The Health Data Cloud & the Virtual Brain Cloud platforms of EBRAINS:

Market & Innovation Report

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EBRAINS

UNIVERSIDAD POLITÉCNICA DE MADRID

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Polytechnic University of Madrid

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Abstract:	The Health Data Cloud (HDC) is a consortium associated to the Human Brain Project/EBRAINS, coordinated by the Charité University Berlin, and based on the trusted Virtual Research Environment (VRE) operated at Charité, with the main objective of providing services for the management, analysis, sharing and storage of sensitive data – such as human brain data - in the neuroscientific field, through a federated platform with General Data Protection regulation (GDPR) accreditation. Its versatility facilitates integration with supporting technologies, extending analysis capabilities for the researcher, such as The Virtual Brain (TVB) to create and simulate personalised brain models – so called human digital brain twins. This report explores technological exploitation possibilities and innovation strategies for HDC/TVB services targeting neurodegenerative diseases such as Alzheimer's and Parkinson's disease. Based on the Horizon Scanning methodology, it identifies the most recent international developments from academia, science, and industry, including search trends related to these diseases. In terms of strategic analysis, a SWOT matrix is initially developed, identifying the internal capacities and the external situation that could affect the positioning of HDC/TVB. In-depth interviews are conducted with neuroscientists and neurotechnology experts to learn about their experience and other assessments related to the use of brain simulation tools and the processing of data in their studies. In terms of business models suitable for innovation environments, a Lean Canvas Model (LCM) adapted to the case study is created and finally, the Abell model is applied, defining the three dimensions of the business, with proposals for innovation and transfer.
Keywords:	EBRAINS, Health Data Cloud, The Virtual Brain, Innovation Strategies, Business Intelligence.
Target Users/Readers:	Brain health professionals, healthcare decision makers, neuroscientists, data scientists, business & innovation leaders.

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INTRODUCTION

The Health Data Cloud (HDC) is a federated research platform conceived to management, analysis, sharing and storage of sensitive neuroscientific data arising from the trusted Virtual Research Environment (VRE) of Charité University Medicine Berlin, with GDPR accreditation. The structure promotes collaborative work from EBRAINS, supported by the consortium participants and its research team, enabling interoperability with other open-source cloud services, such as The Virtual Brain (TVB), to analyse data at different scales for brain simulation and digital twins' creation, strengthening its value proposition.

The growth of data in neuroscience, the rise of artificial intelligence (AI) and the use of neurotechnologies claim efficient innovation ecosystems to address current challenges in the field of neurodegenerative diseases. According to UNESCO (2023), the annual number of publications in neuroscience has tripled since 2000 reaching over 90,000 publications a year in 2021 and, among other aspects, neurotechnological trends are leaning towards more advanced Brain-Computer Interfaces (BCI), epilepsy detection solutions, neuroimaging analysis and brain deep stimulation (DBS), mainly. Together with these advances, regulations and the use of bioethical principles are intensifying on an international scale, in order to promote responsible technological development, as well as the protection of privacy and personal identity.

More and more research units involved in the healthcare system -both public and private- are looking for accurate, efficient, easy-to-use tools that comply with the appropriate standards to manage their data in the lowest time and cost possible. In turn, the availability of open-source initiatives to share databases contributes significantly to the generation of data-driven models and AI (Silva-Spínola et al, 2022), however, they remain limited both for validating hypotheses and for training algorithms, considering the complexity and variety of neurological diseases. A first approach and from an innovation perspective, this report aims to deepen on the mission of the HDC/TVB platform applied in Alzheimer's Disease and Parkinson Disease in its current phase or proof of concept, together with the exploration of its possibilities of exploitation and transfer results. To this end, we will attempt to delimit the market in which it operates, identify technological trends, detect the most relevant needs related to data management and sharing by potential users from the academic and industrial sectors, as well as design strategies for its positioning.

II. OBJECTIVES OF THE REPORT

2.1 General objective

- To evaluate exploitation, commercialization, and innovation strategies for HBP/EBRAINS Health Data Cloud/Virtual Brain Cloud services targeting neuroscience and medical SMEs and start-ups in Europe.

2.2 Specific objectives

- To explore technological trends in the health data services industry aimed at the study of neurodegenerative diseases -mainly in Alzheimer's Disease (AD) and Parkinson's Disease (PD).

- To analyse strategies for exploitation and commercialization of services for other neurological diseases from the HDC/TVB platform.
- To understand the perspective of current and potential users on the use of data-driven model innovation, analytics, and simulation services, including HDC/TVB.
- To discover areas for improvements, innovation and formulate proposals to strengthen its market positioning through strategic analysis.

2.3 Research questions

- What are the technological, scientific, and ethical trends in data modelling and computational simulation focused on Alzheimer's and Parkinson's disease in Europe? What is the expected growth in this sector?
- What are the closest competitors of HDC/TVB worldwide? What positioning strategies do this companies/projects follow in the industry?
- What are the weaknesses and strengths of the HDC/TVB platform? What is the perspective of potential users on the use of these technologies?
- What products or innovations have been introduced in this industry recently?

III. STATE-OF-THE-ART AND THEORETICAL FRAMEWORK

3.1 The Health Data Cloud, the Virtual Brain Cloud and the Virtual Research Environment: Technology presentation and services

The Health Data Cloud (HDC) or Virtual Brain Cloud (integrated in the Virtual Research Environment, VRE) is a consortium led by Charité University Medicine Berlin and composed of members of the Human Brain Project (HBP) and EBRAINS, whose main mission is to provide services for the management, processing, simulation and analysis of sensitive data, aimed at the prevention and treatment of neurodegenerative diseases. The origin of the Health Data Cloud/Virtual Brain Cloud[1] go back to the EOSC project Virtual Brain Cloud[2] that united the efforts of several EU entities including partners that were participants in the HBP Flagship Initiative and the IMI-AETIONOMY project, with a focus on Alzheimer's and Parkinson's Disease (VirtualBrainCloud, 2019). We consider that HDC promotes a holistic approach to the study of brain dynamics and facilitates a collaborative space in which users share and integrate brain imaging data for the simulation of disease models through The Virtual Brain platform.

The Health Data Cloud/Virtual Brain Cloud services are developed in synergy with the Germany National Research Data Infrastructure (NFDI)[3] initiative. The main mission of NFDI is to provide tools to ensure that current research data from the research community follows the FAIR principles (Findable, Accessible, Interoperable and Reusable) for the results of any study to be reproducible, open to other researchers and linked to data within and outside Germany. It was initiated by the German research foundation DFG and consists of non-university higher education institutions, research departments, academies, and other publicly funded institutions (Klingner et al, 2022). Some of the participating institutions maintain close collaboration with EBRAINS, The International Neuroinformatics Coordinating Facility (INCF), The Canadian Open Neuroscience Platform (CONP) and the DANDI platform (Wachtler et al, 2020); a remarkable support for HDC/TVB for data management, protection, and storage.

To reach the goal of a personalised digital medicine, a series of cloud services have been created such as (Schirner et al, 2022): The Virtual Brain (TVB), TVB Image Processing Pipeline, Multiscale Co-Simulation, TVB-HPC, Fast-TVB, Bayesian Virtual Epileptic Patient, TVB Mouse Brains, TVB-ready dataset, TVB atlas adapter, and INCF TVB training space; tools that are part of the TVB software. In turn, the associated interfaces (Siibra, Rest-Api, Unicore) add core services such as the Multilevel Human Brain Atlas, Knowledge Graph, High Performance Computing, Wiki, Office, Jupyter Lab, OpenShift (see details in the figure 1). In order to introduce the platform under study and address its context, some of these services are described in a practical way, starting with those tools related to data and image processing, passing through the core services of TVB as well as other applications for simulation and case studies of interest in clinical practice.

[1] Is financed from the H2020 program with a budget of 15016343,09 euros.
[2] https://eosc-portal.eu/about/eosc-projects
[3] https://www.nfdi.de/?lang=en

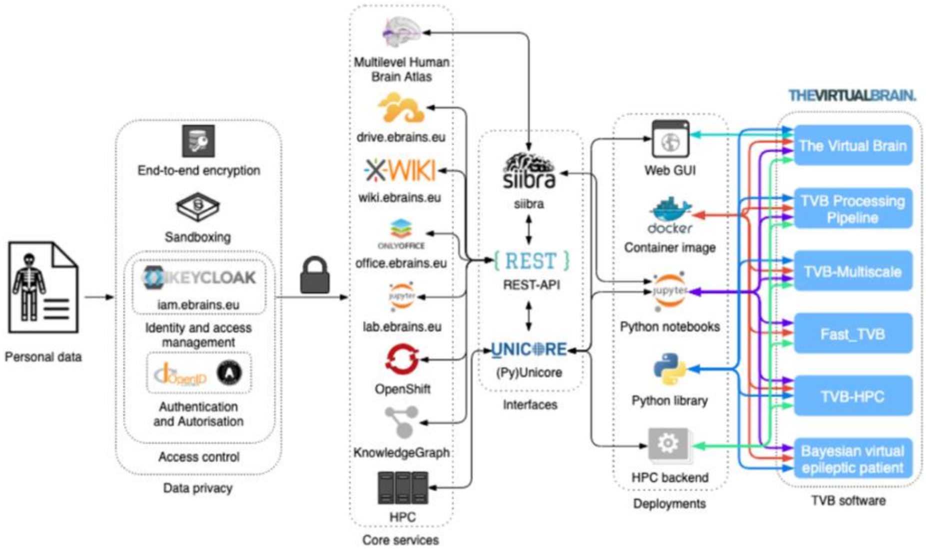


Figure 1. TVB on EBRAINS Cloud Services. (Schirner et al, 2022)

In terms of simulation, **The Virtual Brain** (TVB, www.thevirtualbrain.org), emerged as an open-source software with its first release in 2012 preceding the HBP project that started in 2013 and now being an integral component of the EBRAINS infrastructure[4]. TVB models and simulates large-scale brain networks allowing, among other aspects, the inclusion of patient-specific data from medical evaluations such as magnetic resonance imaging (MRI), diffusion-weighted (fMRI), electroencephalography (EEG), magnetoencephalography (MEG), stereotactic electroencephalogram (SEEG), diffusion tensor imaging (DTI) (Ritter et al., 2013; Sanz-Leon et al, 2013; Sanz-Leon et al, 2015; Falcon, 2015; Schirner et al, 2018; Schirner et al. 2023). As part of the Codesign Project The Virtual Brain – led by partner Charité in the phase SGA2 of HBP – TVB was advanced to enable simulations at the multi-scale level, i.e., from complex neuronal structures of the whole brain or macroscale to microscale levels or individual neurons (Schirner et al., 2018; Schirner et al., 2022; Meier et al., 2022).

Proof of principle studies indicate potential usefulness of the software for neurostimulation techniques such as Deep Brain Stimulation (DBS) in patients with PD (Meier et al, 2022), by virtually simulating the mechanism and its possible effects, in order to determine optimal routes of intervention (see clinical applications section below). Among other aspects, the in-silico experiments of the TVB have shown similarity with results in evaluations such as EEG and other non-invasive brain stimulation (NIBS) techniques such as transcranial Direct Current Stimulation (tDCS). A growing number of experiments are relying on TVB, providing specialists with alternatives to validate their hypotheses in invasive and non-invasive procedures, to deliver data-driven digital models in a wide variety of neurodegenerative diseases. Upon completion of the registration process in TVB, the virtual environment provides specific spaces organised according to the researcher's needs, who can also access different projects, add data, access simulation models, analyse experiments with AI algorithms, define stimuli and deploy connectivity options on a large scale or at a local level. Watch the informative video of the TVB:

[4] The software can be downloaded or can also be accessed from (thevirtualbrain.apps.hbp.eu).

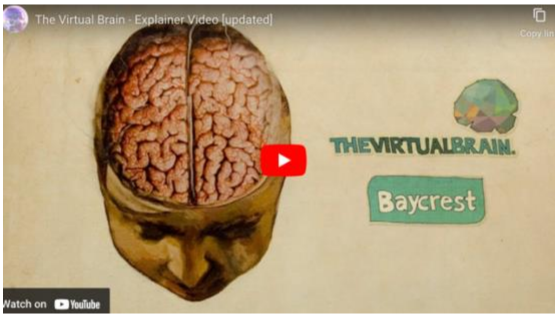


Figure 2. The Virtual Brain (video link)

TVB simulation software is complemented with **TVB Image Processing Pipelines** (Schirner et al, 2015; Schirner et al. 2022) that help to standardize and automate the generation of data derivatives form brain images that can be used to construct brain digital twin models and that contain features to preserve the privacy of personal information in brain images; in addition to other attributes pointed out by the authors, e.g., calculating fMRI time series, functional connectivity, brain surface triangulations, etc. In other words, the pipelines provide a tool that extracts high-dimensional information from these evaluations to analyse them and include them in a simulation model. Nevertheless, the platform offers the researcher a variety of applications for data processing and a flexible interface for data edition. Furthermore, it is supported by complementary platforms such as the EBRAINS Collaboratory, a virtual environment of EBRAINS which provides users with virtual access-controlled or public spaces for exchanging information, manuals, data etc. to provide documentation, tutorials and examples how to use the softare. It is also supported by online platforms such as **GitHub,** in which open-source tools are shared such as DataLad[5] that facilitate integration with multiple datasets and other project tools. As for image processing repositories, they are hosted at Docker Hub[6].

Continuing with simulation services, **Multiscale Co-Simulation** allows the simulation of large-scale brain networks, combining the TVB with other simulators such as PyNEST, ANNarchy, NETPYNE (Neuron), Pyspike and Elephant; through Python toolboxes. To learn more about the TVB simulator with NEST, users can access to the EBRAINS Collaboratory[7] and use Jupyter Hub[8], with online demonstration and no installation required -in case the user wants to use it on his own, it can be accessed for download in Docker Hub[9]. Therefore, these applications provide the researcher with a framework for the computational analysis of neural networks at the mesoscopic and microscopic levels that, together with the TVB, acquires multiple perspectives to understand brain activity. It is known that the human brain involves different scales of connectivity, which have been defined for more than two decades in specialties such as connectomics (Sporns et al, 2005), defining structural connectivity and its links at three scales: microscale -at the level of neurons and synapses-, mesoscale -groups of neurons- and macroscale -between brain regions and their anatomy-, attributes that are intended to be transferred as far as possible to the simulation platform. The co-simulation functionality provided by the TVB is still under development, useful for researchers who need to process multiple data at different scales, given the complexity of factors involved in brain dynamics.

Another interface of interest that incorporates the TVB concerns the Siibra toolbox, which connects to the Multilevel Human Brain Atlas "*a three-dimensional atlas containing cytoarchitectonic maps of cortical areas and subcortical nuclei*" (Amunts et al, 2020, pp. 1), known as Julich-Brain; (Zachlod et al, 2022). This atlas is based on histological sections from 23 post-mortem brains (Ibíd, 2020) and today, it is one of the tools with the highest integration in EBRAINS for the visualisation, analysis, and simulation of the different organisations of the

[5] Datalad, 2022. https://www.datalad.org
[6] https://hub.docker.com/r/thevirtualbrain/tvb_converter
[7] https://wiki.ebrains.eu/bin/view/Collabs/the-virtual-brain-multiscale/
[8] https://tvb-multiscale.apps.hbp.eu/
[9] https://hub.docker.com/r/thevirtualbrain/tvb-multiscale

human brain, reflecting its functional structure and connectivity, at macroscopic and microscopic scale through the "BigBrain" model together with complementary maps.

Other interesting features of this application concern the comparison of functional regions, identifying gene expression related to areas and functions -through a tool called JuGEx from Allen Institute- connecting to databases -from EBRAINS Knowledge Graph- as well as being combined with other atlases and maps to analyse volumetric variations or changes on a microscopic scale between healthy and diseased subjects. In terms of innovation the TVB continues to excel in providing better analysis tools, for example, a forthcoming integration with Human Intracerebral EEG platform from the HBP, developed since the beginning of the project with iEEG datasets from more than 70 clinical centres worldwide.

The two tools TVB-HPC and Fast_TVB provide optimized code for large-scale simulations on High Performance Computing (HPC) clusters of GPUs. On one hand, TVB-HPC automatically facilitates the generation of codes in a programming language of XML called RateML, while Fast_TVB is based on the "Reduced Wong Wang" in C and enables parallel simulation of a brain model on several cores (Deco et al., 2014 mentioned by Schirner et al, 2022). The utility of this system can be applied in experiments or studies that involve large numbers of brain regions (nodes) or large numbers of participants in the studies and therefore a large amount of computation power. Therefore, both the TVB and HDC services are supported by **FENIX**, a supercomputing infrastructure of HBP, formed by six supercomputing clusters distributed over Europe[10].

Once the researchers have completed their experiments with TVB, they have the possibility to share the datasets with other groups of interest, following the FAIR principles, through the Knowledge Graph service and OpenMINDS, mainly. The former is a central meta-data management system that provides guidelines and procedures for meta-data annotation and validation of datasets; while the latter is an open-source tool that grows from third-party contributions on standardized metadata models for neuroscience graph databases. Therefore, the advantages of both services are numerous, because they provide support to researchers in the heterogeneity of the results generated, in metadata models, in the requirements they must follow to make their models reproducible, to establish links with external resources and ontologies related to their virtual libraries, etc.

In this sense, an output of interest is related to **TVB ready data,** in which various datasets can be found, for example, of brain tumor patients with fMRI time series, FC, and SC data before and after surgery (Aerts et al, 2019). According to the expert team, other interesting datasets are available, such as in silico optimization of deep brain stimulation (https://search.kg.ebrains.eu/instances/4efb127d-8393-4c97-b955-90f2c492b526) and case studies that also contain scripting tutorials, code and data to reproduce published results: *Linking molecular pathways and large-scale computational modelling to assess candidate disease mechanisms and pharmacodynamics in Alzheimer's disease*: (https://training.incf.org/lesson/linking-molecular-pathways-and-large-scale-computational-modeling-assess-candidate-disease)

[10] BSC (Spain), CEA (France), CINECA (Italy), CSC (Finland), CSCS (Switzerland) and JSC (Germany)

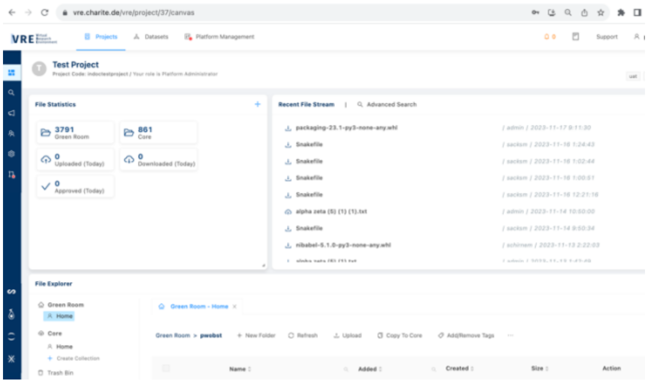


Figure 3. Quick overview of the Health Data Cloud fully operational trusted VRE node project canvas. Source: HDC, 2023.

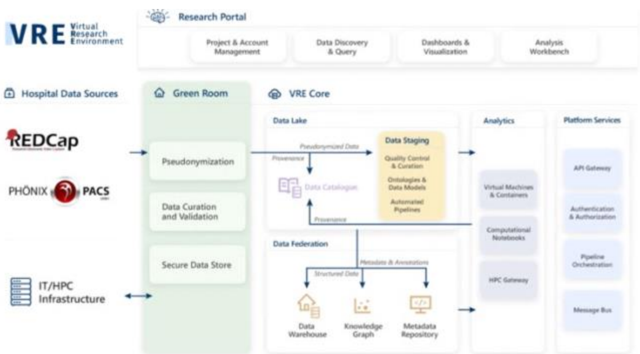


Figure 4. Overview of the Virtual Research Environment (VRE). Source: VRE, 2023.

In sum, some of the described applications integrated in HBP and EBRAINS -especially TVB, laid the foundations for the creation of the Health Data Cloud (HDC) and Virtual Brain Cloud (TVB-Cloud) platforms introduced at the beginning of this section. The HDC (figure 3) is a federated network of trusted **Virtual Research Environmenty (VRE)** (figure 4) – presently with one fully audited node operated and maintained by Charité University Medicine Berlin and connected to EBRAINS – to provide to users services for the management and processing of sensitive data. At the same time, it is integrated with supporting technologies, expanding the analysis possibilities for the researcher: from applications for data exploration, visualisation, programming, education documents to High Performance Computing (HPC) resources.

