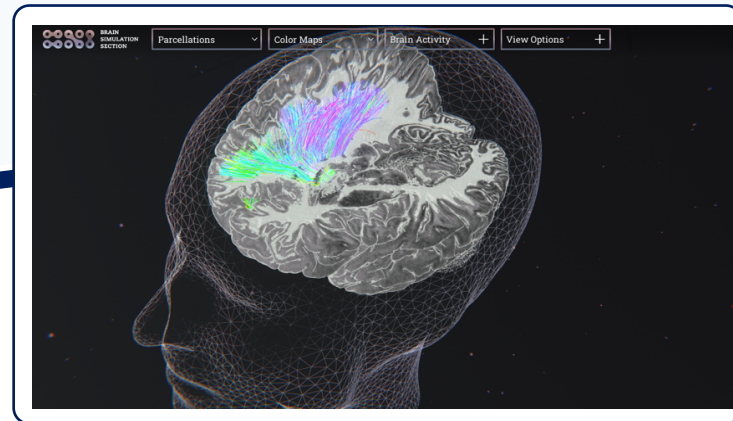




VirtualBrainCloud

Personalized Recommendations for Neurodegenerative Disease



Public deliverable report

D6.5: Final Virtual Brain Cloud Platform is fully integrated and validated documentation of its functionalities

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Dissemination level:	public
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1. Introduction

The central goal of the TVB-Cloud project is the development of a Cloud-based platform, termed TVB-Cloud, for medical research that helps to improve early patient-specific diagnosis and treatment of neurodegenerative diseases like Alzheimer’s disease and Parkinson’s disease. Our long-term vision for TVB-Cloud is to pave the way for a clinical product for personalized medicine that improves the quality of life of EU citizens by enabling targeted prevention, early diagnosis, disease progression prognosis, individual treatment plans and development of novel therapies for neurodegenerative diseases with a focus on Alzheimer’s and Parkinson’s disease. We believe that this vision will be reached by implementing a European cloud-based platform that not only connects two critical streams of biomedical research, systems biology and computational neuroscience but also connects clinics, researchers, patients and students.

2. Description of work performed

This work was performed between January 2018 and May 2023 as part of the EOOSC project Virtual Brain Cloud¹.

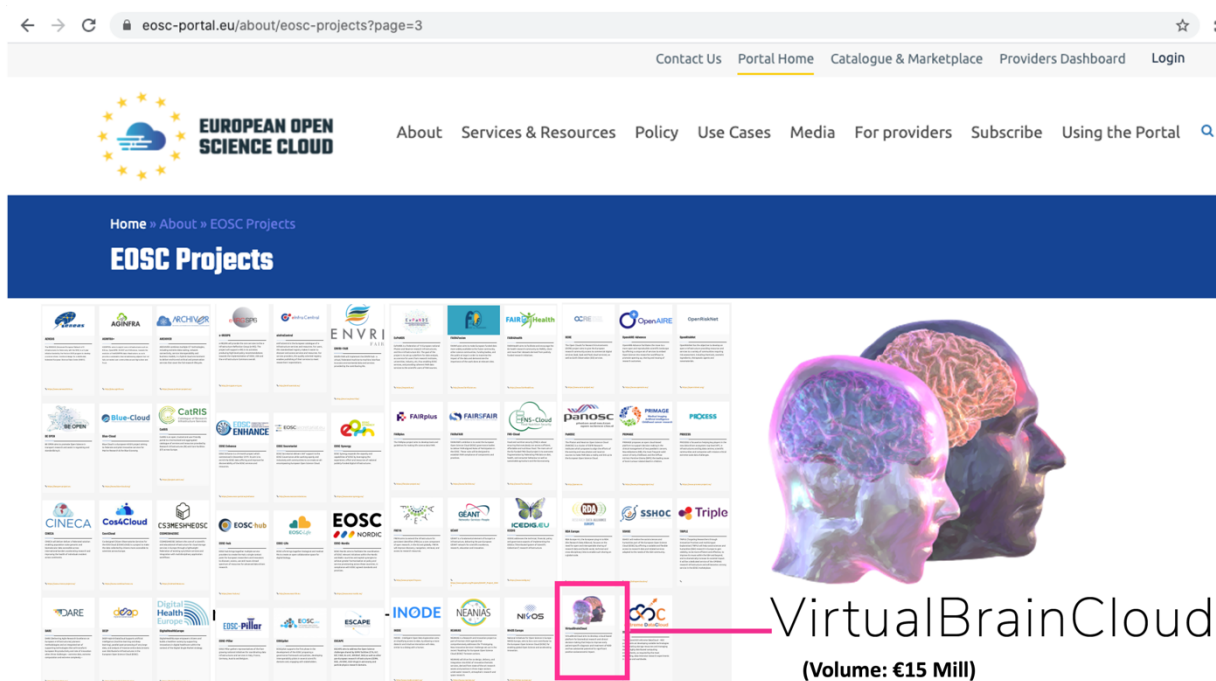


Figure 01: Virtual Brain Cloud is an EOOSC project with the goal to contribute to the implementation of a digital EU-wide research infrastructure. Specifically, the project Virtual Brain Cloud created a secure Virtual Research Environment to manage and process sensitive human health data – and in particular human digital twins – at the service of the research communities.

Health data are of sensitive nature in which case access must be strictly controlled. On the other hand, if a lawful basis exists, it is also desirable that sensitive data can be made accessible for exploitation. To achieve such a solution where data can be used across EU member states, an interoperable suite of software tools was developed that can be composed into distributed technology platforms that make data discoverable via centralised, searchable catalogues of metadata repositories, provide storage and

¹ <https://eosc-portal.eu/about/eosc-projects?page=5>



compute IT infrastructure offering the appropriate information security and privacy standards for each case, and support adaptable data governance processes, reflecting the regulatory requirements that are applicable, which will vary from one jurisdiction to the other, from one sector to the other, and from one use case to another.

3. Results

3.1. Secure Virtual Research Environment

The secure VRE² developed in EOSC project Virtual Brain Cloud provides an open-source data management platform that enables users to store, process and share data in compliance with the EU General Data Protection Regulation (GDPR). The VRE addresses the present lack of digital research data infrastructures fulfilling the need for (a) data protection for sensitive data, (b) capability to process complex data such as radiologic imaging, (c) flexibility for creating own processing workflows, (d) access to high-performance computing. The platform promotes FAIR data principles and reduces barriers to biomedical research and innovation. The VRE offers a web portal with graphical and command-line interfaces, segregated data zones and organizational measures for lawful data onboarding, isolated computing environments where large teams can collaboratively process sensitive data privately, analytics workbench tools for processing, analysing, and visualizing large datasets, automated ingestion of hospital data sources, project-specific data warehouses for structured storage and retrieval, graph databases to capture and query ontology-based metadata, provenance tracking, version control, and support for automated data extraction and indexing. The VRE is based on a modular and extendable state-of-the-art cloud computing framework, a RESTful API, open developer meetings, hackathons, and comprehensive documentation for users, developers, and administrators. The VRE with its concerted technical and organisational measures can be adopted by other research communities and thus facilitates the development of a co-evolving interoperable platform ecosystem with an active research community. Data in the VRE are always encrypted at rest. In the Secure VRE, for processing, data are sent to isolated VMs with strict access control. Only in these protected VM environments can data be decrypted and analysed by researchers, according to the predefined access policy. In cases of the need for HPC resources outside the protected VRE (not all data centres can offer GDPR-audited HPC infrastructure, the data are transferred to an isolated sandbox for processing. The sandbox is a temporary environment that outputs only encrypted results using the authorised user's private key, which deletes all non-encrypted data when expiring³.

² <https://www.bihealth.org/en/translation/network/digital-medicine/bihcharite-virtual-research-environment>

³ Brain Simulation as a cloud service: The Virtual Brain on EBRAINS doi: 10.1016/j.neuroimage.2022.118973

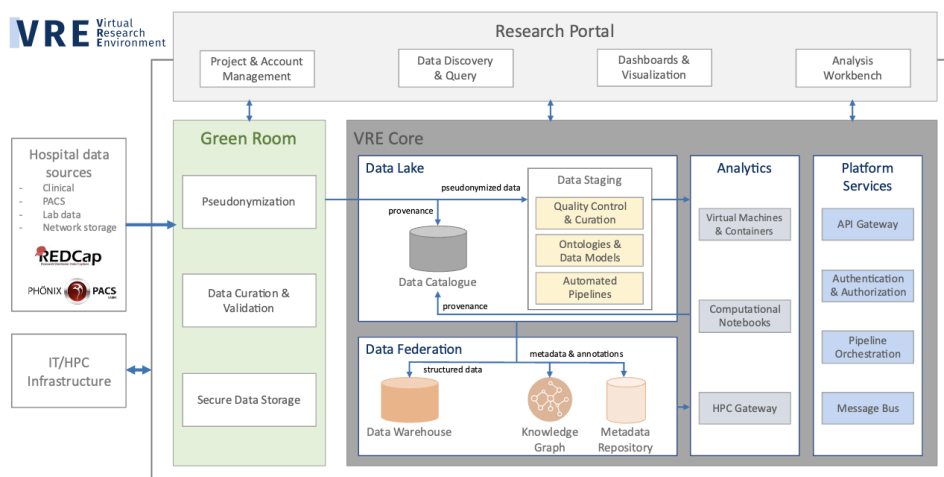


Figure 02: High-level architecture of the secure VRE developed under this EOSC project Virtual Brain Cloud operated at the Charité certified Critical Infrastructure⁴

3.2. Data Discoverability via EBRAINS Research Infrastructure

Non-sensitive metadata of the data inside the VRE can be submitted by data sources to EBRAINS Knowledge Graph⁵ Spaces for discoverability. Dedicated programmatic and graphic user interfaces support the metadata transfer from VRE to EBRAINS Knowledge Graph.

