2022). A team from the Charité in Berlin has generated the first multi-scale model of how a Parkinson’s brain responds to deep brain stimulation, a common treatment, whose outcomes have, thus far, been hard to predict. Simulating electric stimulation across multiple levels of brain networks can help clinicians preview their likely effects and plan therapies accordingly.

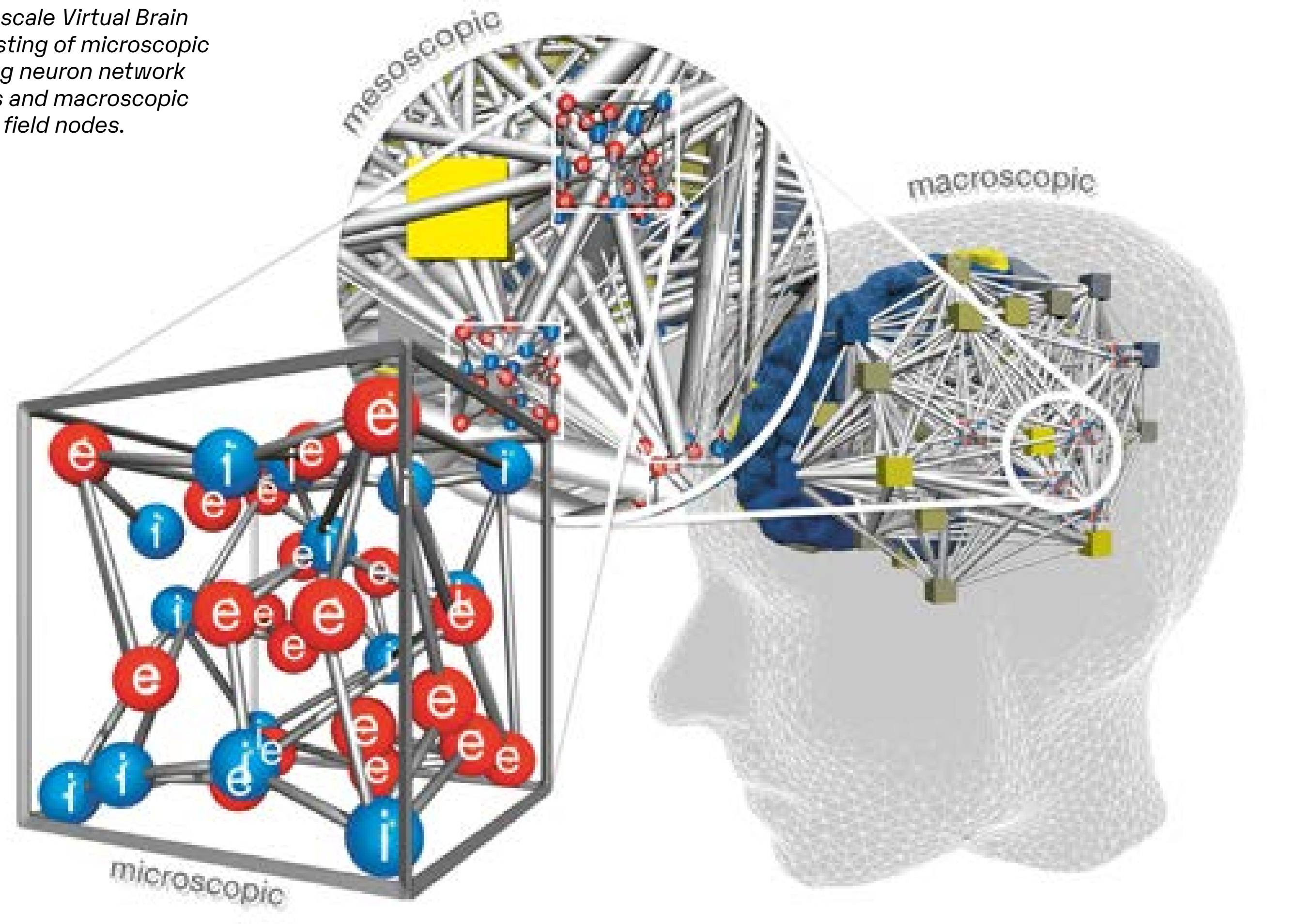
In the case of Parkinson’s, it is not enough to focus on the activity of single neurons or the small subcortical nuclei, because it neglects what happens at the whole-brain scale. The new approach enables researchers to both monitor some structures in high detail, spatially and also at a temporal scale, and to observe the whole-brain effect of the simulation. The study marks the first published case of a multi-scale co-simulation of the human brain applied for a clinical use case, and the methodology has been made openly available on EBRAINS. This could be translated into future medical applications that improve prediction and personalisation when performing deep brain stimulation.

The multi-scale approach is also applied to HBP research on consciousness. Theoretical neuroscientists at the University of Paris-Saclay model brain states from the microscopic scale up to the whole-brain level (Goldman et al. 2023). They work in close collaboration with experimental and clinical colleagues in the HBP who study consciousness and its disorders at the University of Milan and the University of Liège. Other multi-scale approaches have yielded new insights into plasticity, a brain mechanism important for learning (van Keulen et al. 2022) (see p. 51), and into the cerebellum, a part of the brain central for motor control (De Schepper et al. 2022).

While neural modelling and simulation have made their first major steps into large-scale clinical translation, research on basic mechanisms of brain diseases using these approaches has been broad and dynamic. For example, HBP researchers have applied modelling approaches to better understand patient outcomes in ALS (Polverino et al. 2022) and effects of damage to brain connectivity in Multiple Sclerosis (Sorrentino et al. 2022), neural stimulation effects on depression (An et al. 2022) and brain aging (Escrichs et al. 2022), and they have shown how AI-based brain simulations can be used to improve the classification of Alzheimer’s disease, accurately classifying patients at different stages of the disease (Triebkorn et al. 2022).

By necessity, neuroscience has traditionally been separated into top-down and bottom-up approaches. Top-down refers to looking at the whole brain and extrapolating what’s happening at a smaller scale and bottom-up means analysing a smaller scale phenomenon and drawing conclusions on what happens on the whole-brain level. Combining these two approaches is now not only possible, as recent HBP breakthroughs have shown, but indeed necessary (d’Angelo & Jirsa 2022). Multi-scale modelling and simulation have not only added value to research but have become a guiding principle for modern neuroscience.

Multi-scale Virtual Brain consisting of microscopic spiking neuron network nodes and macroscopic mean field nodes.



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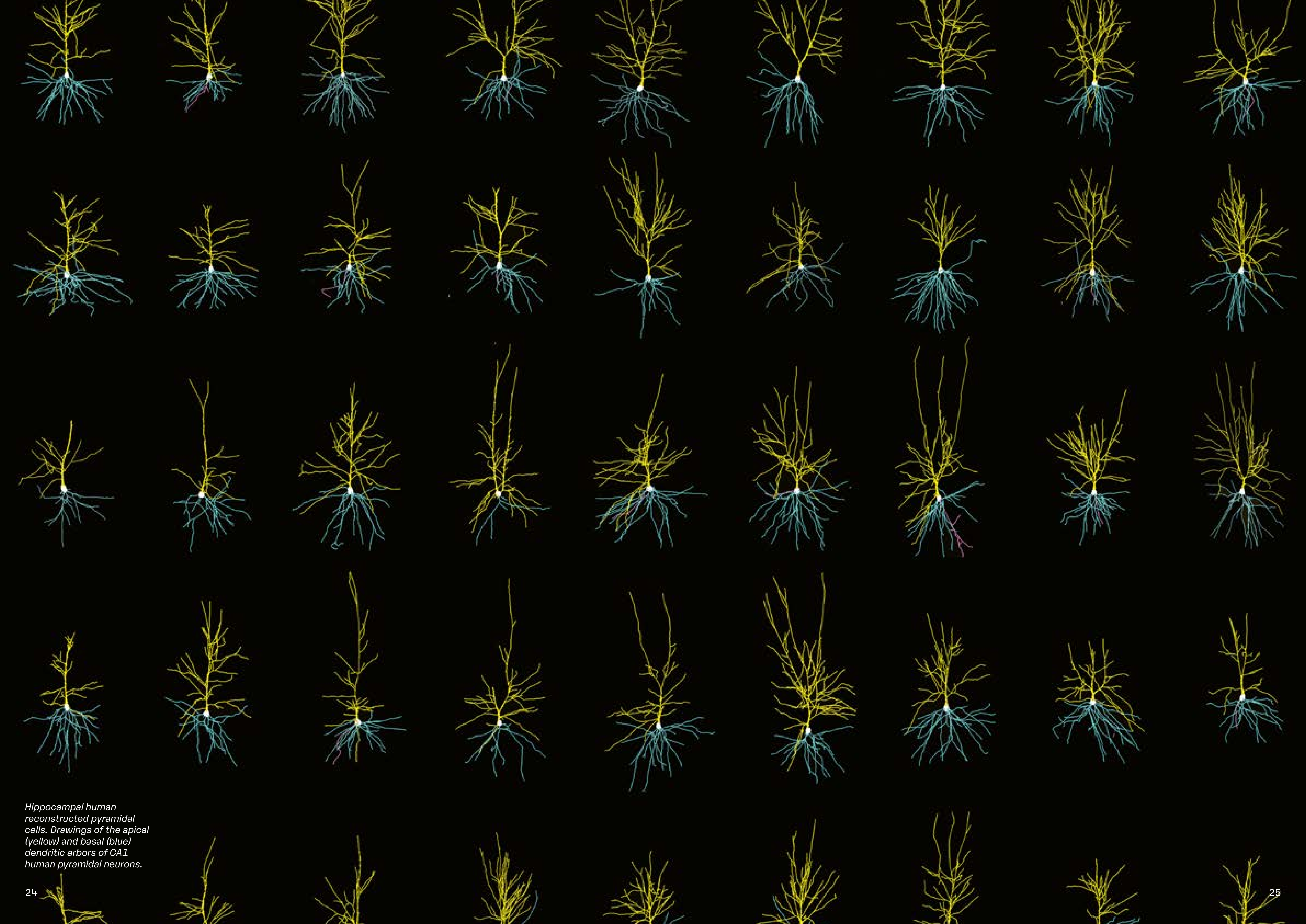
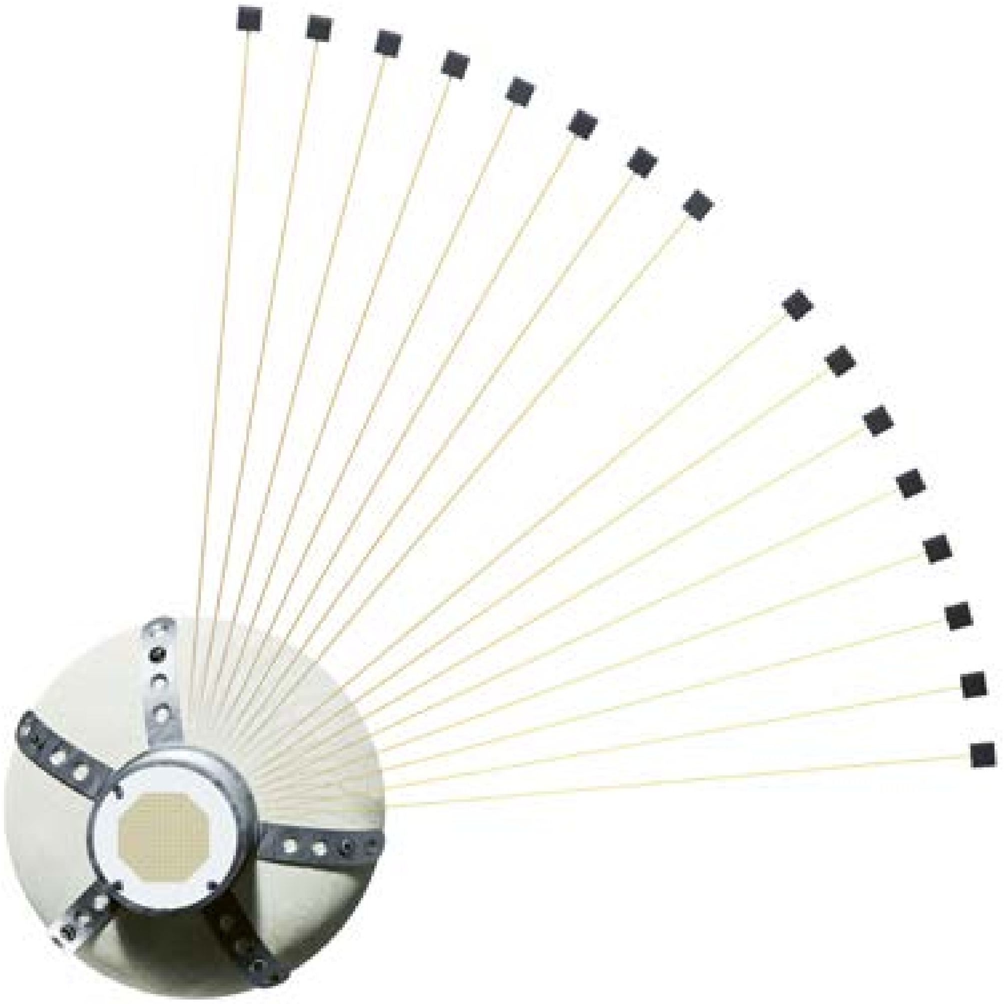


Hippocampal human reconstructed pyramidal cells. Drawings of the apical (yellow) and basal (blue) dendritic arbors of CA1 human pyramidal neurons.

FEATURE

Understanding how the brain makes sense of what we see



The visual neuroprosthesis used by Dutch HBP researchers.

> In the Human Brain Project, researchers are using state-of-the-art measurements, analysis and modelling tools to advance our knowledge of the neural mechanisms underlying our senses, especially vision, which is responsible for a large part of the information we receive from our surroundings.

HBP scientists are advancing our knowledge of how vision works.

From the eyes to the brain

Aristotle regarded our senses as a portal to reality. The Greek philosopher believed that what we see and hear discloses a large part of reality, but humans still require their intellect to understand their environment. 19th century German scientist Hermann von Helmholtz argued that perception requires making predictions about the world based on pre-acquired knowledge. In the 21st century, scientists are still dealing with this question and are trying to better understand how the input from our senses is processed in the brain, enabling us to perceive and experience the world around us.

In a recent study, HBP scientists challenged our current understanding of how vision works. The team from the University of Amsterdam observed in mice how the brain's mechanisms for vision depend on input from other senses as well (Oude Lohuis et al. 2022). They found that the time the brain needs to make a visual interpretation depends on auditory and tactile inputs, not only on the visual properties of the stimuli.

The activity of neurons in the visual cortex varied based on whether the animals had to report only what they saw or also what they heard or felt. In other words, brain signals indicating that visual stimuli had been detected took longer to appear if subjects were also paying attention to sounds or touch.

Previously, our understanding had been that the processing of a visual scene is mainly determined by the complexity of the scene itself. However, visual processing does not occur in isolation and is influenced by sound, touch, smell and other senses.

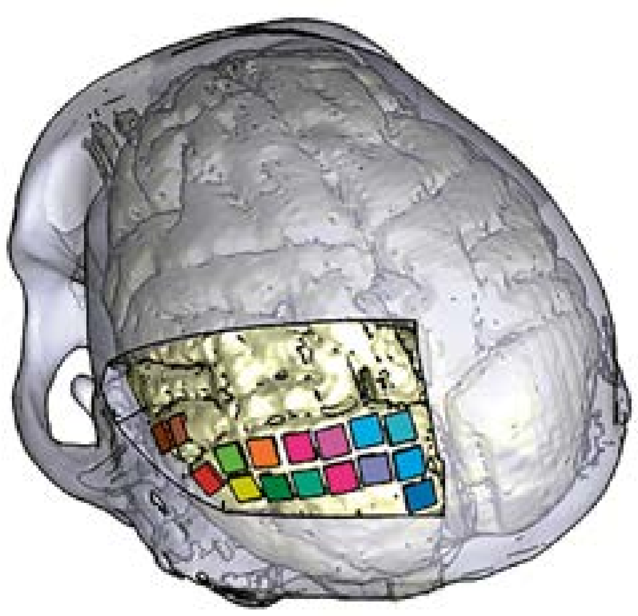
This multimodal view of sensory processing underlies a theory on brain mechanisms of perception and consciousness previously proposed by HBP researcher Cyriel Pennartz, one of the authors of this study.

According to this theory, conscious processing is jointly shaped by multiple senses in an overarching framework that characterises perception as the construction of best-guess representations of our surroundings, and has given rise to computer models built in the HBP.

This theoretical framework, called neurorepresentationalism, states that conscious experience is understood as a sensorily rich, spatially encompassing representation of body and environment, while we nevertheless have the impression of experiencing external reality directly (Pennartz 2022).

Mouse model of vision

Many scientists study mechanisms of vision in the mouse model, because the organisation of the mouse cortical visual system resembles that of primates, albeit with some significant differences.



Electrical stimulation of two areas of the brain that are important for visual perception.

The cortical visual systems of both mice and primates are organised into a primary visual area surrounded by a number of organised higher visual areas. The retinas of primates, however, contain a central region of maximum visual acuity, called the fovea, which is lacking in mice. Consequently, mice don't have a fovea representation in their cortex.

Yet, previous studies have suggested that the mouse retina is not entirely uniform. In a recent study, HBP researchers from the Netherlands Institute of Neuroscience (NIN) used wide-field imaging and modelling to reveal that the mouse visual cortex actually contains a region of improved spatial resolution, which they called the "focea" (van Beest et al. 2021).

