Full integration of atlas services, models and validation including DEMO3 of Showcases 1 and 2 (D1.5 – SGA3)

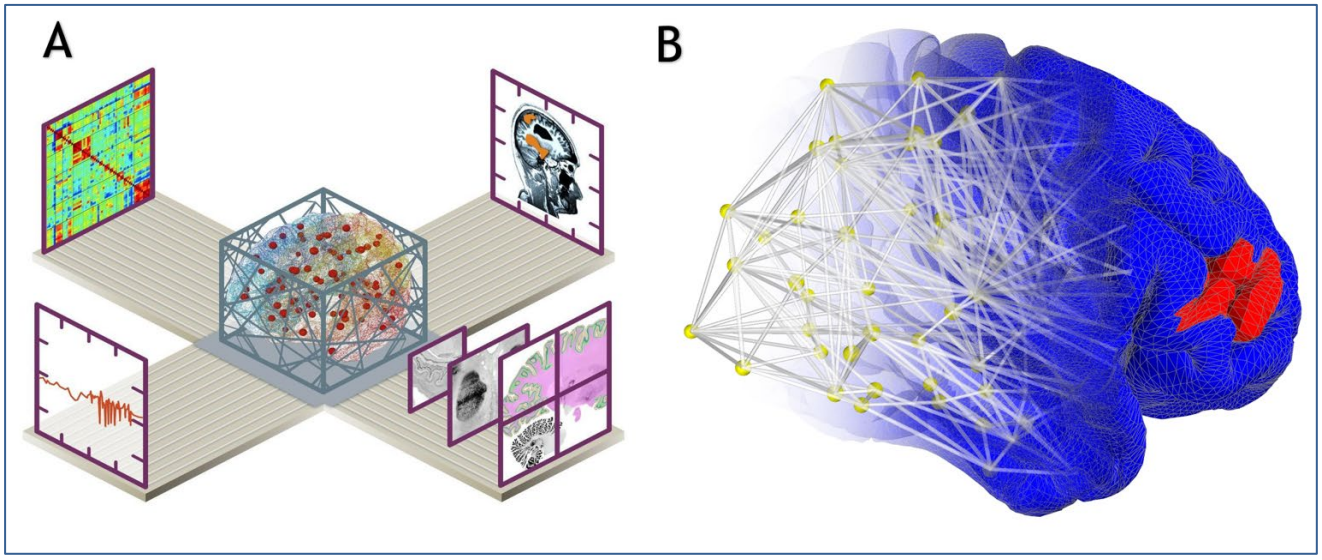

Figure 1: Showcase 1 and Showcase 2

(A) The Virtual Big Brain is a personalised high-resolution virtual brain model, integrating network modelling with multiscale brain data from connectomics and region-variant architecture in the same reference frame; (B) High-resolution virtual brain models represent the human brain on the continuous cortical sheet (blue) instead of a network of connected nodes (yellow), improving accuracy in Epilepsy (red) simulation, diagnosis and prediction of interventions.

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Description in GA:	Software integrating workflows of EBRAINS services (atlas, knowledge graph, HIP) and TVB will be available making full use of the brain reference framework, comprising the release of a variety of models of human brain networks acknowledging population variability, assessment of reliability, and normative data on model parameters in relation to demographic, lifestyle, and cognitive data of large cohorts. Integrated workflows will be available to create personalised brain network models in small detailed cohorts, enabling mutual prediction of brain states in different healthy (rest, cognitive tasks) and diseased conditions. The software will allow demonstrations of the showcases comprising the evaluation of predictive power of epileptic patient brain models, validated on large retrospective cohort (>100 patients), ready for clinical trial testing; as well as demonstrations of sampling of individual degeneracy from empirical functional resting-state imaging data and reconstruction of virtual brain model variability.
Abstract:	This report is the D1.5 Deliverable (M42) as stated in the DoA. It outlines progress in the development of WP1's Showcases 1 and 2, both available in EBRAINS. Showcase 1 develops the workflow for building a virtual brain cohort, which includes data access to the 1000BRAINS cohort, use of EBRAINS' multilevel human brain atlas and The Virtual Brain simulator. Highlights include novel insights into brain aging mechanisms, which confirm some of the leading aging theories. These were initially

	derived cross-sectionally and then confirmed longitudinally for individual brains. Showcase 2 demonstrates how EBRAINS enables advances in personalised medicine through high-resolution simulations. Highlights include progress in high-resolution and multiscale brain simulation for epilepsy, including modelling of intervention scenarios, epileptogenic zone estimation, and co-simulation. The existing functionalities of both demonstrators, including access to the Showcases and future perspectives of this work are also described.
Keywords:	Neuroscience, Big Data, Virtual Big Brain, Variability, Cohort, Personalisation, Epilepsy, Modelling
Target Users/Readers:	Clinicians, computational neuroscience community, computer scientists, Consortium members, HPC community, neuroimaging community, neuroinformaticians, neuroscientific community, platform users, scientific community, students, funders, policymakers.

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1. Introduction

Work Package 1 has developed two Showcases, in which the potential of EBRAINS to elevate the researcher's ability to address profound research questions through interoperable data, models, and methods of digital neuroscience is demonstrated. At the core of both showcases lies the digital twin brain modelling approach where personalized data-driven brain network models are constructed based on individuals' anatomical and functional brain imaging data. Showcase 1 addresses one of the principal obstacles to progress in neuroscience, inter-subject variability; this showcase illustrates the use of EBRAINS for discovery of mechanisms along the example of healthy aging. Showcase 2 highlights the clinical potence of digital neuroscience workflows and demonstrates how drug-resistant epilepsy patients can be better diagnosed using patient-specific digital twins. Both showcases bring the services of EBRAINS into the spotlight and provide a collection of reusable components including workflows, models, and datasets, which together serve as a highly reusable entry-point for prospective scientists and their projects.

2. Showcase 1: Degeneracy in neuroscience – when is Big Data big enough? Demo 3

2.1 Introduction

The identification of causality and mechanisms in neuroscience is major challenge, partly due to the collision of degeneracy and a large intersubject variability. Degeneracy is the propensity for multiple subsystems or mechanisms to support similar functions, appears in all multiscale systems and applies to both empirical data and mathematical models in neuroscience. Individuals can function properly within a given "normal" range of physiological parameters, while each individual's brain differs from each other. The functional loss outside this range, however, varies across different conditions and individuals, and apparently similar structural changes may alter the function substantially in one brain, but may have minimal impact on another. When applying models to empirical data, a substantial amount of data from heterogeneous modalities (e.g., structural and functional MRI, receptors densities, etc.) is needed to draw meaningful conclusions due to this degeneracy. The objective of Showcase 1 is to demonstrate that brain models applied to cutting edge large datasets on structural variability allow to account for degeneracy and can explain and predict the functional variability within and across the individuals.

Human brain ageing is a well-suited paradigm for this task, as large cohorts of healthy subjects and patients with brain disease exist, often comprising multiple brain imaging modalities, and sometimes even longitudinal following. A deeper understanding of aging also aligns with Europe's priority of promoting active and healthy aging among its population. Aging is one of the most prominent factors reflected in brain imaging data, making it a relevant metric for quantifying inter-individual differences. This is also why aging has been a central focus in various brain network studies during SGA1 and SGA2, which generated metrics and paradigms used in SGA3's WP1 and WP2.