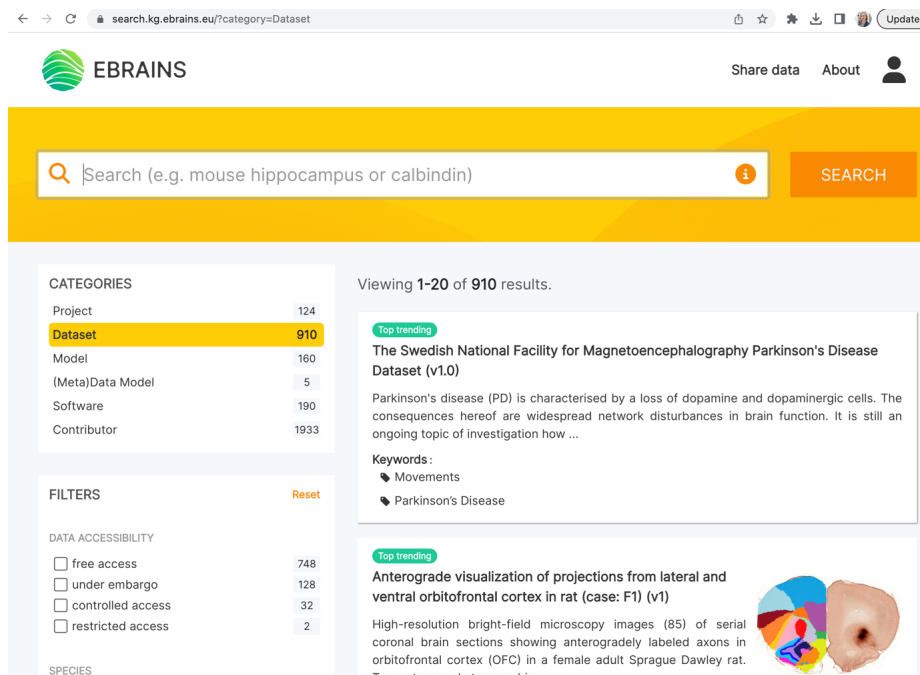


Figure 03: EBRAINS Knowledge Graph is a graph database with a programmatic and graphical user interface for the discovery of data, models, and software tools. KG supports multiple metadata models. A prominent one used in EBRAINS is OpenMINDS⁶

⁴ <https://www.bihealth.org/en/translation/network/digital-medicine/bihcharite-virtual-research-environment>

⁵ <https://search.kg.ebrains.eu>

⁶ <https://github.com/HumanBrainProject/openMINDS>



In EBRAINS Knowledge Graph, each data set is equipped with a data set card (see Figure 03). For sensitive data sets stored in a satellite VRE, the data set card in the "Get data" field informs:

"The data is currently shared via the Virtual Research Environment at Charité – Universitätsmedizin Berlin (<https://www.bihealth.org/en/translation/network/digital-medicine/bihcharite-virtual-research-environment> <<https://www.bihealth.org/en/translation/network/digital-medicine/bihcharite-virtual-research-environment>>). Please contact [data controller name and email address] for access."

Upon conclusion of a data processing agreement and a data protection impact assessment, the data are released to a newly created "project" to which only the new user has access and admin right to admit authorized team members (e.g. processors with whom a processing agreement has been concluded).

The screenshot shows a web browser displaying a data set card. The URL is search.kg.ebrains.eu/?category=Dataset&q=tvb#a696ccc7-e742-4301-8b43-d6814f3e5a44. The card title is "TVB time series and connectomes for personalized brain modeling in brain tumor patients (v1.0)" by Aerts, H.; Schirner, M.; Jeurissen, B.; Dholander, T.; van Roost, D.; Achten, E.; Ritter, P.; Marinazzo, D. The card is divided into several sections: Overview, Data descriptor, How to cite, Get data, Publications, Specimen, and Related resources. It also includes a DOI (10.25493/1ECN-6SM), a license (CC-BY), and project information (The Virtual Brain Tumor Patient). The card lists custodians (Marinazzo, D.) and provides a detailed description of the dataset's content, including BOLD time series and structural connectivity matrices. It also lists studied brain regions, study targets (structural and functional connectivity, brain tumor, connectome), behavioral protocols (Resting State Paradigm), preparation methods (in vivo, in silico), experimental approaches (neural connectivity, neuroimaging, informatics, computational modeling), and techniques (functional magnetic resonance imaging, diffusion-weighted imaging, magnetic resonance imaging, echo planar pulse sequence, simulation). A footer note asks users to report errors or quality concerns to curation-support@ebrains.eu.

Figure 04. Example of a data set card with which each data set that is registered in EBRAINS Knowledge Graph is equipped.

This level of integration is in process of being further advanced, such that metadata can be directly submitted from a VRE / HDC project to the EBRAINS Knowledge Graph.

User Single Sign On (SSO) portal for EBRAINS is an identity broker that allows the collecting of user information and performs requests to KG on behalf of the user. KG management API⁷ allows one to view available spaces, upload datasets, view datasets, define custom types, release information, and more. Collaboratory API⁸ allows the creation and manages collabs, adding or removing users from it and registering a space for the collab.

⁷ <https://core.kg.ebrains.eu/swagger-ui/index.html>

⁸ <https://wiki.ebrains.eu/bin/view/Collabs/the-collaboratory/Documentation%20Wiki/API/>



3.3. Licensing Sensitive Data

The data use agreement terms used for sharing sensitive data correspond to those published by the European Commission (Figure 05):

https://commission.europa.eu/publications/standard-contractual-clauses-controllers-and-processors-eueea_en

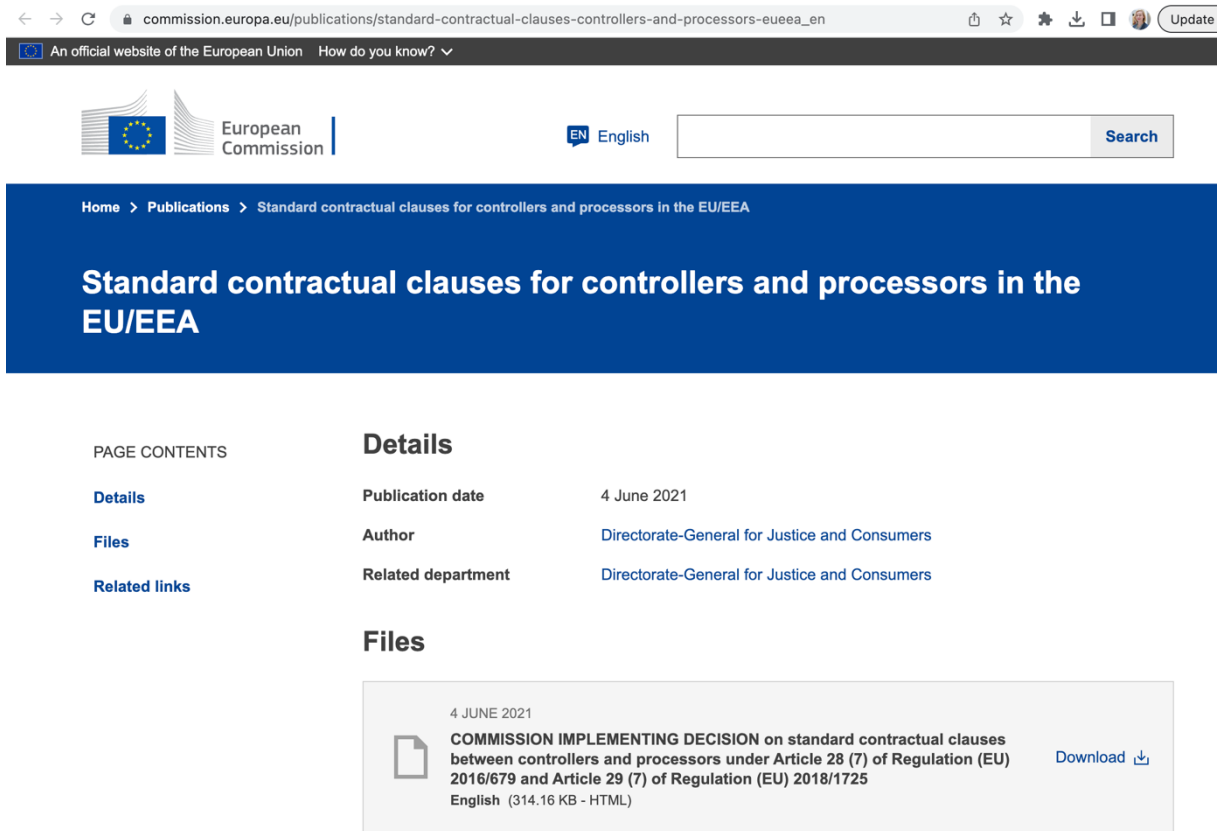


Figure 05: Standard Contractual Clauses (CC) by the EC are used as a contractual agreement between data controllers and processors when sharing sensitive data.