In other words, mice have a cortical specialisation which enhances processing of a particular region of a visual scene, which is located directly in front of and slightly above the mouse. In addition, the researchers found that mice, when exploring a visual scene, take advantage of this higher spatial resolution, by moving head and eyes to keep the focea at this location.

By demonstrating a previously unknown similarity between the visual areas of mice and primates, this study contributes important novel insights for this research field.

From biology to computing

Brain models can have a massive impact on artificial intelligence (AI). Since the brain processes images in a much more energy-efficient way than artificial networks, scientists take inspiration from neuroscience to create neural networks that use significantly less energy. HBP researchers from the Graz University of Technology recently trained a large-scale model of the primary visual cortex of the mouse to solve a number of visual tasks, with high accuracy and versatility (Chen et al. 2022).

This model provides the largest integration of anatomical details and neurophysiological data currently available for the primary visual area V1, which is the first cortical region to receive and process visual information. The model provides an unprecedented window onto the dynamics of visual processing in this brain area and shows how the brain's visual processing capabilities can be reproduced. Scientists hope that such neural networks can serve as blueprints for visual processing in more energy-efficient neuromorphic hardware.

On the path to vision implants

Designing a device capable of helping blind people see has been a long-held dream of scientists – a recent study has shown that this is now in reach.

HBP researchers from the NIN are developing a brain implant that electrically stimulates the brain's visual cortex with high precision. The team demonstrated that they could use the implant to successfully induce visual perception in monkeys (Chen et al. 2020). The device (see image) contains 1,000 micro-electrodes stimulating specific points of the visual cortex to induce "phosphenes", small dot-like percepts in the visual field. The induced pixel-like dots from many electrodes can be used to create the perception of shapes.

In combination with a wearable camera, such implants can translate visual information directly into brain-induced visual experiences – a way of seeing for the blind. The method completely bypasses the eyes and the optic nerve, providing stimulation directly to the brain's visual cortex. This means that, if someday this leads to a successful clinical device, it could help people who lost their vision after damages to the eyes or to pathways leading to the visual cortex.

On a smaller scale, the technological principle has already been transferred into human medicine. The NIN team participated in a joint European–American study where a prosthesis that included a small video camera mounted in a pair of glasses connected to a brain implant with 96 microelectrodes (see image on p. 29). This prosthesis enabled a 57-year-old blind woman to see simple shapes and letters after a training period in a small section of the visual field (Fernández et al. 2021).
At the time of the experiments, she had been fully blind for 16 years.

With our understanding of visual processing in our brains constantly advancing, researchers are making strides towards next-level AI and clinical technologies. State-of-the-art experimental and modelling methods are giving scientists the tools to solve the

A miniature camera connected to an eye tracker built into the frame of glasses transmits visual information to the brain implant.

→ Chen X, Wang F, Fernandez E, Roelfsema PR (2020). Shape perception via a high-channel-count neuroprosthesis in monkey visual cortex. *Science* 370, 6521. doi: 10.1126/science.abd7435

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→ Pennartz CMA (2022). What is neurorepresentationalism? From neural activity and predictive processing to multi-level representations and consciousness. *Behav. Brain Res.* 432:113969. doi: 10.1016/j.bbr.2022.113969

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Measuring consciousness – from the lab to the clinic

Where in the brain does consciousness emerge? Is it possible to detect the faintest signs of consciousness after it has been lost? Is there a way to restore consciousness, "bringing back" a patient after severe brain injury? Scientists in the HBP have been attempting to unravel these and other mysteries of consciousness and have made significant progress: they have developed new methods to better distinguish different states of consciousness on the brain level – from awake to asleep, to anaesthetised, to impaired due to brain injury or disease – and have made advances towards potential new treatments and better care for people who have lost consciousness.

What it means precisely to be conscious is debated among philosophers and scientists, with most definitions centring on the ability to have subjective experiences – an inner sensation of what it is like to see an image, hear a sound, think a thought or feel an emotion. For clinicians working on disorders of consciousness, such questions have to be decided on an even more practical level. Here, diagnosing the conscious states of a patient has to be tied to observables – signs of alertness and responsiveness are the first on the checklist. But what if a patient is unable to respond in any way, yet still retains a level of awareness, feelings or even acute pain in need of treatment?

Magnetic stimulation and EEG readings are used to measure a patient's level of consciousness.

The search for signs of consciousness

Every year, thousands of such patients are sent to emergency services worldwide after severe brain injuries. A correct assessment of the level of consciousness is key for an adequate diagnosis, treatment decision and rehabilitation.

A multinational team of HBP scientists is working on new methods to detect states of consciousness directly at the brain level. With sophisticated experiments, modelling and theory, they are hunting for reliable signs that indicate if a patient is even just minimally conscious and potentially able to recover – in other words, if the patient is "still there".

HBP scientists at the University of Milan have developed a novel non-invasive approach to measure the level of consciousness, called the Perturbational Complexity Index (PCI). For this, a weak magnetic pulse is applied to the head of a patient, momentarily perturbing the electrical brain activity that is always present in the living brain – in the awake and asleep states, during anaesthesia and even during deep coma. The brain response to this pulse is simultaneously measured. The method, which has been tested and verified in collaboration with HBP colleagues at the University Hospital

A patient is treated by clinicians of the Coma Science Group at the Liège University Hospital Centre.

of Liège, reveals that it is not the strength of the response which is indicative of the level of consciousness of a person, but rather its complexity, which can be calculated as a single number (Comolatti et al. 2019, Lutkenhoff et al. 2020). The PCI could therefore become a powerful clinical advance for disorders of consciousness.

In order to better understand underlying patterns of the brain's response to external stimuli and their relation to brain states at the whole-brain level, the clinical scientists collaborated with theoretical neuroscientists at CNRS in Paris to model and simulate these brain states in the computer. These multi-scale computational models of brain networks associated with different states of consciousness enable the understanding of PCI data, and they allow integration of data across different scales – from the level of neurons up to the whole brain (also see page 64).

What is the mechanism behind the loss of complexity measured by the PCI? Clinical studies in the HBP previously showed that the loss of brain complexity during disorders of consciousness is due to a pathological tendency of cortical circuits to fall into silence (or into so-called "OFF-periods") upon receiving an input (Rosanovat al. 2018). In 2022, HBP researchers studied this process in animal models and provided a deeper, dynamic understanding of these OFF-periods, opening doors to potential therapeutic interventions (Camassa et al. 2022).

Distinguishing states of consciousness

Several recent studies coming out of these HBP collaborations have greatly contributed to addressing the challenge of correctly diagnosing levels of consciousness, working towards better clinical care for patients suffering from severe brain damage.

One example is the recent work of HBP researchers from the University of Liège, the Pompeu Fabra University in Barcelona, the Vrije Universiteit Amsterdam, and collaborators, who have developed new techniques that may eventually allow researchers and clinicians to distinguish two specific neurological conditions: the unresponsive wakefulness syndrome and the minimally conscious state (Panda et al. 2022).

Previously known as the "vegetative state", unresponsive wakefulness syndrome is the condition of a patient who wakes from coma (that is, opens the eyes) but remains unresponsive to the environment and verbal commands, showing only reflex movements. By contrast, patients in a minimally conscious state tend to show small signs of awareness such as tracking movements with their eyes or moving a finger when asked.

The researchers used functional magnetic resonance imaging (fMRI) data to assess different aspects of brain structure and network dynamics and demonstrated that these brain-based techniques for functional connectivity measurement are sensitive enough to detect relevant differences for better differentiating these two states in diagnosis.

Inspiration from physics

In search of better theoretical approaches to measuring and modelling levels of consciousness, the HBP team at Pompeu Fabra University, in collaboration with researchers from the University of Buenos Aires and the University of Oxford, has also taken inspiration from physics – namely, the second law of thermodynamics.

For many years inside the HBP, this group had been studying how the dynamics of the brain change in different states. Now, based on a key idea of thermodynamics – that production entropy always increases when an irreversible process occurs in a system – the researchers have developed a new framework for finding precise signatures of three brain states: awake, deep asleep and anaesthetised. The researchers analysed the relationships of different parts of the brain with a large human fMRI dataset and found that, in unconscious states, the measured "non-reversibility" of brain activity decreases (Deco et al. 2022). This turns out to be a very good biomarker for classifying the different brain states.

Help from artificial intelligence

State-of-the-art artificial intelligence tools are also being employed to help clinicians reduce the diagnostic uncertainty for coma survivors. In a recent study, researchers from Korea University collaborated with HBP teams from the University of Liège and the University of Milan, as well as with researchers from the University of Wisconsin to develop novel and unique markers of levels of consciousness using deep-learning technologies (Lee et al. 2022).

The teams analysed electrical measurements of brain function in more than one hundred participants under different conditions of altered consciousness – including sleep, anaesthesia and severe brain injury. They used deep learning to disentangle the components of consciousness from the data.

In addition to tackling the challenge of measuring states of consciousness for diagnostic purposes, HBP researchers are also working on novel therapeutic approaches to help unconscious patients.
HBP researchers from the University of Paris-Saclay and CEA Neurospin have recently made another advance in the search for the next potential treatment. They found evidence that deep brain stimulation (DBS) may have the potential to restore wakefulness and awareness in patients with disorders of consciousness (Tasserie et al. 2022).

Brain imaging studies had already suggested that restoring communication between the cortex and the thalamus might be key to recovering consciousness. The HBP team has now demonstrated that the thalamus centre is the right target for stimulation in order to restore levels of consciousness.

Consciousness, a phenomenon both central to every moment of our being and one of the hardest clinical challenges when disturbed, had long been considered too complex to address and thus outside of the realm of science. With neuroscientists, clinicians and computational theorists breaking new ground,
this picture is beginning to change.

→ Camassa A, Galluzzi A, Mattia M, Sanchez-Vives MV (2022). Deterministic and Stochastic Components of Cortical Down States: Dynamics and Modulation. *J. Neurosci.* 42(50):9387-9400. doi: 10.1523/JNEUROSCI.0914-22.2022

→ Comolatti R, Pigorini A, Casarotto S, Fecchio M, Faria G, Sarasso S, Rosanova M, Gosseries O, Boly M, Bodart O, Ledoux D, Brichant JF, Nobili L, Laureys S, Tononi G, Massimini M, Casali AG (2019). A fast and general method to empirically estimate the complexity of brain responses to transcranial and intracranial stimulations. *Brain stimul.* 12(5):1280-9. doi: 10.1016/j.brs.2019.05.013

→ Deco G, Sanz Perl Y, Bocaccio H, Tagliazucchi E, Kringelbach ML (2022). The INSIDEOUT framework provides precise signatures of the balance of intrinsic and extrinsic dynamics in brain states. *Commun. Biol.* 5(1):572. doi: 10.1038/s42003-022-03505-7

→ Lee M, Sanz LRD, Barra A, Wolff A, Nieminen JO, Boly M, Rosanova M, Casarotto S, Bodart O, Annen J, Thibaut A, Panda R, Bonhomme V, Massimini M, Tononi G, Laureys S, Gosseries O, Lee SW (2022). Quantifying arousal and awareness in altered states of consciousness using interpretable deep learning. *Nat. Commun.* 13(1):1064. doi: 10.1038/s41467-022-28451-0

→ Lutkenhoff ES, Johnson MA, Casarotto S, Massimini M, Monti MM (2020). Subcortical atrophy correlates with the perturbational complexity index in patients with disorders of consciousness. *Brain Stimul.* 13(5):1426-1435. doi: 10.1016/j.brs.2020.07.012

→ Panda R, Thibaut A, Lopez-Gonzalez A, Escrichs A, Bahri MA, Hillebrand A, Deco G, Laureys S, Gosseries O, Annen J, Tewarie P (2022). Disruption in structural–functional network repertoire and time-resolved subcortical fronto-temporoparietal connectivity in disorders of consciousness. *eLife* 11:e77462. doi: 10.7554/eLife.77462

→ Rosanova M, Fecchio M, Casarotto S, Sarasso S, Casali AG, Pigorini A, Comanducci A, Seregni F, Devalle G, Citerio G, Bodart O … Massimini M (2018). Sleep-like cortical OFF-periods disrupt causality and complexity in the brain of unresponsive wakefulness syndrome patients. *Nat. Commun.* 9(1):4427. doi: 10.1038/s41467-018-06871-1

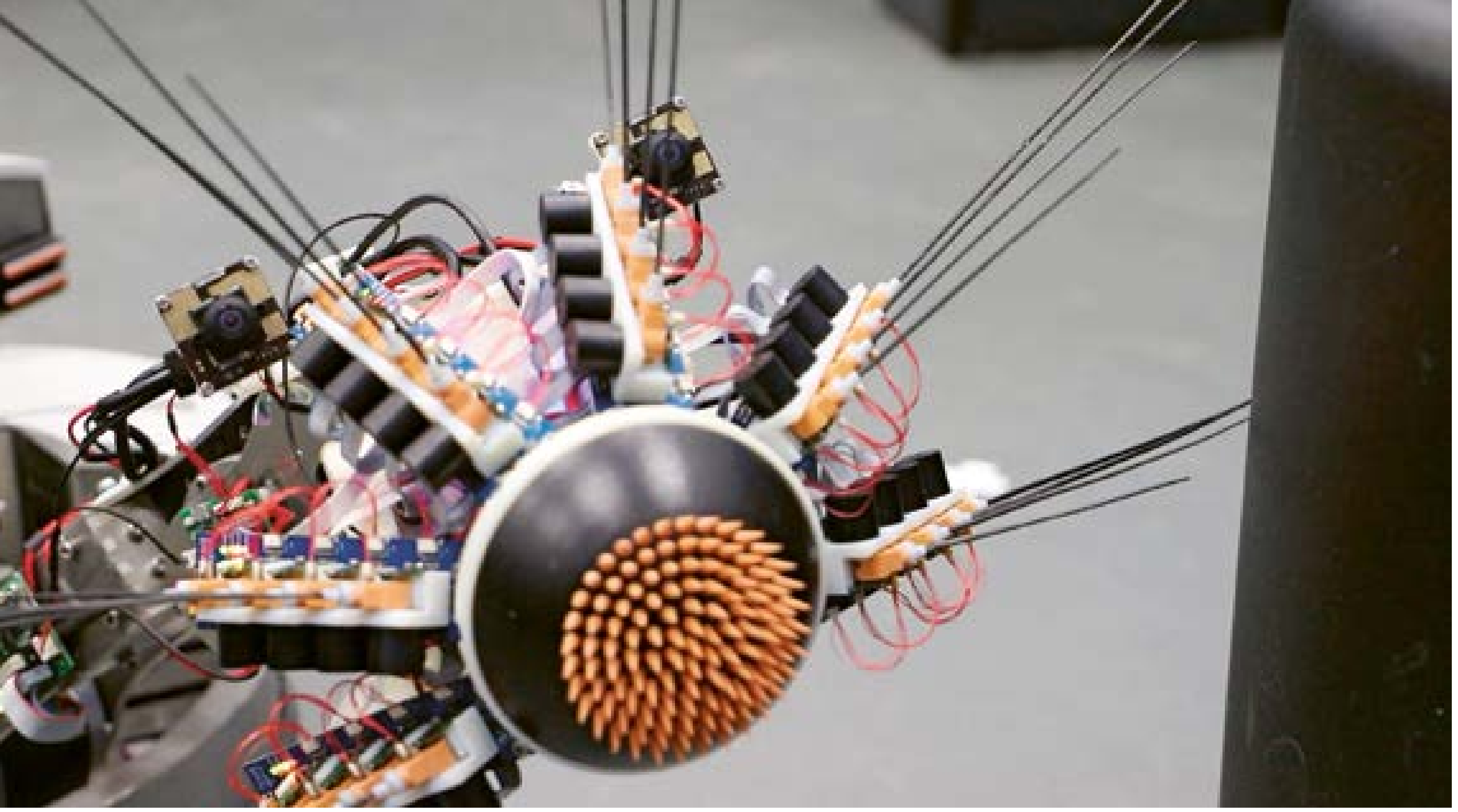
→ Tasserie J, Uhrig L, Sitt JD, Manasova D, Dupont M, Dehaene S, Jarraya B (2022). Deep brain stimulation of the thalamus restores signatures of consciousness in a nonhuman primate model. *Sci. Adv.* 8(11):eabl5547. doi: 10.1126/sciadv.abl5547

Developing robots with brain-derived skills

> The HBP is using neuro-derived technologies to make machines smarter. This not only advances the field of robotics but also helps neuroscientists to better understand how the brain works.

Scuttling across the ground, the robot moves around, nose first, with tendrils constantly waving back and forth, palpating the air. Researchers at the University of Amsterdam and the University of the West of England have taken inspiration from a rat when building it, and it is not hard to see the similarities in both appearance and behaviour. Named WhiskEye, this robot explores the world around it through two small camera eyes and a very large mechanical nose surrounded by 24 artificial whiskers arranged in a circle, much like a rat does. Trained by new computational models developed using the EBRAINS Neurorobotics Platform, WhiskEye is now resembling a rat "in mind" as well as in appearance. The models take inspiration from biological brains, which operate using impulses of electricity (spikes) instead of a continuous flux of information (Pearson et al. 2021). By implementing a more realistic, brain-like architecture, the neuronal model underlying WhiskEye's behaviour is now able to perform object reconstruction – an easy task for us, but one that is considerably harder for robots.

Robot controlled by artificial cerebellum.



The WhiskEye robot.

Some problems that humans and animals would consider trivial – such as recognising that a tree is the same tree when changing the angle of perception – remain big hurdles for artificial minds. Biological brains have been refined by millions of years of natural selection to interact with the world around them; standard computers, while powerful, were never meant to act as brains to control behaviour in an environment, and are, in general, just wired differently.