Brain aging is well described both structurally (e.g. atrophies, micro-lesions, dysconnectivity) and functionally (e.g. adaptations in network architecture and non-efficient recruitment of brain regions), however, to this day, there is no established causality between these observations, albeit several competing hypotheses exist. The substantial interindividual variability in brain structure, function, and cognitive abilities among older individuals presents a significant challenge in unravelling aging mechanisms. Various factors, including genetics, environmental influences, and lifestyle choices, contribute to this variability. Additionally, the different organizational levels within the brain, from molecular and cellular to systems levels, contribute to these effects to varying degrees.

To explore the variability and ultimately explain aging mechanisms, large numbers are required, and a cohort approach is the only viable way of doing so. Moreover, longitudinal cohorts are necessary to validate predictions on individual level. This necessitates substantial constraints in terms of data,

curation, storage, high-performance computing, multiscale modelling, and validation all of which are currently met simultaneously only by EBRAINS. The target paradigm of Showcase 1 is the resting-state brain activity as measured in fMRI. Resting-state activity has been central to the development of HBP's full brain network models during SGA1 and SGA2 and is routinely studied in both basic and clinical research. It is considered a unique fingerprint of an individual's brain, affected by factors like drugs, diseases, age, and cognitive factors.

In this showcase, we integrate detailed multiscale data (brain connectome, region-specific data) in virtual brain models (see Figure 1A), implement the hypothesised ageing mechanisms, and simulate the functional resting-state brain imaging data of a large cohort of individual brains. During SGA3, a novel model inversion process was developed specifically for the resting state, independently validating empirical data against virtual cohort data. This validation demonstrates that neurodegeneration of long interhemispheric fiber tracts is a major causal factor affecting brain activity during healthy aging, aligned with prior hypotheses regarding compensation mechanisms that counteract neural decline. Preliminary findings in Showcase 1 confirm this prediction on the individual level for the longitudinal follow-up, demonstrating support for compensatory scaffolding in aging within a large cohort.

2.2 Technical Specification

Showcase 1 makes use of the Jupyterlab interactive computing interface available in EBRAINS either in the Collaboratory (lab.ebrains.eu), in the Health Data Cloud (hdc.ebrains.eu), or on the individual FENIX sites (e.g. jupyter.cscs.ch). Concise clients and programmatic interfaces for the EBRAINS services and the Showcase components enable efficient usage for a broad range of users with basic computing and programming skills. The user interacts with the Knowledge Graph and the High-Performance Computing infrastructure with user-friendly programming interfaces. Figure 2 shows a detailed workflow diagram of Showcase 1.

The demonstrator for this deliverable integrates 4 main components detailed below covering the interaction with the EBRAINS human brain atlas and the modelling workflow.

The Showcase is connected with the EBRAINS human brain atlas via the software library siibra-python (https://siibra-python.readthedocs.io). The library provides structured access to different parcellations and reference spaces of the human brain, combining the macroscopic scale in MNI and Freesurfer spaces with the microscopic scale of the BigBrain model. Modelling workflows can retrieve spatial properties of brain regions as well as regional data features from different modalities, including regional density measures from different histological experiments, spatial sampling of high-resolution image data from the BigBrain model, and access to different forms of connectivity from imaging cohorts (for the use of the EBRAINS human brain atlas in personalised neuroscience see Jockwitz et al., 2021). In the showcase demonstrator, siibra is used to retrieve spatial maps of neurotransmitter receptor densities. In addition, for datasets, which are not available directly from the Knowledge graph, for example due to sensitive data protection measures, siibra allows seamless integration of local data sources via predefined configuration schemes. Such configurations are specified as simple json files containing all the necessary metadata such as a reference space, parcellation and local file URLs. In the demonstrator we use such local configurations to bring sensitive data of the 1000BRAINS dataset in the common spatial reference framework, and simultaneously harmonise the data access steps across the demonstrator workflows, regardless if the data is publicly available in the KG or made available upon request in a dedicated space on a suitable platform such as the HDC.