3.2 Clinical research cases guide *using the HDC/TVB* services

The main simulation models generated with the HDC/TVB platform for clinical cases of Alzheimer' and Parkinson's disease are described below. In general, proofs of concepts have been obtained -both in groups of patients at the individual level- that simulate brain connectivity at multiple scales. Furthermore, the platform uses structural data from each patient based on diffusion tensor imaging (DTI) to create a virtual macroscale representation, along with mean-field models to simulate local connectivity (Ritter et al., 2013). As observed in column "Patients/Methods & equipment" in each study the TVB achieves an effective integration of multimodal data adapting to the objectives of its researchers (from EEG, fMRI, MEG, PET, DBS, tDCS, TMS, etc.), resulting in a simulation at different scales, oriented to the therapy of these diseases. As part of the outputs, an effective approach to structural connectivity comparable to empirical data, and a prediction of functional connectivity in response to new interventions.

Table 1. Main studies using the platform. *Source: Own elaboration, according to main articles.*

Disease	Patients/Methods & equipment	Neural Mass Model (NMM)	Outputs	Reliability	Reference
Alzheimer's Disease (AD)	33 subjects. Methods & equipment: PET and MRI from ADNI3, dMRI, The Virtual Brain (TVB), frequency compositions of TVB-simulated local field potentials	Amyloid beta distributions and cause-and-effect model, Jansen-Rit neural mass model for healthy control (within TVB)	ML-driven classification of AD/introduction of a mechanistic model for AB-driven effects/improve	Proof-of-Concept ML for AD. More experiments with large cohorts are needed	Triebkorn et al, 2022

	(LFP)/ML: Kernel-based support vector machine (SMV) and the decision tree-based random forest (RF) and its combination		diagnostic classification of AD		
Alzheimer's Disease (AD)	Overview of existing computational models (considering TVB). Methods & equipment: MRI, PET, Diffusion tensor imaging (DTI), Connectomics from imaging data,	Statistical models, sub-cellular models, single-neuron and neural-circuit models, large-scale brain network models (within TVB)	The potential of TVB in AD: Multiscale model (macroscale and mesoscale)	Overview of existing computational models	Stefanovski et al, 2021
Alzheimer's Disease (AD)	124 subjects (73 healthy control, 35 amnestic MCI, 16 AD) from Sydney Memory and Ageing Study (MAS). Methods & equipment: neuropsychological tests, dMRI, rsfMRI, dMRI, AAL parcellations	Reduced Wong Wang model, Whole Brain Network (large-scale brain network), Limbic Subnetwork (within TVB)	Most relevant: a) Correlation between biophysical model parameters and cognitive scores in the Limbic Subnetwork, the Whole Brain Network and Embedded Limbic Subnetwork b) Comparison between clinical groups with diagnosis (aMCI, AD, HC) and the models, c) predict individual clinical phenotype	Proof-of-concept. Quality control, the model fits across disease severity	Zimmermann et al, 2018
Alzheimer's disease (AD) and dementia	(To define, very recent article, not available online)	Whole Brain Nerwork (large-scale brain network), Jansen-Rit neural mass model (within TVB)	Simulate multi-alpha band EEG rhythms (7-8 Hz, 8-9 Hz and 10-11 Hz)/Understand general mechanism of EEG rhythms	(To define, very recent article, not available online)	Al-Hossenat et al, 2022
Multiple models (including AD)	State-of-the-art models using The Virtual Brain (TVB) using empirical data. Methods & equipment: High-resolution T1-weighted MRI, DTI, rsfMRI or EEG-fMRI	Different neural mass models (within TVB)	Brain simulation activity from subcellular scale (spikes, action potentials, oscillations, etc) to large-scale (BOLD activity, EEG, MEG, etc), including empirical data/ Model of brain signals (from LFP to fMRI and EEG signals)	State-of-the-art models in TVB: The efficacy of the simulation is measured by correlating simulation to empirical data	Solodkin et al, 2018
Alzheimer's Disease (AD)	33 subjects (10 AD, 8 MCI, 15 HC) ADNI3 Data. Methods & equipment: PET, T1,T2, DTI, fMRI, Tau PET, Abeta PET, FDG PET, DWI, The Virtual Brain (TVB), EEG	Large-scale brain network models (within TVB), Jansen-Rit model (within TVB), cause-and-effect of abeta in the Jansen-Rit model	TVB simulation of EEG in patients with AD, considering pathogenetic molecular candidate mechanisms, introducing the first virtual therapeutic	Proof-of-Concept. Limited recordings of EEG and LFP in the sample of ADNI, small sample cohort	Stefanovski et al, 2019

		from florbetapir (a tracer)	model with memantine		
Neurodegenerative diseases (focused on Alzheimer's Disease, Frontotemporal Dementia, and Amyotrophic Lateral Sclerosis)	60 subjects (15 AD, 15 FTD, 15 ALS, 15 healthy control). Methods & equipment: Neuropsychological tests, dMRI (3T-MRI, rs-fMRI), AAL atlas and SUIT, TVB	Wong Wang model (within TVB). Large-scale brain network models, cortical subnetwork, and the embedded cerebro-cerebellar network	Analise individual inhibition/excitation of GABA and glutamate concentrations in local networks, role of the cerebellum in neurodegeneration. Simulation of rsfMRI, functional connectivity, compared to experimental data	Satisfactory match with experimental subjects. More studies with large cohorts are needed. Structural/functional brain parcellation influenced by the AAL/SUIT	Monteverdi et al, 2022
Alzheimer's Disease (AD), mild cognitive impaired (MCI)	40 subjects (20 healthy controls, 20 MCI). Methods & equipment: Magnetoencephalography (MEG), dMRI (MRI-, rs-fMRI), Desikan-Killiany atlas	Large-scale brain network models	Simulation of MEG resting state networks of FC in patients with MCI	Satisfactory match with experimental subjects. More studies with large cohorts are needed	Susi et al, 2022
Alzheimer's Disease (AD)	36 (9 Mild Cognitive Impairment (MCI), 10 Alzheimer's Disease (AD) and 17 healthy control subjects). Methods & equipment: MRI, PET (from ADNI); dMRI for structural connectomes; rs-fMRI to fit whole brain; creation of the Balance Dynamic Mean Field (BEI) model. For distributions of Aβ and tau: AV-45 (Florbetapir), AV-1451 (flortaucipir) PET (from ADNI).	Whole Brain Network (large-scale brain network); Balance Dynamic Mean Field or Balanced Excitation-Inhibition (BEI) model (homogeneous reference). Regional distributions of Aβ and tau (heterogeneous reference)	Effects of Aβ and tau in brain neural dynamics and dysfunction (in isolation and in combination). Excitation and inhibition imbalance in AD. Demonstrate the effects of Aβ over tau in Mild Cognitive Impairment (MCI) and protein tau over Aβ in advanced stage of AD	A high-value model for investigating brain dynamics in AD and treatment. Allows to reproduce some experiments, i.e. findings of (Stefanovski et al, 2019) on Aβ burden in early stages of AD and increased excitatory activity were confirmed	Patow et al, 2022
Parkinson's Disease (PD) – Virtual DBS,	2 subjects (1 control, 1 PD) / Methods & equipment: 1) Spiking network model for the basal ganglia by (Maith et al, 2021; Izhikevich, 2004) with mean-field simulations; 2) TVB-multiscale co-simulation toolbox; 3) Connectivity atlas for normative connectome: Tract MRI-based CIT-168 brain atlas by (Petersen et al, 2019); AAL atlas	1) Spiking network model for the basal ganglia by (Maith et al, 2021; Izhikevich, 2004), 2) Mean-field simulations, for cortical regions using the Reduced Wong-Wang-model and TVB-ANNarchy: the Spiking-cortex model (both: TVB-cortex model) 3) Connectivity atlas for normative	Multiscale co-simulation of virtual DBS and/or PD effects at large-scale network, not only for single spiking neural network of the basal ganglia (Microscale and macroscale is considered)	Proof-of-Concept of multiscale modelling with TVB-cortex for virtual DBS	Meier et al, 2022; Maith et al, 2021; Izhikevich, 2004; Petersen et al, 2019

		connectome by (Petersen et al, 2019) combined with individually fitted connectivity data			

On the other hand, some concerns were shared with the expert Ritter about possible measures of reliability of the studies, she explains: "*an appropriate measure of reliability depends on the actual study. A quantification is done for instance in Schirner et al. 2018 and Schirner et al. 2023 where we quantify prediction accuracy with a large number of cross-validations".* Other questions concerned the use of brain atlases using the platform, in this sense, it adapts to any parcellation atlas of the researcher' choice. Ritter explains *in (Meier et al, 2022) we used the Perterson atlas, b/c it provides detailed connectivity information between cortex and the basal ganglia which is relevant for deep brain stimulation. In other cases, we use Glasser parcellation b/c it is based on multimodal features or Schaefer parcellation b/c it is particularly fine grained with its 1000 parcels*."

3.3 Data-driven models & brain digital twins in Alzheimer's and Parkinson's Disease:

Starting with some definitions on data-driven models in neuroscience: "*Models are representations of data that can be useful for recognizing patterns, making predictions, or controlling systems*" (Brunton and Beyeler, 2019, pp. 21). Other definition by (Bielza and Larrañaga, 2021, pp. 3): "*Models are often analytically intractable. Models are compared to experimental data using carefully designed numerical experiments*". In this sense, computational neuroscience is a multidisciplinary scientific area that has specialised in the construction of data-driven models to delve in the study of the brain, applying statistical, mathematical and informatic tools mainly, over a wide universe of generated data.

In general, there are innumerable approaches that have been widely explored, combined, and shared; their classification also differs among experts. We can find for example, biological based models (study of protein, cells, network of cells, brain regions, whole brain), models according to the level of abstraction (mechanistic, phenomenological), hypothesis-driven models and the data-driven models (Eriksson et al, 2022), focusing our attention on the last group. In other studies, in addition to data-driven models, methods that simulate neural activity are described, such as neural mass models -one of the two types of mean fields-[11], oscillator models and conductance based biophysical models (Basu et al, 2018). In the TVB/HDC we can find different types of data-driven models and mathematical models to be selected by the researcher, adapting to the brain scales under study or multiscale models. As an example, the neural mass models related to local dynamics of neural nodes and at macroscale level, up to models at cellular level, such as the well-known Hodgkin-Huxley model. **The neural mass models available in the TVB are**: Generic 2d Oscillator (FitzHugh-Nagumo); Wilson and Cowan; Wong, Wang and Deco (Reduced Wong and Wang); Jansen and Rit (Zetterberg, Jansen and Rit); Stefanescu and Jirsa; Larter and Breakspear (3D chaotic oscillator) (Solodkin et al, 2018).

Thus, the data-driven models are mainly built with datasets and metadata as inputs for automatic simulation, applying statistical and mathematical principles (including AI). One of the current challenges in this field concerns an effective integration of the large amount of data

[11] Within the neural field models there are the neural mass and neural field models (Pinotsis et al, 2014)

generated in neuroscientific studies, among other reasons, due to their typology, quantity, sources of origin, resolution, scales, privacy, etc. In order to comply with the so-called FAIR principles and, therefore, make it possible for other researchers to reproduce studies (Poline et al, 2022). More broadly, the search and publication of datasets has been promoted by recognized projects such as Human Connectome Project (HCP), the HBP/EBRAINS, BRAINS Initiative, BrainMINDS, ENIGMA Consortium, Allen Institute for Brain Science (AIBS), China Brain Project, Israel Brain Technologies (IBT), to specific research projects such as Genes to Cognition Project, International Brain Laboratory, The Myelin Project, Neurotree, Dementia with Lewy Bodies Consortium.

3.4 Specialised initiatives in AD

As for initiatives specializing in AD as a source for experimental data-driven models, the following are some of the most interesting ones (including the cases mentioned in the previous table using the TVB): : The Alzheimer's Disease Neuroimaging Initiative (WW-ADNI), the Allen Institute -providing the Seattle Alzheimer's Disease Brain Cell Atlas (SEA-AD)-, the National Alzheimer's Coordinating Center (NACC), the European Prevention Alzheimer's Dementia Consortium (EPAD), the Alzheimer's Disease Data Initiative (ADDI), the Global Alzheimer's Association Interactive Network (GAAIN), the European Prevention of Alzheimer's Dementia (EPAD), the European Medical Information Framework (EMIF-AD), the AdataViewer, the Neurodegenerative Disease Research (JPND), the Dementias Platform UK (DPUK), the Davos Alzheimer's Collaborative (DAC), Pubmed, the European Platform for Neurodegenerative Diseases (EPND) powered by ADDI's AD Workbench, the Integrative Analysis of Longitudinal Studies on Aging (IALSA). The following table shows in simplified form the main initiatives and the size of the AD-related cohorts:

Table 2. Main dataset initiatives in AD

Major initiatives with AD datasets	**Size**	**Cohort regions**	**Access**
ADNI-1	821 participants: cognitively normal, early MCI and AD	U.S. and Canada population	https://adni.loni.usc.edu/data-samples/access-data/
ADNI-GO	+200 early MCI participants	Same as above	Same as above
ADNI-2	+550 participants with other memory impairments	Same as above	Same as above
ADNI-3	+1200 participants with AD	Same as above	Same as above
ADNI-4	+750 participants: cognitively normal, MCI, dementia. So far, the WW-ADNI has more than 2000 participants	Same as above	Same as above
SEA-AD	6,000 participants: Over 1000 dementia	U.S. population	https://portal.brain-map.org/explore/seattle-alzheimers-disease
NACC	47,772 participants: cognitively normal, impaired, not MCI, MCI, and dementia.	U.S. population	https://naccdata.org/requesting-data/nacc-data
EPND -ADDI' AD workbench-	67 research cohorts, 159,675 participants (AD, PD, LBD, ALS, MSA)	Across Europe (17 countries)	https://epnd.org
GAAIN	535,428 participants, 57 data partners	Worldwide	https://www.gaain.org/
EPAD	3,000 participants	Across Europe (France, Italy, the Netherlands,	Dataset is available on the AD Workbench. Access here:

		Sweden, Spain, Switzerland and the UK)	https://www.alzheimersdata.org/ad-workbench
EMIF-AD Multimodal Biomarker Discovery	11 cohorts, 1,221 participants: 492 cognitively normal, 527 MCI, and 202 AD dementia.	Across Europe	http://www.emif.eu/emif-ad-2/
EMIF-AD 90+	129 participants: 84 cognitively normal, 38 cognitive impaired.	UK, the Netherlands	Same as above
EMIF PreclinAD	285 cognitively normal participants	UK, the Netherlands	Same as above
JPND Global Cohort Directory	175 cohorts; 3,586,109 participants	Worldwide	https://neurodegenerationresearch.eu/jpnd-global-cohort-portal/
DPUK	42 cohorts, 3,370,979	UK	https://portal.dementiasplatform.uk/
DAC	15 cohorts; 30,000 people	Worldwide	https://www.davosalzheimerscollaborative.org/cohorts
IALSA Network	110 cohorts; 1,485,410 participants	Worldwide	https://www.maelstrom-research.org/network/ialsa
ADataViewer	Catalogue of more than 20 AD cohort datasets variables from multiple consortia	Europe, North America, Japan	https://adata.scai.fraunhofer.de/cohorts

Source: NIH; Weber et al, 2021; Salimi et al, 2022; Allen Institute for Brain Science (2023); NACC (2023); IHCC Global (2021); EPAD, s.f; EMIF-AD, 2023; SEA-AD, 2023; EPND, 2023; Maelstrom Research (2021); Bauermeister et al, 2020; DAC, 2023

Many of these initiatives have driven the development of predictive and classification models in a wide range of neurodegenerative diseases and in diverse cohorts. In the field of AI, ADNI alone has contributed some 2,000 publications and 300 scientific articles (Silva-Spínola et al, 2022), also used to train algorithms for diagnostic support. However, these advances invite reflection: is the quantity and quality of data offered by these sources sufficient for data-driven models in neurodegenerative diseases? What is the scope and value proposition of HDC/TVB in the development of personalised models for these diseases?

Different publications explain that the databases are still limited, at least for AI applications, with the use of deep learning, which requires a large amount of data to train its models (Wang et al, 2022; Chang et al, 2022). Two drawbacks are highlighted by experts given this limitation, firstly, the overfitting of models -which would lead to information bias, results not necessarily transferable to a broader context- and secondly, biases in the available datasets, which demands that these AI models be validated on different cohorts. These challenges have motivated researchers to devise combined solutions in AI, such as hybrid machine learning framework, and validate the models with different datasets to reduce the overfitting.

Other obstacles concern working with incomplete datasets, leading to the development of small-scale data exclusion methods that do not maintain important features, in other cases imputation actions for missing data, and the development of deep learning alternatives trained with these limitations (Huang et al, 2016; Chang et al, 2022). In this sense, to obtain a holistic perspective on the risk and progression of these diseases, it is usual to analyse individual data and integrate them accordingly in a multimodal or multi-dataset framework. Therefore, it remains a priority today to have high-quality, standardized cohort data with different characteristics. Other interesting contributions have emerged around the analysis of Alzheimer's Disease data with brain charts, such as brainchart.io (Bethlehem et al, 2022), including MRI scans of participants from very early ages to old age, providing an evolution on structural and neurodevelopmental changes, although with similar limitations on bias and variable diagnoses.

3.5 Main projects of brain digital twins

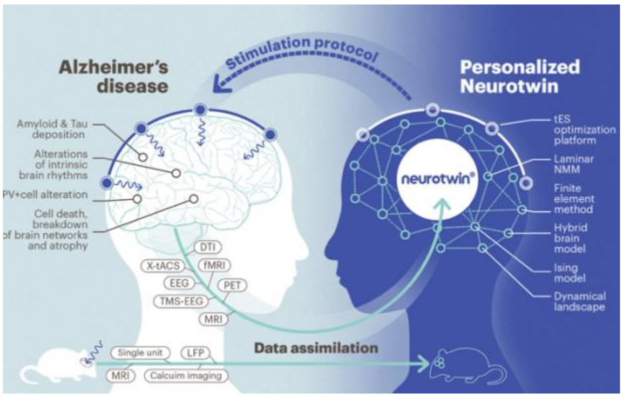


Figure 5. Neurotwin description. Source: Neurotwin, 2023

In Europe, the **Neurotwin consortium** - led by the company Neuroelectrics Barcelona SL- was conceived in 2021 to advance the study of neurological diseases such as epilepsy or Alzheimer's by developing customizable digital models of the human brain that simulate the pathologies and predict the effects of non-invasive neurostimulation therapies. They are based on computational models at different scales, using existing data from healthy and AD individuals, to predict the effects on a mouse and human digital twin, and subsequently create customized neurostimulation protocols (Neurotwin, 2023). Therefore, they explore neural mass models to study the dynamics of neural networks and how the behavior of individual neurons could affect large groups using techniques such as transcranial direct current stimulation (tDCS), transcranial alternating current stimulation (tACS), transcranial magnetic stimulation (TMS), transcranial electric current stimulation (tES), etc (Ruffini, 2023). As an example, one of its research groups has published a study of customizable laminar neural mass model for patients with epilepsy that replicates the electrical activity of a SEEG (Lopez-Sola et al, 2022).

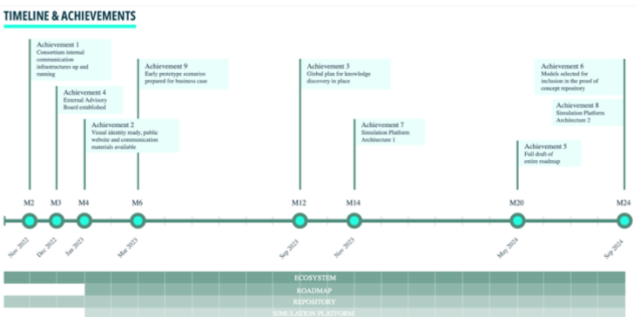


Figure 6. Implementation of European Virtual Human Twin (EDITH). Source: EDITH, 2023

Another consortium funded by the European Commission within the Digital Europe Programme is the **Ecosystem Digital Twin in Health (EDITH),** which aims to link existing digital twin projects in a federated repository. Its objectives include identifying the current landscape of these models, actors, available data, infrastructures, etc. and creating a roadmap for integrating these solutions into a federated cloud repository system.