Robots with a traditional computational architecture are still struggling with object manipulation, naturalistic movement and other tasks that would be intuitive for us, a testament to the intrinsic divide between computers and brains. This is why the intersection of neuroscience and robotics is considered so promising by experts in both fields: neuro-inspired technology that mimics the information flow of a biological brain through spiking neural networks could achieve better task resolution and improve efficiency at the same time.

Robotics as a tool to study brain function

While neuro-inspired technologies mimic the way the brain handles information processing, neuro-derived ones resemble the physical construction of brain architectures and connections between areas. And this is not only a new way of thinking for roboticists: the approach provides brain researchers with a way of testing how their neuroscientific models perform within a body – embodied cognition instead of “brain in a jar”. Advanced brain models can provide us with a lot of information but often exist in isolation from the physical world, in which our brains are immersed through perception and through our bodies. Giving embodiment to a digital brain brings us even closer to how brains operate in their environment, opening up new capabilities for interaction.

Digital brains differ not just in concept and function, but in design and wiring, too. HBP researchers led by a team from Maastricht University, use the HBP’s atlas of the human brain on EBRAINS as the basis to derive the architecture of their robotics platform. This is an example of how an AI-based deep reinforcement learning system can benefit from brain knowledge: the architecture and artificial connections between areas are modelled after a map of the actual areas and neuronal connections in the brain. The resulting brain-inspired cognitive architecture is used to perform robotics learning experiments in a simulated virtual environment, in this case with a virtual copy of the Shadowhand robot, an advanced robotic hand created by the London-based company Shadow Robot. Here, the brain-derived network is trained to learn dexterous manipulations of objects, another task that we humans find very easy, but which is still very complicated for robots. By training the brain-inspired architecture to control the robotic hand, the HBP researchers hope to shed light on how the human brain coordinates complex hand movements. This is possible because the researchers can inspect every detail of the simulated brain, such as the weights of the connections between simulated neurons after successfully learning how to perform dexterous in-hand object manipulation (also see p.65).

Improving robots by mimicking the brain

Precise movements and coordination through neuro-derived AI systems were also achieved by another team of HBP researchers located at the University of Granada. They have linked a detailed artificial neural network that mimics the cerebellum (one of the evolutionarily older parts of the brain, which plays an important role in motor coordination) to a robotic arm (Abadía et al. 2021). Their system learned to perform precise movements and interact with humans in different circumstances, surpassing the performance of previous AI-based robotic steering systems, while also dealing with unpredictable natural time delays. Researchers at the University of Pavia, who specialize in cerebellum modelling, are now experimenting with inserting digital mimics of the cerebellum into robotic controllers on the EBRAINS platform (Antonietti et al. 2022).

It’s not just about building machines that work and learn better on their own: human-robot interaction is expected to rise in the coming years, and with it the necessity for robots that are able to safely collaborate with us – a field of study also known as cobotics. HBP researchers address these issues directly using neuromorphic technology. In a collaborative initiative overseen by the Cognitive Neuroscience department at Maastricht University, HBP cobotics simulations in which robots learn to interact with humans in a safer way are being developed using EBRAINS.

Safer human-robot interaction

Imagine being a worker sharing a factory floor with a robotic arm – how does the robot know where you are? If you disappear momentarily behind a group of boxes, does it still know you are there? Would you trust the robot to hand you a delicate piece of equipment or a sharp tool without inadvertently hurting you? Traditional robotics might try brute force as a solution to these issues through thousands of hours of deep learning or just slowing down the robot, impacting productivity. By using brain-derived neural networks instead, the HBP cobotics system is capable of mimicking the way our brains handle visual occlusion, maintaining a temporal dimension and object permanence. And it also simulates the bone and muscle structure of the human collaborator, modelling the musculoskeletal dynamics and relevant motor circuitry. In this way, it knows when to stop pushing or pulling, and to let go of objects, interacting with you without spraining your ligament by accident.

Despite their current limitations, robots will be a larger part of our lives in the coming years, and the way research and industry will choose to tackle the main questions and issues of robotics will determine just how much smarter, safer and more efficient they will be. Neuromorphic and neuro-derived robotic cognitive architectures might just be the way to go.

Virtual neurorobotics experiment.

→ Abadía I, Naveros F, Ros E, Carrillo RR, Luque NR (2021). A cerebellar-based solution to the nondeterministic time delay problem in robotic control. *Sci. Robot.* 6(58):eabf2756. doi: 10.1126/scirobotics.abf2756

→ Antonietti A, Geminiani A, Negri E, D'Angelo E, Casellato C, Pedrocchi A (2022). Brain-Inspired Spiking Neural Network Controller for a Neurorobotic Whisker System. *Front. Neurorobot.* 16:817948. doi: 10.3389/fnbot.2022.817948

→ Pearson MJ, Dora S, Struckmeier O, Knowles TC, Mitchinson B, Tiwari K, Kyrki V, Bohte S, Pennartz CMA (2021). Multimodal Representation Learning for Place Recognition Using Deep Hebbian Predictive Coding. *Front. Robot.* AI 8:732023. doi: 10.3389/frobt.2021.732023

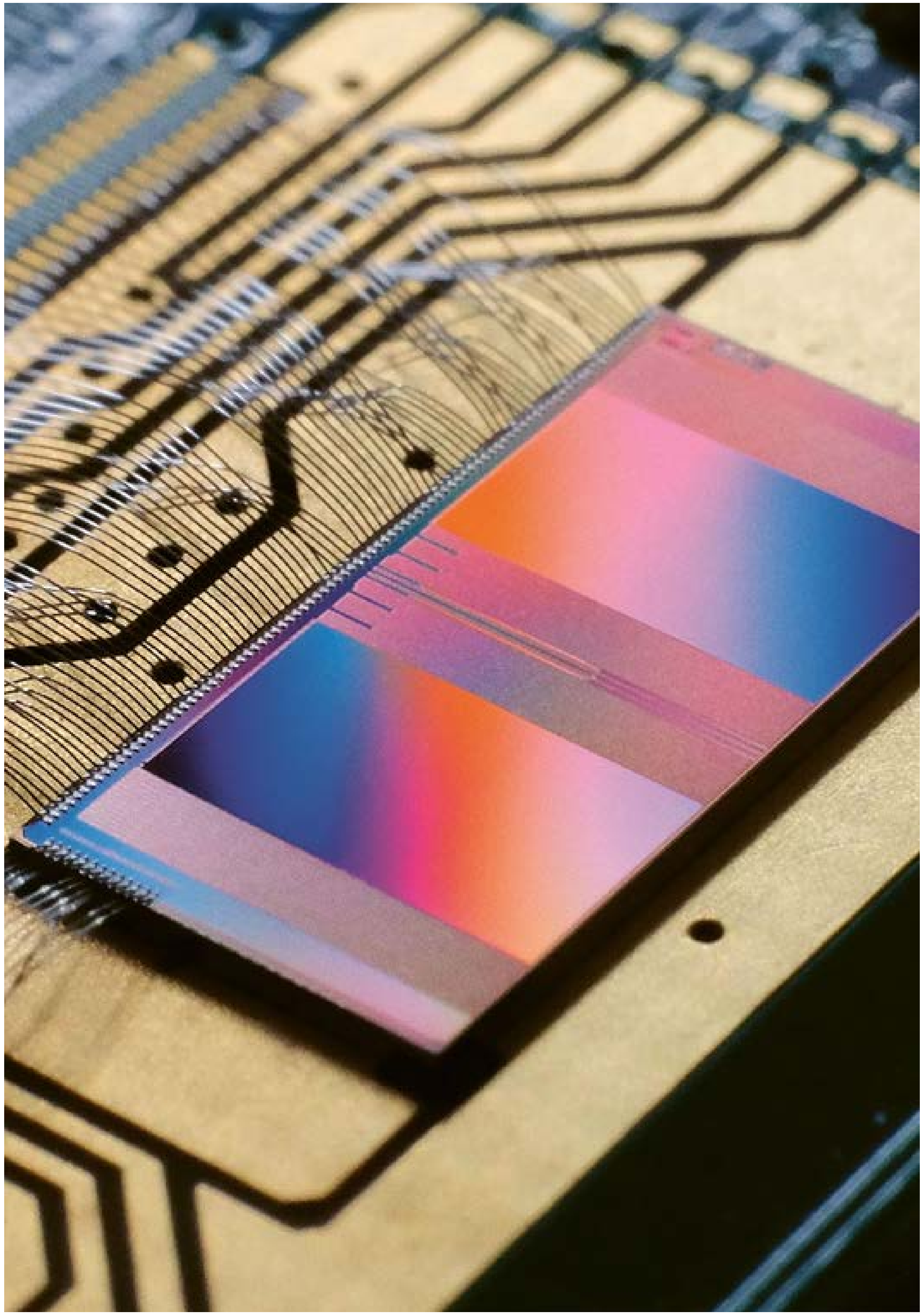
JUWELS at the Jülich Supercomputing Centre (JSC) is one of Europe's fastest supercomputers.

Learning from the brain to make AI more energy-efficient

Energy consumption is one of the main problems facing modern computing. The Human Brain Project has tackled the efficiency issue – potentially changing how computers will be thought of and designed in the future.

As much as computing has progressed, a biological brain still vastly outperforms the fastest calculators in many ways, and with a fraction of the energy consumption. While the demand for computing power is steadily increasing, classical computers can only do so much to become more energy-efficient, due to the inherent principles of their design.

In contrast to power-hungry computers, brains have evolved to be energy-efficient. It is estimated that a human brain uses roughly 20 Watts to work – that is equivalent to the energy consumption of your computer monitor alone, in sleep mode. On this shoe-string budget, 80–100 billion neurons are capable of performing trillions of operations that would require the power of a small hydroelectric plant if they were done artificially.



Close-up view of a BrainScaleS-2 chip.

Progress in neuromorphic technologies

Neuromorphic technologies transfer insights about the brain to optimise AI, deep learning, robotics and automation. Computing systems using this approach have become increasingly refined and are in development worldwide. Like the brain itself, neuromorphic computers hold the promise of processing information with high energy efficiency, fault tolerance and flexible learning ability.

In the Human Brain Project, teams of engineers and theoretical neuroscientists are focused on the engineering and development of neuromorphic devices, which use spiking artificial neurons to train neural networks to perform calculations, and generally take inspiration from the way human brains function. They have built Europe's most powerful neuromorphic systems, BrainScaleS and SpiNNaker, which are both part of the HBP's open research infrastructure EBRAINS.

The first system, BrainScaleS, is an experimental hardware that emulates the behaviour of neurons using analog electrical circuits, omitting energy-hungry digital calculations. It relies on individual events, called "spikes", instead of a stream of continuous values used in most computer simulations. Neurons sending such electrical impulses sparsely to each other is a basic way of efficient signaling in the brain. Mimicking the way neurons calculate and transmit information between each other allows the BrainScaleS chips, now already in their second iteration, to perform very fast calculations while also reducing data redundancy and energy consumption. The large-scale BrainScaleS system is based at Heidelberg University.

The second system, SpiNNaker, is a massively parallel digital computer designed to support large-scale models of brain regions in biological real time. The SpiNNaker neuromorphic computer is based at the University of Manchester. It runs spiking neural network algorithms through its 1,000,000 processing cores that mimic the way the brain encodes information and can be accessed as a testing station for new brain-derived AI algorithms (Furber & Bogdan 2022). At the same time, SpiNNaker has shown promise for developing small low-energy chips that can be used for robots and edge devices. In 2018, the German state of Saxony pledged support of 8 million Euro for the next generation of SpiNNaker, SpiNNaker2, which has been developed in a collaboration between the University of Manchester and TU Dresden within the HBP. SpiNNaker2 chips have since then gone into large-scale production with chip manufacturer GlobalFoundries. A SpiNNaker2 computer system with 70,000 chips and 10 Million processing cores will be based at TU Dresden (also see p. 55). SpiNNaker2 has been chosen as one of the pilot projects of Germany's Federal Agency for Disruptive Innovation, SPRIN-D. A first company for commercialisation, SpiNNcloud Systems, has been founded by the Dresden team.

With the hardware advancing, software is learning from the brain as well. By now, theoretical neuroscientists in the HBP have become highly proficient in developing algorithms that resemble brain mechanisms to a far larger extent than current AI.

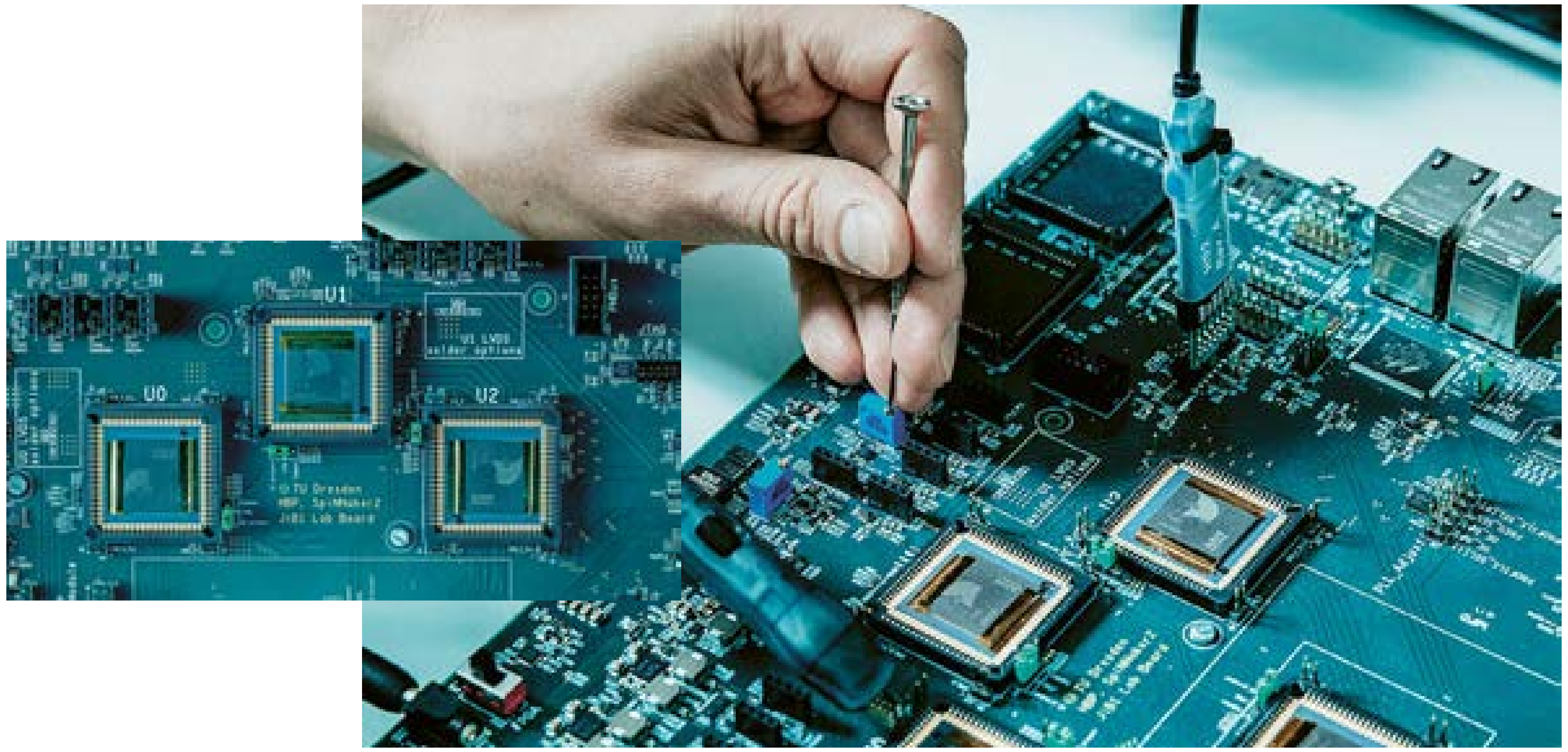
Brain research and AI have always shared connections. The earliest versions of artificial neural networks in the 1950s were already based on rudimentary knowledge about our nerve cells. Today, these AI systems have become ubiquitous, but they still run into limitations: their training is extremely energy-hungry, and what they learn can break down in unexpected ways. Using new insights into biological brain networks, software modelers in the HBP have developed the next generation of brain-derived algorithms. These brain algorithms with higher biological realism have recently proven in practice to massively bring down energy demand, especially when run on a neuromorphic system.

After a series of high-level breakthroughs by several HBP teams (Cramer et al. 2022, Göltz et al. 2021, Bellec et al. 2020), in 2022, a collaboration of HBP researchers at TU Graz together with Intel tested the power of algorithms to bring down energy demand using Intel's Loihi Chip (also see p. 56). The results were an up to 16-fold decrease in energy demand compared to non-neuromorphic hardware (Rao et al. 2022).

A positive feedback loop

Importantly for the HBP and neuroscience in general, more powerful and efficient computing also accelerates brain research, generating a positive feedback loop between highly neuro-inspired computers and detailed brain simulations. In this way, mechanisms that have evolved in biological brains to make them adaptable and capable of learning can be mimicked in a neuromorphic computer so that they can be studied and better understood. This is what a team of HBP researchers at the University of Bern have achieved with so-called "evolutionary algorithms" (Jordan et al. 2021). The programmes they have developed search for solutions to given problems by mimicking the process of biological evolution through natural selection, promoting the ones most able to adapt. Traditional programming is a top-down affair; evolutionary algorithms, instead, arise from the process on their own. This could provide us with further insights into biological learning principles, improve research into synaptic plasticity and accelerate progress towards powerful artificial learning machines.