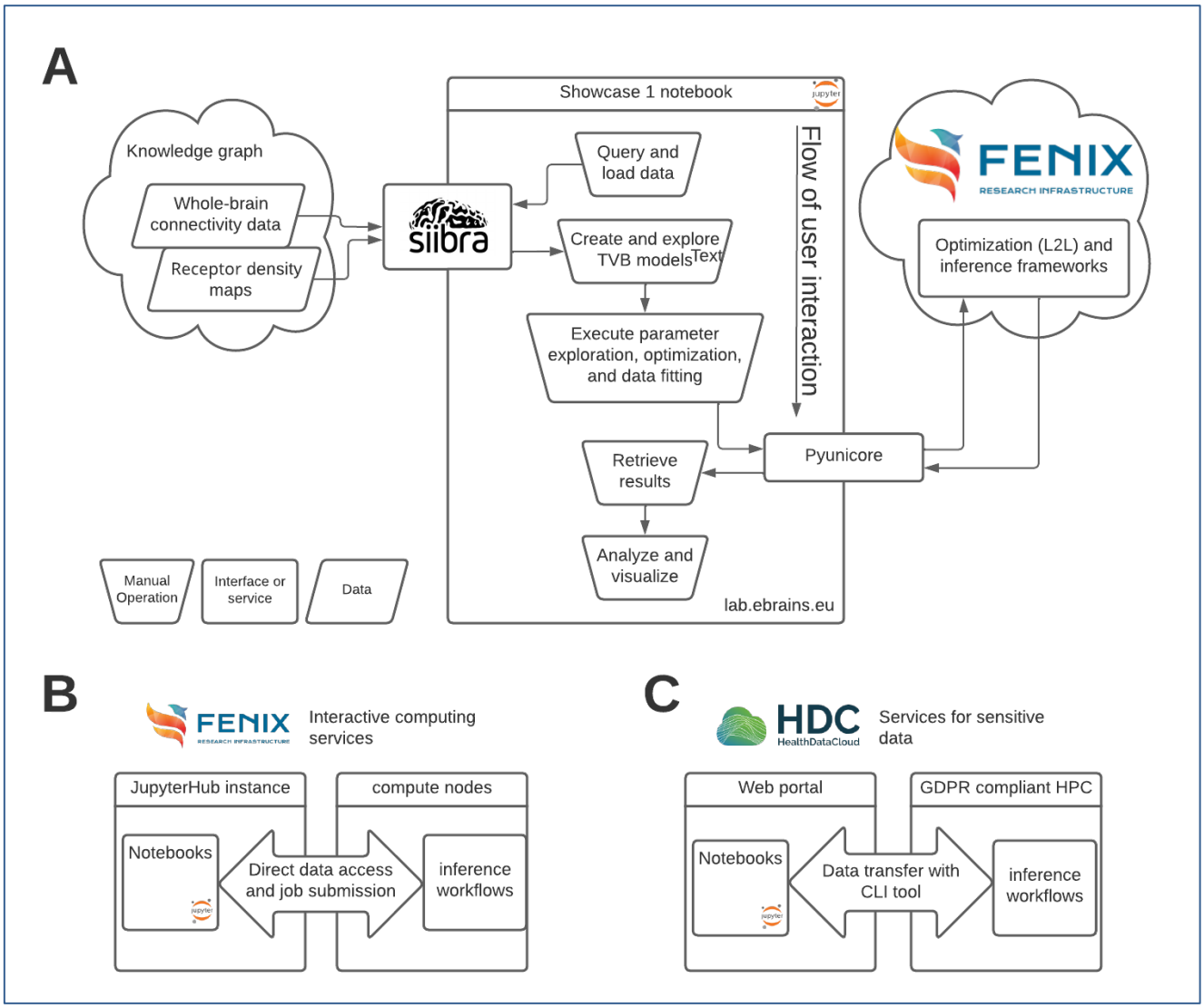

Figure 2: Showcase 1 workflow diagram

The workflow of the showcase 1 running in the EBRAINS collaboratory (A) is portable and can be also executed in the high-performance interactive computing services of FENIX RI, or the services for sensitive data provided by HDC (C).

Showcase 1 addresses the structure-function link through variability across subjects (inter-subject variability parametrised by age) and across brain regions (intra-subject variability parametrised by neuroreceptor density). The study of inter-subject variability is built on the connectivity data from the 1000BRAINS study[1] (Caspers et al., 2014) available in the Knowledge Graph as a dataset with protected access available to EBRAINS users. The access to protected datasets is provided in EBRAINS through the Human Data Gateway[2] (HDG) which allows full access once the user has validated the terms of use. In the implementation of the study on intra-subject variability, we are using the N=294 ROIs (Regions of Interest) parcellation, with the available receptor density datasets (currently measurements are available for 33 brain regions) linked to the Julich-Brain cytoarchitectonic atlas (Amunts et al., 2020). For the remaining regions, their values were extrapolated to the nearest neighbour where the corresponding information is defined. In terms of connectivity data, we have used the connectivity matrices in the same parcellation as above from the Parcellation-based structural and resting-state functional brain connectomes of a healthy cohort[3] available in the Knowledge Graph as a public dataset. The connectivity datasets mentioned above are already accessible via siibra- python, using recently developed support for the new Knowledge Graph API (v3) and Human Data Gateway API. Results of the empirical connectivity analyses are shown in Figure

[1] https://search.kg.ebrains.eu/instances/Dataset/83407c06-b494-4307-861e-d06a5aecdf8a
[2] https://wiki.ebrains.eu/bin/view/Collabs/data-proxy/Human%20Data%20Gateway/
[3] https://search.kg.ebrains.eu/instances/Dataset/d61fc54a-7cc1-4126-93c0-9b6d97775421

3, where a decline in the inter-hemispheric white matter connections is shown in Figure 3A. In the functional data in Figure 3B, an important quantifier of brain flexibility is captured quantitatively by the variance of interhemispheric Functional Connectivity Dynamics (FCD), which declines with age. FCD is a metric capturing the temporal variation of Functional Connectivity, the latter of which is computed by the usual Pearson correlation. FCD represents intuitively a form of fluidity in the brain signals that is particularly informative of age (Battaglia et al., 2020, Petkoski et al., 2023), cognitive performance (Lombardo et al., 2020) and is linked to the perturbational complexity index in the WP2 Showcase 3.

The second major component of the Showcase is The Virtual Brain (TVB) simulation platform (Sanz-Leon et al., 2013), that was largely expanded during SGA1- SGA3 (Schirner et al., 2021). TVB uses empirical structural and functional data to build whole brain models of individual subjects. For convenient model construction, the system is based on a processing pipeline for structural, functional, and diffusion- weighted magnetic resonance imaging (MRI) data. The pipeline combines several state-of-the-art neuroinformatic tools to generate subject-specific cortical and subcortical parcellations, surface- tessellations, structural and functional connectomes, and region-wise aggregated blood oxygen level-dependent (BOLD) functional MRI (fMRI) time-series. The output files of the pipeline can be directly used as input for TVB. The regional heterogeneity was accounted for by the regional variance of GABAa and NMDA receptor densities relevant for anaesthesia through propofol and ketamine. The mean-field AdEx model developed within the HBP was adopted for this variation (Goldman et al. (2022)): a fast (for GABAa) and a slow (for NMDA) synaptic currents were included to the original equations with saturation constants proportional to the receptor density observed from empirical data. Spatial distribution of the GABAa receptor densities was loaded from the Human Brain Atlas via the siibra interface and correspondingly parcellated to constrain the regional parameters. Further parameters of the model, especially the regional gains associated to GABAa receptors, were fitted by running simulations and comparing spatio-temporal statistics of the resulting functional interactions between regions to those observed from empirical BOLD signals. Empirical BOLD from healthy volunteer during resting awake and propofol sedation were fitted to compare the efficacy of accounting for the regional receptor distributions (https://search.kg.ebrains.eu/instances/ceac8277-dc73-4083-8b5b-b029d097f400). GABAa receptor densities were only available for 20 cortical regions out of 214, thus we interpolated missing data. The demonstrator was accomplished in three different versions: employing the standard TVB and employing two alternative backends of TVB that allow for faster simulations: RateML running the simulations in GPUs and TVB-C++ for CPUs.

The third component establishes the distributed execution of systematic parameter exploration and optimisation on the High-Performance Computing (HPC) infrastructure available in the FENIX RI[4]. The unified access to the federated infrastructure is enabled by the pyunicore[5] library providing a concise API to the common tasks such as compute job submission and management. Simplified interfaces for the jupyterlab environment are created for the user to run the parameter explorations. For the inter-subject variability, we have implemented a custom library for distributed simulations compatible with the controlled data access through the Human data Gateway. In the 1000BRAINS cohort, optimising the virtual brain model for each subject for maximal fluidity, the same behaviour of FCD variation is found in simulations in Figure 3C as in the empirical data. For the intra-subject variability, we make use of the “Learning to Learn” (L2L) (Yegenoglu et al. 2022), which is a gradient-free optimisation framework. It defines an API that makes it easy to optimise (hyper-) parameters for any task. The optimization cycle starts when the optimiser generates a set of parameters. Then, the framework evaluates how well this set of parameters performs and returns a “fitness” vector for each parameter in the set. Lastly, the optimiser generates a new set of parameters using the fitness vector it got back. The optimization process involves enhancing the performance of a TVB simulation utilizing the TVB AdEx (Goldman et al., 2023) model. This simulation is generated by RateML (van der Vlag et al 2022) specifically for GPU processing, and it yields a fitness vector at the conclusion of each generation. For this model, you have the option to utilize either a custom-designed or a sample connectome available in the TVB library. It also enables

[4] https://fenix-ri.eu/infrastructure
[5] https://github.com/HumanBrainProject/pyunicore

users to integrate GABA receptor densities by providing the capability to input a vector with values for each brain region. In our implementation, the fitness function is defined to minimise the distance between empirical and simulated BOLD signals through the swFCD observable. Once properly configured, L2L allows running the simulation for a “mean” subject signal built as an average of all individual subjects in the dataset, or for each such individual subject. This execution is distributed on top of the computing capabilities of the Jülich Supercomputing Centre, which allows computing in a matter of minutes which otherwise would take several days. In the current implementation, a systematic parameter sweep was used to guarantee accurately finding a global minimum of the parameters to fit.