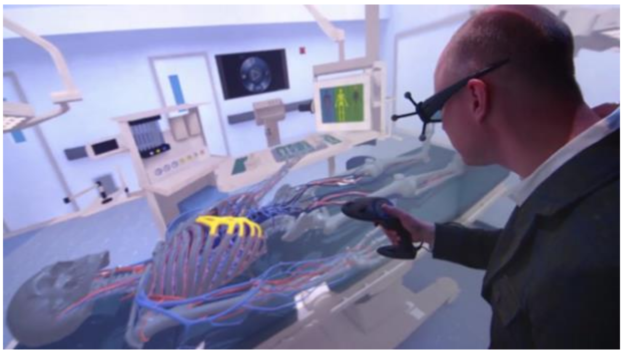


Figure 7. Living Heart Project. Source: Dassault Systèmes (2023)

The well-known **Dassault Systèmes Living Heart Project** seeks to develop a human digital twin in the long term. This project would help in advancing therapies for cardiovascular diseases through simulations, for projects and training in medicine, diagnostic support tools and summary, a better patient-centered service. Alya Red is another similar project on a computational heart developed by The **Barcelona Supercomputer Center** with the support of physicians and bioengineers.

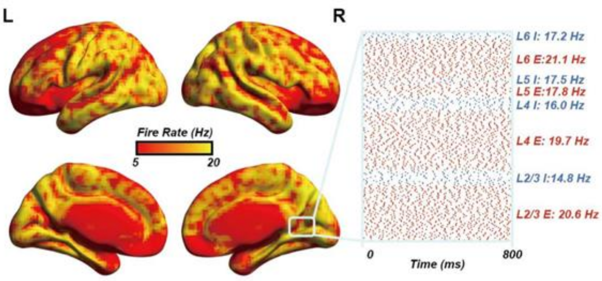


Figure 8. Human brain network simulation (Lu et al., 2023)

The Digital Brain Twin (DTB), China: There is a growing emergence of innovations in digital brain twins from the rise of data in neuroscience and healthcare, the development of new AI algorithms, as well as the financial support that these advances demand. Recently, a group of researchers from Fudan University created a human brain simulation platform called Digital Brain Twin (DBT), together with the support of Shanghai Municipal Science and Technology, Shanghai Center for Brain Science and Brain-Inspired Technology and the National Key R&D Program of China (Lu et al., 2023). Among other aspects, the platform succeeds in simulating the whole brain -86 billion neurons and 47.8 trillion synapses in different scales. They authors suggest that DBT differs from technologies so far developed in 3 main aspects: The application of spiking neuronal network based on sMRI, DTI and PET data, approaching real human brain dynamics. Second, by the efficiency achieved through a partitioning algorithm to minimize traffic between GPUs. Third, they offer a mesoscopic data assimilation method to achieve a more realistic simulation of brain activity and cognitive behaviour.

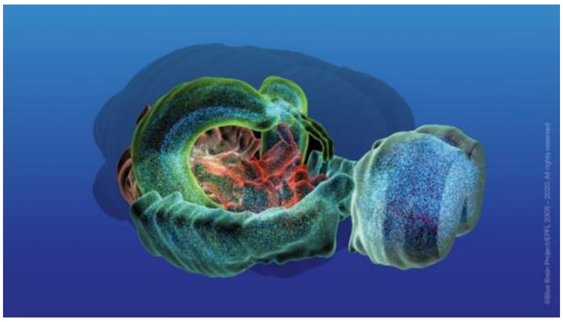


Figure 9. Blue Blain Project/EPFL cell atlas

The **Blue Brain Project** in Switzerland, initiated in 2005 by EPFL, aims to create the first digital model of the entire mouse brain on a cellular scale. Ten years later, they succeeded in reconstructing the microcircuits in the somatosensory cortex of a rat (Markram et al., 2015), with a high precision and detail on some 31,000 neurons, identifying their different types, density, morphological composition, etc.

Figure 10. Digital patient twin. Source: Siemens Healthineers (2023)

The well-known subsidiary of Siemens, **Siemens Healthineers,** the medical technology leader from Germany, is advancing towards a more holistic approach through the digital patient twin. Considering the huge amount of data, state-of-the-art equipment, and AI software at their disposal, they are preparing the ground with the automation of radiological assessments, reducing imaging errors, detection of abnormal tissue, imaging biomarkers. On therapy simulation, support for radiotherapy planning, calculating how patients would respond to treatments, robots to assist in surgical interventions based on this information from the patients' digital twin (Siemens Healthineers, 2023). Regarding data visualisation, useful graphics, with 3D models in VR and AR, to assist the clinician in decision making.

While the HDC/TVB has excelled in the field of research, it would play a relevant role in decision support in the clinical context, as well as in the management, processing, and analysis of data. Only part of its development -TVB- demands for downloads on a regular basis, reaching 53,851 downloads to date (2023-12-02; www.thevirtualbrain.org), however, its clinical application begin with the multicentric clinical trial EPINOV in patients with epilepsy. In terms of intellectual property, the collection of multidisciplinary databases of the Web of Science (WoS) of Clarivate Analytics was consulted, in which we found nearly 70 papers that used TVB software in the research and experimental fields, since its creation in 2012. Figure Nº11 shows the geographical distribution is observed for reference purposes, since most of the publications contain authors associated with different centres internationally, thus their values might be overestimated.

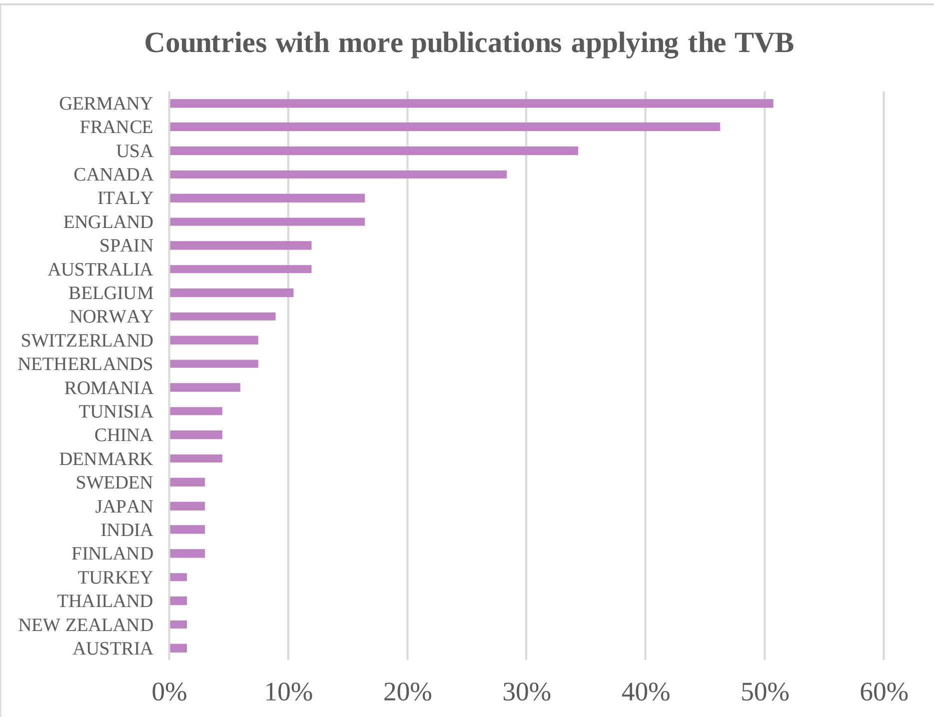


Figure 11. Countries with the highest number of publications using the TVB

IV. METHODOLOGY

This report follows the Horizon Scanning (HS) methodology, defined by the European Commission (2018) offers a broad and practical definition: "*A systematic outlook to detect early signs of potentially important developments, in order to enhance resilient policy-making, address policy makers' needs and concerns regarding new issues, to identify new opportunities by anticipating consumer and societal needs or to prepare society for less expected or rapid changes*". Similar definitions can be found in The International Coalition of Medicines Regulatory Authorities (ICMRA) mentioned by Takata et al, 2022; described it as: "a broad-reaching information-gathering monitoring activity to anticipate emerging products and technologies and potentially disruptive research avenues". Through HS, we can anticipate new developments, devise strategies to enhance what already exists, as well as make better decisions towards possible solutions to the challenges of potential users of HDC/TVB, especially in the highly sensitive area of neurological diseases worldwide.

However, given the convergence between different fields such as neuroscience, medical and informatics, together with accelerated advances among international research groups, there is still no single foresight method that analyses all signals in a single scheme, therefore we explored different avenues in order to deepen the objectives of this research. Specialised public and open databases -scientific articles, industry reports, related company websites, medical journals, grey literature, etc.- were consulted, sources specified throughout the report.

In the next phase, some trends in the healthcare sector in data driven models are described, followed by an internal and external strategic analysis of HDC/TVB through the SWOT matrix. In addition, eleven in-depth interviews were conducted with experts in neurotechnologies and leaders in neuroscientific research in Spain to learn, among other aspects, about their perspectives on the data acquisition process and the use of platforms in their research areas related to neurodegenerative diseases. As for business models, a Lean Canvas Model adapted to the case study was created, an exercise that helped in the search for business models, user segments, existing alternatives, as well as bringing innovation strategies closer to other unforeseen segments. Finally, we adapted the Allen model to the case study in order to get a first approximation on the dimensions of the industry in which it would operate.

V. RESULTS

5.1 International Patent Application

In terms of IPR, following the international classification in which the invention of the group is framed (Ritter et al., 2013) G09N and its subclasses G06N 3/10; G06N 3/04; G06N 3/49. Specialised databases were used such as Patentscope of the World Intellectual Property Organization (WIPO), Espacenet of the European Patent Office and Google Patents. The nomenclature of the International Patent Classification (IPC) is considered, in the case study G06N is defined as *Computing arrangements based on biological models*, and its subcategories: G06N 3/10 *interfaces, programming languages of software development kits;* G06N 3/04 *architecture* and G06N 3/49 *temporal neural networks.* Likewise, heterogeneous results were found among the different databases, either due the multidisciplinary nature of these developments with other fields of research -which overlap with other techniques-, dates of application and/or breadth of search.

In a simplified manner, the technology under study is based on three main aspects: the Virtual Research Environment (VRE) as a neuroscientific research platform, the Virtual Brain Simulator (TVB) and the Health Data Cloud (HDC). In this sense, the searches were analysed in two stages: A first stage that, in addition to considering the IPC, the keywords related to the *virtual brain model* were included, obtaining 331 results in the last five years (Patentscope, 2023). The applicants who lead this segment are Samsung Electronics Co, LTD., Korea Advanced Institute of Science and Technology, Hangzhou Dianzi University, Beijing University of Technology, Nvidia Co., Nanjing University of Posts and Telecommunications, Tsinghua University, Baycrest Centre for Geriatric Care, JLK Inspection, Semiconductor Energy Laboratory Co, LTD.

In a second search stage keywords related to health data cloud and brain, obtaining results closer to the HDC and VRE platforms. 1,247 records were obtained, mostly from the USA, as shown in figure Nº12. Among the leading companies in these areas we find: Magic Leap, Microsoft Tech Licensing, Strong Force IOT, Koninklijke Philips, Bao Tran, Medtronic, Theator, Zoll Medical. Figure Nº15 brings together the related technical areas, following the IPC described above:

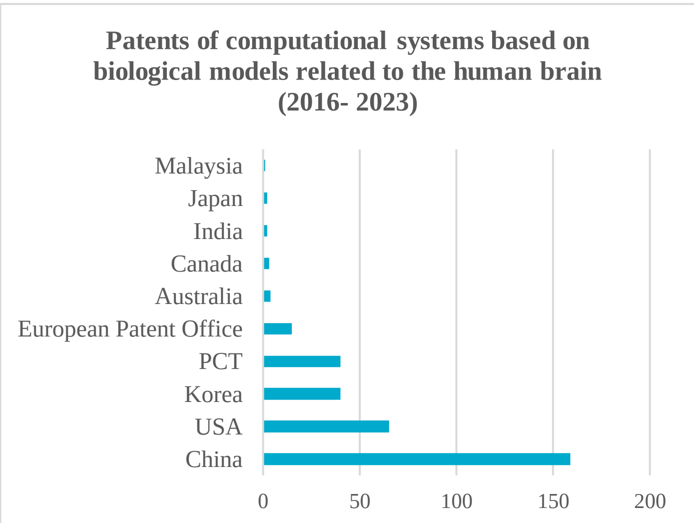


Figure 12. Patents related to health data and neuroscience, following IPC. Source: Patentscope (2023)

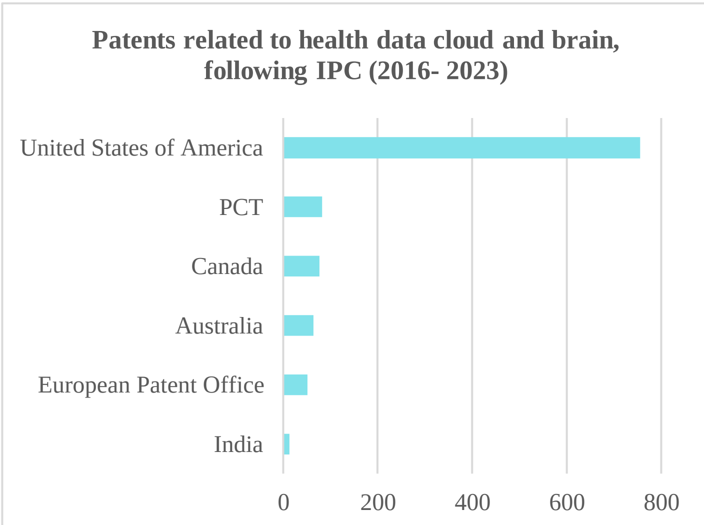


Figure 13. Patents of computational systems based on biological models related to the human brain. Source: Patentscope (2023)

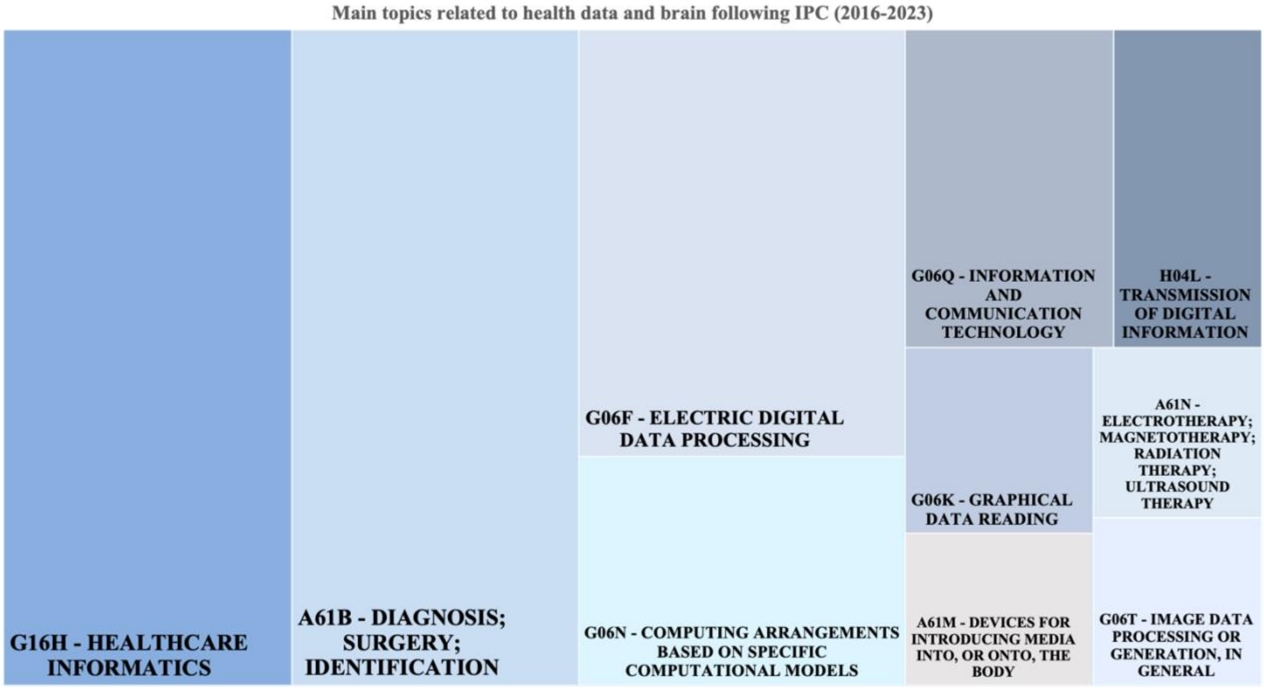


Figure 14. Own elaboration. Source: Patentscope, 2023

Figure 15. A view of the Samsung Medical Center (SMC)

The inventions of **Samsung Electronics** rely on AI methods - machine learning and deep learning - that seek to emulate human brain functions such as cognition, reasoning, recognition, etc. from a user's behavioural data. However, the published records do not reflect solutions to support medical diagnosis *per se*, but rather as applications that extract real-time data from a user's wearable device, data that can also be sensitive. Other innovations include methods for generating images based on a keyword with AI, models that improve as they learn on their own. The Korean multinational company also has the **Samsung Medical Center (SMC)** (Figure 15) in Seoul, South Korea, with cutting-edge technologies and supported with 5G networks, streamlining the hospital's internal communications in real time.

Figure 16. Gamma knife radiosurgery device. Source: Korea Biomed, 2020

The centre has specialties in severe diseases such as cancer, heart disease, organ transplantation, etc. and services oriented to personalised medicine, open and collaborative research. In neurology, they also have state-of-the art equipment, diagnostic services, and treatment of brain tumours. Among the surgical treatment options, they specialise in transcranial surgery, skull-based surgery, endoscopic brain surgery, awake craniotomy, Gamma Knife radiosurgery (figure 16) -as a surgical method with intense gamma rays without the need to penetrate the bone or make incisions, proton therapy or radionation therapy -post-surgery or in those cases in which a complete resection of the cancerous tissue is not possible-, in addition to chemotherapy. It is considered a reference hospital for brain tumour and gamma knife surgery in South Korea. In addition, the centre has strengthened its competitive advantages with AI, generating predictive models based on medical data, organizing the necessary personnel to improve healthcare, given the volume of patients, including robots to move medical material.

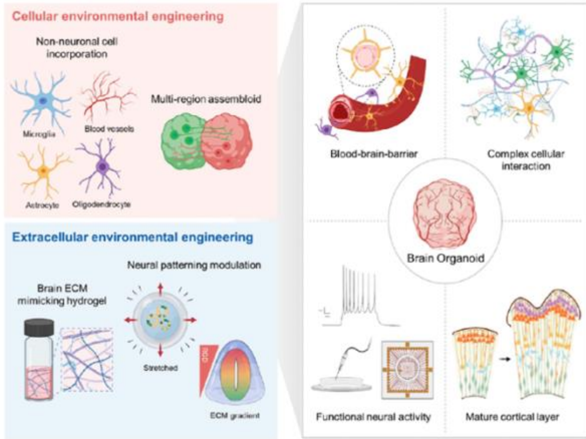


Figure 17. Summary of engineering approaches to recapitulate the brain environment. (Authors: Jeong et al, 2022)

Other innovative developments supported by Samsung - although not patented yet - are brain organoids, emerged just a decade ago and are conceived as 3D structures that replicate areas of the human brain. According to the expert team (Jeong et al, 2023), organoids can contain a variety of neuronal cells and chemical signals (figure 17), however, they do not fully mimic the human brain given the cell culture system in which it develops. To overcome these limitations, engineering techniques are being applied that mimic the environment of the cells, including, for example, vascular networks to provide nutrients to the cells, glial cells, fuse organoids, and techniques to facilitate their culture. Therefore, these are methods in early stages with potential application for modeling neurological diseases from patient's cells and in drug testing; in cases where animal experimentation is not accurate or cannot be extrapolated to humans. Neurodevelopmental, neuropsychiatric diseases -such as schizophrenia and major depression - and neurodegenerative diseases - AD, PD, Huntington's disease, and brain cancer- are some examples of the current approaches of the technique.

The inventions from **Korea Advanced Institute of Science and Technology (KAIST)** in this category are related with brain computer interfaces (BCI) for behaviour prediction and decision support based on brain signals. These applications seek to estimate a cognitive state and predict user behaviour from an EEG or functional near infrared signal. Other innovations include AI algorithms that learn about user behaviour to control learning tasks by stimulating brain regions noninvasively. In this sense, they generate a computational brain model that activates regions depending on task performance. In terms of BCI, researchers of KAIST have already developed systems that decode brain signals to control robotic arms without the need to train the algorithm (Chang, 2022), analysing computational models that detect cognitive processes in imaginary motion signals.