In the last few years, impressive neuromorphic breakthroughs have made tangible what was previously only theorised regarding the advantages of the technology. As the limitations of traditional AI and classical computers become more and more obvious, learning from the brain has emerged as one of the most powerful approaches for moving ahead.



Above: *SpiNNaker chip.*
Centre: *SpiNNaker2 circuit board.*
Left: *Close-up view of SpiNNaker2 circuit board.*

→ Bellec G, Scherr F, Subramoney A, Hajek E, Salaj D, Legenstein R, Maass W (2020). A solution to the learning dilemma for recurrent networks of spiking neurons. *Nat. Commun.* 11(1):3625. doi: 10.1038/s41467-020-17236-y

→ Cramer B, Billaudelle S, Kanya S, Leibfried A, Grübl A, Karasenko V, Pehle C, Schreiber K, Stradmann Y, Weis J, Schemmel J, Zenke F (2022). Surrogate gradients for analog neuromorphic computing. *Proc. Natl. Acad. Sci. U. S. A.* 119(4):e2109194119. doi: 10.1073/pnas.2109194119

→ Furber S, Bogdan P (eds.) (2020). SpiNNaker: A Spiking Neural Network Architecture. Boston-Delft: *now publishers.* doi: 10.1561/9781680836523

→ Göltz J, Kriener L, Baumbach A, Billaudelle S, Breitwieser O, Cramer B, Dold D, Kungl AF, Senn W, Schemmel J, Meier K, Petrovici MA (2021). Fast and energy-efficient neuromorphic deep learning with first-spike times. *Nat. Mach. Intell.* 3:823-835. doi: 10.1038/s42256-021-00388-x

→ Jordan J, Schmidt M, Senn W, Petrovici MA (2021). Evolving interpretable plasticity for spiking networks. *eLife* 10:e66273. doi: 10.7554/eLife.66273

→ Rao A, Plank P, Wild A, Maass W (2022). A Long Short-Term Memory for AI Applications in Spike-based Neuromorphic Hardware. *Nat. Mach. Intell.* 4:467–479. doi: 10.1038/s42256-022-00480-w

Making powerful supercomputing available to the research community at large

The Fenix infrastructure, set up by Europe's leading supercomputing centres, emerged from the Human Brain Project and now offers invaluable computing and data resources for the entire scientific community.

The TGCC computing centre of the French Alternative Energies and Atomic Energy Commission (CEA) is part of the Fenix infrastructure.

The human brain contains around 80-100 billion neurons with trillions of contact points, so-called synapses, forming a complex network. A full comprehension of how the brain functions requires bridging the many levels of brain organisation, from molecules to neurons and their manifold connections. This involves handling massive amounts of multilevel data and places high demands on computing – the motivation to build Fenix.

BigBrain, a three-dimensional reconstruction of one human brain stained for cell bodies at near-cellular resolution of 20 micrometres, exemplifies the volumes of data that are involved. As part of the HBP's Multilevel Human Brain Atlas, the BigBrain serves as an anatomically realistic reference space into which other data can be spatially anchored in a functionally relevant dimension. The original dataset is based on 7,404 histological brain sections and comprises around one terabyte of data. Presently, work is ongoing to develop a model with an even higher resolution of one micrometre that will produce data in the range of several petabytes (Amunts & Lippert 2021).

Collecting, processing, storing, sharing and analysing this kind of data is very computationally demanding, and when linking data from further levels of brain organisation the computational demands increase even more. To address the requirements of neuroscientists, the Human Brain Project is building the EBRAINS infrastructure, which provides access to a range of tools, data and computing services, many of which rely on powerful supercomputing systems. The required computing, cloud and storage resources are currently provided via the EU-funded Interactive Computing E-Infrastructure for the Human Brain Project (ICEI), the first implementation project of the federated infrastructure Fenix.

The Fenix infrastructure has been set up by five of Europe's leading supercomputing centres – BSC in Spain, CEA in France, CINECA in Italy, CSCS in Switzerland and JSC in Germany – and offers high-performance computing (HPC), cloud and data resources to the scientific community (Alam et al. 2022). Fenix has been established in a way that allows further partners to join. In 2021, CSC in Finland, which hosts one of the pan-European pre-exascale supercomputers, LUMI, joined the federated infrastructure.

The EBRAINS and Fenix infrastructures form two separate service layers with distinct targets: EBRAINS provides platform services that are highly specific for the brain research domain, whereas Fenix serves as a basal infrastructure offering more generic computing services upon which the different EBRAINS services are built.

Fenix has emerged from the Human Brain Project and has been designed based on use cases from brain research. Recent examples of projects using Fenix resources include a study by HBP researchers from the University of Pavia who have used the supercomputing resources to perform single-cell simulations that predict a new role for stellate cells of the cerebellum (Rizza et al. 2021) and a study from Forschungszentrum Jülich that used Fenix computing services to simulate large-scale spiking network models of the macaque brain (Tiddia et al. 2022).

While some specialists access Fenix resources directly, most users from the brain research community avail of its services via EBRAINS, for example, by running embodied simulation experiments on the EBRAINS Neurorobotics Platform, by linking structural and functional brain data in the Multilevel Human Brain Atlas or by generating personalised brain models and simulating multi-scale networks with The Virtual Brain. Other EBRAINS services building upon Fenix include Data and Knowledge Services, the Medical Informatics Platform, the Collaboratory, various simulation tools and others. Such services are often hosted on the cloud resources offered by Fenix.

At the same time, the Fenix services are generic enough to serve scientific communities beyond neuroscience. This is a major advantage in the way the two service layers of EBRAINS and Fenix have been set up because it ensures most efficient use of resources. Research fields for which Fenix resources may be of particular interest include materials science, geoscience, genomics, physics, fluid dynamics, oceanography and biomedicine.

In April 2020, Fenix launched a call offering fast-track access to its resources to researchers working on topics related to the Covid-19 pandemic. The projects that have benefited from this offer include a study by researchers from Barcelona, which led to new insights on the infectiousness of different SARS-COV-2 variants, a large virtual screening of potential anti-COVID-19 compounds headed by HBP researchers from Jülich and state-of-the-art simulations of SARS-CoV-2 proteins as potential drug targets carried out by researchers from Sorbonne University in Paris (Jaffrelot Inizan et al. 2021).

When the HBP started, the neuroscience community was – compared to other communities – only in its infancy with regards to HPC usage. Neuroscience is benefiting greatly from Fenix, because there is no minimum allocation size and hence also small and medium-sized projects can benefit. Before Fenix, access to supercomputing resources was only possible via large-scale calls, which require the ability to use a significantly large allocation, restricting access for smaller projects. Now, with the establishment of Fenix, a large number of researchers from all over Europe can access powerful supercomputing resources much more easily. The combination of cloud and supercomputing services within one framework is unique and enables easy access from a single account, saving valuable time.

As computing demands are rising, Europe is preparing for the exascale era: In June 2022, the European High Performance Computing Joint Undertaking (EuroHPC JU) has announced that Fenix partner Jülich Supercomputing Centre (JSC) will host Europe's first exascale supercomputer, JUPITER. EuroHPC JU is a joint initiative between the EU, European countries and private partners and will acquire the system, which will be capable of performing more than one trillion calculations per second. JUPITER represents a major milestone for Europe and will help to address urgent scientific questions including in the fields of climate change, public health and sustainable energy. The brain research community will benefit from JUPITER's analysis of very large data volumes, which will enable the intensive use of artificial intelligence.

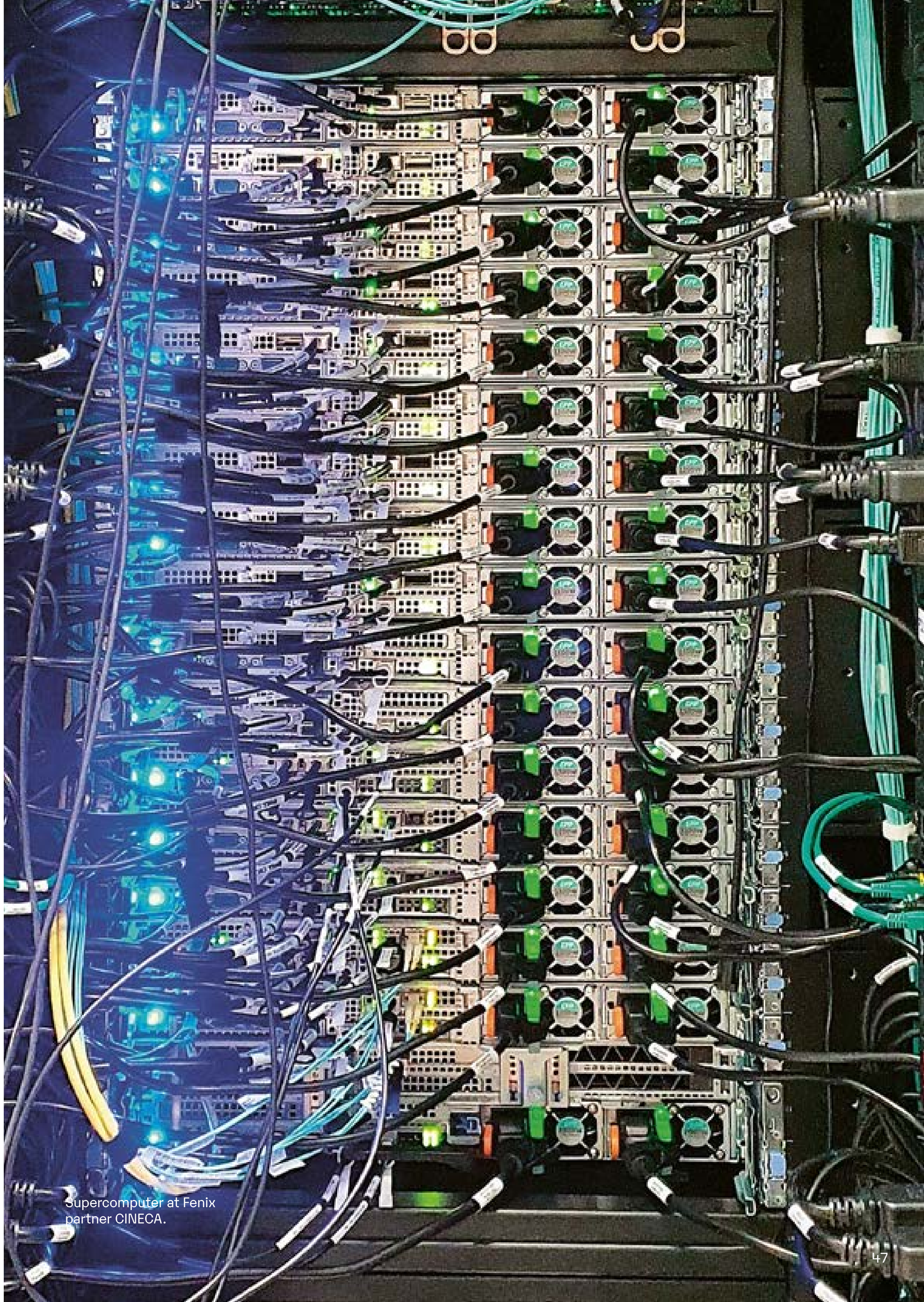
→ Alam SR, Bartolome J, Carpene M, Happonen K, Lafouciere JC, Pleiter D (2022). FENIX: A Pan-European Federation of Supercomputing and Cloud e-Infrastructure Services. *Commun. ACM* 65(4):46-47. doi: 10.1145/3511802

→ Amunts K, Lippert T (2021). Brain research challenges supercomputing. *Science* 374(6571):1054-1055. doi: 10.1126/science.abl8519

→ Jaffrelot Inizan T, Célerse F, Adjoua O, El Ahdab D, Jolly LH, Liu C, Ren P, Montes M, Lagarde N, Lagardère L, Monmarché P, Piquemal JP (2021). High-resolution mining of the SARS-CoV-2 main protease conformational space: supercomputer-driven unsupervised adaptive sampling. *Chem. Sci.* 12(13):4889-4907. doi: 10.1039/d1sc00145k

→ Rizza MF, Locatelli F, Masoli S, Sánchez-Ponce D, Muñoz A, Prestori F, D'Angelo E (2021). Stellate cell computational modeling predicts signal filtering in the molecular layer circuit of cerebellum. *Sci. Rep.* 11(1):3873. doi: 10.1038/s41598-021-83209-w

→ Tiddia G, Golosio B, Albers J, Senk J, Simula F, Pronold J, Fanti V, Pastorelli E, Paolucci PS, van Albada SJ (2022). Fast simulation of multi-area spiking network model of macaque cortex on an MPI-GPU cluster. *Front. Neuroinform.* 16:883333. doi: 10.3389/fninf.2022.883333



Supercomputer at Fenix partner CINECA.

Spotlights on recent research

The Human Brain Project has driven outstanding advances in the fields of brain research and the development of brain-derived applications in medicine and technology. Many of the most recent scientific advances were born directly as a result of the HBP's ambitious efforts; for others, the HBP has acted as a catalyst, providing the enabling environment for exceptional breakthroughs.

Sample of neurons imaged simultaneously in the auditory cortex, identified after digital image processing.

Strange dreams might help your brain learn better

A study by HBP researchers from the University of Bern suggests that dreams – especially those that appear realistic, but, upon closer look, are actually bizarre – help our brain learn and extract generic concepts from previous experiences. The study offers a new theory on the significance of dreams using machine learning-inspired methodology and brain simulation.

→ Deperrois N, Petrovici MA, Senn W, Jordan J (2022). Learning cortical representations through perturbed and adversarial dreaming. *eLife* 11:e76384. doi: 10.7554/eLife.76384

How visual information travels in our brains

Using extremely high-resolution functional imaging methods, a HBP team at the German Center for Neurodegenerative Diseases (DZNE) has provided a new view of how different kinds of visual information travel in the human cortex and within areas of the hippocampus. They found that two functional routes characterise this circuitry: one specific scene-processing route and another functional route that shows no preference for scene or object information.

→ Grande X, Sauvage MM, Becke A, Düzel E, Berron D (2022). Transversal functional connectivity and scene-specific processing in the human entorhinal-hippocampal circuitry. *eLife* 11:e76479. doi: 10.7554/eLife.76479

New implant offers promise for the paralysed

An implant developed at HBP Partners EPFL and CHUV in Lausanne enables patients with complete spinal cord injuries to stand, walk and even perform recreational activities like swimming or cycling (also see p. 57). In order to design and place the implants, the team simulated the spinal cord of each patient. An important element to the success of this endeavour is a digital atlas of the human spinal cord including computational models of neural circuitry, which were created in the HBP. The spine atlas was presented in a 2022 publication that described the approach in detail.

→ Rowald A, Komi S, Demesmaeker R, Baaklini E, Hernandez-Charpak SD, Paoles E, Montanaro H, Cassara A, Becce F, Lloyd B, Newton T, … Courtine G (2022). Activity-dependent spinal cord neuromodulation rapidly restores trunk and leg motor functions after complete paralysis. *Nat. Med.* 28(2): 260-271. doi: 10.1038/s41591-021-01663-5

HBP brain atlas research featured in a special issue of *Science*

HBP researchers from the University of Oslo have reviewed the current state of atlas-based data integration for mapping the connections and architecture of the rodent brain. In a second article from the same special issue of *Science*, colleagues from Forschungszentrum Jülich discussed the nested design of human connectomics and connectivity data integration in human brain atlases (see also p. 14). The HBP has made the Waxholm Space Rat Brain Atlas and the Multilevel Human Brain Atlas openly available on EBRAINS.

→ Axer M, Amunts K (2022). Scale matters: The nested human connectome. *Science* 378(6619):500-504. doi: 10.1126/science.abq2599

→ Leergaard TB, Bjaalie JG (2022). Atlas-based data integration for mapping the connections and architecture of the brain. *Science* 378(6619): 488-492. doi: 10.1126/science.abq2594

Neuronal assemblies shape sound perception

The cortex organises itself in specific neuronal assemblies when consciously perceiving sounds, generating "creative" patterns of activity. This is the conclusion of a study carried out by HBP researchers at CNRS, University of Paris-Saclay in collaboration with researchers at the Pasteur Institute in Paris. While awake, hundreds of nerve cells at a time can coordinate to form these sound-specific patterns. The study combined *in vivo* experiments and computational analysis.

→ Filipchuk A, Schwenkgrub J, Destexhe A, Bathellier B (2022). Awake perception is associated with dedicated neuronal assemblies in the cerebral cortex. *Nat. Neurosci.* 25, 1327–1338. doi: 10.1038/s41593-022-01168-5

Insight into cellular origin of autism

Oxytocin is an important signalling molecule linked to social bonding and empathy. Attempts at counteracting autism symptoms have relied on administration of oxytocin nasal spray, with varying efficacy. HBP scientists from Forschungszentrum Jülich, together with a team from the University of Regensburg, have shown how an autism-linked genetic variation changes the structure and function of the oxytocin receptor, affecting downstream events. The insight could contribute to future pharmaceutical intervention against the disease.

→ Meyer M, Jurek B, Alfonso-Prieto M, Ribeiro R, Milenkovic VM, Winter J, Hoffmann P, Wetzel CH, Giorgetti A, Carloni P, Neumann ID (2022). Structure-function relationships of the disease-linked A218T oxytocin receptor variant. *Mol. Psychiatry* 27, 907–917. doi: 10.1038/s41380-021-01241-8

Simulations reveal molecular mechanisms behind learning

Simulation has helped a multinational HBP team to uncover molecular mechanisms of enzymes that are key to brain plasticity and learning. The results provide insights into the dynamic interactions between so-called adenylyl cyclase enzymes and the proteins that regulate their activity. Higher-level models then tracked how this mechanism influences processes at the synapse that involve signalling molecules like dopamine, which are crucial for memory reward learning.