The fourth component integrates a Bayesian framework for inference of the full posterior values of the parameters using Simulation Based Inference (SBI; Gonçalves et al., 2020). A deep neural estimator is trained to provide a relationship between the parameters of a model (black box simulator) and selected descriptive statistics of the observed data. Neurotransmitter modulation is quantified by the working point G and is estimated independently using SBI (Figure 3D). As numerous repeated simulations are at the core of the training phase of SBI (sampling of the prior parameter distributions), the implementation reuses the infrastructure for the systematic parameter sweeps on the HPC infrastructure. Specifically, for inter-subject variability, an estimator was trained on 2,000 simulations per subject to independently retrieve the parameters linked to neuromodulation (in particular dopaminergic subsystems) hypothesised to provide compensation mechanisms in healthy aging. Virtual aging of a young individual brain is simulated by gradual degeneration of inter-hemispheric connectivity in Figure 3E. The inference of coupling strength G in Figure 3F independently validates the increase of G with age for each individual subject when maximising the fluidity in Figure 3D and E. Furthermore, for a subset of the subjects (N=220), longitudinal data from a follow-up visit (mean 5 years) was studied. The distribution of rate of change of the structural interhemispheric connectivity confirmed the negative cross-sectional trend (Figure 3G). The virtual aging model predicts an individual increase of the global strength of G to maintain a high degree of fluidity. Failure of such compensation would result in loss of cognitive performance. Figure 4H confirms this prediction and shows increased compensation for larger loss of structural connectivity on an individual basis. This relationship holds particularly well in cases of large cognitive decline (Figure 3I). The empirical fMRI time series data have not been made publicly available yet at time of writing, and the procedure is thus demonstrated in the Jupyter notebooks on simulated data only.

All the previous steps are implemented as a series of Jupyter notebooks and Python scripts with very low barrier for adoption by scientists with intermediate level of training in digital neuroscience. The demonstrator is portable across the EBRAINS services providing support for interactive computing in JupyterLab such as the Collaboratory, Health Data Cloud, HIP, and the individual sites of the ICEI. The diversity of the interactive computing services is reflected in the demonstrator by examples of relevant steps tailored to the individual sites. For example, the computational resources of the Collaboratory lab are rather modest, allowing basic data and model exploration, however, are accessible to all users of EBRAINS. This basic exploration can serve as a stepping stone for a user to apply for access to one of the ICEI sites, where the user can continue with the other parts of the demonstrator dedicated e.g. to customized parameter inference. Finally, the same project structure and codes support the modelling and analysis of the sensitive data of the 1000BRAINS in the HDC. Here, a dedicated section of the documentation of the demonstrator helps the prospective users to transfer the data between the HDC core and secured HPC infrastructure and run the compute intensive steps of the workflow.

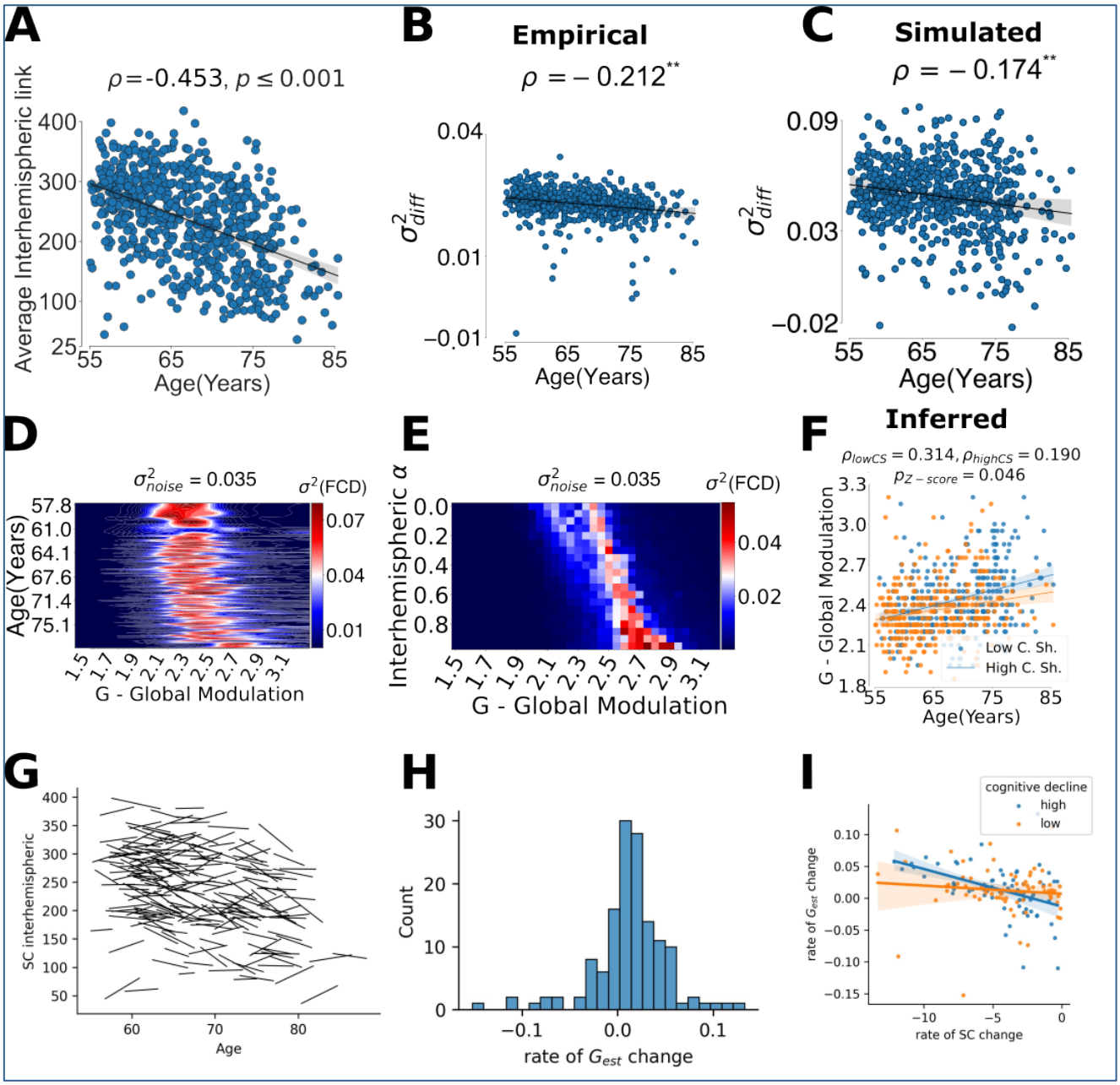

Figure 3: Inter-individual variability of structure and function in empirical and virtual ageing

The structural decline in interhemispheric connectivity (A) is accompanied by the functional decline reflected in decreased fluidity of brain activity (B). Personalized brain models built on the structural data replicate the empirically observed functional decline (C), while showing gradual increase in network modulation of empirical cross-sectional data (D) and simulations of virtual aging (E). The increase in modulation is larger for subjects with higher cognitive decline (F). In the longitudinal data, the structural decline (G) is confirmed. The virtual aging model predicts an individual increase of network modulation, which is also confirmed in the longitudinal data (H). The rate of the structural decrease correlates with the rate of network modulation increase in subjects with high cognitive decline (I).