KAIST has promoted innovative programs around neuroscience, applying robotics in rehabilitation medicine with haptic technologies, AI for clinical assessment by automating processes and tele-rehabilitation with virtual reality (figure 18). For example, the **Renew** project, seek to understand the effect of rehabilitation in neuroplasticity, based in a model of stroke. First, the model analyses the electrophysiological signals during the rehabilitation, adjust the electrical stimulation to the cells and evaluate its effects in the genes and proteins related with neuroplasticity (see Renew, 2019). With this information they build a computational model to predict the outcomes of this rehabilitation in patients, based on the analysis of the brain motor network. Thus, they created a BCI that shows the motor intention of the user in rehabilitation sessions using real-time EEG, an interface that applies an algorithm that identify the movement intention, a muscle synergy model and home rehabilitation programs with 3D printed wearables. In short, this project not only integrates a computational model based on patient data, but also embeds various platforms for a comprehensive and personalised treatment, a model that could be followed by the HDC/TVB.

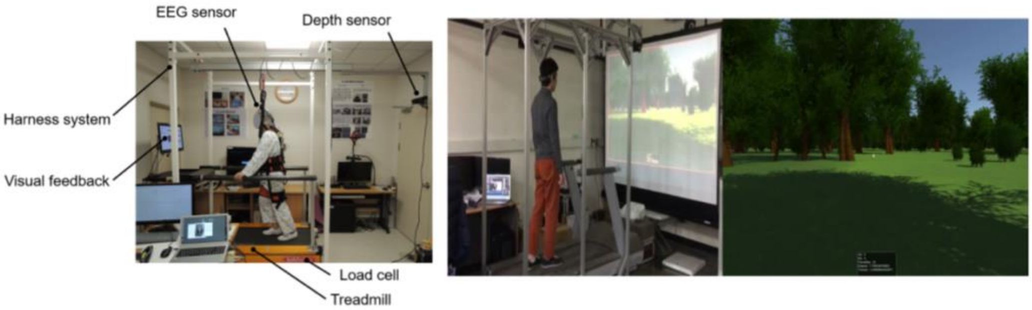


Figure 18. Virtual Reality for rehabilitation. Dept. of Mechanical Engineering KAIST

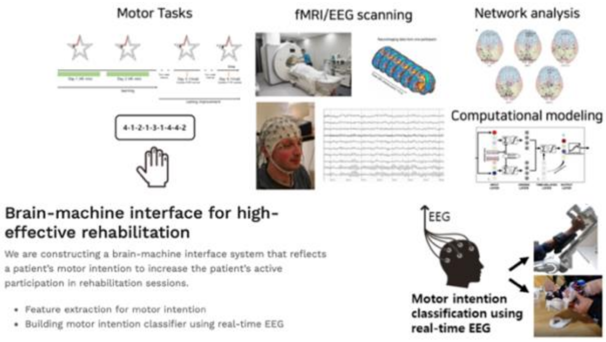


Figure 19. BCI for high-effective rehabilitation. Renew project (2019)

Other applications of the group that focus on neurodegenerative diseases incorporate a model that measures cognitive reserve (CR) or what is known as the difference between actual and estimated cognitive function (Lee et al, 2022). Using neuroimaging techniques such as MRI and PET they created a model that reflects the cross-sectional and longitudinal effects of CR on cognitive function in cognitively unimpaired and Alzheimer's disease patients. The study could support the development of early and personalised interventions in these patients, as well as in pharmacological therapies that could delay the progression of the disease.

The **Beijing University of Technology** also presents interesting proposals in human brain simulation applying AI that seeks to contribute to the early diagnosis of neurodegenerative diseases. In their most recent records, they share a method to identify the human brain effect connection with adversarial generative network (GAN), useful to understand -from a cause-effect perspective- the relationship between affected areas in these diseases and their connections, with special application in fMRI data. In the neuroimaging field, two methods of effects recognition are differentiated: one based on model driving -as a method that verifies the effects of connections in a previous model using structural equation models (SEM) and dynamic causal models (DCM)- and another based on data driving -which does not require training but directly extracts causal relationships in brain regions from data, using Granger Causality (GC), a Linear Non-Gaussian Acyclifower model, a Generalized Synchronization model (GS), Bayesian Networks (BN), etc-.

However, they argue that the GAN method is efficient in unsupervised learning tasks that combine a *generator* and a *discriminator*. In a first stage, the application learns about a real data set and then a discriminator checks whether the data is generated or real. Therefore, these

GANs generates fMRI-like data, which then goes through a model driving method (SEM), with outputs consistent with the real data, with a high level of effectiveness in understanding these causal relationships. According to the authors, their differentiation stands out for combining a traditional driving model with an adversarial generative network, which requires no prior knowledge and offers realistic data on the effects of brain connections from brain imaging tests.

Another related innovation registered by the **Beijing University of Technology** relates to a method for estimating brain age and chronological age from a MRI, achieving high reliability. In general, if the brain age is higher than the chronological age, it is inferred that a person has a faster rate of brain ageing (Yu J, et al, 2022). This group has found a method that distinguishes itself from current techniques given its effectiveness in predicting the brain age, using a 2D convolutional neural network (CNN) with vector machine for regression (Lin et al, 2020). The model reaches prediction through a high-dimensional modeling that captures morphological changes from a structural MRI, which can also be used as a biomarker of neurodegenerative diseases.

Regarding sample size or amount of data, they grouped samples of different sizes and trained the data with each one, obtaining six different models. Smaller samples did not fit the model, but those between 20% and 40% of the entire cohort, so their method achieves the best results with samples of 120 participants and above (Ibíd, 2020). Certainly, these studies contribute to the scientific progress by approximating chronological brain age in a personalised way, not only to enhance the understanding of neuroanatomical functions, but also to plan and employ therapies in a timely manner. In this sense, the TVB/HDC has considered studies that analyse brain aging in patients with Parkinson's disease (PD) by training ML models (Eickhoff et al, 2021), including these regional annotations into the nodes of this tool, therefore, this platform will continue to support new studies to enrich its models.

Another line of research concerns to emotional recognition methods, applications registered by the **Hangzhou Dianzi University.** Developments that seek to overcome the limitations of the common methods with AI and EEG, the former through ML and DL with CNN and a recurrent neural network (RNN). The authors comment that main barriers of DL are twofold in this field, on the one hand, little emotional facial data limits the training of the algorithm, while a larger amount of data requires a powerful computer platform to process it. On the EEG side, beyond its advantages in precision and facial recognition tasks, they require the intervention of the researcher and place it every time a new task is started. Therefore, their invention is based on a version that adapts the data processing requirements called ***brain-computer collaboration***.

The underlying dynamic of this solution is characterized by a human-machine interaction framed within a co-space in which the processing or cognitive capacity of the brain after a task (images) is shared to the ML and serves as a guide for its learning together with an EEG. With this data analysis an image modal primary representation is obtained, helping in the creation of a feature extraction model. In short, the main strengths of this innovation lie in facilitating a common space in which EEG data and image data converge, making it unnecessary to search for a large amount of facial emotion data to train a model, saving the use of computational resources and a high level of accuracy in terms of real-time emotional recognition effect.

To obtain a more comprehensive picture from a technological sovereignty perspective, in 2017 the China's State Council announced the *New Generation Artificial Intelligence State*[12], a plan

[12] State Council of China, 2017

based on the advantage of the first move, in whose objectives are delineated strategies towards creating an innovative country and becoming a global leader in almost everything related to AI by 2030. The new generation described by the Asian giant is framed by theories such as **big data intelligence, cross-media intelligence, group intelligence, hybrid augmented intelligence and autonomous intelligent systems**. Through the theory of *hybrid augmented intelligence*, the aim is to enhance the cognitive capabilities by combining human-machine intelligence, together with the development of architectures to support these applications. Methods such as behavioral augmentation, brain-computer collaboration, collaborative computing methods for cloud robots, are just a sample of the applications in these categories that might have a relevant influence in the coming years. Ambitions that are also reflected in the “China Brain Project” (Poo et al, 2016) in a combination of brain-disease diagnosis and brain-inspired technologies.

The records of **NVIDIA** in this category -a global leader in the manufacturing of graphic processing units (GPUs)-, covers those related to artificial neural networks (ANN). The experts agree once again that the use of these methods requires considerable computational resources and time, so some of their inventions stand out in minimizing these needs by tracing paths through networks, speeding up their performance. In general, the company has a favourable impact in the healthcare sector with digital solutions, examples such as the computational platform *NVIDIA Clara* which brings together smart sensors to monitor patients remotely by applying AI in audio and video anywhere in the hospital. For neurological interventions, they incorporate brain tumour segmentation applications, supported by pre-trained medical imaging models. Recently, one of its many partners, King’s College London, announced the forthcoming publication of the world’s largest curated database of synthetic brain imaging, powered by the supercomputer of the company, the Cambridge-1.

Figure 20. Whole brain segmentation using large UNesT annotation model and inference with 3D Slicer. Source: Yu et al., 2022

Another project cofounded by **NVIDIA and King’s College London** is called MONAI (see MONAI, 2023), an open-source platform based on deep learning for medical imaging, in which academia, industry and clinics contribute. In the neurological field, its data-driving applications and visualisation tools are used in surgical planning to delineate brain tumours, assess intervention possibilities with high-resolution tools and obtain real data. This process provides continuous information to train its AI models and link them to the patient’s medical records. Although the brain models published in their platform are few, the following image (figure 20) shows an example as 3D transformed-based model for whole brain segmentation, in collaboration with the Vanderbilt University and the MONAI team (Yu et al, 2022). Noted that although the project is open-source and aimed at scientists and researchers, NVIDIA offers a version for developers in the business domain the **MONAI Enterprise, a paid service**. The latter includes support for implementation options, contact with engineers to optimise configuration and performance, customized AI workshops and training, etc. A business model where certain aspects could usefully be transferred to HDC/TVB.

Another innovative development comes from the **Nanjing University of Posts and Telecommunications,** concerns the implementation of memristors[13] in neuronal circuits and neurons, with a utility model in which memristors facilitate storage and processing of signals like a human brain. The novelty lies in the fact that these systems or *memristors neurons* are connected to a cell and can extend their range to be used on a large scale, transmitting signals between them, and building new connections. Therefore, each memristor neuron can both bind to a synaptic connection and transmit information to multiple neurons at the same time, building large-scale neuron networks. On the whole, the usefulness of these systems emerges as an alternative to the current proposals to make neural simulation methods less energy-consuming and more efficient.

Nor should we disregard the patents related to photonic devices for learning, memory, and decision recognition, registered by the same university. Given the convergence between disciplines such as AI and neuroscience, two technical paths can be distinguished for the development of devices that attempt to simulate the human brain: those usually based on CMOS technology, and memristor-type synaptic nerves, explained above. However, it is understood that both methods have significant limitations at present and are still far from reaching the capabilities of the human brain. According to the inventors, their device is the first to use electron-substitution photons as a way to simulate the transmission of neurotransmitters in neurons and synapses, with memory, learning and decision-making capabilities.

On the other hand, institutions such as **The Cornell University** highlights in retinal prostheses, restoration of neural functions in mammalian subjects, methods for data and imagine analysis and processing with novel computer vision algorithms, etc. Other non-patented developments provide a complementary perspective, for example, an associated research group has developed personalised techniques for the treatment of brain tumours or glioblastomas, through biological models with stem cells that augment human cells, the mentioned brain organoids (see Weill Cornell Medicine, 2020). Most recent development includes AD models (Karaman et al, 2022) through deep learning to predict whether cognitively normal subjects could develop MCI or AD, over a five-year time horizon. The authors share the high accuracy achieved in the prediction of CN to MCI at one year, useful for timely treatment of the diseases.

Wider searches related to virtual brain models detected records from centres such as: Fouzhou University, South China University of Technology, HITIQ Limited, Cancer Center of Guangzhou Medical University, Casibrain Tech (Beijing) company, Hunan Normal University, Koninklijke Philips NV, Suzhou Institute of Biomedical Engineering and Tech Chinese Academy of Sciences, Universite D'AIX Marseille (AMU) and Xi'An Jiaotong University.

[13] According to *Jimenez-Fernandez et al, 2012* a memristor is a resistor or basic circuit device that has the capability of storing its resistance even when the current flow is interrupted. Its origin dates from 1971 by the electrical engineer León Chua of the University of California, and its practical demonstration was carried out by Hewlett Packard in 2008.

5.2 Market & Industry Overview

5.2.1 Trends in the universe of data-driven human brain simulation models

In the social sphere, among the current range of applications that facilitate trend analysis, we start with Google Trends. This tool has a simple format to broadly search terms both globally and by country, or also with keywords related to the problem or topic. The disadvantage of this application -at least in our study case- is the difficulty in finding results with specific or highly technical keywords, so we use terms such as artificial intelligence, Alzheimer's Disease and Parkinson's Disease, obtaining a comprehensive picture in these domains (the figures do not symbolise the absolute search volume, but a result of a normalisation in their databases, according to the company).

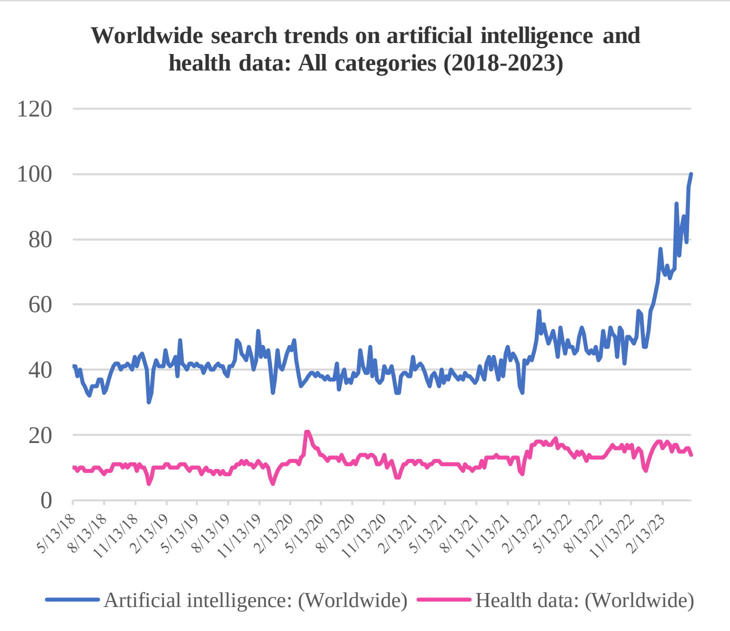


Figure 21. Search trends, all categories. Source: Google Trends

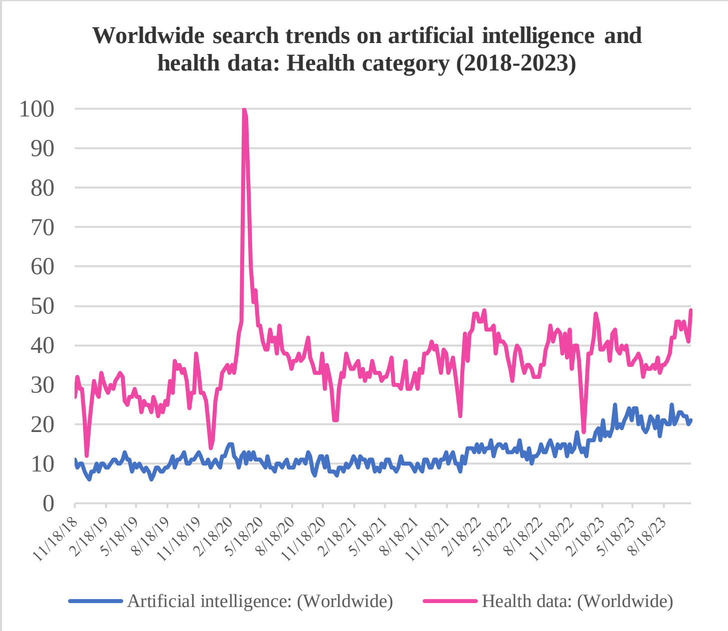


Figure 22. Search trends, health category. Source: Google Trends

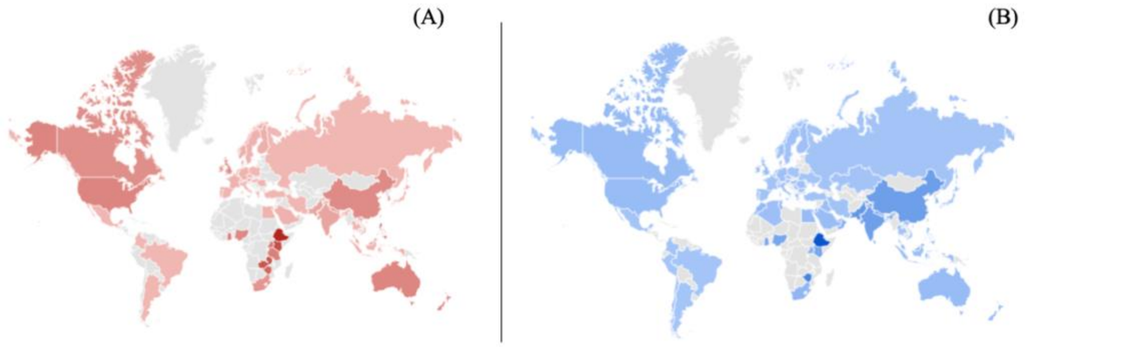
The figures 21 and 22 show two different perspectives on search trends in AI and health data worldwide. Figure 21 indicates how the interest in learning AI has grown, with an upward trend so far in 2023, with a myriad of influencing aspects. New proposals of companies such as OpenAI, Meta AI, IBM, Palantir, Microsoft, Google, X, etc. -*mostly from Silicon Valley*- have attracted the world's interest with projects based on deep learning (i.e. generative AI, self-supervised learning, etc). Among the neuroscientific developments adhered to these companies and have gained popularity are MetaAI, with a non-invasive technology to decode speech from brain recordings in patients with traumatic brain injury or those people unable to speech, one of the few groups that have managed to come close to such advances.

One of the differentiating and promising aspects of this solution is the AI models that the company has developed in recent years -among them self-supervised and deep learning (see Défossez et al, 2022) and which have been applied in MEG and EEG analysis[14]. These are methods that, although not specified in the searches, together reflects a social impact. On the

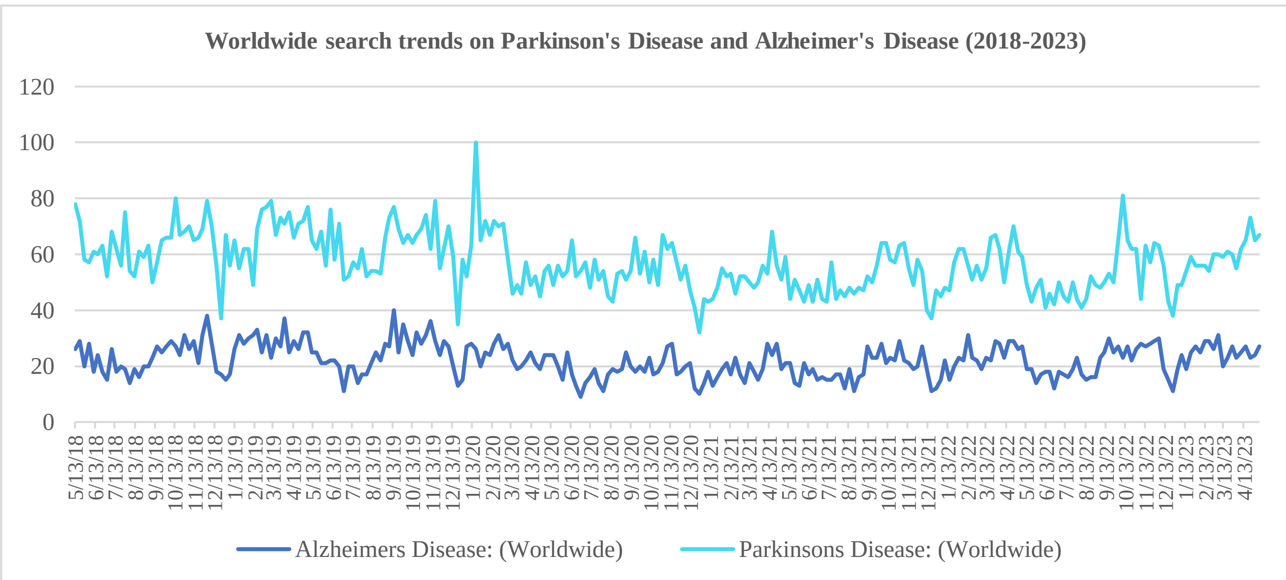
[14] Other interesting studies from their research groups that have been highlighted in this field recently relate to natural language prediction using predictive code (Défossez et al, 2023).

other hand, figure 22 frames the searches in the Health category, thus its peaks and valleys show more pronounced shifts. Not surprisingly, the highest peak in health dates back to March 2020 due to the COVID-19 pandemic, while the valleys reflect a (descending) pattern in the last week of each December. In contrast, AI searches show a lower volume, but an increasing trend in this category. The main topics that have aroused the interest of users range from AI concepts, its benefits in medicine, in the healthcare system, in pharmacy, in clinical trials, to chatGPT.