→ van Keulen SC, Martin J, Colizzi F, Frezza E, Trpevski D, Cirauqui Diaz N, Vidossich P, Rothlisberger U, Hellgren Kotaleski J, Wade RC, Carloni P (2022). Multi-scale molecular simulations to investigate adenylyl cyclase-based signaling in the brain. *Wires* e1623. doi: 10.1002/wcms.1623

Why Ritalin affects everyone differently

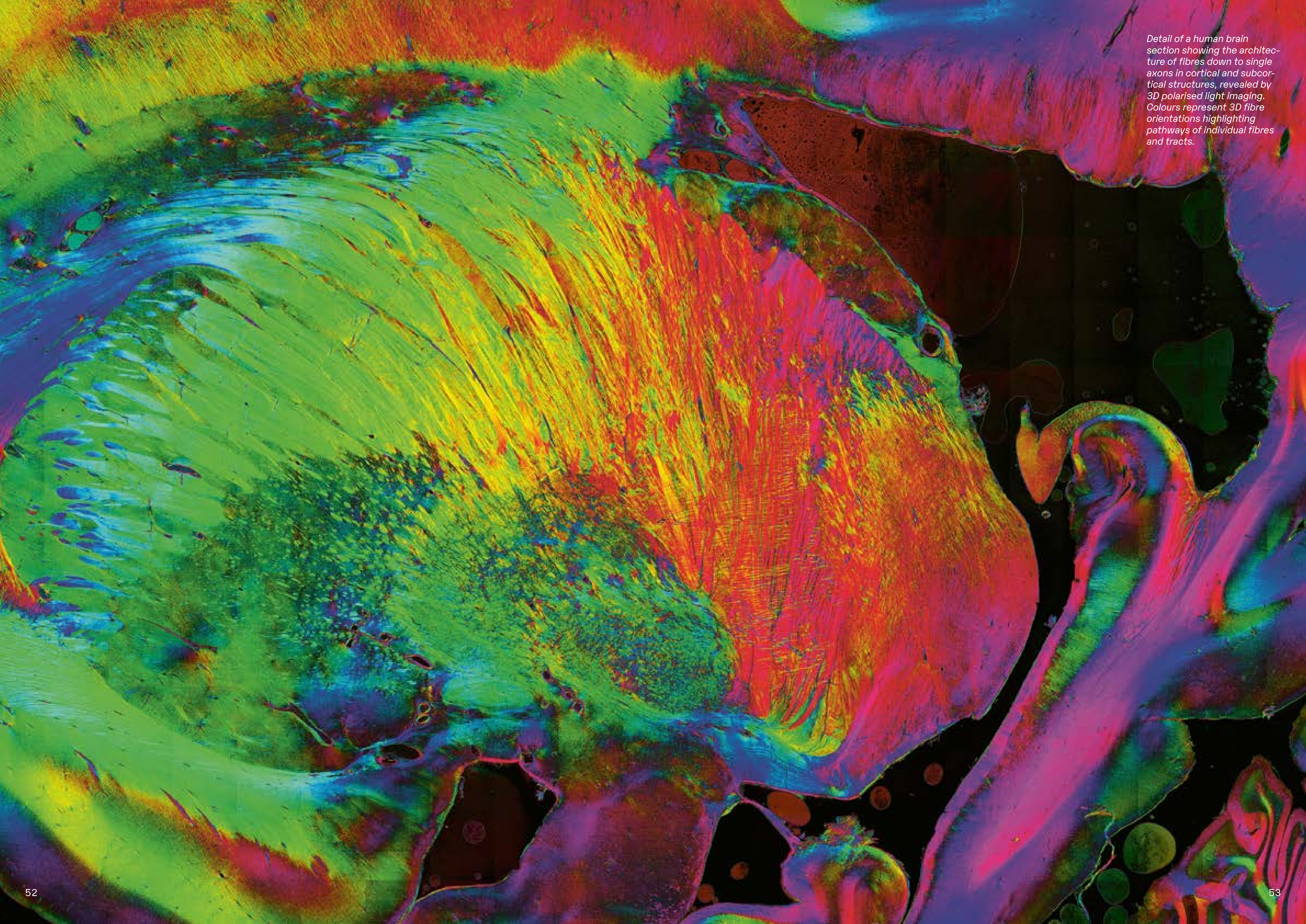
Researchers at the Donders Institute for Brain, Cognition and Behaviour have moved closer to understanding why methylphenidate, the active compound in Ritalin®, which is the most common drug to treat ADHD, affects people differently. Their results showed that the effects of this compound on learning depend on the baseline levels of dopamine in a person's brain.

→ van den Bosch R, Lambregts B, Määttä J, Hofmans L, Papadopetraki D, Westbrook A, Verkes RJ, Booij J, Cools R (2022). Striatal dopamine dissociates methylphenidate effects on value-based versus surprise-based reversal learning. *Nat. Commun.* 13: 4962. doi: 10.1038/s41467-022-32679-1

A novel atlas of "short-distance" brain connectivity

Researchers at CEA Paris-Saclay have created the first atlas of the short-distance fibre bundles of the human brain. While long-range fibre connections had been investigated before, the local short-range connectivity had never been mapped in such a comprehensive way. The atlas is composed of 525 bundles of superficial short association fibres along the whole brain, providing a better picture of the human connectome.

→ Román C, Hernández C, Figueroa M, Houenou J, Poupon C, Mangin JF, Guevara P (2022). Superficial white matter bundle atlas based on hierarchical fiber clustering over probabilistic tractography data. *NeuroImage* 262: 119550, doi: 10.1016/j.neuroimage.2022.119550



Detail of a human brain section showing the architecture of fibres down to single axons in cortical and subcortical structures, revealed by 3D polarised light imaging. Colours represent 3D fibre orientations highlighting pathways of individual fibres and tracts.

Spotlights on Innovation

The HBP has in recent years seen exciting developments at the interface between science and application, in the form of collaborations, spin-offs, patents and clinical trials. Some of these innovations are direct results of HBP activities, others are built upon breakthroughs that have been achieved within the HBP.

HBP research has contributed to targeted spinal cord stimulation that has helped patients with paralysis walk again.

Patents for new drug candidates

HBP researcher Giulia Rossetti has applied for patents for drug candidates against neurodegenerative disorders identified with molecular modelling and simulations. She is now building on this work using Fenix computers and EBRAINS to further investigate these candidates. Currently, she is focussing on the molecular mechanism leading to long COVID and its effects on the brain in a collaboration of several HBP Partners called BRAVE. The team is investigating how inflammatory reactions in the brain can be averted; these reactions are implicated in the long-term "brain fog" experienced by many, even long after infection has been overcome.

Spin-off company SpiNNcloud develops brain-inspired AI

The brain-inspired supercomputer SpiNNcloud has been selected as one of the first breakthrough innovations by SPRIN-D, Germany's Federal Agency for Disruptive Innovation. It builds on research within the HBP on the SpiNNaker neuromorphic computing system. The next generation of SpiNNaker – SpiNNaker2 – has been created by teams at TU Dresden and the University of Manchester, together with chipmaker GlobalFoundries and German chip design house Racyics. Commercialisation is already underway in the form of SpiNNcloud Systems GmbH, a spin-off of TU Dresden. SpiNNcloud Systems delivers solutions in brain-inspired AI, from small-scale edge nodes to the large-scale SpiNNcloud composed of 70,000 SpiNNaker2 chips, which is the largest platform for real-time AI worldwide. Industrial pilot projects with BMW, Infineon and others already use the new system. SpiNNcloud and SpiNNaker2 will advance impactful AI models in computer vision, robotics, industry 4.0 and autonomous systems, where fast reaction times, low latency and energy efficiency are essential.

→ spinncloud.com

Spin-off company VB-Tech develops virtual brain models

SATT Sud-Est has granted an exclusive worldwide license to the start-up VB-Tech for The Virtual Brain (TVB) technology developed by the INS (Institute of Systems Neurosciences) of Aix-Marseille University. The technology targets the treatment of brain pathologies and combines neuroscience, brain modelling and machine learning, which together have enabled a first clinical trial in epilepsy. Several patents were recently awarded for TVB applications. This use of computational modelling in the clinic has been pioneered by Viktor Jirsa within the HBP. In 2021, he received one of the first HBP Innovation Awards for this work.

Collaboration with Dassault Systèmes for epilepsy clinical trial

The EPINOV collaboration works to improve epilepsy surgery through personalised brain modelling. The approach is being tested in a large-scale clinical trial in France (also see p. 22). The collaboration involves industry partner Dassault Systèmes, the largest company for 3D experience in Europe. The clinical trial is expected to conclude in 2025. If successful, Dassault could provide the brain-modelling software as a product to clinics.

→ 3ds.com/stories/living-brain

Innovation to detect consciousness in coma patients

Marcello Massimini from the University of Milan received the HBP Innovation Award 2021 for his innovative approach for detecting consciousness in coma patients. The approach uses combined transcranial stimulation (TMS) and EEG measurements of brain waves. It has been comprehensively refined, tested and advanced in the HBP (also see p. 31), and its base mechanisms are better understood through EBRAINS modelling showcase 3 (p. 64). Now, Massimini is preparing for larger steps: together with Finnish company Nextstim, which specializes in targeted brain stimulation, the UMIL team is testing a brand new TMS-EEG prototype device in Milan. Moreover, with support from the Tiny Blue Dot Foundation, TMS-EEG devices have been shipped to major US neurological hospitals, in preparation for a multi-centric clinical trial of the consciousness-measuring method. Finally, a spin-off was recently incorporated to facilitate the introduction of this method into hospitals.

Collaboration with Intel for a neuromorphic breakthrough

In 2022, HBP researchers at TU Graz in Austria collaborated with Intel to bring AI closer to the energy efficiency of the brain. The team develops brain-inspired algorithms which can be implemented on spiking neuromorphic systems of the EBRAINS infrastructure or external industry collaborators. The latest result, an up to 16-fold decrease in energy demand on Intel's Loihi Chip, was published in the prestigious journal *Nature Machine Intelligence*. This demonstration is a major step toward new AI algorithms that function with only a fraction of the energy demand while exhibiting enhanced performance (also see p. 40–43).

EPFL spin-off Onward Medical helps paraplegic people walk again

Onward Medical is a spin-off of HBP Partner EPFL that develops a treatment for people with paralysis after spinal cord injury using targeted electrical stimulation through a neuroprosthetic implant. Within the HBP, the research team behind this approach created simulation models of spinal circuitry that are used to guide the placement and design of the electrodes. This early cooperation has contributed to a series of sensational breakthroughs with this approach. Today, even patients with complete sensorimotor paralysis have been helped to regain their movement (also see p. 49). In 2021, Onward Medical made the major step of becoming listed on the European Stock Exchange Euronext.

→ onwd.com

NIN spin-off company Phosphoenix working to cure blindness

Blindness is curable – that is the credo of the Dutch company Phosphoenix, a spin-off by HBP Partner NIN Amsterdam. The company aims to commercialise an approach that uses direct stimulation of the visual areas in the brain to evoke visual perception via an implant. Connected to a camera, this can enable some basic vision functions for blind people (also see p. 28). As final application in humans will require very precise knowledge of the structure and dynamics of the visual field, the team collaborates with brain mapping and perception researchers in the HBP. In 2022, Phosphoenix went into a successful pre-seed funding round and licensed NIN patents for the prosthesis design.

→ phosphoenix.nl

EBRAINS

A key enabler for advancing brain science

To facilitate the integration of brain science across disciplines and borders, the HBP is building a digital research infrastructure: EBRAINS is an open platform that provides access to a plethora of digital tools, models, data and services, enabling collaboration on a very large scale. In 2021, EBRAINS was added to the ESFRI Roadmap for Research Infrastructures – a strong demonstration that it is on track to becoming an important part of the European research landscape. EBRAINS will remain available to the scientific community as a lasting contribution of the HBP to global scientific progress. All researchers are welcome to join the EBRAINS community.

Service Categories

Services on the EBRAINS Research Infrastructure are highly interconnected.

Data and Knowledge

EBRAINS Data and Knowledge services facilitate sharing of and access to research data, computational models and software. These services revolve around an expert-driven Knowledge Graph which combines metadata ingestion pipelines, human-user input and multiple quality assurance processes to help contributors and users by ensuring data consistency and quality.

Atlases

Brain atlases provide spatial reference systems for neuroscience, giving the ability to navigate, characterise and analyse information on the basis of anatomical location. Atlases define the shape, location and variability of brain regions in common coordinate spaces and allow interpretation, integration and comparison of observations and measurements collected from different sources and different brains.

Simulation

Simulation is a powerful instrument for understanding the human brain, which is a complex dynamic system with a multi-scale architecture. The complexity and versatility of the brain, and the variations from one brain to another, are major scientific challenges and are driving the development of simulation technology.

Brain-Inspired Technologies

EBRAINS offers brain-inspired tools and services to understand and leverage the computational capabilities of spiking neural networks. In contrast to standard deep neural networks, which consume considerable amounts of energy, spiking neural networks shed light on the human brain's ability to continuously learn and express higher cognitive functions while consuming much less power – only 20 W.

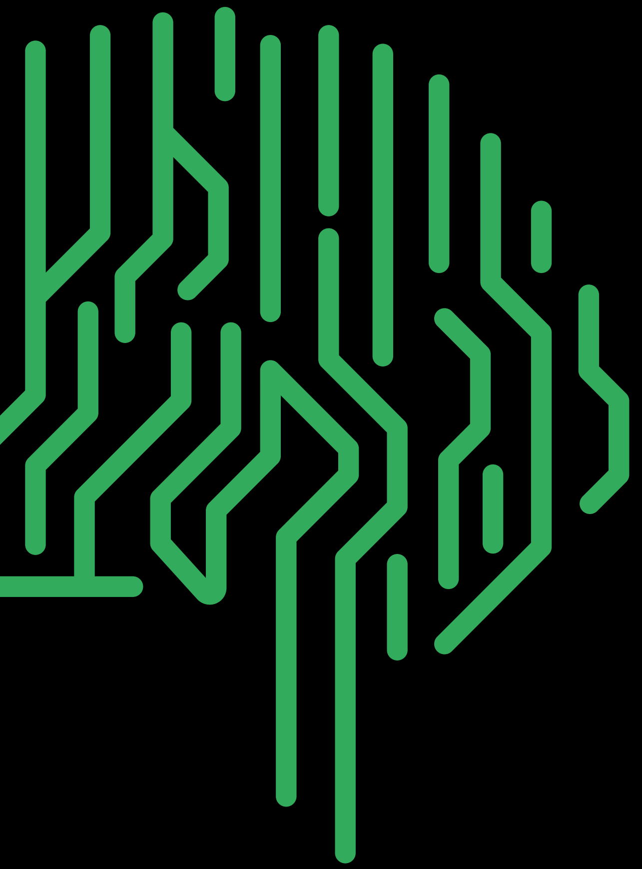
Medical Data Analytic

The Medical Data Analytics service currently hosts the Medical Informatics Platform (MIP), a unique EBRAINS platform providing advanced analytics for diagnosis and research in clinical neuroscience.

The road to EBRAINS

2013

The HBP proposal is chosen for funding, together with the Graphene proposal. The Flagship sets sail into the "Ramp-up Phase". Work begins on the six initial platform prototypes: Neuroinformatics, Simulation, Medical Informatics, Neuromorphic Computing, Neurorobotics and High-Performance Computing.



2012

The public proposal for the Human Brain Project as an FET Flagship is submitted to the European Commission. It summarises the goal of the HBP:

> "The Human Brain Project should lay the technical foundations for a new model of ICT-based brain research, driving integration between data and knowledge from different disciplines, and catalysing a community effort to achieve a new understanding of the brain, new treatments for brain disease and new brain-like computing technologies."

→ The HBP-PS Consortium, Lausanne (2012). The Human Brain Project: A report to the European Commission.

2016

The six initial platforms are formally opened during an event in Geneva.

A concept paper published in *Neuron* further specifies that the platforms are to become an integrated research infrastructure for brain research and related fields. A co-design approach is established to guide the development in response to scientific needs.

→ Amunts K, Ebell C, Muller J, Telefont M, Knoll A, Lippert T (2016). The Human Brain Project: Creating a European Research Infrastructure to Decode the Human Brain. *Neuron* 92(3), 574-581. doi: 10.1016/j.neuron.2016.10.046

2018

The ICEI Grant for interactive Supercomputing Services becomes part of the Flagship. It leads to the creation of the multi-purpose computing infrastructure Fenix within the HBP.

2019

A paper in *PLOS Biology* gives a first view of the HBP Joint Platform. The EBRAINS AISBL is founded.