CC BY4.0 license on human health data could be construed as misleading due to its incompatibility with GDPR as the creator of the health information depicted e.g. in our MRI data is the data subject and it doesn't result from the creative process of a scientist that could give us the right to waive copyright protection. If such a license is applied it must be clear that it only pertains to very limited aspects of the data set, like for example how the files and folders are organized, but not to the health information stored inside the files. We suggest as License Statement: Data sharing/processing agreement according to GDPR to be concluded with the data controller.

CHARITE and UNIVIE team are planning to submit an article on the “Licensing of personal data in Europe” to the current Frontiers in Neuroinformatics Research Topic: Navigating the Landscape of FAIR Data Sharing and Reuse: Repositories, Standards, and Resources⁹.

⁹ <https://www.frontiersin.org/research-topics/48468/navigating-the-landscape-of-fair-data-sharing-and-reuse-repositories-standards-and-resources>



3.4. GDPR Compliance Audit

The VRE operated at the Charité underwent a comprehensive external independent GDPR compliance audit which confirmed the GDPR readiness of the infrastructure.

In October 2022 the European Data Protection Board (EDPB) endorsed a GDPR certification scheme for the first time: The Europrivacy certification hands now out the European Data Protection Seal to certify GDPR compliance. The certification criteria were drafted by European Center for Certification and Privacy Europrivacy certification is registered in the public register of certification mechanisms and data protection seals and marks.

We presently explore the possibility to achieve additionally to the already successful external audit a European Data Protection Seal to facilitate researchers/users to demonstrate compliance when using the VRE for their processing of sensitive data.

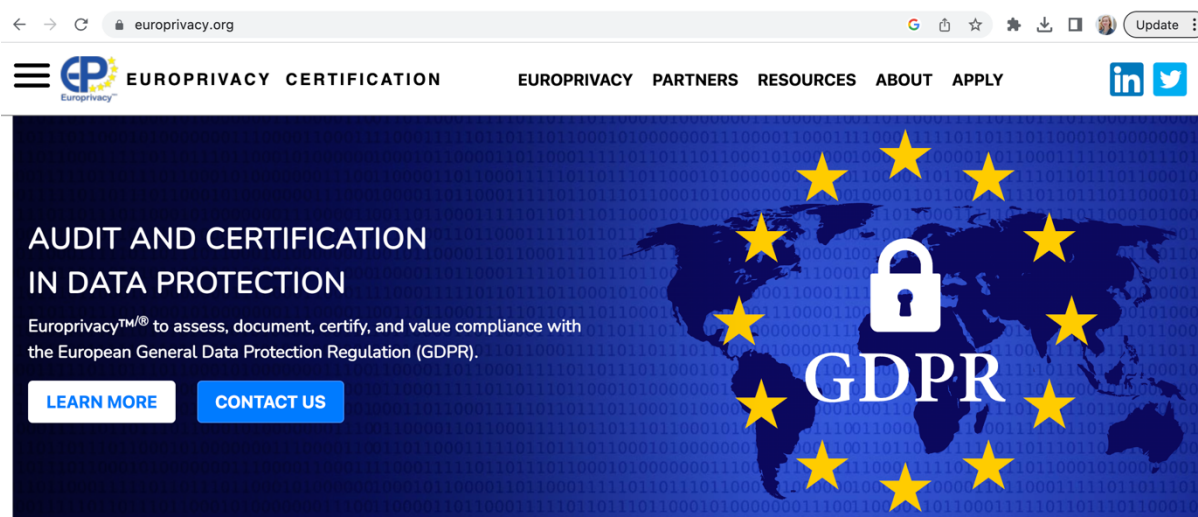


Figure 06: The Europrivacy certification hands now out the European Data Protection Seal to certify GDPR compliance.

3.5. Access to the Secure Virtual Research Environment via EOSC Marketplace

The secure Virtual Research Environment at Charité is discoverable and accessible via EOSC Marketplace¹⁰.

¹⁰ <https://marketplace.eosc-portal.eu/services/secure-virtual-research-environment-vre-for-sensitive-data>



The screenshot shows the EOSC marketplace page for the 'Secure Virtual Research Environment (VRE) for sensitive data'. The page includes a navigation bar with 'About EOSC', 'Browse Marketplace', 'Providers Hub', 'Monitoring', 'Status', and 'Contact us'. The main content area features the VRE logo, a description of the service, and a 'Access the service' button. The description states that the VRE is an open-source data management platform that enables medical researchers to store, process, and share data in compliance with the EU General Data Protection Regulation (GDPR). It also lists the organization as Charité University Medicine Berlin, Berlin Institute of Health, and Brain Simulation Section. The page includes a star rating of 0.0/5, a 'Webpage' link, and a 'Helpdesk' link. On the right side, there are sections for 'SCIENTIFIC CATEGORISATION' (Medical & Health Sciences) and 'CATEGORISATION' (Data Management, Access, Compute, Other).

Figure 07: The Secure Virtual Research Environment is discoverable via the EOSC marketplace.

The screenshot shows the RIsources website page for the 'BIH / Charité Virtual Research Environment (BIH/Charité VRE)'. The page features the DFG (Deutsche Forschungsgemeinschaft) logo and the RIsources logo. The main content area includes a 'Details' section with a 'Back' link. The description of the VRE is identical to the one in Figure 07. On the right side, there is an 'Address' section with the following information: Robert-Koch-Platz 4, 10115 Berlin, Berlin, Deutschland, and a 'To website' link.

Figure 08: Germany's research foundation lists the secure Virtual Research Environment in its registry of research infrastructures¹¹.

¹¹ https://risources.dfg.de/detail/RI_00560_en.html



re3data.org

Repository details

BIH / Charité Virtual Research Environment

General Institutions Terms Standards

Name of repository	BIH / Charité Virtual Research Environment
Additional name(s)	Berlin Institute of Health / Charité Virtual Research Environment BIH / VRE
Repository URL	https://www.bihealth.org/en/translation/network/digital-medicine/bihcharite-virtual-research-environment
Subject(s)	Medicine Life Sciences
Description	The Virtual Research Environment (VRE) is an open-source data management platform that enables medical researchers to store, process and share data in compliance with the European Union (EU) General Data Protection Regulation (GDPR). The VRE addresses the present lack of digital research data infrastructures fulfilling the need for (a) data protection for sensitive data, (b) capability to process complex data such as radiologic imaging, (c) flexibility for creating own processing workflows, (d) access to high performance computing. The platform promotes FAIR data principles and reduces barriers to biomedical research and innovation. The VRE offers a web portal with graphical and command-line interfaces, segregated data zones and organizational measures for lawful data onboarding, isolated computing environments where large teams can collaboratively process sensitive data privately, analytics workbench tools for processing, analyzing, and visualizing large datasets, automated ingestion of hospital data sources, project-specific data warehouses for structured storage and retrieval, graph databases to capture and query ontology-based metadata, provenance tracking, version control, and support for automated data extraction and indexing. The VRE is based on a modular and extendable state-of-the-art cloud computing framework, a RESTful API, open developer meetings, hackathons, and comprehensive documentation for users, developers, and administrators. The VRE with its concerted technical and organizational measures can be adopted by other research communities and thus facilitates the development of a co-evolving interoperable platform ecosystem with an active research community.
Contact	vre-support@charite.de

Figure 09: Registry of Research Data Repositories¹² lists the secure Virtual Research Environment.

Presently the VRE is in process of also being included in the registry

- FAIRsharing.org
- Nature Scientific Data repositories <https://www.nature.com/sdata/policies/repositories#healthsci> under health repositories category

3.6. Open-Source Community Project

The already developed secure VRE at Charite data centre (accessible via EOSC Marketplace¹³) is a full stack automated *infrastructure as code* (IaC) - open source under EUPL and equipped with detailed deployment and operation documentation.