2.3 Progress from M21

The M21 Deliverable D 1.2 (D8) constituted all the steps of the complete workflow of the Showcase 1 together with curated data available in EBRAINS and established scientific results on the inter-individual variability.

The progress from M21 to M42 comprises the following:

1) Integration of all data inputs with the atlas services through Siibra-python

2) Portable implementation of the demonstrator with examples for the Collaboratory, ICEI interactive computing environments, and Health Data Cloud
3) Extension of the aging analysis to the longitudinal aspect of the data and validation of virtual aging model.
4) Use of interactive widgets to lower the barrier of entry for beginner users.

2.4 How to access the Showcase

Showcase 1 is implemented as a series of interactive Jupyter notebooks covering the individual logical steps and can be accessed in a dedicated public EBRAINS Collab. The Collab can be found at: https://wiki.ebrains.eu/bin/view/Collabs/sga3-d1-5-showcase-1

The EBRAINS Collab consists of interlinked Drive, Bucket, Wiki, and Lab. The Drive provides small file storage and contains the notebooks and all supporting code. The Bucket is a large file storage service and holds the pre-computed results of the extensive parameter sweeps and model optimisations to allow skipping the computationally demanding steps. The documentation of the Showcase implementation is collected in the Wiki. The Lab service is an instance of JupyterLab—an interactive computing environment where the notebooks can be run and worked with. The notebooks in this Collab will load all required Python modules including siibra and The Virtual Brain, and the interfaces for launching the computationally demanding parts in the HPC infrastructure. Running the notebooks requires an EBRAINS account with permissions to access the Lab and the Knowledge Graph API. In addition, to be able to interact with the HPC infrastructure, the user must have access to an active allocation on the corresponding FENIX site. Depending on the scope and character of the data, the showcase can be also executed in the other interactive computing environments of EBRAINS beside the Collaboratory: The Health Data Cloud for sensitive data processing and the jupyterlab instances on the individual FENIX sites (e.g. http://jupyter.cscs.ch/ or https://jupyter-jsc.fz-juelich.de/) for more feature-full access to the HPC resources.

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3. Showcase 2: Improving epilepsy surgery with the Virtual Big Brain, Demo 3

3.1 Introduction

About 50 million patients worldwide suffer from epilepsy. First line therapy consists in anti-seizure medication, which is successful in about two thirds of the cases. Patients with drug refractory epilepsy can be candidates for surgery, which targets to remove the most epileptogenic part of the brain. The success rate of this procedure resides around 60% to 70%. A precise delineation of epileptic and non-epileptic tissue is required for a seizure-free outcome with few adverse effects. Computational methods have been developed to aid in this identification, which use patient specific empirical imaging data, such as MRI and SEEG to construct a structural model of the patient brain. Usually, the brain is divided into around 160 brain regions, where the precise location and extent of each region is given by structural T1w MR imaging. Each brain region is equipped with a dynamical neural mass model, the Epileptor (Jirsa et al. 2014), which describes epileptic neural activity. From diffusion weighted MR imaging and tractography the connections between regions are derived to form a brain network along which seizure activity can propagate. Inference and machine learning methods, together with the patient's empirical SEEG seizure recordings, are applied to estimate the parameters, i.e. the epileptogenicity, of each region in the network model. This personalized modelling approach is called the “virtual epileptic patient” (VEP) and has fully been developed in HBP during SGA1, SGA2, and SGA3. It has been initially validated in a retrospective study of a cohort of 50 patients (Jirsa et al. 2017, Wang et al. 2023) and is currently being confirmed in the clinical trial EPINOV with 356 prospective epilepsy surgery patients.

Showcase 2 targets the construction, simulation and inference of high-resolution patient specific epilepsy brain models. It uses neural fields, which represent the brain on the level of ~1 mm^2, instead of the previously applied approach of neural masses, which approximated the activity of a full brain region by a single point in space, representing on average a surface area of ~16 cm^2. Neural activity

can now propagate locally along the cortical surface and globally along white matter pathways. Local propagation can account for phenomena such as travelling waves, which have been observed empirically in seizure recordings. Below we display the construction, simulation and inference on the high-resolution virtual brain model.

3.2 Technical Specification

The final demonstrator for Showcase 2 constitutes an uninterrupted workflow for the construction of an individual high-resolution virtual epileptic brain model. It comprises all steps for the construction of the high-resolution brain personalized model using individual's data, simulation of synthetic SEEG data and model inversion for estimating the patient-specific epileptogenic zone. Figure 4 shows the detailed workflow diagram of Showcase 2.