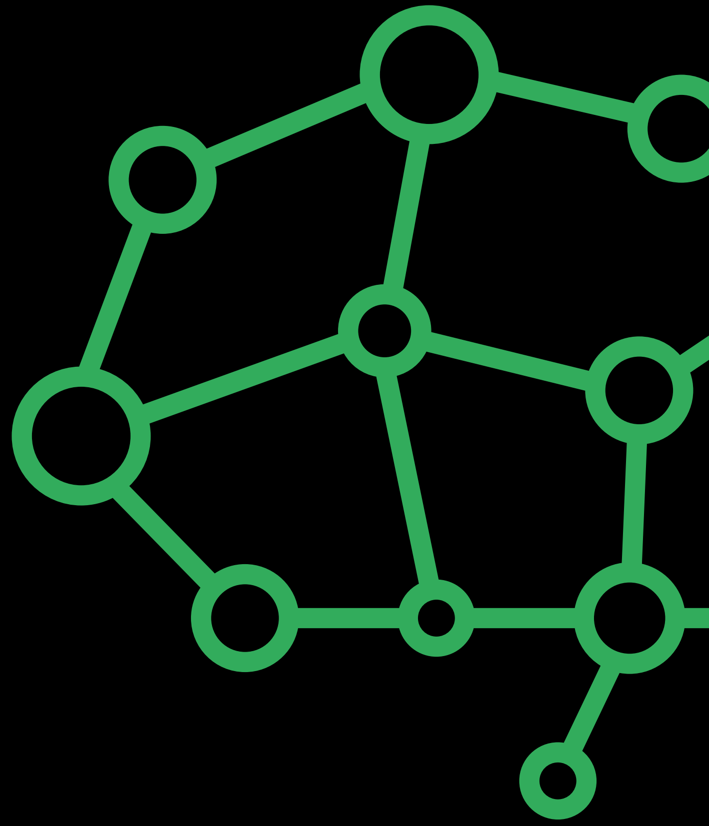
→ Amunts K, Knoll AC, Lippert T, Pennartz CMA, Ryvlin P, Destexhe A, Jirsa VK, D'Angelo E, Bjaalie JG (2019). The Human Brain Project—Synergy between neuroscience, computing, informatics, and brain-inspired technologies. *PLoS Biol.* 17(7): e3000344. doi: 10.1371/journal.pbio.3000344

2021

EBRAINS is selected for the ESFRI Roadmap of European Research Infrastructures.

EBRAINS is presented in a position paper in eNeuro highlighting a paradigm shift in brain research.

→ Amunts K, DeFelipe J, Pennartz C, Destexhe A, Migliore M, Ryvlin P, Furber S, Knoll A, Bitsch L, Bjaalie JG, Ioannidis Y, … Jirsa V (2022). Linking Brain Structure, Activity, and Cognitive Function through Computation. *eNeuro* 9(2) doi: 10.1523/ENEURO.0316-21.2022



2020

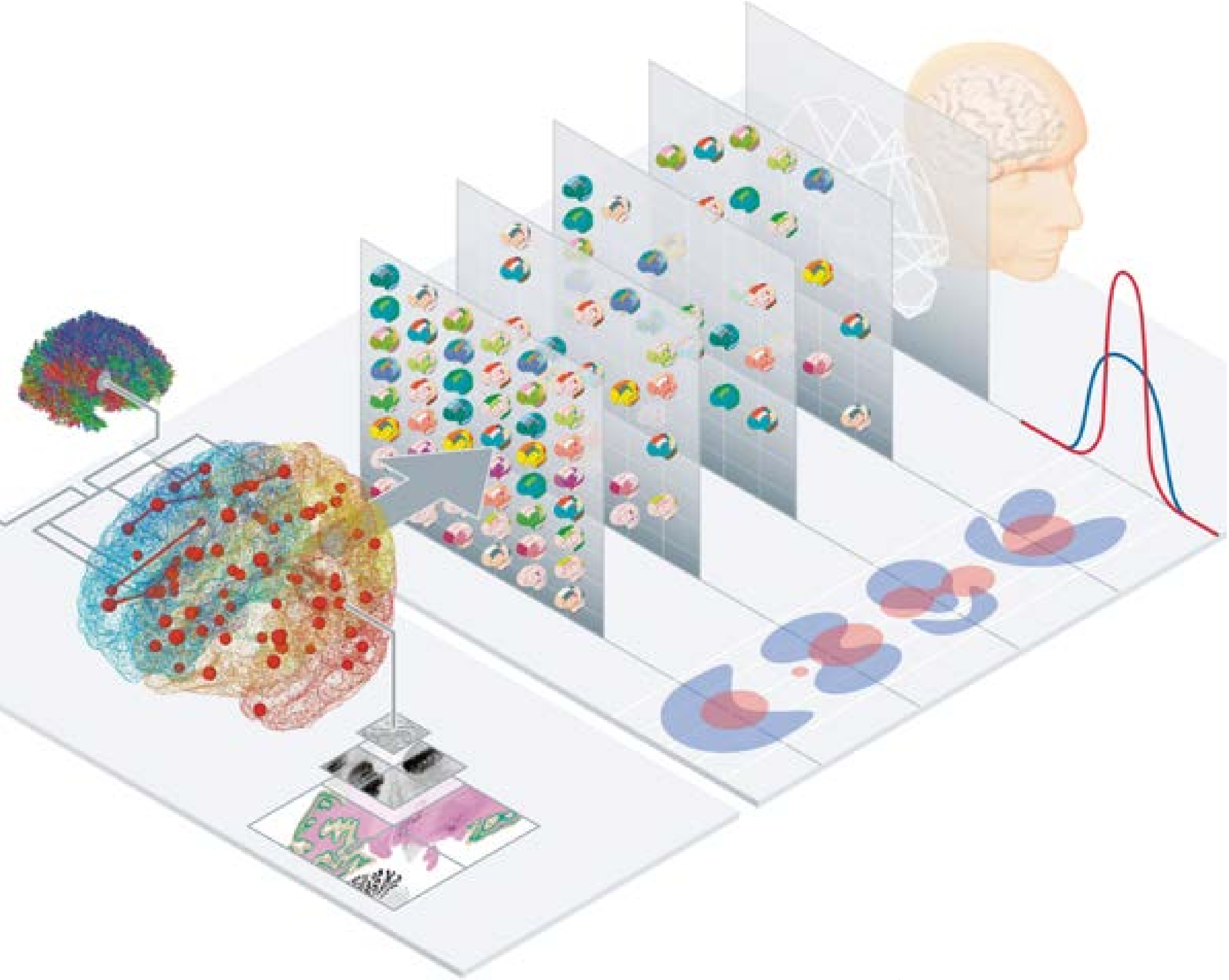
The EBRAINS research Infrastructure is formally launched with a central hub in Brussels. EBRAINS services become increasingly interlinked, allowing cross-platform workflows for complex scientific aims. EBRAINS Showcases are set up as example workflows.

2022

EBRAINS' first national nodes are being formed; more than 40 institutions from 12 European countries have joined EBRAINS. The infrastructure has become firmly integrated in the European brain research landscape.

Showcasing EBRAINS

How can the tools and services offered by the HBP's EBRAINS infrastructure enable cutting-edge research? Six interdisciplinary showcases demonstrate how EBRAINS is pushing the field of neuroscience forward.



Showcase 1 models brain complexity.

SHOWCASE 1

Degeneracy in neuroscience - when is Big Data big enough?

Even though every human brain has a different structure, individual brains function similarly. This is due to a phenomenon called degeneracy: multiple configurations can lead to the same functional outcome. For this reason, structural changes may cause loss of function in some brains and have no consequence in others. Degeneracy represents a key obstacle in neuroscience, as it makes it harder to understand how brain activity corresponds with brain function. HBP researchers tackle this challenge by building whole-brain models using detailed datasets on structural variability from a large cohort. They simulate the ageing process with these models in order to test hypotheses about ageing mechanisms by comparing their simulation results with *in vivo* data from older individuals of the cohort. The researchers are hoping to better understand the difference between healthy and pathological aging and apply their findings to other diseases, for example, in Parkinson's disease or other forms of dementia. The showcase establishes a link between the Multilevel Human Brain Atlas and The Virtual Brain simulator.

SHOWCASE 2

Improving epilepsy surgery with the Virtual BigBrain

Epilepsy affects over 50 million people worldwide, of whom one third are resistant to drugs. Thus, surgical removal of the area of the brain where seizures emerge is often the only option. However, the targeting of the epileptogenic tissue must be extremely precise, and current success rates still average at 60%. Using The Virtual Brain (TVB) simulator on EBRAINS, HBP scientists are developing personalised brain models to more precisely identify the location where seizures emerge in an individual patient's brain. A clinical trial is already ongoing in 11 French hospitals, involving almost 400 patients. The aim is to provide neurosurgeons with a precise tool to help individual surgery decisions and improve outcomes by increasing surgical precision. Via EBRAINS, the researchers are able to make multiple data sources compatible with TVB, for example, the Multilevel Human Brain Atlas, which includes the high-resolution BigBrain dataset that will help to enhance accuracy. EBRAINS also provides access to deep-learning applications and other computational tools to further boost the accuracy of the models.

SHOWCASE 3

Brain complexity and consciousness

Each year, about a million patients worldwide are sent to emergency services after a brain injury. While determining their levels of consciousness is crucial for deciding on treatment, this assessment is also difficult. Understanding fundamental mechanisms of consciousness could lead to better diagnosis and guide recovery. Clinical and research scientists of the HBP have established methods that allow assessing levels of consciousness directly from brain activity with unprecedented sensitivity. This approach involves non-invasive magnetic stimulation of the brain and measurement of the complexity of the brain's response with an electroencephalogram (EEG). Researchers are also developing virtual brain models to simulate different brain states and levels of consciousness (awake, asleep, anaesthetised, coma and more) and how they respond to stimuli. These computational models can integrate data across different scales of the brain – from the levels of neurons up to the whole brain – and simulate the dynamics of different brain states. Simulations have been made for three species: human, macaque monkey and mouse, which have matched models to recorded experimental data. A multi-centric clinical study is currently in preparation.

SHOWCASE 4

Object perception and memory

How do we perceive objects, navigate between them and remember where they are situated in a physical space? The neurobiological mechanisms at the basis of activities which are very natural to us still require deeper investigation. To better understand them, HBP scientists have built a robot capable of exploring and learning from the environment, taking inspiration from a rat. The rodent-inspired robot called WhiskEye has two camera eyes and 24 artificial whiskers arranged in a mechanical nose, which constantly palpate into the space around them. The similarities with rodents aren't just in appearance and behaviour: WhiskEye also employs an array of internal cognitive models inspired by biological brains. The neuromorphic architecture of its processors operates in pulses of electricity (spikes) instead of a continuous flux of information, emulating the way biological brains process information. One of the models is now able to recognise objects and reconstruct them from different viewing angles and whisker touches, improving navigation. As the robot learns to localise itself in space, scientists are gaining insights into how perception and cognition work as well as into how to build more advanced, neuro-inspired robotics platforms.

SHOWCASE 5

Dexterous manipulation – how the brain coordinates hand movements

It is easy to take for granted how complex our hand movements are, but the skillful manipulation of objects is one of the abilities that make humans unique. Even hand movements that may seem simple, like holding a cup of coffee, are actually complex and engage a large-scale brain network encompassing sensory, association and motor regions. This complexity makes it challenging to imitate the brain processes that underlie hand movements. HBP researchers are using the EBRAINS infrastructure to simulate a robotic hand developed by the Shadow Robot Company, achieving a human-like level of object manipulation. Artificial neural networks are trained with reinforcement learning at the Swiss National Supercomputing Centre and are constrained to better mimic the biological neural network involved in hand movement in the human brain. The artificial neural network learns how to move every joint of the hand in a simulation involving thousands of iterations. This work combines deep learning, robotics and neuroscience with the aim of shedding light on how the brain coordinates complex hand movements.

SHOWCASE 6

Brain-based technology to support safe human-robot collaboration

As factory floors become more and more automated, humans and robots will increasingly interact with each other in shared working environments. How should a robot move and behave to make sure humans around them avoid injuries and life-threatening situations? The HBP has developed a co-botics platform to explore methods for the safe collaboration between humans and robots in a shared space. Using the EBRAINS infrastructure, the scientists have built a virtual factory floor in which they can insert and simulate functional neural models developed within the HBP. These brain-inspired neural models involve perception, cognition, planning, motor control, real-time visual processing of information, object manipulation and more. The models can be integrated into the platform and model situations where robots and humans coexist and collaborate, with the goal of reducing uncertainty and potential harm. It is a testing ground for practical applications of HBP technology, including neuromorphic tools such as SpiNNaker, while also providing a way to integrate previously separate research threads.

Simulated robotic hand performing in-hand object manipulation (Showcase 5).

3D rendering of the vasculature network in the whole mouse brain imaged with light-sheet fluorescence microscopy by HBP researchers at the European Laboratory for Non-Linear Spectroscopy (LENS)/University of Florence.

INTERVIEW

"A data revolution"

New ways of sharing data are central to the HBP, and one of the main elements of EBRAINS is a data service for brain researchers. No one has a better overview of this area than HBP Infrastructure Development Director Jan Bjaalie. Here, Bjaalie, who is Professor at the Institute of Basic Medical Sciences of the University of Oslo and the EBRAINS Special Advisor for Neuroinformatics, shares his perspective on the challenges of data sharing and how EBRAINS is making it easier for researchers to organise, share and access information.

What is the importance of data sharing for the advancement of brain research?

Science as a whole is currently undergoing a data revolution, and the neuroscience field is no exception. It is a major shift and may be one of the most meaningful changes going on in research today. New ways of data sharing are absolutely essential to this.

From a purely scientific perspective, there were for a long time two primary ways of communication: scientific publications – journal articles, primarily – and meetings where people present and discuss their findings and ideas. What has been missing was access to the underlying experimental data that the researchers' interpretations and scientific articles are based on. Yet, scientific progress depends to a large extent on accessing the data underlying interpretations and conclusions. This is the big change: It is now fully possible to share original research data, as openly as possible (for data in general) and as restricted or controlled as necessary (for data from research based on human subjects).

This has a major impact: The leading journals in the world are all emphasising that we are in a reproducibility and replicability crisis. Reproducibility means that you can obtain the same results based on given data that has been collected. Replicability means that you can obtain the same results by redoing all the experiments. Reproducibility depends on access to the data, and replicability depends on good documentation of all the experimental steps. Both aspects are challenging and at the same time fundamental. It would be very hard to think that we are working efficiently today if our research was not reproducible and replicable.

Data sharing sounds so easy – what are the obstacles?

The reasons for not having access to the data were previously mostly technical and practical. Many of those aspects have been solved, and it is now possible to exchange large amounts of data in many areas of research.

Now, the question is: how do we do that in the most efficient way? Addressing this question has been one of the main motivations for constructing the EBRAINS Data and Knowledge services. EBRAINS invites the community to share data and builds a system to efficiently exchange and work with it. This is different from the past, where you more or less had to rely on information available in research articles, which often would only be the tip of the iceberg.

It also requires a cultural change: A major issue has been that data sharing is usually not part of the "business model" – the modus operandi of science. In contrast to publishing scientific articles, which is clearly part of doing research and which is also rewarded, it is less clear to researchers whether they will be rewarded if they share their data. This is one of the reasons explaining why less time and money are invested in data sharing than in publishing in journals.

> "Those who are preparing for the future will build data sharing into the research process."

In this regard, we are currently undergoing a change. The business model, the model for how we are doing science, is slowly changing, and those who are preparing for the future will build data sharing into the research process – FAIR* research by design'. But it will take time. With the EBRAINS Data and Knowledge services, we are trying to facilitate that process. We are learning a lot from the researchers sharing their data, allowing us to improve the data-sharing service over time. I believe that this will be very important for science in the future.

How do the EBRAINS data services help researchers share their data?

It is not enough to share your data just anywhere. If we are again comparing to scientific articles, we find that it makes a big difference whether you find information in a journal, and especially a renowned journal, or whether you just find some information somewhere on the web. The same is true for data: if you find data in a data repository, taken care of by a data-sharing service such as the one provided by EBRAINS, this makes a big difference. The benefits are many: Standardisation of the metadata – "the data describing the data" – makes it easier to find and interpret the data. A well-structured presentation of the data makes it easier to understand what the data represent and how they were generated. Finally, in addition to providing access to the data, EBRAINS provides information about relevant tools for visualisation and analysis, and in some cases, also workspaces for analysis of new combinations of data.

What is the role of the HBP in the EU and global context?

The HBP is developing the research infrastructure

EBRAINS and its data and knowledge services – without the HBP this would not have been set up. EBRAINS provides solutions for the field of neuroscience, the brain research area and brain-inspired research. There has not been any major service like this at the European level. Thus, we are filling a gap.

What makes EBRAINS unique at the global level is that it is more horizontal than any of the other infrastructure services in our field. There are many examples of what I would refer to as vertical initiatives: they go deep into a particular area, a particular category of data, and build around that. EBRAINS, in contrast, is open to any kind of neuroscience data, making it broader – more horizontal.

Access to the EBRAINS Data and Knowledge services is not restricted to Europe – it is open to the world. EBRAINS user accounts that you need for certain types of operation inside the system can be requested from almost anywhere in the world, if you have an institutional affiliation, or another reason that can be justified. Hence, EBRAINS plays in a global arena.

Is there collaboration with other global initiatives?

Yes, we collaborate with them, for example, in order to standardize metadata – the way that we describe data. Needless to say, standardisation is only meaningful if it is also done in a similar way by others. There is a joke saying that the nice thing about standards is that there are so many of them, but the point is that a standard is meaningful if it is followed in different places.

We develop standardisation in an international collaboration also connected to the INCF International Neuroinformatics Coordinating Facility, and it involves interactions with initiatives in different locations around the world. The aim is to establish standards that people will actually use.

We also exchange data and workflows across initiatives on a global level. For example, researchers from the US Brain initiative use some tools that originate from the HBP. And *vice versa*, we are also using data and tools from the US. There are many of these kinds of exchanges, which are built naturally into global science today, where the borders are dismantled.

With solutions for data sharing becoming more wide-spread, what are some of the longer-term impacts that could be expected?