The Software is made available under the open-source license European Public License (EUPL) established by the EC under European law. Compatible Licences' according to Article 5 EUPL are: GNU General Public License (GPL) v. 2, v. 3; GNU Affero General Public License (AGPL) v. 3; Open Software License (OSL) v. 2.1, v. 3.0; Eclipse Public License (EPL) v. 1.0; CeCILL v. 2.0, v. 2.1; Mozilla Public License (MPL) v. 2; GNU Lesser General Public License (LGPL) v. 2.1, v. 3; Creative Commons Attribution-ShareAlike v. 3.0 Unported (CC BY-SA 3.0) for works other than software; European Union Public License

¹² <https://www.re3data.org/repository/r3d100014127>

¹³ <https://marketplace.eosc-portal.eu/services/secure-virtual-research-environment-vre-for-sensitive-data>



(EUPL) v. 1.1, v. 1.2; Québec Free and Open-Source Licence — Reciprocity (LiLiQ-R) or Strong Reciprocity (LiLiQ-R+). All documentation that is not owned by third parties is licensed under the Creative Commons License CC-BY-SA-4.0: <https://creativecommons.org/licenses/by-sa/4.0/legalcode>.

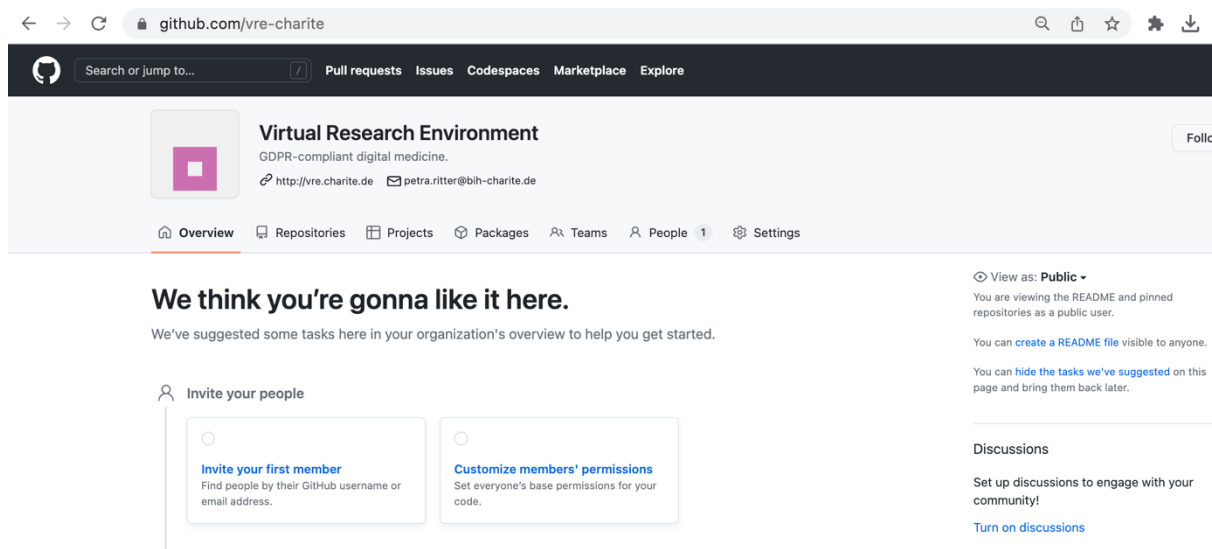


Figure 10: VRE open-source code is accessible via github¹⁴ and licensed under EUPL.

The VRE is a project under the lead of Charite with a contribution by contracted partner Indoc Research. Development of the platform started in April 2020 as a community-driven, iterative effort in which the input of stakeholders (researchers, IT, management, and data protection officials) informs the ongoing development of the features, front-end interface, and backend architecture. Charité coordinates bi-weekly meetings open to stakeholders from BIH/Charite and external organizations interested in the VRE. In these sessions, the development team updated the community on the progress of the VRE and collected feedback on features and new requirements. Stakeholders and participants presented research use cases and formed new collaborations and synergies between groups. The VRE development project has thus engaged a community of ca. 200 individuals from >30 institutions in >10 countries across Europe and North America. Since the first production release in September 2020, the number of users performing acceptance testing has grown to ca. 100 beta users in 22 test projects and has yielded positive feedback that is shaping the future development priorities of the platform. The VRE supports FAIR data principles in the developer community by publishing and updating open-source development code and documentation in the VRE Wiki and by deploying and supporting the use of open-source workbench tools that are commonly used among the research community (Jupyter notebooks, Python libraries, Docker containers, Apache Guacamole remote desktop gateway, Apache Superset and XWiki).

Subsequent Developments: Peer-to-peer Network of Secure Virtual Research Environments – EBRAINS Health Data Cloud

The secure VRE technology developed under the EOSC project Virtual Brain Cloud is being used as foundational architecture for EBRAINS Health Data Cloud¹⁵ developed presently under the lead of CHARITE in the EU Flagship Human Brain Project (Task 6.15, Jan 2022-Sept 2023). It consists of a peer-

¹⁴ <https://github.com/vre-charite>

¹⁵ <https://www.healthdatacloud.eu/>



to-peer network of equally privileged secure VREs in line with the roadmap of the European Health Data Space (EHDS). While each VRE is fully functional and autonomous, they are all interoperable and can exchange metadata, data and code.

The Secure Virtual Research Environment¹⁶ being developed under the lead of CHARITE comprises a federated peer-to-peer (P2P) network, which is a network of interoperable equally privileged nodes that all exist autonomously. Each node is fully functional and serves its individual user groups with an individual user-facing front. Nevertheless, the HDC P2P framework connects these nodes and enables the exchange of data, metadata and code between nodes. Thus, metadata from data stored at a network node can be sent to a central Knowledge Graph (located at ESFRI RI EBRAINS) and published after passing the quality control and curation process. Data in distributed data centres thus become discoverable centrally via a single search interface. After discovery users can send access requests which are delivered to the respective data controllers. Upon approval by data controllers, data (minimized for the specific processing purpose in accordance with GDPR) are made accessible to the new users who conclude a sharing or processing agreement and thus become lawful controllers or processors.

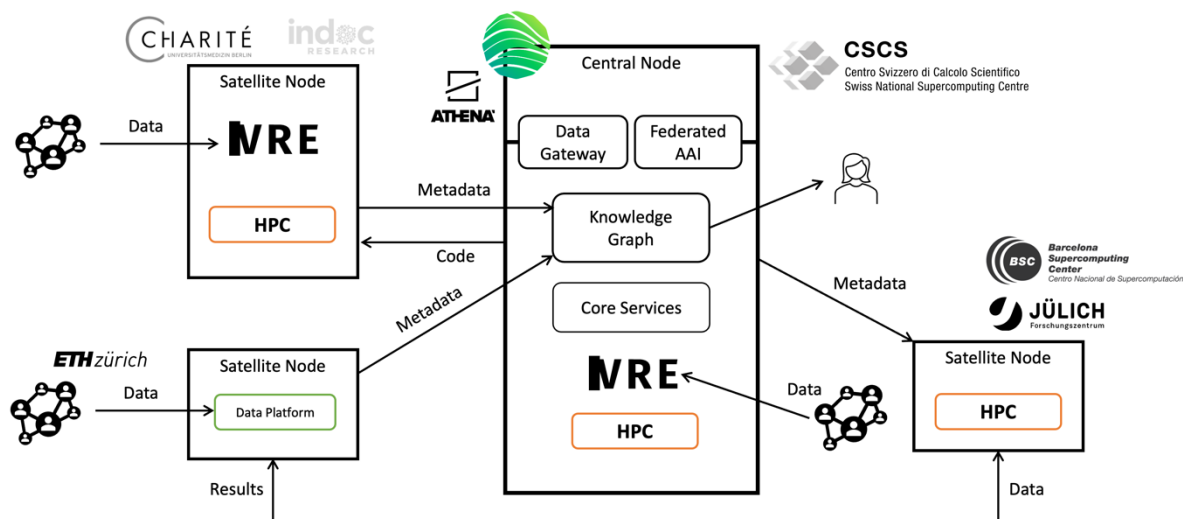


Figure 11: CHARITE leads EBRANS Health Data Cloud, a network of equally privileged autonomous interoperable nodes (data and compute centres) that builds on secure VRE technology developed in the EOSC project Virtual Brain Cloud. This development is funded under EU Flagship Human Brain Project SGA 3 (Jan 2022-Sept 2023)

3.7. Subsequent Developments: Deployment of the VRE on EGI-ACE resource

In 2022, CHARITE has submitted a proposal for a call by the European Grid Infrastructure¹⁷ (European access to computing resources initiative, Figure 12).

¹⁶ <https://www.bihealth.org/en/translation/network/digital-medicine/bihcharite-virtual-research-environment>

¹⁷ <https://www.egi.eu/egi-ace-open-call/>



egi.eu/egi-ace-open-call/

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Open Calls

EGI-ACE: Call for Use Cases

Apply and get access to Services, Tools, Training & Support!

With this call for use cases, the EGI-ACE project offers individual researchers, national and international research projects, and communities access to infrastructure and platform services, dedicated user support and training. The services, support and training are sponsored by the European Commission and various national funding agencies and are free to access to the use cases that will be selected through the call.