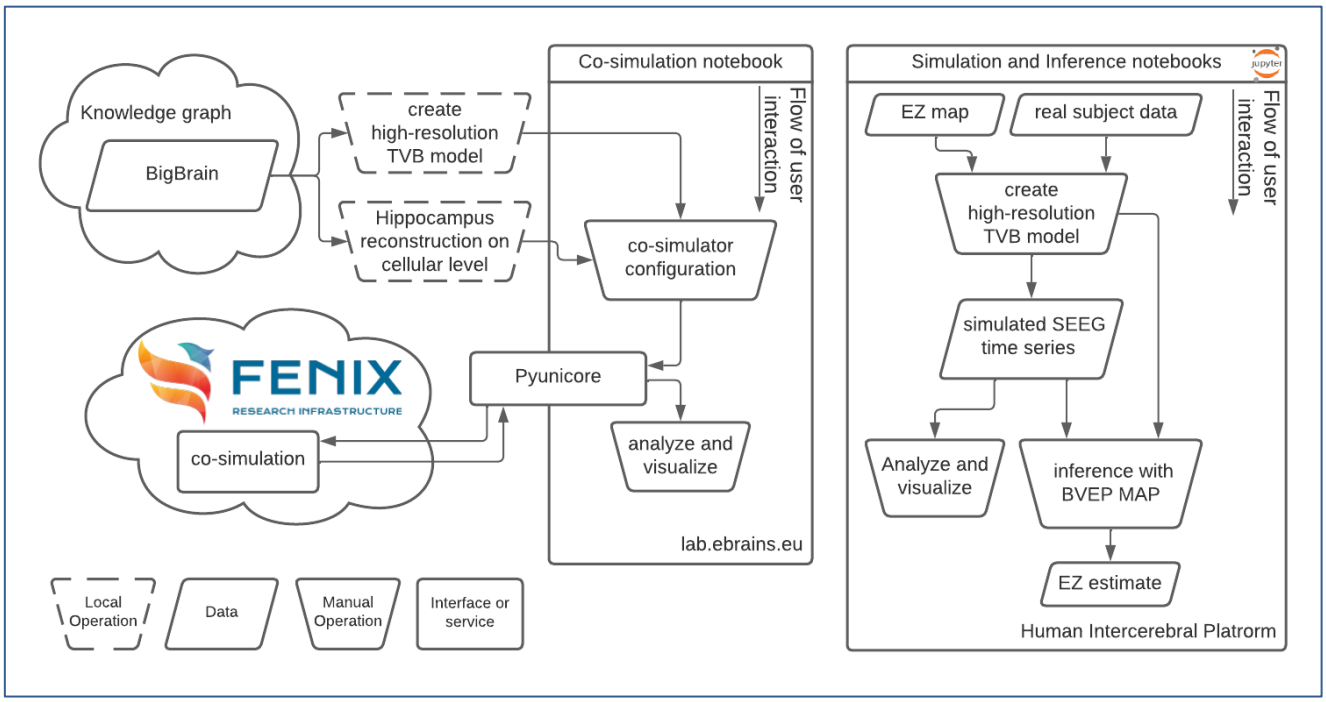

Figure 4: Showcase 2 workflow diagram

3.2.1 High-resolution virtual brain model of epilepsy

To construct the virtual brain model we use an image processing pipeline based on the software toolboxes Freesurfer (Dale et al. 1999), FSL (Jenkinson et al. 2012) and MRtrix3 (Tournier et al. 2019). T1w structural MR images are processed with Freesurfer to reconstruct the cortical surface and obtain a subcortical grey matter segmentation. On the resulting triangulated surface mesh single vertices represent on average an area of 0.8 mm2. Subcortical nuclei are represented by volumetric grids. Diffusion weighted MR images are processed using FSL and MRtrix3 to estimate white matter connectivity. The intersection of single tracts with the cortical mesh or subcortical grids is computed (Figure 5A) to obtain a full brain global connectivity matrix (Figure 5B). Local, intracortical, connections are estimated by a distance-based approach. Connection strength between neighbouring vertices decreases exponentially with increasing distance. In order to compare surface structures with volumetric structures (i.e. subcortical nuclei), each cortical vertex is assigned a volume, according to the cortical thickness. This volume is used to weigh the local connectivity matrix.

In Figures 5 and 6 we used data from a patient with drug-resistant focal epilepsy, with an epileptogenic zone estimated to be in the left anterior temporal lobe (Figure 5C). The rest of the brain is assumed to be sufficiently stable, i.e. not epileptogenic or healthy zone, so it does not interfere with the seizure. We equipped the patch of cortex with a dynamical model, the 2D

Epileptor, and parameterized it to be in an excitable regime. Thus, in the absence of perturbations, the system would settle on the stable focus point (Figure 6A). However, slight perturbation can cause the system to do an excitation which can travel through the network and excite other parts of the system. This model was chosen to model re-entry dynamics in seizures. Re-entry happens when a previously activated part of the system goes through its refractory period and is activated again by incoming excitation. This phenomenon has previously been observed in in-vitro studies (Keren et al. 2016). To simulate the excitable system we initialised the full cortical patch on the stable focus, only the onset zone (Figure 5C), was initialised slightly below in order to kick-off the seizure. Snapshots of the seizure simulation can be seen in Figure 5D. The cortical patch is shown from the mesial side. The seizure starts from the onset zone on the most anterior part of the temporal pole and a wave of activity passes to the posterior parts of the patch. Re-entry due to delays in long range connections excites anterior parts of the cortical patch again sustaining the seizure. This example of the re-entry phenomenon illustrates a unique application of high-resolution virtual brain modelling that would not have been addressable by precedent approaches.

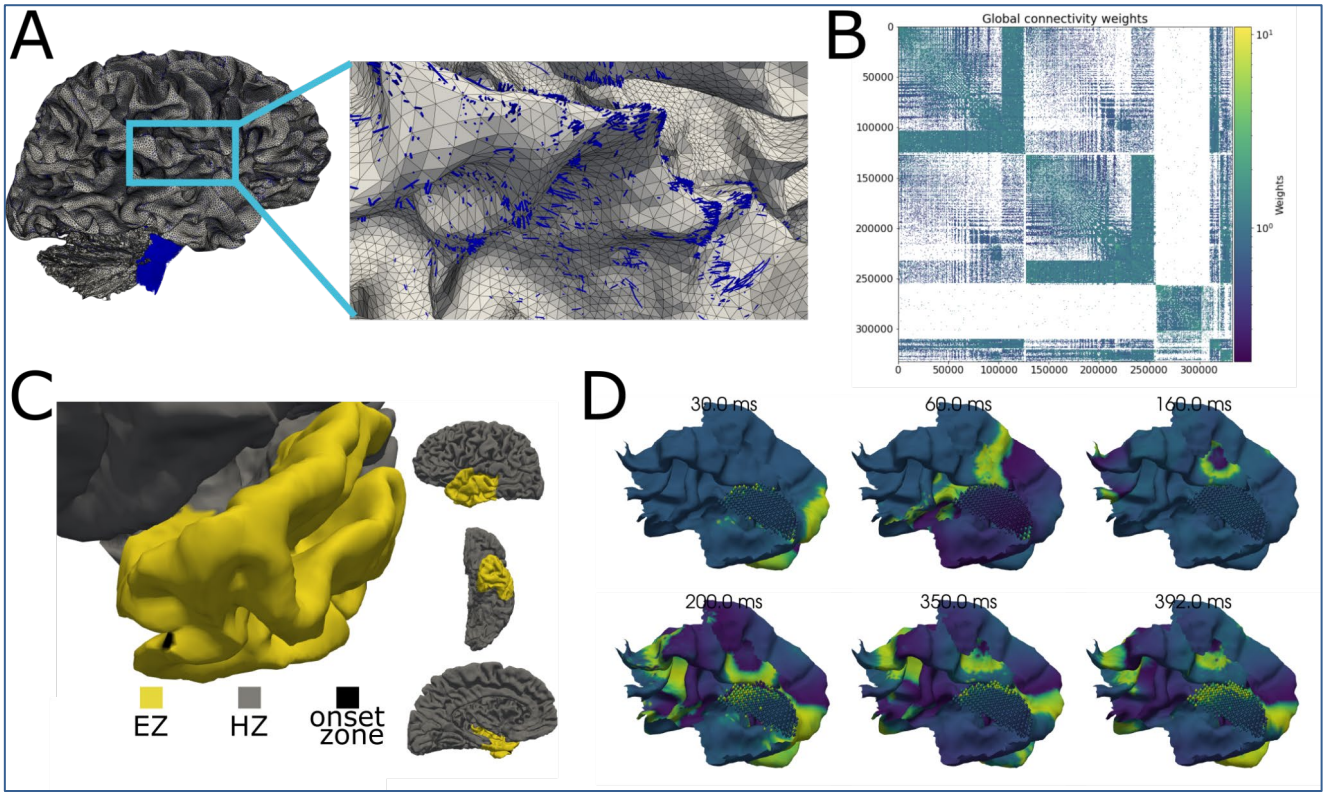

Figure 5: Construction and simulation of patient-specific high-resolution brain networks

(A) Construction of the high-resolution connectome, by calculating intersections between fibre tracts and the cortical surface. (B) Resulting high-resolution connectivity matrix. (C) Simulated epileptogenic zone (EZ) in the left anterior temporal lobe, while the rest of the brain is assumed to healthy (HZ). (D) Simulated seizure on the epileptogenic zone showing travelling waves and re-entry dynamics. Each panel is a snapshot of the cortical surface at different time points (indicated by the numbers above the panel), to show the temporo-spatial evolution of the seizure.