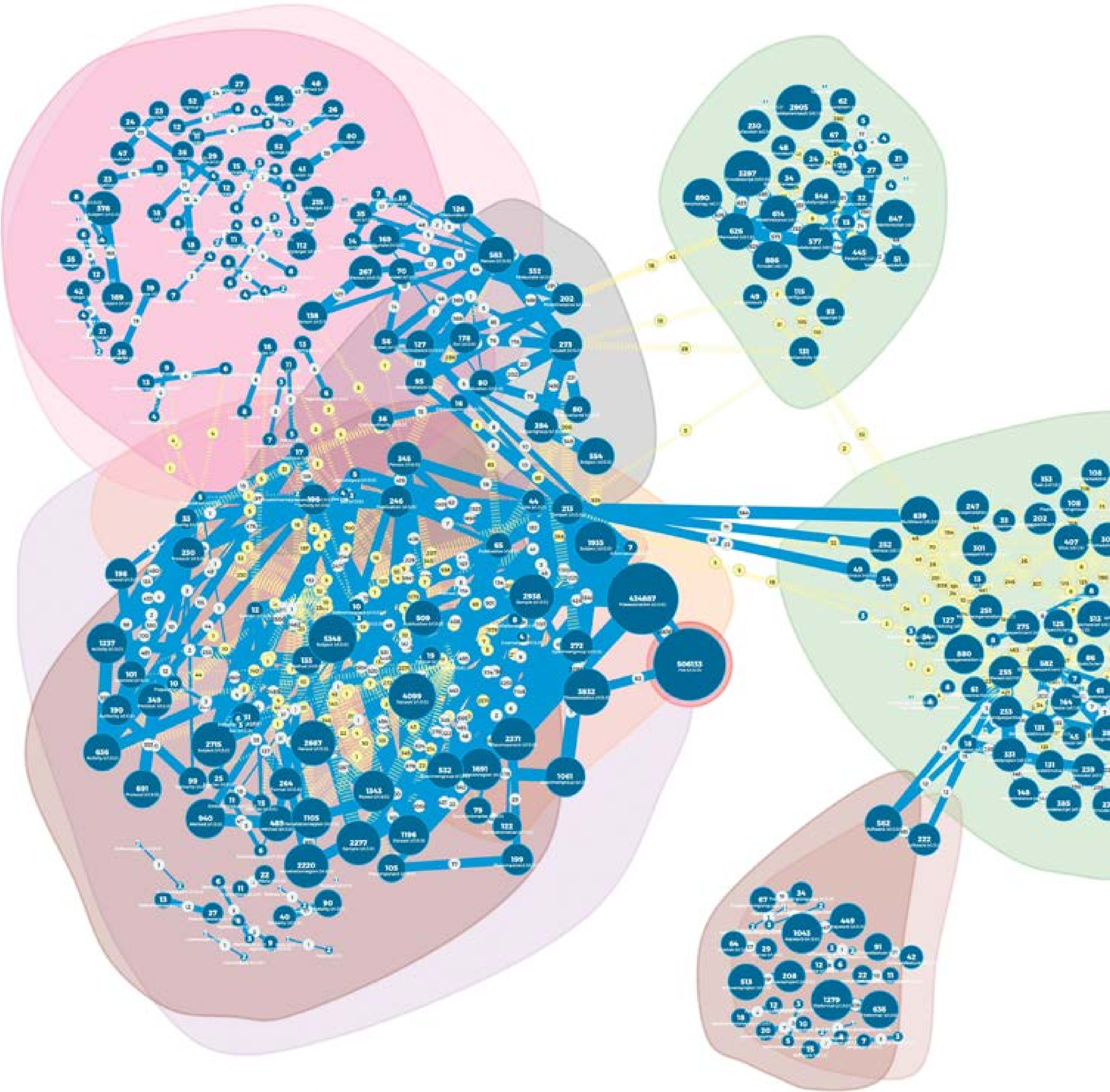
I believe that having access to data will become a natural part of how we do science. I think this is unavoidable, because it's just not logical not to have the data together with the interpretations. A field that doesn't solve this will not be successful in the future. We are contributing to a new kind of ecosystem for how we do brain science, including how we share data.

→ Eke DO, Bernard A, Bjaalie JG, Chavarriaga R, Hanakawa T, Hannan AJ, Hill SL, Martone ME, McMahon A, Ruebel O, Crook S, Thiels E, Pestilli F (2022). International data governance for neuroscience. *Neuron* 110(4):600-612. doi: 10.1016/j.neuron.2021.11.017

→ Nature Portfolio Webcasts (2022). Making small data big: Building a graph database from experimental brain research. https://www.nature.com/webcasts/event/making-small-data-big-building-a-graph-database-from-experimental-brain-research/

→ Bjaalie JG, Goble C, Sansone SA, Nakamura R, Martone ME (2022). Perspectives on Data Sharing and the New NIH Policy from the European Union. *Harvard Data Science Review* 4(3). doi: 10.1162/99608f92.bcd0b999

* FAIR describes data that is findable, accessible, interoperable and reusable.



Graph structure of the active and continuously developing content of the EBRAINS Knowledge Graph (derived from https://kg.ebrains.eu/statistics/).

“Conceptual clarity is key”

Brain research and emerging neurotechnologies can have ethical and societal implications – and even impact our self-perception as humans.

Arleen Salles, deputy leader of the Responsible Research and Innovation work package of the HBP, speaks about the ethical challenges facing neuroscience and how the HBP is addressing them. She is a senior researcher in Philosophy at the Centre for Research Ethics and Bioethics (CRB) at Uppsala University and leads NeuroeticaBA (NEBA) in Buenos Aires, Argentina.

Which ethical issues emerge from the Human Brain Project, and how are they addressed?

From its inception, the HBP has been aware that its research was likely to have ethical, philosophical and societal implications. On the one hand, brain research touches on questions that go to the heart of who we are. On the other hand, it can have immediate and long-term practical implications. For this reason, the HBP ethics and society team has developed a number of structures, mechanisms and strategies to identify, reflect upon and manage the ethical, social and philosophical issues raised.

The ethics and society team, constituted by social scientists, ethicists and philosophers, has been tasked with implementing RRI (Responsible Research and Innovation) in the HBP, and we have done so working across the whole project and engaging with scientists and other stakeholders. Our goal is to strengthen the ethical robustness of the research and of the project.

Which issues does the ethics and society team work on?

The issues range from things that could happen during the research process to potential implications of the work. There are practical issues such as research integrity, data governance and the potential for dual use and misuse of neuroscientific findings, but also more philosophical ones related to issues raised by studies on consciousness, for example. Regarding the more practical and urgent questions, in addition to scientific publications, we have issued three Opinions, which are joint research documents on topics identified as particularly relevant for the HBP. Each of the Opinions focuses on one topic: data protection, dual uses and misuses and artificial intelligence. We identify main concerns and provide recommendations for different actors and stakeholders.

We have also addressed more theoretical concerns: to illustrate, some HBP scientists conduct research on and build models of the brain for many different uses, others try to understand the underpinnings of conscious processes. In addition to the practical impact of these types of research, there is also the issue of the potential impact of the findings on a number of beliefs that people may have about what the brain is and what humans are.

A significant aspect of the work of the neuroethics team in the HBP has been conceptual analysis and clarification of the main scientific and philosophical notions. Conceptual clarity is essential to understanding the problems that science addresses and to identifying and managing the ethical and social issues raised. This also requires special attention to the terminology used. Language matters, it shapes concepts. How we use terms, and when we use them can influence perception and impacts the ethical debate.

> “Philosophers, ethicists and social scientists work collaboratively with the neuroscientists to explore ethical and societal dimensions of the research.”

What are the biggest challenges for neuroethics?

One obstacle is the somewhat prevalent view that all there is to ethics is compliance. The belief that complying with the law and with some basic ethical principles is enough hinders careful reflection on the ethical aspects of the research and its potential impact. Compliance is, of course, very important, but it is the bare minimum.

Another challenge is: How can we enhance the integration of ethical and societal considerations with science? In the HBP, we have acknowledged this challenge, and as the project evolved, we have created a number of mechanisms and structures in order to make implementation easier. But we are trying to do more. In this respect, we have also joined forces with the International Brain Initiative’s Neuroethics Working Group to jointly address the issue of neuroethics integration, some existing roadblocks (conceptual, structural) and how to measure successful integration.

So how do you achieve real integration of ethics in a large scientific project like the HBP?

The HBP is organised into a number of work packages that focus on different research questions. Within these work packages, we now have embedded ethics tasks. These embedded tasks are a very important structure to implement ethics within the research, because we are integrated into the scientific work instead of working as an external group. Philosophers, ethicists and social scientists work collaboratively with the neuroscientists to explore ethical and societal dimensions of the research.

Embedding ethics in this way reinforces the idea that ethics is part of the research itself. We are not the ethics police but colleagues working together towards understanding what the issues are and what we can do to solve them. This builds trust and enables genuine collaboration insofar as it promotes the idea that ethical reflection is part of the scientific process.

You are one of the co-authors of a position paper on the future of digital brain research that introduces the concept of a digital twin of the human brain. What are the ethical considerations around this concept?

We were very much involved in the discussion around the conceptual issues raised and very mindful of the fact that we need to be as clear as possible about the meaning of the terms we use.

Considering that terms such as "virtual" and "twin" may have different connotations and even meanings for different publics, lack of clarity regarding the concepts of the "virtual brain" and the "digital twin of the brain", on what they are and what they are intended to do, might increase hype and, thus, lead to either unjustified worries or unrealistic expectations.

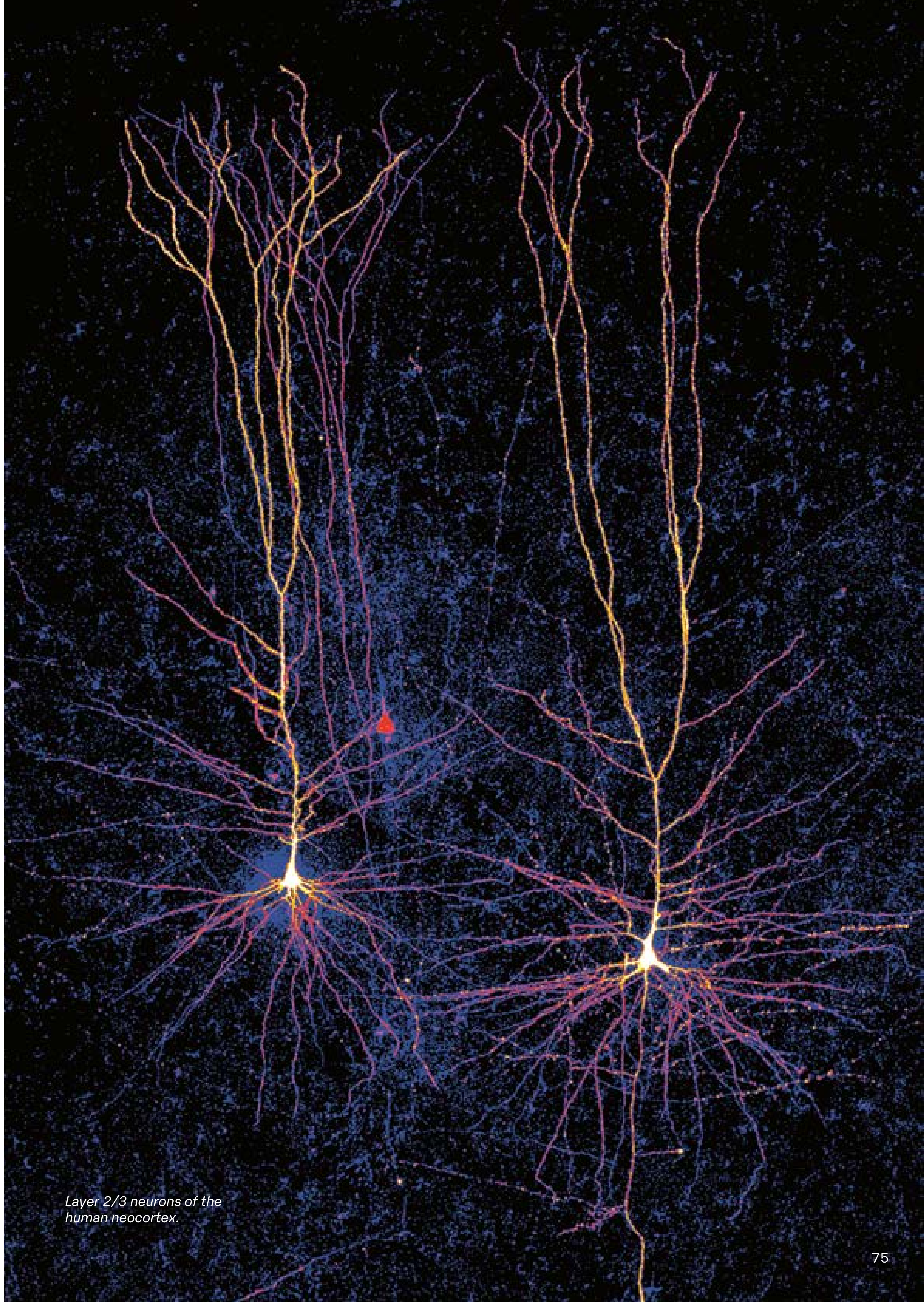
The current version of the paper that you are referring to makes clear distinctions between these concepts of different brain models (more about the digital twin concept on p. 81). This will counteract possible misconceptions around these ideas.

Considering the importance that rich engagement with different stakeholders has for the development of responsible science and innovation, conceptual clarity is key.

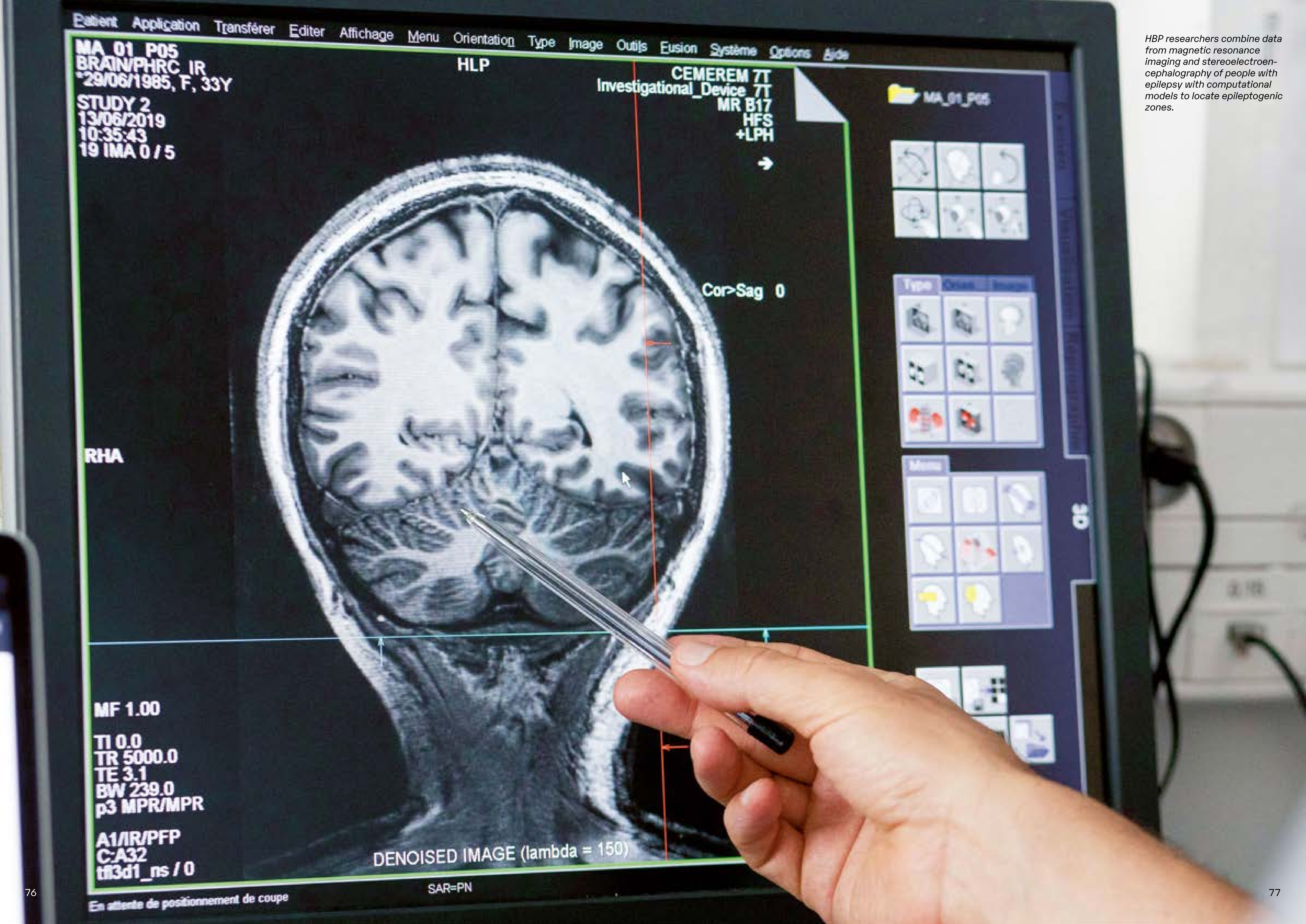
> "Language matters, it shapes concepts. How we use terms, and when we use them can influence perception and impacts the ethical debate."