[Apply now!](#) [More about EGI-ACE](#)

Figure 12. The Virtual Brain Cloud project under the lead of CHARITE was applied successfully for a Use Case in the EGI-ACE project. Consequently, the VRE is being deployed in collaboration with FRAUNHOFER at the EGI infrastructure. Thus, it becomes available as an additional node to the EOSC community.

3.8. Subsequent Developments: Horizon Europe project EBRAIN-Health and Digital Europe project TEF-Health

The VRE builds the foundational Architecture for several subsequently funded EU projects, such as:

- PHRASE¹⁸: Personalized Health cognitive assistance for RehAbilitation
- AISN¹⁹: Integrating AI in Stroke Neurorehabilitation
- eBRAIN-Health²⁰: Actionable Multilevel Health Data
- TEF-Health²¹: Testing and Experimentation Facility for Health AI and Robotics

In projects the VRE technology will be further advanced and the scope of functionalities and available nodes extended.

3.9. BrainX3

BrainX3²² is the visualization software of TVB-Cloud. It is a neuroinformatic tool for the exploration, analysis, modelling and simulation of brain data using interactive visualizations that facilitate the exploration and discovery of new insights by scientists and clinicians. It is a standalone multiplatform software that supports multiple workflows for data analysis.

BrainX3 can be used as a front-end application for the TVB simulation software. It integrates the TVB-rest-client, a component that allows communication with a TVB server, interchange data and executes operations on the server. This section describes the features to interact with the TVB server: authentication, data exploration and visualization, and the new TVB-Knowledge base feature.

¹⁸ <https://cordis.europa.eu/project/id/101058240>

¹⁹ <https://cordis.europa.eu/project/id/101057655>

²⁰ <https://cordis.europa.eu/project/id/101058516>

²¹ <https://www.tefhealth.eu/>

²² <https://www.brainx3.com/>



Authentication

The first step is to launch the connection to the TVB server from the BrainX3 menu and authenticate the connection. For that the user must provide the URL of the TVB server²³ and the software will open a browser to request the credentials of the user, using the Keycloak authentication manager integrated into the TVB-Server (Figure 13).

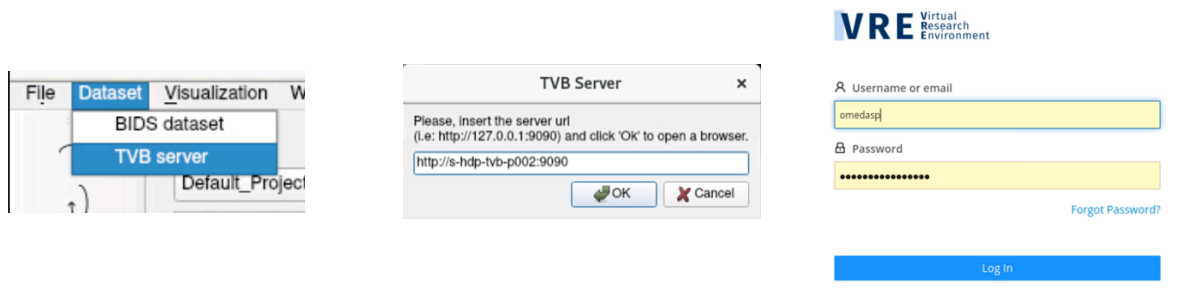


Figure 13: On the left, the option in the BrainX3 menu to launch the connection to the TVB server. In the center, the widget in BrainX3 introduces the URL of the TVB server (tvb-rest-api) and on the right the authentication box in the browser.

Data exploration

BrainX3 allows exploration of the projects stored in the TVB server and their data; this information is displayed in the dataset window. From this window, the user can select the project and the data is displayed (Figure 14).

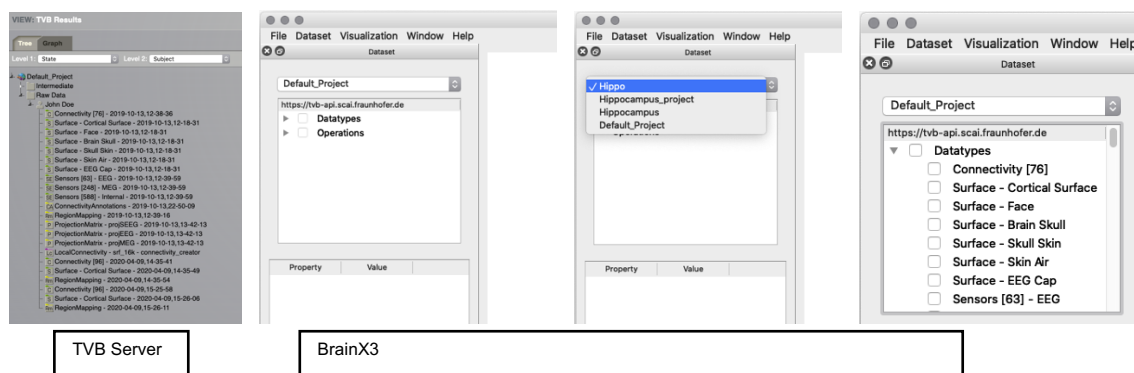


Figure 14: Dataset exploration from BrainX3. On the left, it shows the project and the data as displayed in the TVB Server. On the right, it shows the interface to explore the project from BrainX3.

TVB Data visualization and exploration

From the dataset widget the user can click on the listed data and visualize it. In the background, BrainX3 downloads the data to a temporary location in the VM to be used more efficiently by the software and it is displayed in the appropriate widget. If it is a mesh, volume or 3D object, it will be loaded in the 3D visualization widget and, if it is a signal, it will be loaded in the signal viewer. Once the data is loaded, the user can explore the data interactively. In the visualization window, the user can use basic functionalities like zoom and rotation and can modify the properties of the data. In the current version, we have integrated the following datatypes: Connectomes, Meshes, Electrodes, Timeseries and Volumes.

²³ <https://vre.charite.de/tvb-rest>



Connectivity data

When the user clicks on the connectivity data, it is downloaded from the TVB server to the VM where BrainX3 is running (all in the same protected network of the VRE) and it will be visualized as a 3D graph where each node corresponds to a brain area and each edge represents a measure of connectivity between the nodes. In the example below (Figure 15) we show the visualization of a connectome as a network of interconnected nodes, showing different visualization options.

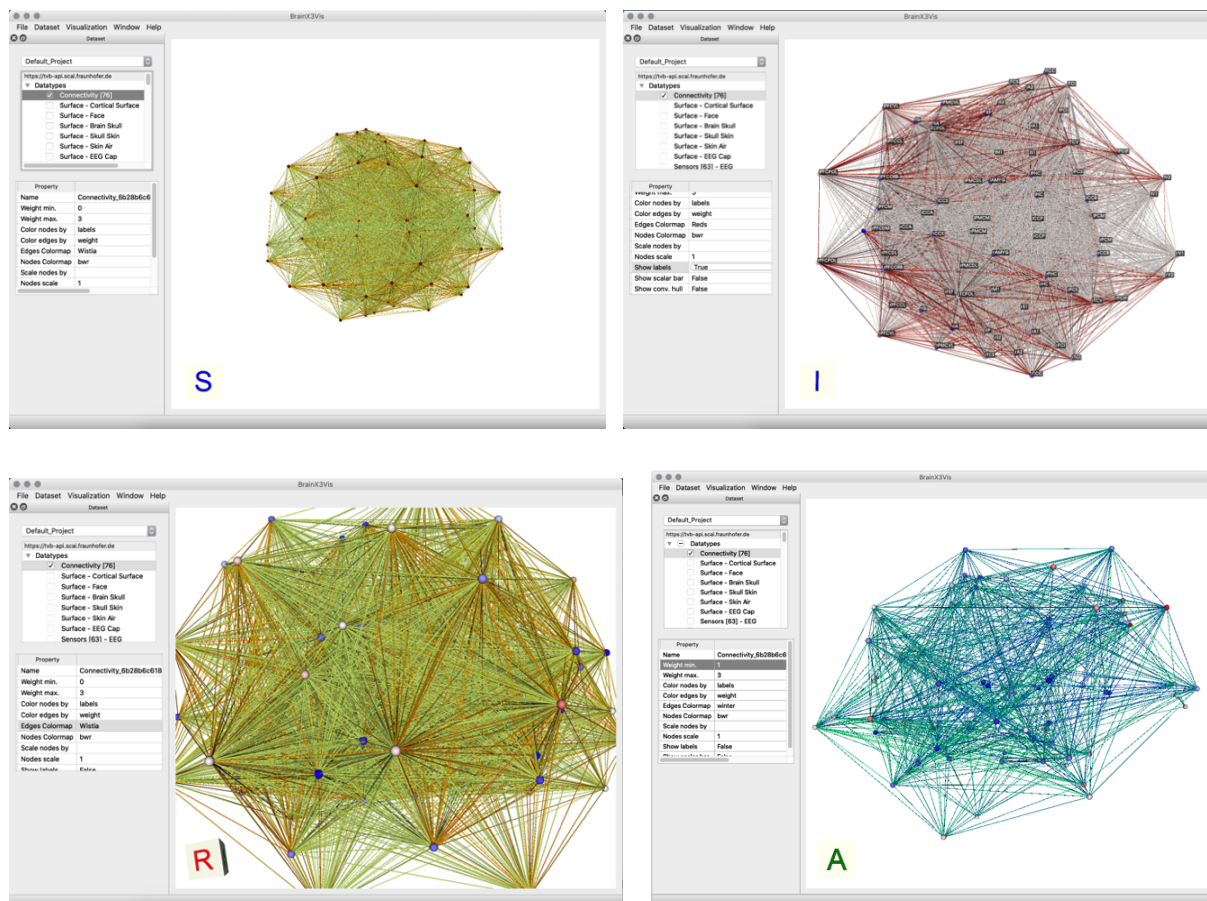


Figure 15: Connectome visualization in BrainX3 using different properties and options. In the top left is the default view, on the top right, the labels associated with the node location of the brain atlas are displayed, the node sizes have been increased and, on the bottom right, it is using a different colour map for the edge connections and is filtering the connections using the weight property of the edges.