These global searches have a special interest in the learning of a multitude of applications with DL, such as the chatbots offered by the aforementioned companies, images generation, arts, videos, etc. In the healthcare field, searches are focused on the application of AI in radiology, healthcare systems and medicine in general. On the *health data* side, African countries rank highest for job searches in these areas and offers from hospitals and research institutes working on health programmes within and outside the continent. In Ethiopia, for example, we find the Ethiopian Artificial Intelligence Institute, with projects related to data management and brain tumour detection[15], also well-known foundations such as Bill and Melinda Gates that have managed programs to help their population in health and nutrition. In broad terms and without attempting to delve into specific causes, it is not surprising that during the COVID-19 pandemic, the emergency to find a vaccine globally accelerated the acquisition and sharing of health data, increasing the search for related terms. The regions are summarized in the figure below:



(A) Interest by region in health data search (B) Interest by region in artificial intelligence search



[15] Aic.et

In terms of AD and PD, if we evaluate the behaviour at the regional level, the percentage of searches is mostly accentuated in countries such as Germany (AD, 45%; PD 55%), the Netherlands (AD, 42%; 52%), Sweden (AD, 40%; PD 60%), Philippines (AD, 34%; PD 66%), Niger (AD, 33%; PD 67%). Clearly, this is not enough information for the TVB/HDC to position itself in these regions in the future, but there are some signs of the need and interest of society to learn about these diseases, mostly framed in searches for symptoms, treatment, and common factors such as Parkinson's disease dementia and its stages (figure 25). Although the variations are not accompanied by an explanation and are result from multiple factors, we find that the highest peaks coincide, for example, with Dementia action week (18-21 September), or other related news[16]. Similarly, in PD searches, peaks coincide with the incursion of novel treatments, such as India, in which apomorphine is introduced for the first-time following agreements between the pharmaceutical company Britannia from UK and the Vikram Hospital Bengaluru (see Biospectrumasia, 2018), as well as Parkinson's action week (11 April) as other examples.

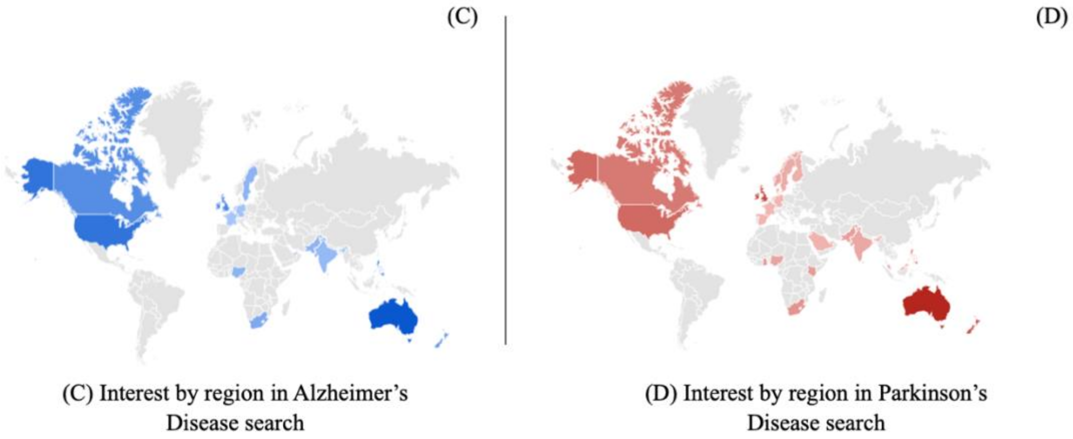


Figure 25. Interest by region of searches (2018-2023). Source: Google Trends

Therefore, **we consider that a strategy to enter these markets and raise awareness about the scope of TVB/HDC is to approach certain periods as ranges to reach potential users**, based on the most pronounced peaks in demand for information, through awareness programmes, learning and activities on significant dates. It would also help to publish reports on the platform and showcase studies, highlighting the benefits that the medical and research community has gained from AD and PD research. Furthermore, it is noted that the social interest in both conditions is mostly concentrated in countries such as Australia, United States, the Philippines, the United Kingdom, Ireland, Canada, New Zealand, South Africa, Pakistan, Sweden, Nigeria, the United Arab Emirates, India, the Netherlands, and Germany. We perceive this behaviour as a possibility for TVB/HDC to offer services (in addition to those countries with which they have had previous experience, such as the US or Canada).

Due to the social demand to find accurate, simply, and quick information that helps to understand neurodegenerative diseases, the platform could contribute to reducing this uncertainty by creating online marketing strategies, as well as disseminating courses and organising specialised programms for these markets. This first approach would be framed in four main segments (see market segmentation section): Students, healthcare professionals and technicians, and finally to a public comprising those affected and relatives, also demonstrating

[16] Ex. The finding on the risk of the APOE4 gene affecting the function of the brain's immune cells, microglia. Involving universities in Finland and Australia (EurekAlert!, 2019).

a social commitment, through awareness-raising campaigns. Other aspects such as collaborating with leading academic institutions or research centres to organise these programmes -in which the team also has experience-, and ideas aimed at cutting edge in VR and AR companies are possibilities in these markets.

In the healthcare sector, we look at the volume of clinical trials that have used similar technologies to TVB/HDC. In general, there are limited AD trials focused on testing the effectiveness of AI algorithms, data-driven brain simulation models and virtual network models, as shown in figure 26. As these methods relatively new in the scientific field, we note that the oldest clinical trial is from 2014, 33% of which have been completed, and nearly a half (47%) are recruiting subjects. In addition, the countries with the highest concentrations of records are the United States and United Kingdom, while the rest (Finland, Republic of Korea, Israel, Taiwan, Turkey, Australia, Sweden, Greece) record a single trial. Only in specific cases are multicentric (Greece, for example).

In terms of PD, the number of records compared to AD are similar, with the highest number in the US and Italy (UK, Germany, Greece, France, and Denmark; with single records). The oldest clinical trial dates to 2013, 22% could be completed and less than half (44%) are still recruiting. Overall, there are fewer clinical trials registered in both conditions, however, we are excluding records involving treatments (drugs, brain recording devices, etc.) which affects these limited results. Regarding the TVB/HDC, it is known that it has no active clinical trials, however, it should be noted that previous studies demonstrate its potential to find information that is hidden or difficult to obtain with current equipment (see section *Clinical research cases guide using the HDC/TVB services*), **in this sense, its application on larger cohorts of AD is highly important, therefore, organising a clinical trial in the near future would be within this possibilities.**

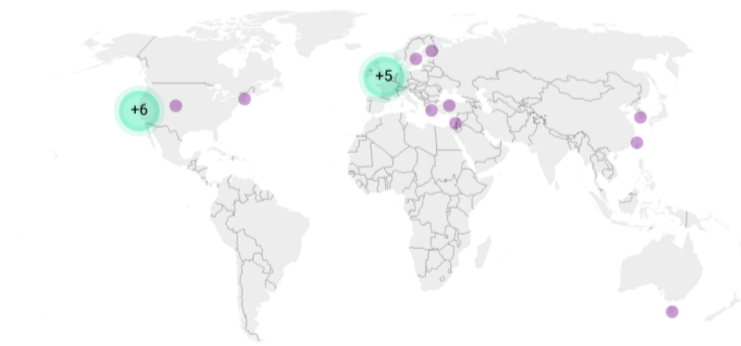


Figure 26. Registered clinical trials with artificial intelligence and data-driven brain simulation applied to Alzheimer's Disease. Source: Clinicaltrials

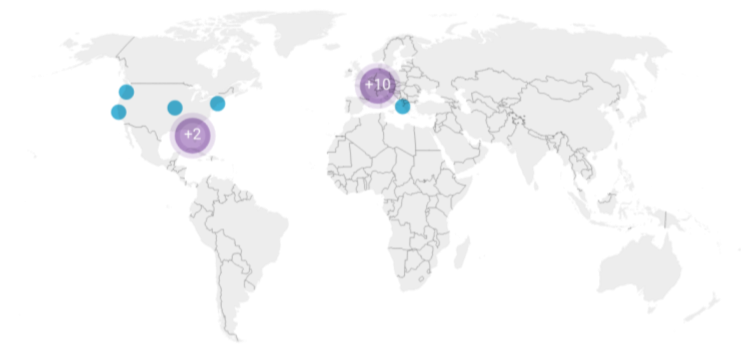


Figure 27. Registered clinical trials with artificial intelligence and data-driven brain simulation applied to Parkinson's Disease. Source: Clinicaltrials

Among the variety of open access resources to identify the companies that excel in an industry as complex and in constant technological growth as the health sector, we share the work of company Datavant (2023) titled “Healthcare Data Ecosystem”. This diagram shows a snapshot of the main organisations operating in three main segments: Originators, Intermediaries and Use Cases. In a simplified manner, the first group (EHR Software, Distribution, Pharmacies, Claims Clearinghouse, Labs, Information Exchanges, Government Entities and Socioeconomic & Behavioural Data) is oriented towards the acquisition of data from patients assisted by the health system, the second group would act as intermediaries, i.e. they store, organise, and analyse the data obtained (Registries and Consortia, Aggregators, Enterprise Data Warehousing) and the third group focuses on how the system handles privacy and data security issues (Services for Providers, Services for Patients, Services for Risk-Bearing Entities and Services for Biopharmaceuticals).

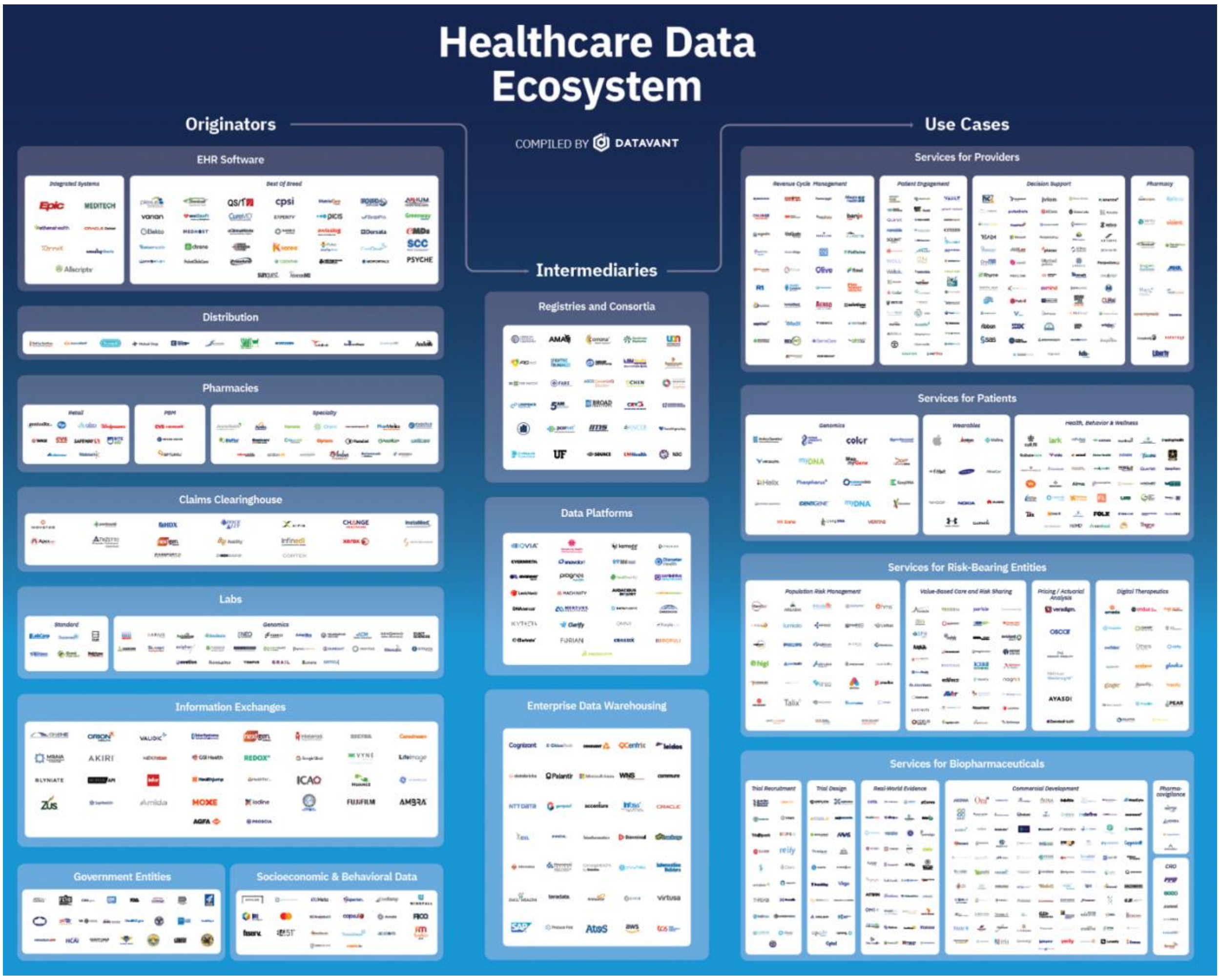


Figure 28. Healthcare Data Ecosystem, by May, T. Source: Datavant, 2023

Following the ecosystem designed by Datavant (figure 28), the HDC/TVB services would be distributed among the following groups: 1) Enterprise Data Warehousing group through the services of FENIX consortium, 2) Services for Providers group, subcategory Decision Support, and 3) Services for Biopharmaceuticals group, subcategory Real-World Evidence. In addition to identifying competitors, it is also noted that only a limited number of businesses offer their services in these categories in parallel, which would give to HDC/TVB in EBRAINS a competitive advantage. Well-known multinationals with storage, computing and management software capabilities include Microsoft Azure, Amazon Web Services, SAP, Google Cloud Service Health, among others.

5.3 HDC/VRE SWOT Analysis

The SWOT analysis is a well-known tool in market research to try to assess the internal capabilities of a project or company and the external situation. The model is composed of *Strengths*, *Weaknesses*, *Opportunities* and *Threats*, the first two are adapted to the internal analysis and the last two to the environment. It follows a practical approach, adapts to different industries, allows for a concise assessment of the project's benefits, and relates it to the context. Other authors (Namugenyi et al, 2019) have studied its theoretical and practical approaches, identifying some disadvantages as, for example, the lack of prioritisation of problems, of providing alternative solutions and the lack of control of external factors such as inflation or the cost of raw materials; designing a matrix oriented to services of digital ecosystems. Thus, the model has some limitations, since it does not originally propose the search for solutions or innovation ideas, but rather is a tool that helps to make strategic decisions. In this sense, we believe that the exploration of weakness and risks can open a path of reflection in these areas, and this has been the case for HDC/VRE.

The **Strengths** in this context are understood as "the capabilities that enable your company or unit to perform well-capabilities that need to be leveraged" (Pahl and Richter, 2009), for the case study, twelve items or internal capabilities were obtained that will help it to growth in the industry. Some of these are described in more detail in section III, regarding technical features.

STRENGTHS

1. Compliance with the European regulatory framework on data protection, following of FAIR principles and protocols for data standardisation.
2. The integration of HDC with the TVB generates an alternative way for receiving new data, as well as attracting new users.
3. Access to multiple cohort datasets for the validation of experimental hypotheses in neurodegenerative diseases, mainly AD and PD.
4. International scientific recognition and support from HBP/EBRAINS generating greater confidence for new users to explore and access the platform.
5. Supporting multiple HBP/EBRAINS developments (see section III), strengthening simulation capabilities and integration with new tools.
6. Technical development and regular updates, including measures to protect data privacy, such as restricted access, encryption, etc.
7. Support of supercomputing infrastructure FENIX to cover storage and computing server needs.
8. It provides a secure virtual environment for the storage, exchange and analysis of data (sensitive, pseudonymised and anonymised) for both research groups and intergroup.
9. Charité University of Berlin as a coordinating node of HDC, with know-how and experience from the VRE.
10. Interoperability with a wide set of EBRAINS services: (Multilevel Human Brain Atlas, Knowledge Graph, XWiki, The Virtual Brain) and interoperability with management tools common to external research groups (such as REDCap).
11. Supports any format (.json, txt., csv., BIDS, etc.)
12. Organised user guides, FAQs, educational videos about the platform.
13. Intellectual and industrial property actions: 2 registered patents and a variety of scientific publications.

In the next step, we assess the **Weaknesses** or "characteristics that prohibit your company or unit from performing well and need to be addressed" (Ibid., 2009). In this sense, the major limitation of HDC accessible from EBRAINS portal is the lack of GDPR certification, so interested users will have to wait for approval or use the services of its counterpart platform, VRE, which is operational from the servers of Charité Institute, Berlin.

WEAKNESSES

1. Multiple platforms and partnerships associated with HDC with different guides, manuals and online links, hindering efficient processing of content to facilitate access. More unified user guides would be helpful.
2. Considering the wide range of neurological diseases and thus lines of research in neuroscience that process different types of data, formats and scales; the HDC does not describe the areas on which it initial focus.
3. The access to HDC from EBRAINS is waiting GDPR certification, so those users who wish to enjoy the service will have to access the counterpart platform Virtual Research Environment (VRE), associated to Charité.
4. Unlike other health data management platforms, both the description of datasets that can be explored and the statistical or AI algorithms are not displayed on the project page.
5. The HDC service provider and its sub-services cannot guarantee the quality and accuracy of the data that can be accessed. This could influence other teams to consider HDC as an alternative to validate their hypotheses or results obtained.
6. As with current brain simulation techniques, there is still a gap between the resulting simulation models and clinical practice, medical expertise is still essential.
7. Limited capacity of long-term storage services.

As for the **Opportunities** quadrant, we evaluate the external factors that HDC/VRE can leverage in order to achieve its objectives, other authors define it as "trends, forces events, and ideas that your company or unit can capitalise on" (Ibid, 2018). Some of the favourable elements for HDC/VRE could be the increasing need for research groups to have more secure storage infrastructures, without compromising sensitive data. Another opportunity identified relates to the most recent publication of the WHO[17] on the use of AI in health and the creation of six areas for regulation in which they will begin to require external validation of data. HDC/TVB would have a significant advantage over other international competitors, not only because it is part of the EBRAINS infrastructure, but also because it will require maintaining and increasing neurodegenerative disease datasets from different cohorts, possibly at a greater level of detail (e.g. gender, race, and ethnicity), as specified by the organisation. The factors assessed and identified are shown below:

[17] See "WHO outlines considerations for regulation of artificial intelligence for health" October 2023.

OPPORTUNITIES

1. Increasing need of research centres for storage resources and large-scale computing services.
2. Open-source resources for the development of AI algorithms, including generative models that are being explored in the medical field.
3. The WHO recently published a series of regulations for the use of AI in health (see WHO, 2023). Among other aspects, external validation of datasets in the health sector will be requested to avoid bias. If HDC/VRE manages to become more specific on diseases and increase its available data, it could be an alternative for the validation of models from other projects and external researchers.
4. Possibility of integration with other federated platforms of HBP/EBRAINS such as the Medical Informatics Platform (MIP) with a wide range of data on different neurological diseases.
5. Emergence of European initiatives for the development of digital twins in neuroscience. Positioning of HDC/TVB as a reference platform for diverse neurological diseases aimed at personalised medicine.
6. Growing need in Europe to leverage limited financial resources in R&D projects. Advanced platforms for diagnostics and brain simulation that enable an eventual cost reduction in basic and preclinical research are valued.
7. Increase chance to include experimental datasets and cohorts from other regions with different clinical characteristics, through their partners in Canada.
8. Possibility to achieve licensing agreements with pharmaceutical companies, laboratories, medical device developers and biotechnology companies; as an R&D alternative for its cloud storage and neuronavigation systems.