Next to the exploration of seizure dynamics across the parameter space we test different intervention approaches. Beside epilepsy surgery, less invasive methods such as laser ablation or radiofrequency thermocoagulation have been developed which target the epileptogenic tissue with more precision and introduce lesions in the brain (Shamim et al. 2022). We implemented this approach in our high-resolution model by placing 3 virtual lesions into the white matter of the left anterior temporal lobe (Figure 6C). Any tracts passing through these virtual lesions have been removed from the connectome, thus weakening connectivity in the network. Exemplary simulations of the network without (Figure 6B) and with (Figure 6D) lesions show that the intervention effectively stopped prolonged seizure activity. Apart from lesioning, closed-loop electrical stimulation devices are used in clinical practice which have an electrode implemented into the estimated epileptogenic

zone and sense ongoing neural activity (Shamim et al. 2022). As soon as the measured signal surpasses a set threshold, a stimulus is delivered to the brain area aiming to stop the developing seizure. Currently used clinical closed-loop stimulation devices administer a burst of high frequency pulses. However, it has also been found that a single phase-dependent pulse could terminate seizure activity in-vivo (Osorio et al. 2009) and in after-discharges clinically (Motamedi et al. 2002). We tested this in the high-resolution model by implementing virtual electrodes into the brain and computing the electrical field they would exert onto the neural tissue (Figure 6E). A seizure is simulated, and one contact is used to measure the electrical signal produced by the neurons (Figure 6F). From the signal we compute the instantaneous phase and deliver 3 phase-dependent pulses, effectively stopping the seizure.

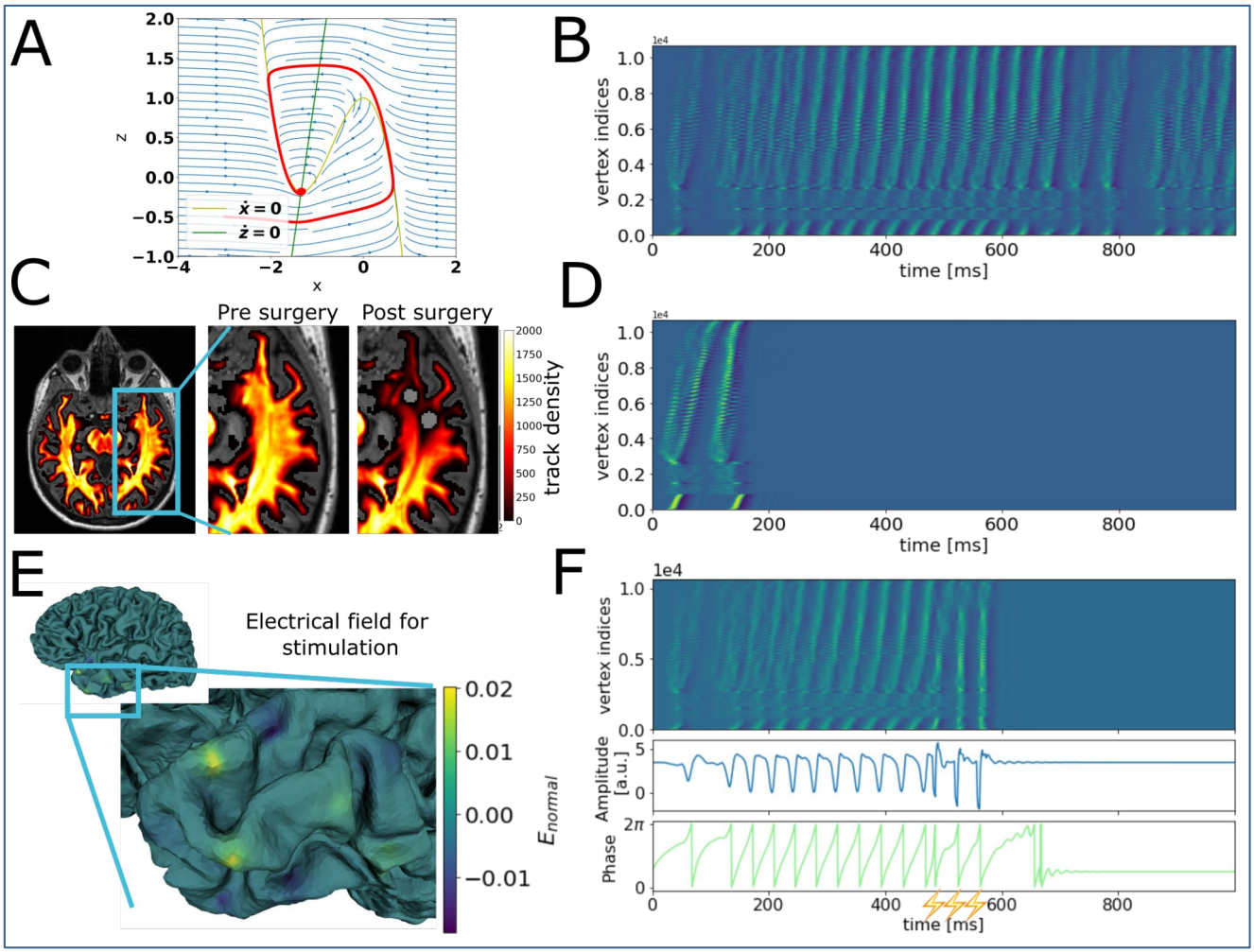

Figure 6: High-resolution seizure simulation and virtual interventions

(A) Phase plane of the excitable dynamical model, used to model seizure dynamics on the neural field. (B) Time-space plot of a simulated seizure. (C) Probing the model by introducing a lesion into the white matter, causing disconnections which could prevent seizure propagation. (D) Seizure simulation after disconnection, which results in only brief excitatory activity but no prolonged seizure. (E) Electrical field estimation after virtual implantation of contacts for electrical stimulation. (F) Seizure simulation with electrical stimulation. After sensing seizure activity on a given contact for 500ms (middle panel, Amplitude), a 3 phase-dependent pulses are applied to the neural field, effectively terminating ongoing seizure activity.

3.2.2 Model inversion with high-resolution virtual brains

The limited spatial resolution of the parcellation-based BNMs is one of the key limitations also for the model inversion used for estimation of the epileptogenic zone in the Virtual Epileptic Patient (VEP, Jirsa et al 2017). However, increasing the resolution of the model inversion is very challenging as the evaluation of the gradients, required to perform the inversion, is even more computationally intensive than the already expensive forward simulation. Furthermore, the dimensionality of the

parameter space scales linearly with the spatial resolution. In this demonstrator we employ a novel technique where the continuous neural field of the cortical surface is mapped onto a spherical surface and the parameter space is reparametrized to the spherical harmonic mode coefficients using a pseudo spectral method. This results in a tractable Bayesian model inversion for the Epileptor model on a continuous domain of the cortical sheet.