Surface and sensors data

BrainX3 allows to exploration and visualise 3D data such as surface meshes and sensors. When the user clicks on this data it is loaded in the 3D widget and the user can explore it. The data is aligned to a common 3D space, allowing the exploration of different modalities at the same time (Figure 16).

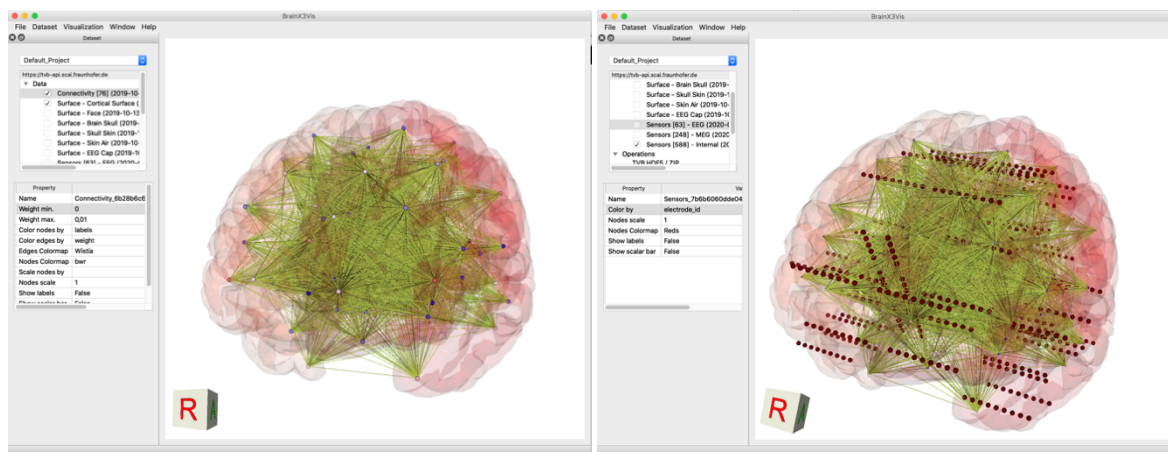


Figure 16: On the left connectivity data and the cortical surface mesh, on the right image the intracranial sensors location is added to the visualization.

Functional Connectivity

A recently added functionality in BrainX3 is to visualise intermediate connectivity from a running simulation. A port can be opened to a direct connectivity matrix and whenever a user clicks on “Load Connectome” a new connectivity matrix will be loaded from the running simulation. This functionality helps the user to visualise functional connectome from the intermediate steps of simulation (Figure 17).

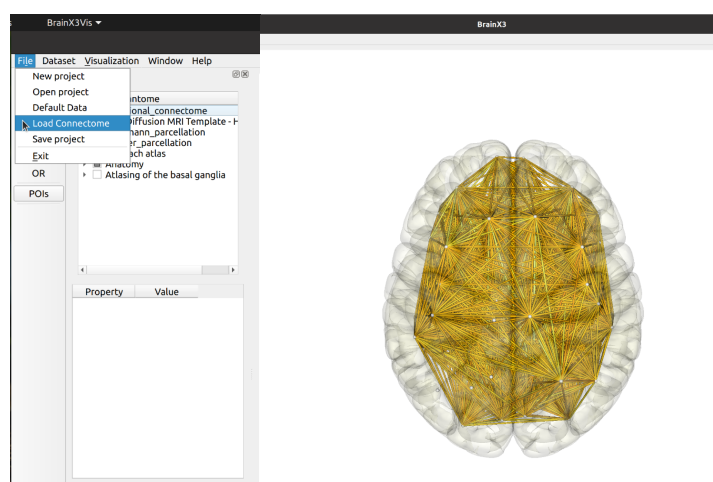


Figure 17: Visualisation of functional connectivity from intermediate steps of the running simulation.

Operations

TVB offers the possibility to perform operations on the data. We integrated in BrainX3 the functionality to launch operations; this can be done by right-clicking on the data object in the dataset widget. A contextual menu appears showing the available operations and the user selects the operation to be performed on the data. When the operation is selected, it is launched and executed on the TVB Server using the TVB API. On BrainX3 the user can get a list of launched operations and their status on the dataset widget (running, finish ok or finish with error is indicated with an icon) (Figure 18 left)

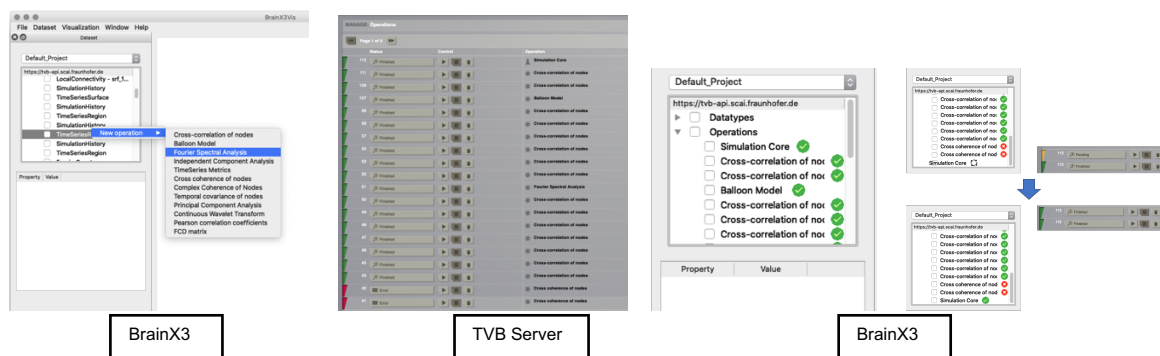


Figure 18: The steps to launch and operation on a dataset using BrainX3 and TVB. On the left the operation is launched on the selected data, the operation is launched in TVB server (second image), and the result is downloaded and the status is shown on the BrainX3 interface (third and fourth images to the right).

Simulations

The main feature of TVB is to perform brain simulations. We integrated in BrainX3 the functionality to launch simulations on the TVB Server. We have integrated in the interface a function to launch a predefined simulation on the server by right-clicking on *Operations* and clicking on *New Simulation* (Figure 19). The simulation is launched on the TVB server using the TVB API and the status is reflected in the BrainX3 interface. We plan to expand this functionality to allow the user to choose the models and the parameters of the simulations.

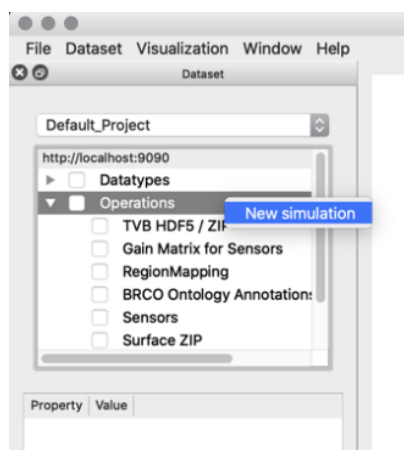


Figure 19: Interface to launch TVB simulations from BrainX3

The result of a simulation in TVB is a TimeSeriesRegion. More precisely, the signals generated by the simulation on each of the nodes of a Connectivity. Once the simulations are finished, the user can click on the result and visualize them with the reference data (connectivity matrix and surface) (Figure 20).