Finally, **Threats** are elements external to the company that act as obstacles to the achievement of its objectives, also defined as: "Possible events or forces outside of your control that your company or unit needs to plan for or decide how to mitigate" (Ibid. 2018). Among the most unfavourable external trends -not only for HDC/TVB- but for the health system as a whole, is the increase of cyber incidents in Europe, considering the first report from ENISA (2023). Only between 2021 and 2023, hospitals showed the highest percentage of attacks (89%), followed by health agencies and authorities (30%), pharmaceutical industry (18%), research institutes (11%), among others. Other aspects that hinder the adoption of digital health platforms or applications are related to the approvals or the ethics committees, which paradoxically promote efficiency and good practice on the protection of sensitive data, while on the other hand intensifying restrictions on the use and development of innovative tools by research teams and healthcare professionals.

THREATS

1. New potential users depend on the approval of the ethics committee to transfer their data, bureaucracy that slows down the signing of agreements between institutions.
2. Emergence of multiple public and/or private federated projects specialising in neurological diseases which overshadows the need to use tools such as HDC.
3. Increased data and AI regulations that may affect the use of the platform.
4. Generally, research groups generate their own data, follow different processing and methods and protocols; which makes it difficult to transfer them to other platforms.
5. Leading companies with positioning in the medical industry, with virtual models incorporated into their visualisation equipment.
6. Published studies of neurological diseases in PD and AD using the platform are limited. Considering the variety of supply in AI platforms for these diseases and the rapid technological acceleration, it could be unfavourable for HDC/TVB in the long term.
7. Increase in cyberattacks on the healthcare sector globally. In Europe alone, health providers had witnessed 53% of the total attacks between January 2021 and March 2023, with hospitals being the most affected with 42% (ENISA, 2023). The attacks came in the form of ransomware, data-related threats and intrusion, mainly.

5.4 Interviews

In September 2023, a report entitled "*Acquisition, management and use of clinical data in neuroscience and artificial intelligence*" was published, the result of a collaboration between the Polytechnic University of Madrid (UPM) and the Carlos III Health Institute (ISCIII). The objectives of the report focused on exploring the needs of the NHS in Spain in terms of data in the area of experimental and clinical neuroscience, together with the use of HBP and EBRAINS tools. The methodology included, among other aspects, questionnaires, and in-depth interviews with researchers and/or physicians in Spanish health research institutes and hospitals associated with neuroscience projects.

The number of questions to evaluate the use of human brain simulation technologies specifically was limited, as the objectives of the report focused on other aspects, however, some of the reflections offered insights applicable to the current case study. The aspects that we evaluate in this study are: 1- Current use, needs and most valued aspects about human brain simulation platforms and 2- Use of third-party tools used for clinical data processing, storage, and analysis services. The opinions described below correspond to their interviewees, they may not coincide with those of their organizations, in addition, the identity of the participants is omitted for privacy reasons. These conversations prompted a search for further interviews with researchers and neurologists specialising in Parkinson's and Alzheimer's, the diseases addressed in our study. We also contacted companies developing neurotechnologies aimed at these or related conditions, in order to find out about their interest and usefulness in their current projects.

Interviewed group 1: Two neuroscience research groups specialised in the field of neuroimaging and molecular neuroscience were interviewed. In healthcare, the health information system of their autonomous community is usually restrictive regarding the use of external or unauthorised programs, including virtual brain simulators or cloud storage. Clinicians can upgrade to the latest software to performs analysis on certain test or use a tool with a technical application, such as optimizing the measurement of volume in an image.

However, they are not allowed to use any simulation or prediction technology and apply it in a clinical case, for example, to determine the probabilities of the appearance of a tumour, or if it is malignant or not. They collaborated punctually with companies on COVID-19 related projects, which allowed them to use third-party platforms for data processing and neuroimaging, with informed consent. On the other hand, the Translational Neuroscience team analyses molecular data, so they do not use brain simulation tools. As for training programs, so far, the researchers have not received specific courses for data curation in their centre, although it is planned in the next training programs.

Interviewed group 2: The team belongs to a laboratory whose line of research is oriented to the neurobiology of circuits and at the same time collaborates with an associated hospital. Their major need lies in the cloud storage of raw data in large volumes, so they invest significant resources annually to maintain their current servers. In terms of data management, they perform experiments with animals and other projects involve human volunteers, however, they do not work with sensitive data directly, they receive them anonymised. Researchers follow their own methodology for storage, and data are not unified or follow a common standard for sharing. In addition to storage needs, they value servers that provide simulations or analysis, and have agreements with supercomputing centres in Spain. They have extensive experience using neural network simulation software and libraries, however, to explore new simulation tools they require them to be easy to use, with a programming language such as Python, which is used by most of the researchers in their laboratory.

Interviewed group 3: Regarding medical data platforms in health, in their hospital they use SAP, while in the field of research they have created a variety of databases in neurological diseases. In some pathologies no interest has been shown in using these databases, such as multiple system atrophy (MSA). Likewise, collaboration with other projects allows them to explore different medical platforms, such as the multicentre project called Parkinson's Progression Markers Initiative (PPMI)[18] or the Healthy Brain Aging (HeBA), the latter is supported by REDCap for the input of non-sensitive data. On the other hand, in healthcare practice, they have nor required the use of human brain simulation tools or virtual experimentation platforms.

Interviewed group 4: Neurologists are aware of the tools associated with EBRAINS; however, they have not used its services due to lack of knowledge on how to access, how it works and how they could contribute. Among other aspects, they find the technological offer very interesting; although they need to find out more about what these platforms offer, the technical limitations and the IT resources they can use to conduct their analyses. Similarly, the role of health research institutes in these initiatives should be analysed, in addition to finding out which of these applications can be transferred from basic to clinical research.

[18] PPMI is a project that offers the scientific community an extensive repository of clinical, imaging, and biological data from different cohorts for the identification of biomarkers in Parkinson's Disease and to assess disease progression.

The experts generally publish their own raw data (non-sensitive) and, while they are familiar with other databases, they require personalise advice on how they can benefit from the resources offered by the project. In terms of research lines, they work on a wide range of neurological diseases, especially cerebrovascular and movement disorders. One of their research projects focusses on the analysis or objective quantification of movement in neurological diseases through optical motion capture and they have published studies in this regard. As for data platforms, in addition to building their own databases, they use external proteomics platforms, among them, *Uniprot*, for the study of proteins. In general, their data are processed internally, anonymised for sharing, and get support from scientific journals for publications. Regarding human brain simulation tools, they have not had the need to use them, however, remain open to explore its possibilities as training for their researchers as an application at a theoretical level.

Interviewed group 5: The team of neurologists interviewed specialise in stroke and from the hospital they also coordinate several projects on these and related diseases. They do not share data because it should not leave the hospital, but through their federated data-based platforms they have succeeded in integrating a consortium with European public and private partners. They have experience with projects such as Harmonics to harmonise data between Spain, Belgium, and Portugal, in which they have created algorithms based not only on retrospective data but have been validated to avoid bias or discriminatory data. With this information they generate *proof-of-concepts* and are deposited in an internal repository in which the algorithms are trained locally. Subsequently they are distributed to a federated network server, which feeds a central node that is continuously improved, while allowing their analysis, without exposing patient data, due to the associated encryption system. Among other aspects, they lead another initiative for the management and analysis of various types of data throughout the stroke process within the hospital. The main challenge -both inside and outside Spain- is to streamline ethics committee approvals, to improve mechanisms for accessing research data and to be able to use them in an orderly and legal manner. In terms of virtual brain simulators, they have not had the need to use these techniques in their projects.

Interviewed group 6: They study neurodegenerative diseases such as dementias, interested in the acquisition and analysis of a large number of biomarkers, from samples of encephalorachidian fluid, blood, and neuroimaging tests; mainly. They build their own databases, managed by a health platform centralised in their research centre. They use specialised international platforms such as GAAIN and ADNI, although they would be interest in finding data from other cohorts to validate their studies, such as dementia with Lewy bodies. They do not require the using brain simulation platforms, however, they are interested in learning how they get the results of the simulations and delve deeper into what they could do.

Interviewed group 7: As a neurologist and member of a scientific association, he has extensive experience in organising training courses, publications, editorials, and other dissemination activities related to new technologies and AI. Among the medical platforms they teach to share data and work collaboratively is REDCap, other trainings include programming foundations to manage, tabulate and visualise data with R, mainly. He is interested in technological modernisation and the possibility of using advanced tools to share or analyse data such as those offered by HBP/EBRAINS, which go beyond what is usually employed in clinical neurology. He understands the usefulness of virtual brain simulators, however, he has not had the need to use or teach them, noting that he would have to delve deeper into the possibilities of clinical applications. As for virtual brain simulators, he is very interested in the cases explained about HBP/EBRAINS epilepsy or Parkinson’s Disease. He values the possibilities of new technologies in the identification of lesions, as well as in the simulation of the progress of a disease, cognitive impairment, etc. In his experience as a neurologist, it seems necessary to have complete datasets of study series, from clinical data, neuroimaging, digital biomarkers, etc., in a cross-sectional and longitudinal basis.

Interviewed group 8: Two experts were interviewed at the same research biomedical research centre, both working in different teams and techniques. On the one hand, the Magnetic Resonance Imaging (MRI) facility, which also provides analytical services, and on the other hand, the biobank platform, the coordinating centre for human biological samples. Both specialists are aware of the HBP/EBRAINS project and have participated in some related activities, however, they are not familiar with health data platforms, including HDC. In this sense, the common barrier when it comes to managing their data and sharing it, is related to authorisation by the ethics committee, as well as many of the research groups.

From the MRI service, data storage and analysis are performed locally, mainly using PACS (Picture Archiving and Communication System) for neuroimaging data and follow the BIDS format. Their current systems for these processes are insufficient, so they are striving to adopt a new platform for the management and sharing of images between associated health centres. On the biobank side, they use specialised LIMBS management software -for biobanks and biorepositories-, in which they can share image data once authorisation is acquired by the ethics committee[19] (non-omics data, for the moment). With the authorisation, they proceed to prepare the data, and a Data Transfer Agreement (DTA). In this sense, both groups have limitations to share their data to other platforms, not only because of the necessary approval of the committees, but also because of the need for IT and human resources.

Another aspect to highlight, platforms for sharing and managing health data are used on a daily basis, in contrast to human brain simulation software. Regarding the latter, only the MRI service has used them on an occasional basis. The main activity of the group is to provide a service to other researchers through neuroimaging assessments, so the decision to use a particular simulation tool is made by its main users, although they could suggest some useful technology or innovation. Given the nature of biobank services, they do not require the use of brain simulation technologies in their services. As for lines of research, the MRI group studies a wide range of neurological diseases from child to adult neuropsychiatry, neurodegenerative (Alzheimer's, Parkinson's, Sclerosis, Huntington, etc.) both in animals and humans, as well as behavioural studies. In the neurological tissue biobank there are samples also associated with these diseases, as well as Down syndrome and tumours.

Interviewed group 9: Spanish startup dedicated to the development and commercialisation of medical devices for the prediction of epileptic seizures through a headset with personalised 3D design. The technology has a sensor that monitors electrical brain activity and works together with a real-time predictive algorithm and an app, making it possible to anticipate seizures by alerting the patient and their caregivers, keeping a record for data analysis by the healthcare professional.

The company has created a platform for the management and analysis of its own and the hospitals' data. As medical devices, they have to comply with the relevant regulations, such as the Medical Device Regulation (MDR), ISO standards, as well as audits for compliance with the General Data Protection Regulation (GDPR). Its leader shares that the data belongs to its

[19] In Spain, regulated by the Biobank law: Ley 14/2007.

patient and/or users, so its use is restricted to the purposes reflected in the disclaimers, such as programming new models adapted to each patient.

Interviewed group 10: The research group interviewed specialises in neuroacustics, in a laboratory associated to the University. They have published a variety of scientific articles focussed on the influence of binaural acoustic stimulations in patients with neurodegenerative diseases and in animal models, mainly. They are unaware of the platforms associated to the project except for the presentation in the interview. As for the tools to share and manage data, in the one hand, they use their own resources through CeSViMa, a university platform that provides internal networks, storage and virtual servers; services they use daily. On the other hand, the Zenodo database is used to share data from their publications, nevertheless, they are interested in exploring the platforms of EBRAINS. On one occasion they intended to use REDCap, for this they required training and a dedicated researcher, and they decided not to continue with the process.

In other respects, they have had no inconvenience in sharing data and usually share them in their own files containing the original signals in binary. They do not follow specific standardisation pathways and the formats used are not related to BIDS, because they do not work with images but with electrical signals. As for the management of authorisations and agreements, they contact to the university's ethic committee.

Regarding tools for visualising the human brain, they have not found a suitable platform, which is why they have not used them in their laboratory. In this sense, they would like to explore the technological offer of EBRAINS, to understand how they work and the level of difficulty in learning how to work with them. This would help to decide whether they should initially apply them independently or, instead, collaborate with a researcher in the project who has further expertise in the modelling tools. Some time ago, an international researcher was recruited for a PhD programme and shared with them that tools were being developed to simulate brain response of auditory circuits and motor activity, so he would also find it useful to identify these tools in the project.

Finally, they are interested in tools to model EEG in response to sound stimuli or innovations that complement their studies. Examples include testing photic driving EEG response or simulating the circuits that process motor and sound activity. At the moment they are not looking for specific datasets but better technologies to simulate and model.

Interviewed group 11: The laboratory is associated with a reference hospital in their autonomous community, so they work in both sectors. Their lines of research focus on brain connectivity, both in healthy and diseased subjects, using different neuroimaging techniques, especially MRI. They work on brain connectivity from the chemical, neurodegenerative, autism, epilepsy, traumatic brain injury, among others. There were not familiar with the health data platforms presented, with the exception of the Human Intracerebral EEG Platform (HIP). The main factor that makes it difficult for the laboratory to use these platforms are the regulatory procedures and the associated bureaucracy to share the data, they already have experience with other European projects. Another aspect is that their studies are longitudinal and not cross-sectional, so the effort to properly code and share them is higher.

At present they work with UK Biobank data, they have access to a wide range of longitudinal data on subjects and pathologies, from genomics, sequencing, among others. They consider the platform as a valuable source of different types of data (including imaging) and also use their analysis platform, in this sense, they have several funded projects and thesis in development that use their services. On the hospital side, they are not an end-user when it comes to sharing data with other platforms, unlike their laboratory. Technical barriers to working and sharing their data are not an obstacle, they have their own repositories with unidentifiable, coded, and organised information.

Another aspect to highlight when it comes to sharing data refers to the consent of the participants in their retrospective studies. In their experience, they would have to request it for each patient, and this implies a significant effort, unlike prospective studies, in which forms or instruments could be sent that allow the option of removing at any moment. Regarding data format at the hospital, when working with neuroimaging they follow the DICOM format, while NIFTI in research and as a standard or organisation, BIDS. As for analytical tools, the group has extensive experience with Machine Learning (ML) techniques, also value visualisation tools, cluster, variable classification, basic analytics mainly.

5.4.1 Analysis of interviews, insights, and suggestions

Platforms such as TVB/HDC would have a great difficulty in being introduced into the Spanish public health system (NHS), from the perspective of acquisition and management of clinical data in healthcare practice, therefore they would have better acceptance in the context of research. **We believe that both TVB and HDC require strengthening the marketing strategies of their online resources, as well as offering personalised technical support to access these services.** These actions help to attract the interest of research groups, considering that most of them have a high workload in healthcare, have less time to devote to research and receive training outside the work environment. Given the sample interviewed, from small teams to multidisciplinary groups of more than 30 people, in which physicians, psychiatrists, psychologists, neuroimaging technicians, students, among others participate; the use of brain (and neuronal) simulation tools is limited, while data storage, management and analysis services are playing an increasingly important role.

On the other hand, the HDC team offers a fully operational workflow to EBRAINS users - compatible with the regulations required in terms of data protection - via the VRE node operated and maintained at the critical (certified) infrastructure of the Berlin Institute of Health Charité. The complex onboarding process – that is required by GDPR – is documented in an EBRAINS Collaboratory[20].

Notably, HDC/VRE provide a tool that enables users to demonstrate that they process sensitive data in compliance with GDPR. As given by EU law (GDPR) the users become processors or controllers of the sensitive data and this involves responsibilities.

A common problem observed is that there is a general lack of training and education what these responsibilities do imply and how they can be fulfilled. The HDC/TVB team strives to contribute to provide this education, e.g. by providing tutorials, documentation, templates and support to users.

[20] https://wiki.ebrains.eu/bin/view/Collabs/health-data-cloud/HDCVRE%20onboarding/

Likewise, we highlight that most processing activities of health data require a data protection impact assessment (DPIA) that also takes into account the **differences on regulatory commitments and the responsibilities that stakeholders must fulfil in terms of using platforms for health data management**.

In general, the prior legal and technical procedures that must be followed differ between hospitals, research institutes, biobanks and B2B2C medical technology companies. Providing an increasing set of blueprint use cases helps to navigate through these differences and accelerates the completion of the complex onboarding workflows. This includes varying strategies e.g. for hospitals, where restrictions on data sharing may go beyond GDPR and imply institutional use and access committees, compared to health research institutes and laboratories that often have a less centralized approach where individual researchers act as controllers of the sensitive data. In any case, processing activities often involve the need for approval of ethical committees and other requirements such as the authorisation of processing by the data subjects participating in their studies.

As for biobanks, they are regulated by specific laws (although not isolated from the health system), depend on the approval of ethics committees and in some cases sign Data Transfer Agreements (DTA). There are biobanks that are increasingly developing better technologies to share their data and perform analysis, since it is a fundamental part of their service, such as UK Biobanks, All of Us in the US, etc. In this sense, they would have less need to use third-party platforms for health data management. As far as B2B2C companies that develop medical devices for both patients and professional use, the commitment suggests being higher, as they must comply with standards and regulations for both hospitals and research institutes, certifications on their devices, audits in terms of data, as well as informing users of any use and modification of their data.

In the side of HDC/VRE, first of all, the General Terms of Use must be accepted, which describes, among other aspects, the procedures, and conditions that users must follow prior to the transfer and storage of data to the platform. The types of processing, the liability of each party, restrictions, intellectual property aspects, etc. Secondly, a Nondisclosure Agreement (NDA), must be signed to ensure protection of confidential information between the parties.

Therefore, by exploring the difficulties faced by interested centres and researchers in using and sharing scientific data, we suggest increasing personalised support considering that each centre has particular policies and researchers generally depend on other members for decision-making. Another aspect is **to follow up these processes to ensure that users feel supported in technical issues**. It would also be valuable if it could **include legal advice or training that would simplify the processes required by HDC/VRE**, which for the sample are unknown. For example, **offer assistance to describe the different research agreements applicable both to the interested party and on the platform itself**: Nondisclosure Agreement (NDA), Data Transfer Agreements (DTA), Data Processing Agreement (DPA), Clinical Trial Agreement (CTA), etc. (see University of Calgary, 2023). Another point is to offer recommendations for submitting applications to research ethics committees, considering the experience of the VRE team with other researchers and studies.

By facilitating data minimized for the research purpose (i.e. all information not required is removed and excluded from the sharing/processing activity) and compliance with the corresponding regulations regarding the protection through technical and organizational measures, users are enabled to demonstrate GDPR compliance for all kinds of health and personal human data in principle – but need to be aware that as of GDPR law each processing activity requires a risk evaluation and mitigation documentation in the form of a comprehensive DPIA with involvement of the relevant data protection officers (of the involved users' institutions). **On the TVB side, the key aspect in the clinical and research field is the usefulness for neurosurgery groups, which need sophisticated neuronavigation systems, as well as medical students in these specialties**. These user segments would have a higher priority to introduce TVB/HDC.

The need for storage services in the field of research constitutes an opportunity to offer the HDC platform. Notably, data can be stored and processed in HDC without fulfilling any standards. Only if users wish to make their data FAIR (findable, accessible, interoperable, re-usable) and discoverable via EBRAINS Knowledge Graph, they need to prepare metadata following for instance the openMINDS schema. As of law it is the user/researcher who is responsible for lawful processing of their sensitive data. HDC does not claim to provide control, rather it gives users a well-documented resource at hand that enables them to demonstrate compliance with GDPR when managing sensitive data. Infrastructure that enables users to demonstrate GDPR compliance is largely lacking in Europe and hence the HDC/VRE provides a unique solution for human digital twin researchers. The platform could provide customised sessions that address these management prerequisites for those interested in publishing their studies.