→ HBP SP12 and WP9. (2021). Social, ethical & reflective work in the Human Brain Project (Version 1). *Zenodo*. doi: 10.5281/zenodo.5521270

→ Amunts K, Axer M, Bitsch L, Bjaalie J, Brovelli A, Caspers S, Cichon S, Cools R, Changeux JP, Costantini I, D'Angelo E, … Zaborszky L (2022). The coming decade of digital brain research – A vision for neuroscience at the intersection of technology and computing (Version 3.0). *Zenodo*. doi: 10.5281/zenodo.7319334



Layer 2/3 neurons of the human neocortex.



HBP researchers combine data from magnetic resonance imaging and stereoelectroencephalography of people with epilepsy with computational models to locate epileptogenic zones.

"A systematic approach will be essential to meet the challenges of the future"

The Human Brain Project launched its final phase in April 2020 and will conclude in September 2023. We spoke to HBP Scientific Director Katrin Amunts and EBRAINS Chief Science Officer Viktor Jirsa about how the HBP has permanently changed the way brain research is carried out and how they envision the future of the field of digital brain research.

Katrin Amunts is a full professor and Director of the C. and O. Vogt Institute for Brain Research at Heinrich-Heine University Düsseldorf and Director of the Institute of Neuroscience and Medicine (INM-1) at Forschungszentrum Jülich. Her research focuses on organisational principles of the brain and how its structure relates to function and behaviour. Her team has developed the Julich Brain Atlas.

Viktor Jirsa leads the HBP's multi-scale connectome work package. He is Director of Research at CNRS (Centre National de la Recherche Scientifique) and Director of the Inserm Institut de Neurosciences des Systèmes (INS) at Aix-Marseille University. His research is focused on gaining a deeper understanding of the mechanisms underlying the emergence of brain function and dysfunction from network dynamics. His team leads the development of The Virtual Brain – personalised models to simulate the human brain.

In an overview paper published in *eNeuro*, you state that the field of neuroscience is "at the beginning of a new paradigm for understanding the brain." What characterises this paradigm shift?

Amunts: The way we study the brain has changed fundamentally in recent years. In the past, separate communities have often focused on specific aspects of neuroscience such as cognitive neuroscience or cell biology, and the problem was always how to link the different worlds, for example, in order to explain a certain cognitive function in terms of the underlying neurobiology. The Human Brain Project has brought together communities from different disciplines and countries in a large-scale approach to work collaboratively on a common goal.

The human brain is one of the most complex systems known, and we still don't understand many of the basic principles of its function. One challenge is that the brain is organised on multiple spatial and temporal scales. Consequently, brain data often are very large and complex. They need to be integrated in order to gain a comprehensive understanding of this extremely complex system, and we need to link data about structure and function. In the Human Brain Project, we have tackled this challenge by building a new digital, collaborative research platform (EBRAINS). Building such a platform was the focus of the Human Brain Project from the very beginning. EBRAINS enables the integration of data from various research groups from different countries and with distinct approaches. It provides a range of different digital tools and services supporting brain researchers. This also includes access to powerful supercomputing systems via the infrastructure Fenix, which has been set up by Europe's leading supercomputing centres as part of the HBP and will serve communities beyond brain research.

How have technological advances affected brain research?

Amunts: Modelling and simulation but also deep-learning and machine-learning-based analysis are becoming increasingly relevant. Digital tools allow us to perform new experiments that would otherwise not have been possible in the human brain – or even in the mouse brain. In this way, technological advances have opened up a second line of research in addition to the empirical work.

Jirsa: We are now combining a bottom-up with a top-down approach. The bottom-up approach tries to explain a very complex function starting from the building blocks in the brain and is applied, for example, in the construction of computational brain models. The top-down approach starts from behaviour and cognition and then tries to better understand what the biological substrate of a certain function is. In the past, these two approaches were often discussed as excluding each other – this has been regarded as one of the biggest challenges in neuroscience. Now, we see it as a necessity to take a mixed approach to understand the brain. You need to integrate the two and use one approach in order to better explain the other and *vice versa*. The reason for this is the brain's multi-scale and nonlinear nature, meaning that, on the one hand, multiple mechanisms within the brain can give rise to the same behaviour – a property referred to as neurodegeneracy – and, on the other hand, the same regulatory system can induce multiple distinct behaviours. In order to find a good solution within this complex system you need to tackle it from two sides using the bottom-up and top-down approaches in synergy.

Did it require a large-scale initiative like the Human Brain Project to achieve the paradigm shift that you describe?

Amunts: Yes, for several reasons. Firstly, the large number of researchers involved: To advance a research field to this extent, a critical mass of researchers needs to be united under a common umbrella. It required researchers from the whole of Europe because the different countries and institutions have different strengths. With this large-scale approach, we were also able to cover the full spectrum of human brain research.

The second reason is the time span. Developing collaboration but also technological solutions that go beyond one's own research discipline simply needs a lot of time and also systematic planning with a time perspective that allows for the achievement of ambitious goals.

> “Digital tools allow us to perform new experiments that would otherwise not have been possible in the human brain.”
>
> Katrin Amunts

The third reason is that the brain is the most complex research subject you can have and this requires a flagship approach rather than a multitude of single small projects which, in the end, do not come together. What makes the Human Brain Project stand out is that we have very strong specialised research projects in the individual disciplines and, at the same time, we also have a common understanding of how we want to decode the human brain – these have resulted from intense scientific exchange and discussions over many years.

Jirsa: And it is not enough that the different domains are connected and able to speak to each other. You also need to have dedicated research personnel that enable interoperability between the domains. For example, you need informaticians who develop tailored application programming interfaces that enable applications of different domains to communicate with each other. We have achieved major breakthroughs thanks to an exceptionally high level of interoperability. This has been critical and its emergence was only possible within the framework of the Human Brain Project.

How can this type of large-scale, collaborative research be continued after the HBP flagship ends in 2023?

Jirsa: The first prerequisite, and perhaps the most important one, is that EBRAINS is now on the ESFRI Roadmap of European research infrastructures – clear recognition of its lasting value to the research community. With EBRAINS, we have the platform and the tools to continue brain research in a highly collaborative way after the flagship, and it will now be crucial that the infrastructure is continuously developed according to the needs of the research community.

The field is progressing from generic modelling at low resolution to high-resolution models with applications in clinics. Projecting this development into the future, our vision is to build digital twins of individual brains: virtual brain models that are continuously informed and updated by real-world data. We can, for example, feed patient-specific functional and structural data to the digital twin, but potentially also environmental data. It is important to note, however, that such models will not capture every single detail – rather, they would always be constrained by data from their biological counterpart. Such virtual models allow us to perform simulations under the same conditions as appropriate for the individual patient to improve diagnostics and therapy. They also allow us to test basic research hypotheses about the brain's organisation, and they will pave the way for novel neuro-technology.

Amunts: We are currently discussing the future of the research field beyond 2023 with the scientific community at large. Together, we are writing a position paper identifying common goals and outlining our scientific vision for the next decade. We have published the vision paper on Zenodo and have invited the entire community to enter the discussion by commenting. We aim to engage a broad community beyond the Human Brain Project and hope that this open discussion will drive progress in the broader field of neuroscience. A systematic approach will be essential to meet the challenges of the future – this is true for brain medicine and technology alike.

In November 2022, the third version of the science vision position paper was published (Amunts et al. Zenodo 2022), with contributions from 80 authors from 15 countries and 90 institutions.

Categories of digital brain models

Brain models
Brain models are digital representations of the brain. The term is used in different contexts; common examples include digital atlases, artificial neural networks, anatomical models, network models, cognitive and behavioural models and mathematical and data-driven models.

Personalised brain models
Personalised brain models are special types of models that are personalised by integrating specific data of one individual into a more general model (e.g., as enabled by the Virtual Epileptic Patient).

Digital twins
Next-generation personalised brain models that continuously evolve by being informed with real-world data. They are designed in a purpose-driven way, integrating data relevant for a specific research question.

Full replica
The idea of a complete digital representation of all aspects of a brain at all levels (hypothetical concept)

The position paper “The coming decade of digital brain research” presents the digital twin of the brain as a future vision for neuroscience. It clearly distinguishes the concept of a purpose-driven digital twin from other types of virtual brain models (Amunts et al. *Zenodo* 2022).

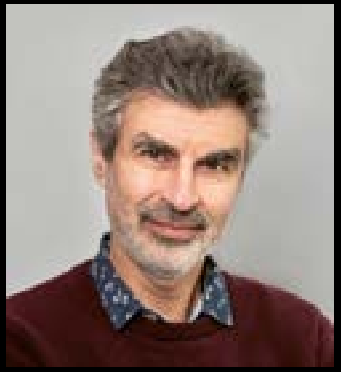
→ Amunts K, DeFelipe J, Pennartz C, Destexhe A, Migliore M, Ryvlin P, Furber S, Knoll A, Bitsch L, Bjaalie JG, Ioannidis Y, … Jirsa V (2022). Linking Brain Structure, Activity, and Cognitive Function through Computation. *eNeuro* 9(2) doi: 10.1523/ENEURO.0316-21.2022

→ Amunts K, Axer M, Bitsch L, Bjaalie J, Brovelli A, Caspers S, Cichon S, Cools R, Changeux JP, Costantini I, D'Angelo E, … Zaborszky L (2022). The coming decade of digital brain research – A vision for neuroscience at the intersection of technology and computing (Version 3.0). *Zenodo*. doi: 10.5281/zenodo.7319334

HBP researchers like Philipp Schlömer use 3D polarised light imaging to visualise brain fibres at high resolution.

What others say about the HBP

“The investment in neuroscience, in particular forming a critical mass of talent and forming explanatory theories of experimental data, key elements of HBP, are very likely to be crucial ingredients in bridging the gap between current state-of-the-art in AI and human-level intelligence.”



Yoshua Bengio

Leading AI expert, A.M. Turing Award recipient, Full Professor at Université de Montréal and Founder and Scientific Director of Mila – Quebec AI Institute

Angela Friederici

Leading expert in neuropsychology and linguistics, Director at the Max Planck Institute for Human Cognitive and Brain Sciences in Leipzig, 2014-2020 Vice President of the Max Planck Society

“The HBP is a thriving neuroscientific enterprise providing a powerful basis for advances in brain science and their clinical and industrial implications. It demonstrates impressively that insight into the fundamental mechanisms of brain function precedes and leads to effective applications. This project is a first successful step which must be followed by further continuous steps.”

Ivica Kostović

Founder and Honorary Director of the Croatian Institute for Brain Research, former Croatian Minister of Science and Technology (1995-98)

“HBP achievements will have a major impact on prevention, diagnosis and treatment of mental and neurological disorders with benefits at the personal level and for society at large.”

“The Human Brain Project has in an unprecedented way enabled cross-European collaborations with excellent neuroscience that otherwise would not have happened. The next big step is to capitalise on the experiences and also to deepen the knowledge to bring it closer to resolve some of the big challenges in brain disorders, such as epilepsy and loss of neurological function.”

Gitte Moos Knudsen

Professor at University of Copenhagen, Chair of Neurobiology Research Unit, Rigshospitalet, Chair of Center for Experimental Medicine Neuropharmacology, member of the HBP Science and Infrastructure Advisory Board (SIAB)

Simon Privett

Advocate for greater awareness and inclusion of people with epilepsy in clinical trials and government policy, has formed and leads epilepsy patient expert groups

“Computational neuroscience gives us interdisciplinary approaches to develop novel diagnostic tools and treatment options not just for epilepsy, but potentially for learning disabilities and other brain conditions. The possibility of faster, more reliable diagnosis, more effective treatments, and improved prognosis means that there are brighter futures in sight for people currently not benefitting from the existing treatment pathway.”

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Markus Axer, Katrin Amunts, INM-1, Forschungszentrum Jülich and Roxana Kooijmans, Netherlands Institute for Neuroscience (p. 1, top, 52–53, 88, left); sprind.org (p. 1, bottom, 42–43, left, centre, 88, right); Katrin Amunts, INM-1, Forschungszentrum Jülich (p. 2, 17, 87); EPFL/Jamani Caillet (p. 4, 54); Hartmut Mohlberg, Katrin Amunts, INM-1, Forschungszentrum Jülich (p. 5, 14, 16); EBRAINS, https://kg.ebrains.eu/statistics/ (p.5, 70–71); Mareen Fischinger (p. 7, 12–13, 15, 18, right, 79, left, 82–83); BigBrainProject (CC BY-SA) (p. 17, left); Sascha Münzing, Nicole Schubert, Philipp Schlömer, Felix Matuschke, David Gräßel, Markus Axer, Katrin Amunts, INM-1, Forschungszentrum Jülich (p. 18, left); Markus Axer, INM-1, Forschungszentrum Jülich (p. 19); Charité/Petra Ritter (p. 20–21, 23); INS UMR 1106 (p. 22, 76–77); Modified from Benavides-Piccione et al. (2020). doi: 10.1093/cercor/bhz122 (p. 24–25); 2020 Blackrock Microsystems, LLC (p. 26); University Miguel Hernández (p. 28); Xing Chen (p. 29); Russ Juskalian (p. 31); Coma Science Group/GIGA Consciousness – CHU Liège-ULiège (p. 32); Ignacio Abadía (p. 35); Human Brain Project (p. 36); TU Munich Neurorobotics (p. 37); Forschungszentrum Jülich/Sascha Kreklau (p. 38–39); Heidelberg University (p. 41); Forschungszentrum Jülich (p. 43, top); ICEI Consortium Partners (p. 44–45, 47); Joanna Schwenkgrub (p. 48); Viktor Jirsa (p. 62, 79, right); Mario Senden (p. 65); Francesco Saverio Pavone (p. 66–67); Christian Wangberg (p. 68); Albert Gidon & Matthew Larkum, Humboldt University of Berlin; Felix Bolduan & Imre Vida, Charité – Universitätsmedizin Berlin (p. 75); Camille Gladu-Drouin (p. 84, top); Uta Tabea Marten, fotografa/Berlin (p. 84, bottom).

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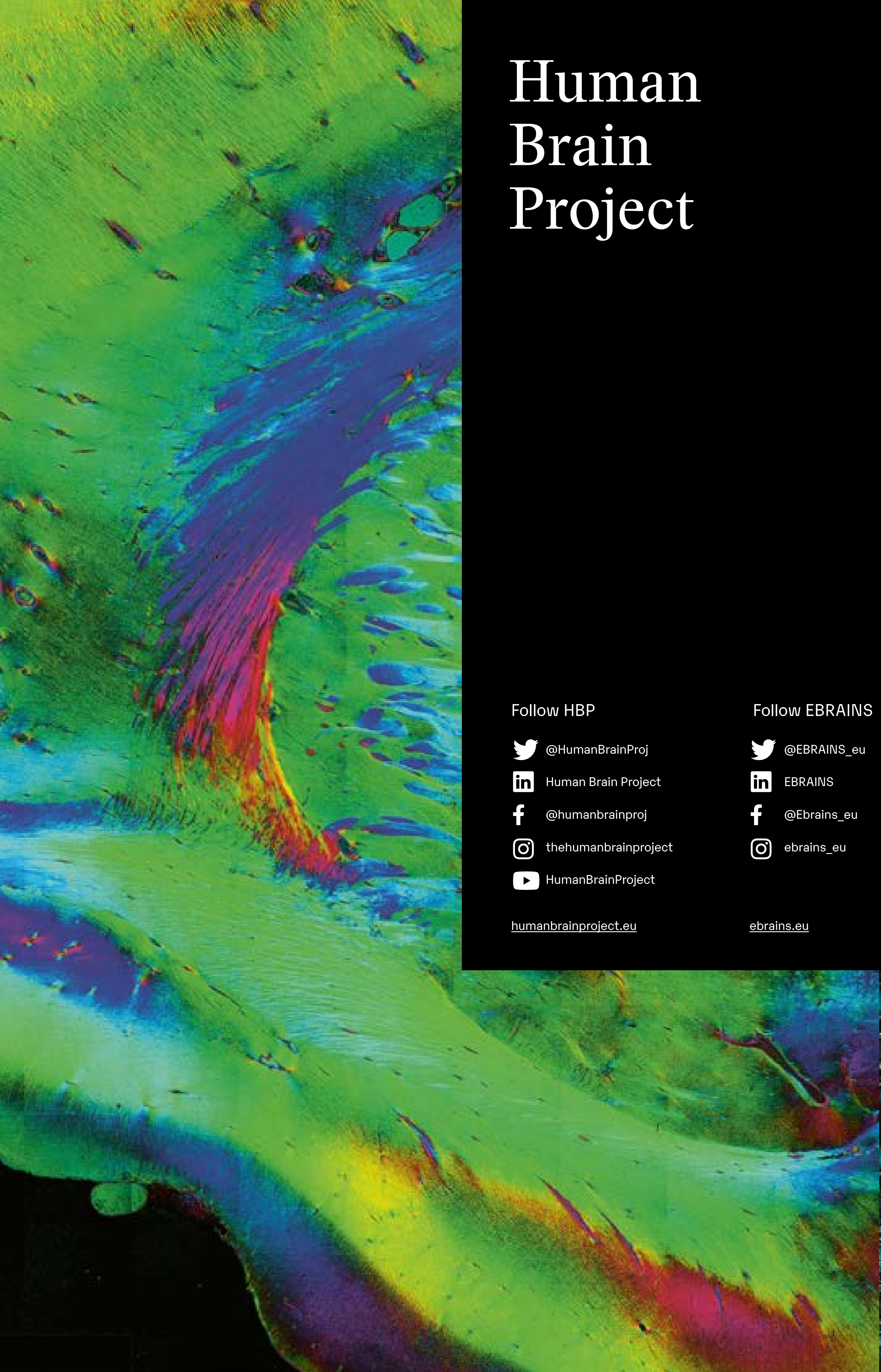

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