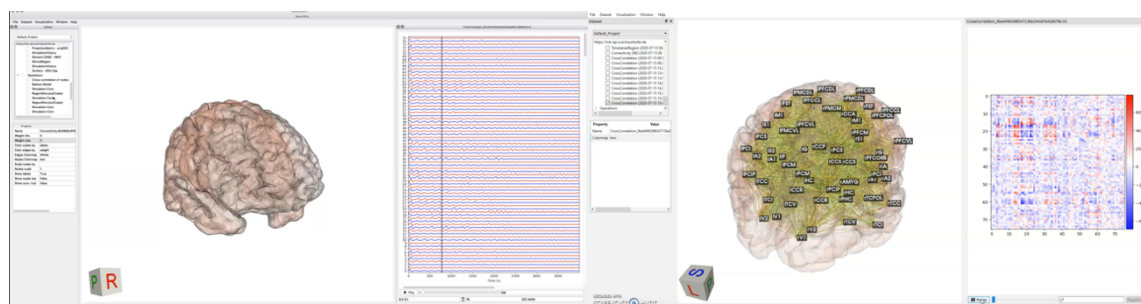


Figure 20: Visualization of brain datasets and TVB simulation results in BrainX3.



TVBase

BrainX3 integrates the functionality of the TVB Knowledge Base Adapter TVBase, a method that maps information from automated literature mining derived knowledge bases to the 3D space of brain network models – as built with TVB simulation software. Users can select any search terms or combinations to generate spatial feature maps from the knowledge base SCAIView that subsequently can inform multi-scale brain simulations. This approach allows mapping in real-time information from the literature-mining knowledge base of SCAIView to a 3D brain space for effortless integration of biological information in multi-scale whole brain models. This method has been implemented in Python code that can be used in a Jupyter Notebook.

The TVBase functionality has been integrated into BrainX3 to facilitate the use and expand the possibilities to explore the results in a 3D brain space. A graphical user interface has been created to introduce the search terms and show the results produced by the library, an interactive plot of the cortical surface of the Glasser atlas showing the relevance of the results in a colour scale (Figure 21)

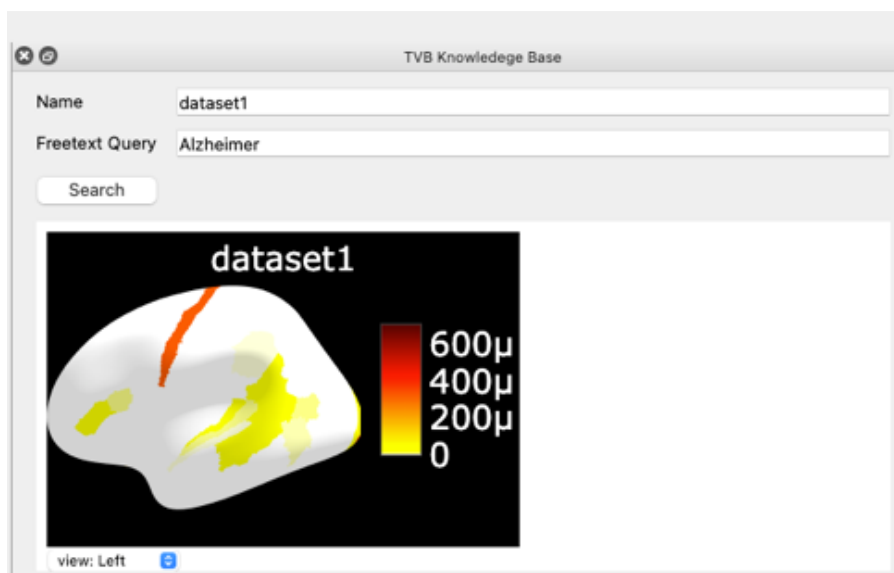


Figure 21: The interface of TVBase in BrainX3

To allow interactive exploration of results linked to semantic knowledge, a 3D representation of the Glasser Atlas in MNI space has been integrated. The results of TVBase are mapped to the 3D presentation and are displayed in the main window, allowing the alignment of multiple modalities with the results of TVBase and exploration.

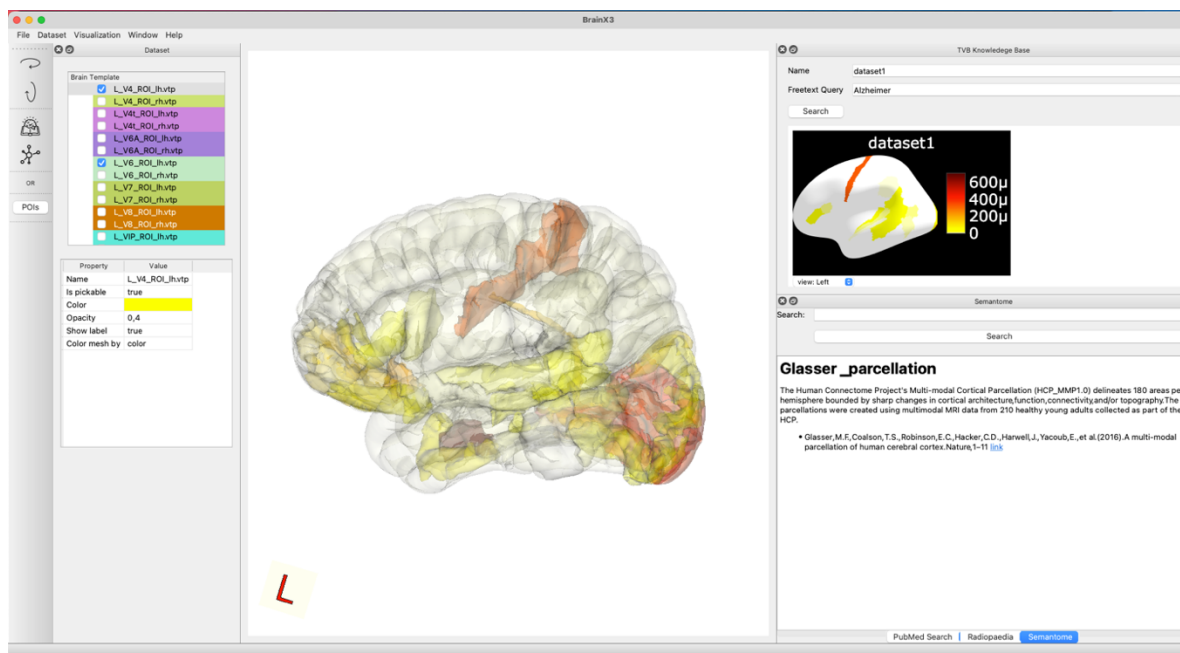


Figure 22: Results of TVBase mapped into brain areas of the Glasser atlas, showing the relevance of the result in colours

The user can start to explore and interact with the results in the anatomical representation. The areas can be selected and they will be highlighted with the name of the area. Semantic information and searches into knowledge base databases will be triggered from these selections as a next step.

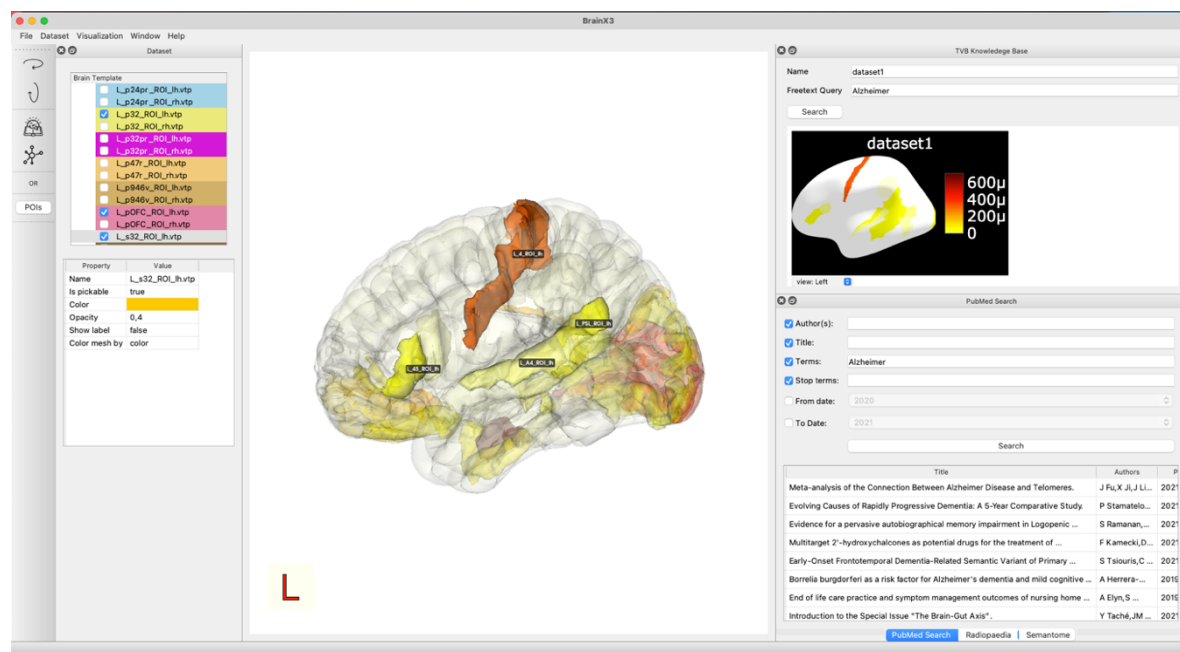


Figure 23: Highlighted areas of the Glasser atlas and the identification of Additional data that can be loaded, like MRI images and tractography.