The alternative platforms similar to HDC/VRE that the researchers have used, are not free of difficulties either. Cases such as REDCap (Research Electronic Data Capture) widely known tool in the community for managing and storing sensitive data, naturally requires a specialised technical human resource – and also a positive GDPR audit which typically is lacking. It is therefore essential for both HDC/VRE/TVB and EBRAINS services to **expand their human resources specialised in the platform** and to **increase publications with other teams** so that their technical *know-how* can be spread.

Finally, by way of reflection, in the article cited earlier with the ISCIII, part of the study included a questionnaire sent to the innovation units of the 18 nodes and 100 centres associated to its network in Spain. One of the questions explored the assessment of the usefulness of data, simulation, and experimentation (figure 29). Again, although the sample is not representative and the needs of these segments of interest should be further explored, of the six items shown, the following tools were rated as *very useful* and *useful* by part of the sample: Analysis and processing of clinical data (87,03%), Platforms for sharing data with other researchers (83,33%), AI applied to medical data (70,37%), Digital brain atlases (61,11%), Simulation of the human brain (46,29%) and Neurorobotics platforms (38,89%).

In general, the results suggest a valuable opportunity for HDC/TVB to enter these segments, considering its performance in four of the six categories assessed. However, at the other extreme, there is a part of the sample that finds some of these tools *unhelpful* and *nothing useful* in their current studies, such as Simulation of the human brain (29,63%), neurorobotics platforms (25,93%) and even AI applied to medical data (14,82%). It does not mean that these technologies are not beneficial for this fraction of the sample, but rather other factors are related, likely a lack of knowledge that human brain data are sensitive health data that fall under GDPR and that processing them – even including them in brain simulation comes with obligations for the researchers that require GDPR compliant infrastructure. The lack of knowledge or proper handling of health data can be particularly seen in researchers of technical disciplines (simulation, robotics) compared to those researchers with medical backgrounds that are better educated in the management of health data.

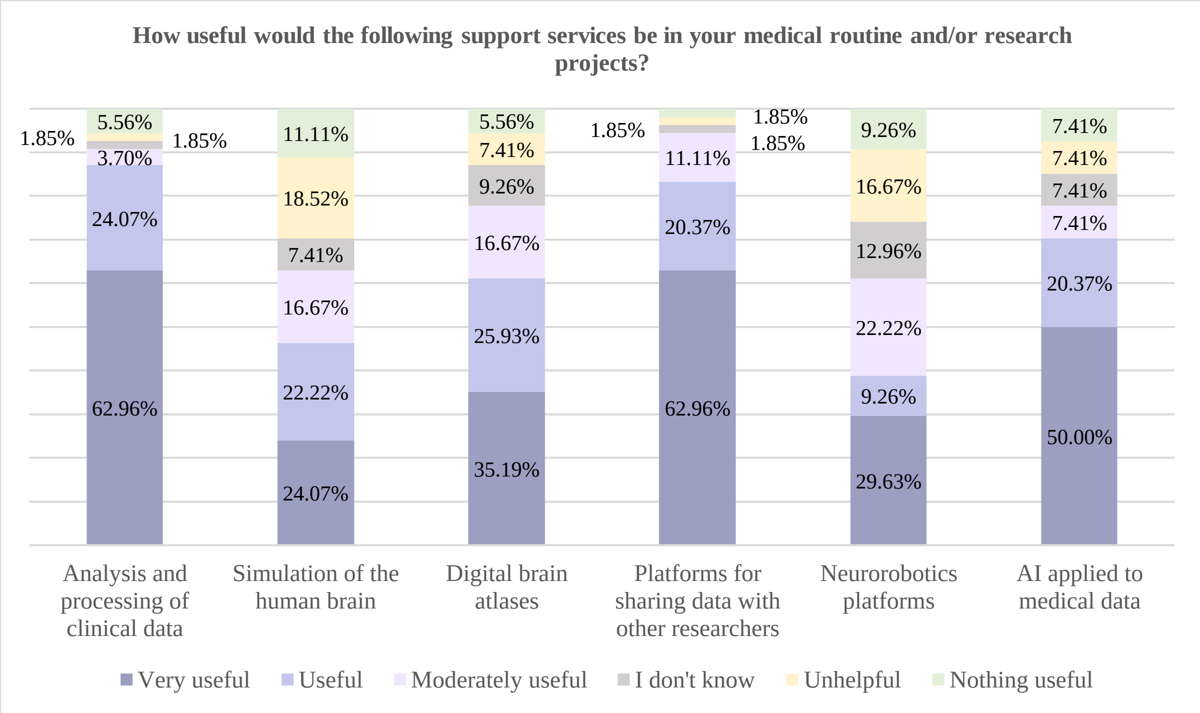


Figure 29. How useful would the following support services be in your medical routine and/or research projects?. Source: Duran, García and Velasco, 2023.

5.5 Lean Canvas Model for HDC/TVB

One of the models derived from the **Business Model Canvas** that has been successfully adapted in the field of innovation is known as the **Lean Canvas Model**, created by Ash Maurya[21] in 2010 and has been updated since then. In the author own words, the model is suitable for use when "*you're working really fast and under conditions of extreme uncertainty, as is required for Continuous Innovation, you can't afford to rely on static plans- you need dynamics models*" (Maurya, 2022, pp. 4). The **Lean Canvas Model** is the framework that we have developed for HDC/TVB, that could also be adapted to the different technologies related.

We do not intend to develop static frameworks as business models, nor extensive pages that show a long-term financial forecast in this report. Instead, a first practical exercise has been carried out with Lean Canvas which contains many of the sections of a business plan and which has inspired useful ideas that will in turn accompany the strategic framework presented in the next section. It is known that the neurotechnology market is at an emerging stage worldwide, including the EBRAINS platform with its associated services, so a dynamic workflow from an entrepreneurship perspective could be the key to boosting HDC/TVB, as presented below:

[21] Ash Maurya is author of two bestselling books "Running Lean", "Scaling Lean" and the Lean Canvas framework. He has also served as a consultant to entrepreneurs internationally. (See Maurya, 2022)

PROBLEM

1- Lack of audited GDPR compliant infrastructure.
2- Limited datasets of neurological diseases to validate hypotheses and brain simulation models in healthy brains and pathologies.
3- Lack of tools and services supporting FAIR data management and reproducible workflows for human digital twins.

EXISTING ALTERNATIVES

*Search for external providers.
*Data repositories oriented to the type of extraction.
*Advice from the legal service, mainly ethics committees.
*Multiple open-source software tools.

SOLUTIONS

*Neuroscientific data processing, computation, visualisation and validation services.
*Advanced platforms and user-friendly design (UX).
*Development, refinement and validation of brain digital twins/ patient digital twins.
*Virtual Clinical Trials Support Platforms.
*Platforms that provide access to cohorts, complete datasets: Not only transversely but longitudinally.

KEY METRICS

*(1) 2 patents filled *(2) TVB: 52,496 downloads (Oct. 2023) *(3) VRE: 93 Members, 17 projects, 177 GB Data, 21 Virtual Machines, 244 Cores, 1503 GB RAM *(4) VirtualBrainCloud (TVB-Cloud): 38 Peer reviewed articles, 3 demonstrations *Available datasets: Unknown *Types: Unknown *Users per month: Unknown *No revenue.

UNIQUE VALUE PROPOSITION

*Health Data Cloud (HDC) with its Virtual Research Environment (VRE) as a platform to collect, process, share and store data from neuroscience and clinical studies, complying with European GDPR regulations and international standards easily and safely.
Others: *Workflows and integrated modules to facilitate data processing at all stages. *Training and educational resources to learn how to use the platform comprehensively. **UPM Innovation Ideas for the HDC/TVB:** (see section below)

HIGH LEVEL CONCEPT

*HDC/VRE for neuroscience data management.
*TVB for brain digital twins.

UNFAIR ADVANTAGE

Leading companies in the development of medical technologies and with an experience curve. They control important market shares through their subsidiaries, distribution channels and suppliers; advantages that facilitate the adoption of their technological platforms.

CHANNELS

*Online: HDC/VRE/TVB official websites, EBRAINS website, social media platforms, publication in scientific journals, dissemination of grey literature *In-Person events: Participation in congresses, sponsorship in digital health events *Networks of collaborations, support of the members of its consortium: University hospitals, research institutes. *By references(word-of-mouth) *Direct sales.

CUSTOMER SEGMENTS

Segments **by type of service** in HDC/VRE (See services in Revenue Streams):
Health and biomedical research institutes (associated with hospitals), laboratories, company leaders and spin-offs developers of neurotechnology with digital platforms, Contract Research Organisations (CRO).

EARLY ADOPTERS

Principal researchers in neuroscience groups in health/ biomedical research institutes, laboratories and centres associated with hospitals and clinics.

COST STRUCTURE

Direct Costs: Cost per service and maintenance of infrastructure (data centres, networks) / Human resource costs (salaries and incentives of administrative, engineers and technicians, management, operations, research, etc.) / Cost per integration of technologies developed by HBP/EBRAINS groups, licensing costs (if applicable). **Indirect Costs:** Sales and after-sales service, advertising and marketing / R&D expenses: Costs for service redesign, updates, IT improvements / Office rental, electricity consumption, consumables / IPR costs: *Scientific journals publications: Article Publishing Charge (APC), costs for patent registrations / Costs for legal services and agreements with other entities.

REVENUE STREAMS

Free basic platform and annual or monthly subscription-based model.
Type of services:
1) Storage service and support in the transfer of data to the platform.
2) Consultancy for the validation and testing of models: Analysis, visualisation, simulation, digital twins creation service.
3) Long-term storage and access to specific datasets in compliance with the GDPR.
4) Training services for data management and analysis.
UPM Innovation Ideas for the HDC/TVB: See section below.

Source: Own elaboration, template adapted from the Lean Canvas Model created by Ash Maurya. Other references: (1) HDC/VRE Patent N° (2) Thevirtualbrain.org, 2023 (3) https://vre.charite.de/vre/ (4) TVB-Cloud results, EC CORDIS.

5.5.1. CUSTOMER SEGMENTS

Before starting to define customer segments, it is important to clarify that we have classified them according to the **type of service** of HDC/TVB. Another essential step is the distinction between users and customers, the latter being the agents who would pay for the product or service. Naturally, this process is more complex in the health and research field, considering the multiple actors involved in the procurement processes.

According to the type of service offered in HDC/VRE, **customers** - or those who would pay for the service - can be from both public and private sector. The two segments differ not only in the type of financing and purchasing power, but also in the administrative processes for acquiring or renewing their technologies. A buyer with high negotiation power for HDC/VRE - a private clinic, for example- in a market of strong competitors, will try to find the best prices given the wide range of alternatives in its market or because of the reachability of *substitute services* -other data management platforms -. These differences in the segmentation will influence in the future strategic decisions to address or not a certain segment.

For the case study, Customer Segments will simply include health and biomedical research institutes (associate with hospitals), laboratories, university hospitals, companies belonging to the neuroscientific field and possibly Contract Research Organisations (CRO). As in Spain, public hospitals in many countries are intensifying controls and restriction on the use of acquisition, data, and analysis platforms outside the authorised systems, more so than in research institutes themselves, given the acquisition of sensitive data resulting from healthcare practice. With no intention of excluding such a relevant sector, the indirect or common way to address this segment would be through research institutes or other centres, such as laboratories. Therefore, the customer segment is represented by legally independent entities, and in the case of the public sector, the purchase of technology must be implemented - at least in Spain- through mechanisms such as Public Innovation Procurement [22].

On the **user** side, HDC/VRE requires the signing of a Non-Disclosure Agreement (NDA) by the interested centre, being the Principal Investigator (PI) of the group who will manage the projects within the HDC/VRE platform and grant the permissions to the rest of her/his team (if required) for data management. This is since GDPR compliance needs to be demonstrated by each user (data controller) and hence they are required to be informed about the proper technical measures in place to provide a high level of information security and data privacy. This requires disclosure of sensitive information about the IT infrastructure and hence an NDA is to be concluded to prevent distribution of this sensitive information.

In addition, we include other scientists related to the project, innovation specialists, business and technicians who can influence other groups (who are unaware of the services of the platform), acting in turn as influencers or mediators in the transmission of information related to HDC/VRE.

[22] In turn, Public Innovation Procurement is done through two methods: Pre-commercial Public Procurement (PPP) and Public Procurement of Innovative Technology (PPI). Principado de Asturias, SEKUENS, 2019.

5.5.2. EARLY ADOPTERS

As described in the previous section, the main users of HDC/VRE are the PIs of research teams on neuroscience and neurotechnologies disciplines, who will use the service for their research projects.

5.5.3. PROBLEM

From the list of problems identified in this sector that can be reduced using HDC/VRE, the three with the highest priority are selected, those for which the client would use the platform:

1- **Lack of audited GDPR compliant infrastructure** that makes processing of human digital twins containing personal and health information law and regulation compliant.

2- **Limited datasets of neurological diseases to validate hypotheses and brain simulation models in healthy brains and pathologies**: Greater access to clinical data (digital biomarkers, neuroimaging, genomics, etc) is needed not only transversely but longitudinally.

3- **Lack of tools and services supporting FAIR data management and reproducible workflows for human digital twins**

5.5.4. EXISTING ALTERNATIVES

In the following we outline the different ways in which early adopters seek to solve the problems described above. For the HDC/VRE they are shown below:

- **Search for external cloud storage providers and data analysis providers:** Multinationals with experience and infrastructure distributed worldwide such as Amazon Web Services (AWS), Microsoft Azure, etc. However, while Cloud providers may claim GDPR compliance, the actual service workflows lack GDPR auditing and users are not supported in receiving the Data Protection Impact Assessment that implies a detailed account of technical and organizational measures in place to protect the data of specific use cases during storing, sharing and processing. Thus, often, users who are liable when processing sensitive data are not aware that they are processing the data not in compliance with EU law.

- **Data repositories oriented to the type of extraction:** Solutions specialised in radiological images, pathological anatomy, etc. and other biomarkers in neurological diseases. However, they are still limited and often do not offer access of individuals from multiple institutions / external individuals to the organization that offers the service.

- **Advice from the legal service and ethics committees**: Depending on the type of institution associated with the health system – hospital, labs, research institutes, etc.- advice will be sought from the legal service, mainly from the ethics committees. In other cases, the informed consents of the subjects will be requested again. We are not aware of alternative ways to obtain quick approvals from committees, and they can take up to six (6) months. HDC/VRE offers the opportunity to keep consents and ethics votes once they exist for future secondary data users. Nevertheless, for their specific processing purposes additional ethics votes may be required by the users' institutions. The availability of ethics votes of the original data study and the subject consents yet facilitates this process.

- **Multiple open-source software tools** for automatic data acquisition, anonymisation, standardisation, etc. These may vary according to each processing stage, methods and tend to be independent, i.e. they do not easily integrate with other platforms and tools.

5.5.5. UNIQUE VALUE PROPOSITION

In this section it should be highlighted why the product or service is different from what already exists, the qualities or characteristics that could be relevant to potential users (this information is developed in more detail in the first sections of the report), in a nutshell:

> *Health Data Cloud (HDC) with its Virtual Research Environment (VRE) as a platform to collect, process, share and store data from neuroscience and clinical studies, complying with European GDPR regulations and international standards easily and safely.*

More benefits

- Workflows and integrated modules to facilitate data processing at all stages.
- Training and educational resources to learn how to use the platform comprehensively (including associated HBP/EBRAINS technologies), highlighting the benefits associated with its adoption.
- Others (*see section III)*

Our Innovation Ideas for the HDC/TVB

- **Agreements/collaborations with Contract Research Organisations (CRO)** for the management and support of virtual clinical trials by applying HDC/TVB, which can be empirically validated.

- **Possibility of initiating research partnerships with neurotechnology and pharmaceutical companies through the platform,** in order to help research teams with HDC/VRE-stored datasets have the potential to be applied in clinical trials (and who are also interested in initiating collaborations).

- **Short trainings on legal aspects and agreements**, recommendations for Ethics Committees.

- Partnerships with specialised brain injury centres **for war and defence veterans to support individuals who are more likely to develop neurodegenerative and mental diseases after trauma**.

5.5.6. HIGH LEVEL CONCEPT

According to Maurya (2022), this exercise intends to create a “high-concept pitch” that simplifies in a very concise way the idea of the product or service, not to be used on a landing page but in contexts after the introduction, easy to understand with few words. For our case study:

HDC/VRE for neuroscience data management.
TVB for brain digital twins.

5.5.7. SOLUTION

In coherence with the identification and selection of the problems in the previous segment according to the level of priority, possible solutions using the platform are described below:

- **Neuroscientific data processing, computation, visualisation, and validation services:** Access to a network of professionals associated to HDC/VRE as data managers and related personnel.

- **Advanced platforms with user-friendly design (UX)** for neuroscience data processing and analysis.

- **Development, refinement, and validation of brain digital twins** of healthy people and those with neurological diseases, for treatment simulation and rehabilitation (including normal and pathological ageing).

- **Virtual Clinical Trials support platforms,** that allow the comparison of real and experimental study groups through HDC and TVB.

- **Platforms that provide access to cohorts, complete datasets:** Access to data and biomarkers most needed by AD and PD research groups (digital biomarkers, neuroimaging, genomics, etc.) not only cross-sectionally but also longitudinally.

5.5.8. CHANNELS

Clearly, this segment seeks to describe the available options in which a product or service reaches potential customers. The model highlights the usefulness for start-ups of following the process of “customer discovery/interview” (Maurya, 2022). Although this method has been successfully developed in this report, the sample interviewed is not representative, however, it helps to identify the different needs that are common among the groups. The channels for our case study are simplified below:

- **Online:** HDC/VRE/TVB official websites, EBRAINS website, social media platforms, publication in scientific journals, dissemination of grey literature.
- **In-Person events:** Participation in congresses, sponsorship in digital health events.
- **Networks of collaborations, support of the members of its consortium:** University hospitals, research institutes.
- **By references:** (word-of-mouth).
- **Direct sales.**

5.5.9. REVENUE STREAMS & COST STRUCTURE

The model recommends evaluating the prices of the product or service being offered from the early stages, helping to define the type of customers of the company. However, since it is a first exercise, it does not delve into the possible strategies. We will develop a few that could be applied to the case study. There are numerous ways to determine base prices and adjust them. Some experts define three main marketing strategies in terms of pricing and, from there, other aspects for pricing must be considered (Kotler and Armstrong, 2018). The three basic strategies are: *Pricing based on value for the client, pricing based on an adjusted value and pricing based on the competition*. We will focus on two of those that could be considered for HDC/TVB.

In simplified terms, **price fixing based on the value-based** pricing puts the customer's need first, in contrast to cost-based pricing, which is usually defined after the team has created the product or service, that is, it sets prices at a later stage to cover costs. However, in this case it is the customers who perceive its value and decide whether it meets their needs. For HDC/TVB, many of the potential users have a wide experience in neuroscience data management and analysis software, with many teams using *open-source* software, therefore, the perceived value of HDC/TVB would play a key role as a pricing strategy for access to some of its services. In turn, within this strategy, two pricing approaches can be followed: value-adjusted and value-added (Ibíd, 2018).

The most important difference is that in the first there is a combination of high-quality service for a fair price, variable depending on the economy and value perceptions, while in the second approach, companies offer enhancements or additional features that help differentiate them from the competition, i.e. they do not lower the price to match other companies but provide more value to their customers. Ultimately, the choice of one or the other will depend on the marketing objectives of HDC/TVB's future startup.

The second is the **competitor based-pricing**, as the name suggests, where competitors 'prices are used as benchmarks. Similar services to HDC, VRE, TVB can be found independently in both paid and *open-source* software. However, platforms that integrate at their core the most advanced technologies for neuroscience research, neurodegenerative diseases datasets, analytical tools, brain visualisation, data storage, supercomputing, etc. expert consultancy from the HBP (just to name some features of the case study); are not found in large numbers in the neuroscientific community, nor in the industry, for better or for worse. The neurotechnology market is still growing and the pricing for HDC/VRE/TVB services in this concept will depend on the perceived value of other users in similar businesses.