The user can also start to define Regions of Interest (ROI) and add annotations (See Figure 24).

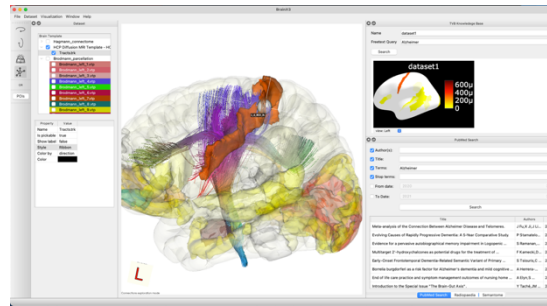


Figure 24: On the left, the results of TVB aligned with an MNI template. On the right, the TVBase results are shown with an average tractography template.

Atlas integration

Since BrainX3 works with a variety of neuroimaging modalities, it is critical to have access to a variety of atlases to map information to specific brain areas. Our goal is to make BrainX3 not just beneficial for researchers, but also a useful tool for physicians. To map spatial data onto the highly parcellated atlas, we decided to use the Glasser atlas. We also merged the Desikan-Killiany atlas to address the spatially poor data in the case of Electroencephalogram or Magnetoencephalogram (EEG/MEG) data onto the average parcellated brain atlas.

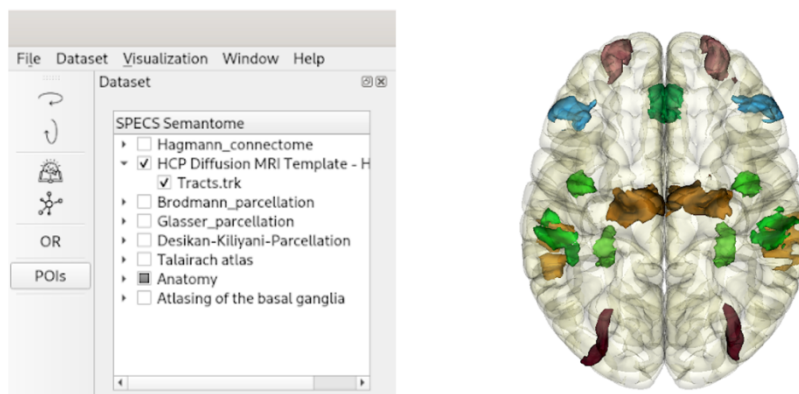


Figure 25: On the left panel, the newly added atlases are displayed. From the atlas of interest, one can visualise structures on the 3D MNI template. For example, the labels from the Glasser atlas are shown in the image below

To process the MRI volume, we utilized the Python packages nibabel and Nilearn. The MRI volume containing label information was first resampled to MNI space using the MNI152 template, after which the volume was partitioned on one axis to capture only one hemisphere. Using the Python VTK module, each hemisphere was then used to produce 3D brain surfaces and using BrainX3, the surfaces were displayed.

Semantome

A widget of most utility - Semantome. Our team has created a one-of-a-kind widget that retrieves pertinent data and presents it to the user in the most appropriate way. **The semantome is a search-based platform that combines the brain's region of interest with recent research and medical intervention from a library of databases.**

The semantome is a living, dynamic project that, unlike static databases, never gets old. It allows the user to stay up to date on the latest developments around the world. We are always attempting to merge freshly created databases because the project is perpetual. The program allows the user to filter



the information they get; they may limit the information by selecting a certain year, author, or other criteria. **Our objective is to make semantome a "go-to SEM" toolbox for researchers and clinicians who want to keep up with new advancements.**

Alongside our in-house database, we have integrated another AI-based search engine “Semantic Scholar” to look up relevant and recent research articles. The semantic scholar provides a list of relevant articles which can be further directed to a web browser for details.

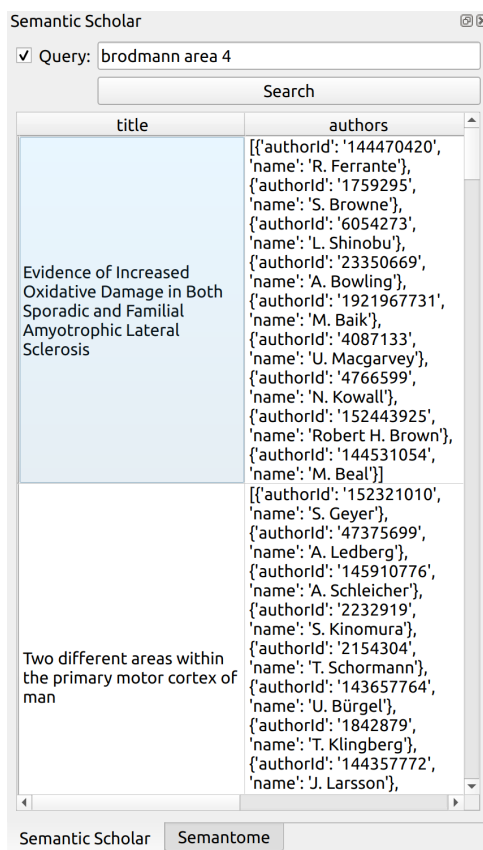


Figure 26. AI-based search engine (Semantic Scholar) to look up research articles.

Use cases: Radiology

We're striving to integrate many neuroimaging modalities, which will allow us to bring together researchers, physicians, and students on a single platform. We're also working on making machine learning a core feature of our tool. The task will be to classify MRI images based on structural abnormalities and lesion identification. We're working on the customization of the MONAI (<https://monai.io/>) module to use AI for lesion detection. The next stage would be to characterize the functional component by identifying key features from the fMRI and M/EEG recordings across a wide range of medical disorders.

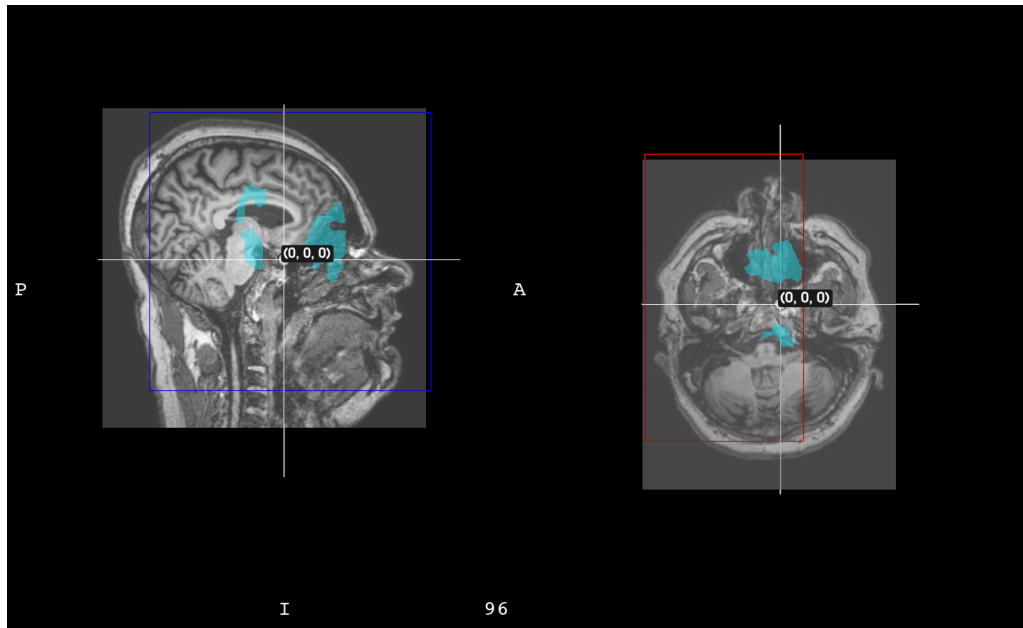


Figure 27. Improving AI-based automated lesion detection and morphology estimation.

We'd like to take it a step further and introduce patient-specific treatment, in which our technology can help predict disease progression and aid in early detection. The ability to link the neurorehabilitation regimen to the disease's predicted progression will be one of the most significant characteristics.

Signal processing and, eventually, functional connectivity will be the focus of the project's second phase. This feature will aid physicians and researchers in determining the effects of lesions or other medical disorders on brain activity.

Integrating semantome with TVB Knowledge Base is the most important aspect of the software.

Searching for relevant literature and extracting information from TVB can be done with the indicated brain lesions. The semantome will help researchers and physicians communicate more effectively. The widget will gather information from a variety of databases and display it on a single screen. The tool can be customized and asked to display results based on the user's preferences, such as the year of publication, author information, journal preference, and so on.

4. Conclusion, next steps

As one main output of the EOSC project Virtual Brain Cloud, we have developed a secure Virtual Research Environment for the management and processing of complex sensitive health data and human digital twins. This environment provides novel technologies that foster research and innovation and that drive several subsequent large-scale EU projects.