As an example, among the NVIDIA company's product lines (see section V), there is a free or *open-source* MONAI platform (see Medical Open Network for Artificial Intelligence, 2023) to train its AI algorithms in neuroimaging analysis, while on the other hand it offers paid plans for companies of the NVIDIA AI line starting from 4,500$ (about 4,119€) just one year of subscription. In our Lean scheme, a free basic platform and annual or monthly subscription-based model is proposed for HDC/TVB. **As for the services that can be offered to companies as subscription model are**: 1) Storage service and support in the transfer of data to the platform. 2) Consultancy for the validation and testing of models: Analysis, visualisation, simulation, creation of digital twin's service 3) Long-term storage and access to specific datasets in compliance with the GDPR, 4) Training services for data management and analysis.

Other aspects to be considered for pricing and adjustments are the different life cycles of the technology, such as the **earliest stage of market introduction, others such as geographic location, intensity of competitors, customer value, psychological pricing,** among many others. As mentioned above for HDC/TVB, a price fixing by segments could also be considered, which varies according to them (subscription model for companies, free for other types of users). Depending on the competitors (companies such as NVIDIA, Microsoft Azure, Amazon Web Services (AWS), etc.), also by product line (AI services, validation with HDC/TVB, for example).

Finally, from an innovation perspective and consistent with the ideas suggested in previous points, the proposed services that could be included to enhance HDC/TVB's value perspective are:

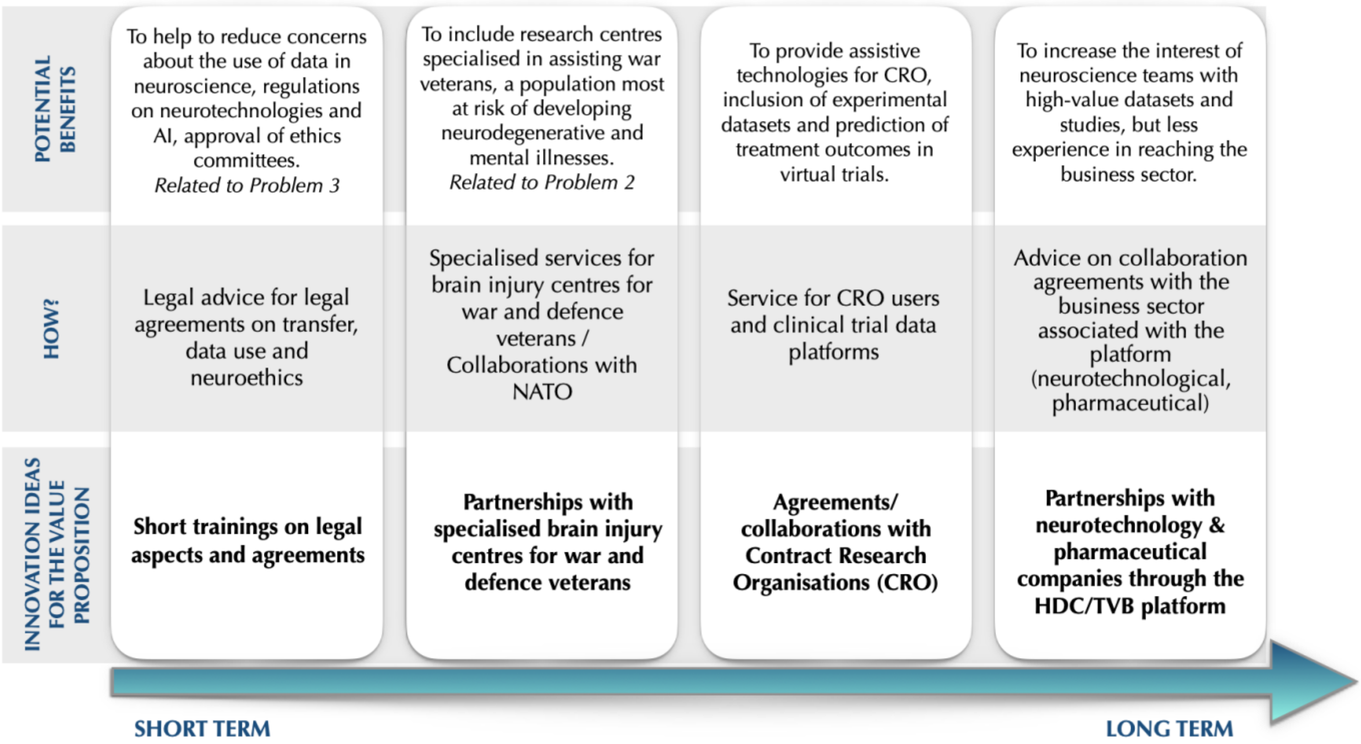


Figure 30. Suggestions of new services to be included in HDC/TVB. Own elaboration

5.6. Dimensions of the competitive environment

From a macro perspective there are some classifications or nomenclatures of business activities, such as the North American Industry Classification System (NAICS)[23] applied in Canada, the United States and Mexico; the National Classification of Economic Activities (NACE)[24] by the European Union, or the Global Industry Classification Standard (GICS)[25] by the MSCI. These codes differ among international standards and delimit economic activities in a generic basis; however, they allow an initial approximation to the competitive environment in order to identify HDC/TVB related businesses. Starting from the NAICS classification (2022 v1.0), the services would possibly fall under classification 541710 "Research and development in the physical, engineering and life sciences" in subgroups such as "Medical research and development laboratories or services (except clinical)" or "computer and related hardware, research and development services".

A next method aimed at better definition of the competitive environment derives from the three-dimensional strategic model, proposed by Abell (2010), adapted to the industry where platforms such as HDC/TVB operate. The dimension proposed are: 1) The customer groups or those who purchase the product, 2) the functions that the product performs for these customers, and 3) the form that the product takes or the technique it uses to fulfil its function; the key ones are shown in the diagram below:

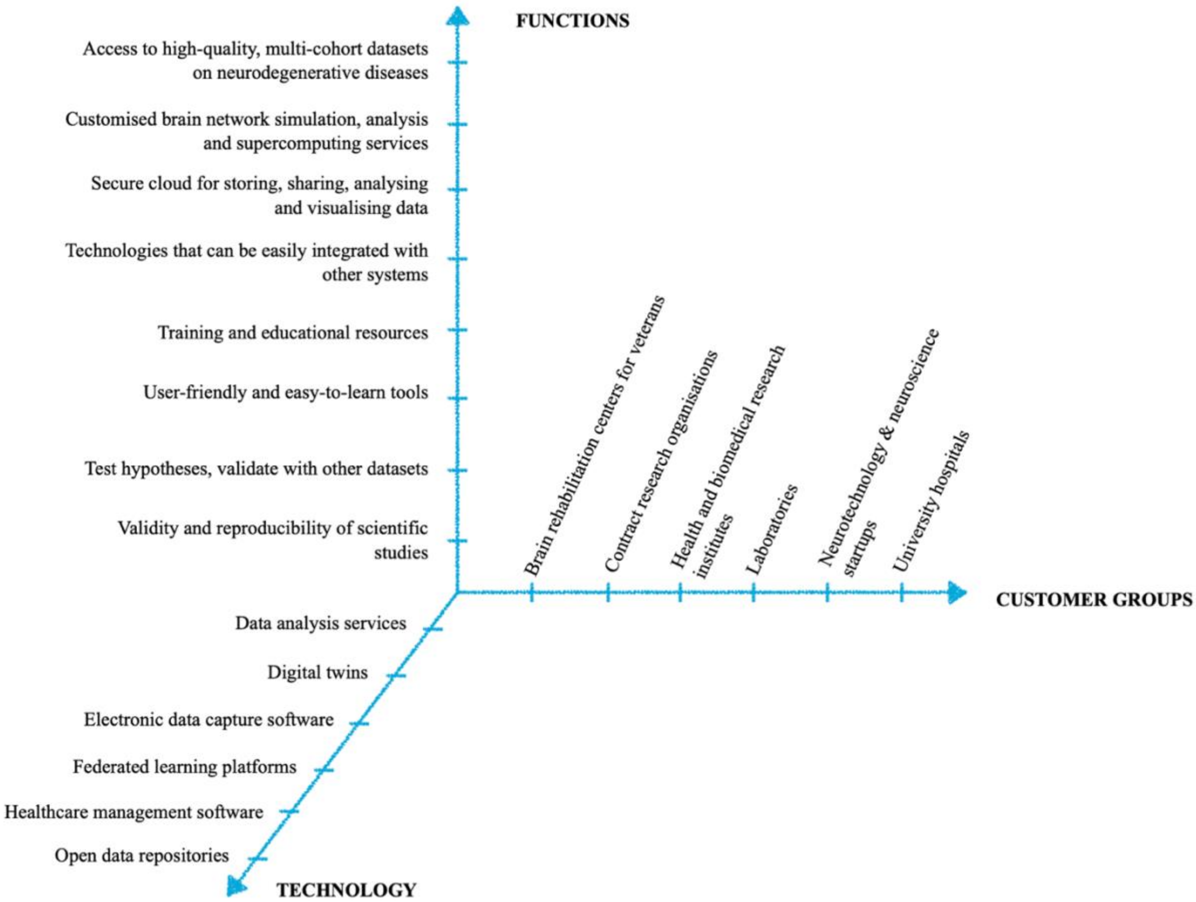


Figure 31. Own elaboration, following the Abell model (2010)

[23] https://www23.statcan.gc.ca/imdb/p3VD.pl?Function=getVD&TVD=1181553
[24] https://nacev2.com/en
[25] https://www.msci.com

Some of the strategic suggestions in this report include **the possibility of stablishing agreements with Contract Research Organisations (CRO)** and brain rehabilitation centres for veterans equipped with research departments, part of the Customer Groups. A more precise definition of a CRO is provided by the European CRO Federation (EUCROF, 2023) "*is a person or an organisation (including commercial, academic and non-profit) that provides services to industry and other stakeholders such as governmental organisations, foundations or hospitals, on a contract basis and within the scope of clinical research (experimental or observational), as well as other activities in connected domains.*" In 2014, around 1,110 CROs were estimated worldwide (Spainhour, 2014), in Europe alone, these organisations currently number 450 EUCROF partners. In addition, the CRO market is expected to reach more than 65.5 billion dollars by 2028, with a compound annual growth rate (CAGR) of 6,4% between 2022-2028 (FactsFactors, 2021).

In recent years, the role of the CRO has become increasingly diversified, offering services for wide range of medical specialties and diseases, tasks that can be contracted outsourced on a part-time basis. Therefore, services may range from the organisation of clinical trials, protocols, ethical and regulatory aspects, patient recruitment, to the design of strategies for future approval and commercialisation. However, some studies reflect the problems many CROs face in practice globally -lack of quality, inadequate documentation of work and data, poor protection of intellectual property, security, communication problems, etc.- and share some suggestions regarding the use of CROs (Spainhour, 2014). Others analyse the main drivers that delay the startup of global randomised clinical trials (Lai, 2021) and, among other aspects, suggest the inclusion of telemedicine and decentralised clinical trials (DCTs) -trials in which the patient is monitored remotely, e.g. from home, in order to increase trial efficiency.

In this sense, the HDC/TVB platform could be a useful alternative for CROs and other sponsors of clinical trials in pre-clinical and clinical studies. First, as a support tool in the storage and analysis of data, part of the range of services offered from a CRO. Secondly, as a source of information on other studies in neuroscience together with the possibility of contacting their principal investigators (at least for those projects that would like to be visible within the platform) and thirdly, as part of the feasibility studies carried out by sponsors or CROs before venturing into a clinical trial (some type of studies in Rajadhyaksha, 2010). In exploring opportunities and constraints, HDC/TVB's simulation and modelling functions could help redefine trial designs or research hypotheses for CRO and principal investigators, saving costs and time in new studies. On the other hand, preclinical CROs specialise in animal model testing, following internationally established ethical principles in animal research and protocols[26]. Thus, using HDC/VRE services in these projects could increase the value proposition, considering that data in animal experiments do not maintain the same confidentiality restrictions as human data.

A further strategic proposal in this report relates to **the possibility of collaboration with military health research centres – in accordance with EU and national regulations and EU defence agency (EDA) programs[27] - to adopt TVB/HDC services and its associated brain data recording platforms**, to promote specialised lines of research in the diagnosis and treatment of neurological diseases for veterans and active military.

[26] International Ethics Codes, European Union Regulations 86/609, among others (Reyero et al, 2000)

[27] https://eda.europa.eu/what-we-do/research-technology

Several publications indicate that traumatic brain injury (TBI) and post-traumatic stress disorder (PTSD) in military environments increases the risk of developing neurodegenerative diseases, such as AD (Weiner et al, 2013; Tate et al, 2021). Among the most frequent consequences for military survivors are amputations, spinal cord injuries, and traumatic brain injuries, being the most common cause improvised explosive device (IED) blasts (Spelman, 2012). Among other concerns identified, the need to follow standardised clinical procedures for the diagnosis of TBI in neuroimaging equipment is highlighted, as well as the identification of Common Data Elements (CDEs), to be shared by the specialised centres, being the ENIGMA consortium an international initiative promoting these methods (Tate et al, 2021). However, more effort is required for data standardisation, understanding the methods and instruments for acquiring the datasets available in TBI, current limitations, among others. The medical platforms of EBRAINS could be a valuable alternative to these current challenges and first proof of principle has already been provided (Good et al, 2022).

In North America, participation in the pilot programmes of Defense Innovation Accelerator for the North Atlantic (DIANA) "Pilot Challenges" which, as a NATO partner, has a strong interest in building relationships with innovators, investors, and industrial partners to address defense and security challenges in dual-use technologies (see DIANA, 2023). The 30 startups selected for the annual programmes will be granted 100,000 in phase 1 and 300,000 in phase 2, in addition to being included in an accelerator or Boot-camp (Figure 31). The Test Centres and the Accelerators can be seen on the map of the figure 32, in which France and Germany have a greater number of test centres. In Spain, the Universidad Politécnica de Madrid (UPM) has been selected as a Test Centre, through two strategic units "*NeuroTechAI, focused on neurotechnology and artificial intelligence, and UPM-DQC focused on quantum technologies and cyber security*" (CTB-UPM, 2023). Likewise, opportunities could be explored for platforms such as HDC/TVB as alternatives for data storage and management in the development of some projects.

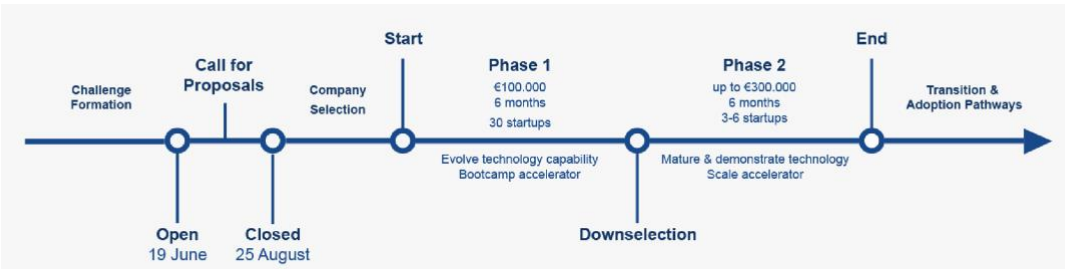


Figure 32. Selection phases for the DIANA accelerator programme. Source: DIANA, 2023

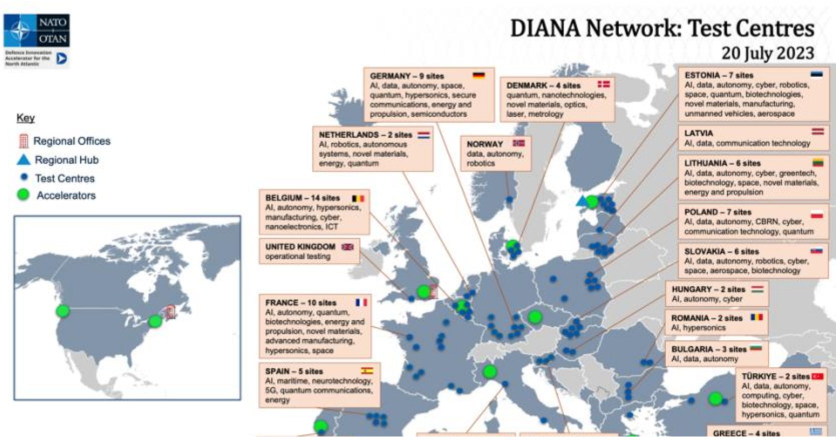


Figure 33. Diana Network. Source: DIANA, 2023

In Europe, In January 2023 a new excellence facility has started – the Testing and Experimentation Facility for Health AI and Robotics (TEF-Health)[28] under lead of Charité. The project is funded by €60 million for 5 years and will continue its operation after the five years funding period. The project develops virtual and physical testing and validation services for startups and SMEs to facilitate bringing innovative products through certification and to the market. HDC/TVB are health data and human digital twin simulation services that will likely constitute a major service supporting the private sector in developing, validating and certifying human digital twin technologies in Europe.

[28] https://tefhealth.eu/home

CONCLUSIONS

The HDC/VRE platform is a technology for the management, sharing, analysis and storage of data, part of the Human Brain Project and EBRAINS that, together with TVB contribute to the designs of personalised therapies through digital brain twins. From an intellectual property perspective, the platform debuts in the scientific community with two registered patents - additional to those of TVB, its associated simulator-, considering its recent launch. These actions not only give an advantage in terms of exploiting its innovation vis-à-vis its competitors and as a marketing strategy, but also in terms of putting the proofs of concept achieved or computational biological models for the study of neurodegenerative disease into practice.

While a wide range of related patents was found, based on the IPC nomenclature and its sub-classifications, in which powerful multinationals specialised in different technological areas, laboratories, start-ups, universities and science and technology institutes stand-out; mainly from China, USA and South Korea, it is noteworthy that HDC/TVB are the only human digital twin cloud based platforms that are developed with data protection according to EU law by design and by default. A fraction of the global competition around neurotechnologies and neuroscience is reflected, allowing us to explore where the efforts of these organisations are being directed, to understand how HDC manages to differentiate itself from the current technological offer and to find efficient strategies to successfully transfer its results.

Other market behaviour explored are related to worldwide search trends in AI and health data in the last five years, reflecting a growing interest in these applications in specific periods and regions. Global impacts as the COVID-19 pandemic, the emergence of start-ups and unicorns promoting the massification of generative models, are the most pronounced variations. At the same time, circumstances of lower global impact such as the approval of novel treatments, innovative companies, campaigns to raise awareness of neurodegenerative diseases, etc. have also had an effect on search behaviour. As for the health sector, the volume of clinical trials aimed at testing the effectiveness of AI algorithms or data-driven brain simulation models in the field of AD and PD are limited, the former mostly in the USA and UK, while the latter in the USA and Italy.

To begin with the strategic analysis, a SWOT matrix was designed identifying the capabilities of the case study and the external situation. In sum, thirteen strengths or most important attributes were detected, some of which are the integration with EBRAINS technologies, technical capabilities, educational resources, among others. Seven weaknesses that could influence reaching new users or stand out from other initiatives in the sector. As for environmental factors, eight opportunities were detected, highlighting the growing need for storage and computing resources, recent publications of WHO for the validation of datasets in the health sector, etc. in terms of threats, seven elements could become a challenge for related platforms, such as the strengthening of federated projects with a higher level of specialisation in neurodegenerative diseases, increasingly sophisticated and more frequent cyber-attacks, etc.

Moreover, assessments obtained from interviews with researchers, leaders, and other health professionals in the development of studies in neuroscience were key. The contributions made it possible to deepen the needs of potential segments and obtain insights for the design of innovation strategies, marketing, user experience, legal aspects, and agreements, among others. Suggestions such as increasing marketing and dissemination actions about the functioning of HDC/TVB, to provide guidelines and more unified access to the platform, advice on legal agreements and ethical aspects, personalisation, and monitoring of services to both potential users and clients to help determine the match between the tools offered and the research lines, among other aspects.

As for business models, the Business Model Canvas (BMC) is developed, a framework originally proposed by Ash Maurya (2010), suitable for scenarios of uncertainty, rapid changes, and continuous innovation. The exercise helped to profile customer segments, determine early adopters, select the most relevant problems, identify alternatives, highlight the unique value proposition, generate innovation proposals for the platform and models for service delivery. Likewise, the strategic Abell model (2010) on three dimensions of the competitive environment is considered and adapted to the case study, delimiting customer groups, functions, and technologies. Finally, some innovation proposals from BMC are developed, mainly HDC/TVB agreements with Contract Research Organisations (CRO), partnerships with specialised brain injury centres for veterans and particularly promising is the perspective of becoming a central service offering of the new EU Testing and Experimentation Facility for Health AI and Robotics (TEF-Health).

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