The workflow was evaluated first on synthetic data with respect to the hyperparameters such as the cortical mesh resolution or number of spherical harmonic modes, and the signal to noise ratio. The method provides good performance in terms of precision and recall for the spatial resolution from the whole range between 8192 to 32,768 vertices and is robust to observation noise (Figure 7A, C). The accuracy of the EZ estimation decreases for higher numbers of considered spherical harmonic modes (L_{max}>25, Figure 7B), implying that earlier truncation not only helps to lower computational complexity, but also helps to reduce the structural degeneracy of the model.

Validation of the workflow was performed on a retrospective cohort of 12 patients who underwent the surgery, and for which the outcome of the surgery was known (7 seizure-free). The precision and recall are higher for the seizure-free group implying the predicted EZ matched with the resection area in successfully operated patients but showed a mismatch for patients where the surgery failed (Figure 7E). Furthermore, when compared to the low-resolution workflow (Figure 7D), the high-resolution model inversion significantly improved the precision, reducing the number of areas falsely identified as epileptogenic.

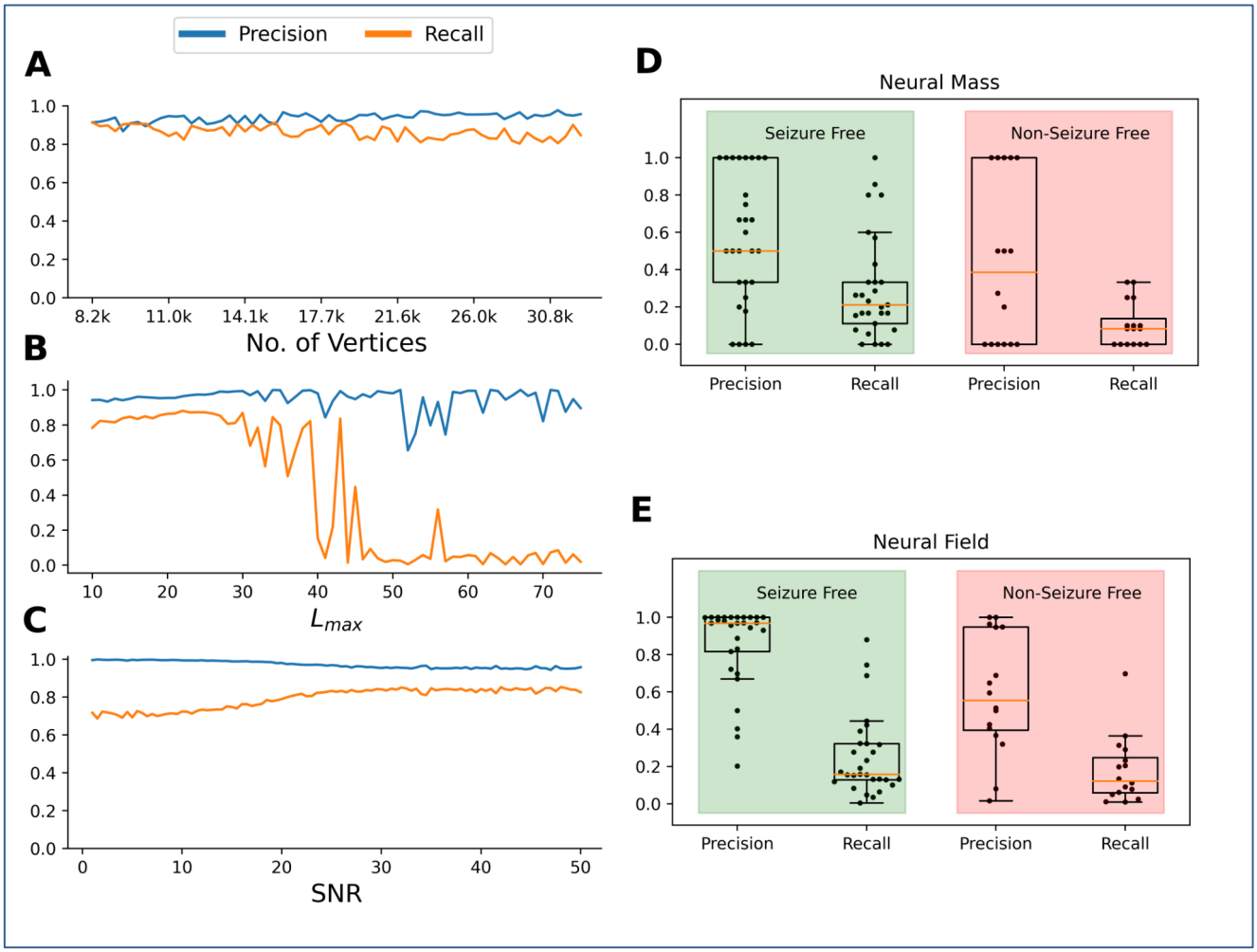

Figure 7: High-resolution model inversion

The model inversion with high-resolution model was evaluated on the synthetic data with known ground truth (left column), and validated on empirical data (right column). While the precision and recall for the synthetic dataset was not affected by the increased resolution of the mesh (A) or signal to noise ratio (C), the high numbers of spherical harmonic modes decreased the recall (B). On the empirical dataset based on a retrospective cohort, precision for the high resolution model (E) is improved over the low-resolution model inversion (D) for patients with positive outcome of the surgery.

3.2.3 Co-simulation

Fundamental questions related to epilepsy such as the mechanisms of ictogenesis have to be addressed taking both the micro- and macro-scopic scales into consideration. Showcase 2 integrates co-simulation technology developed during SGA3, where a selected region of interest is represented at cellular scale and connected to a high-resolution neural field model of the rest of the brain (Kusch et al. 2022). Construction of this model is enabled by the unique data available in EBRAINS that is the microscopic resolution images of the BigBrain, and the high-resolution connectivity.

Here, the CA1 subregion of the right hippocampus was constructed using an automatic cell-body-placement analysis based on grayscale image thresholding in order to obtain a realistic cell density distribution. The CA1 network connectivity was computed starting from the realistic morpho-anatomical connection strategy adopted for the point-neuron modelling of the mouse CA1 hippocampal subregion (Gandolfi et al. 2023).

The interface between the two simulators translates the activity between the TVB nodes connected to CA1, and the neurons in the NEST model. In one direction, the continuous activity of the TVB nodes is converted to spike trains using inhomogeneous Poisson generators, and in the opposite direction the spiking activity is reported as instantaneous firing rate. While both of the simulators are running in parallel, the simulation of the human CA1 microcircuit relies heavily on high-performance computing resources of the EBRAINS. The current demonstrator assesses the construct validity of the co-simulation by the response to single-pulse stimulus within single transversal slices (Figure 8). In agreement with the empirical observations, the stimulation of the slice in the proximity of the CA3 side showed a strong activation directionality towards Subiculum. In addition, the stimulation of the slice in the proximity of the Subiculum showed no backpropagation towards the CA3 region, as expected from empirical findings.

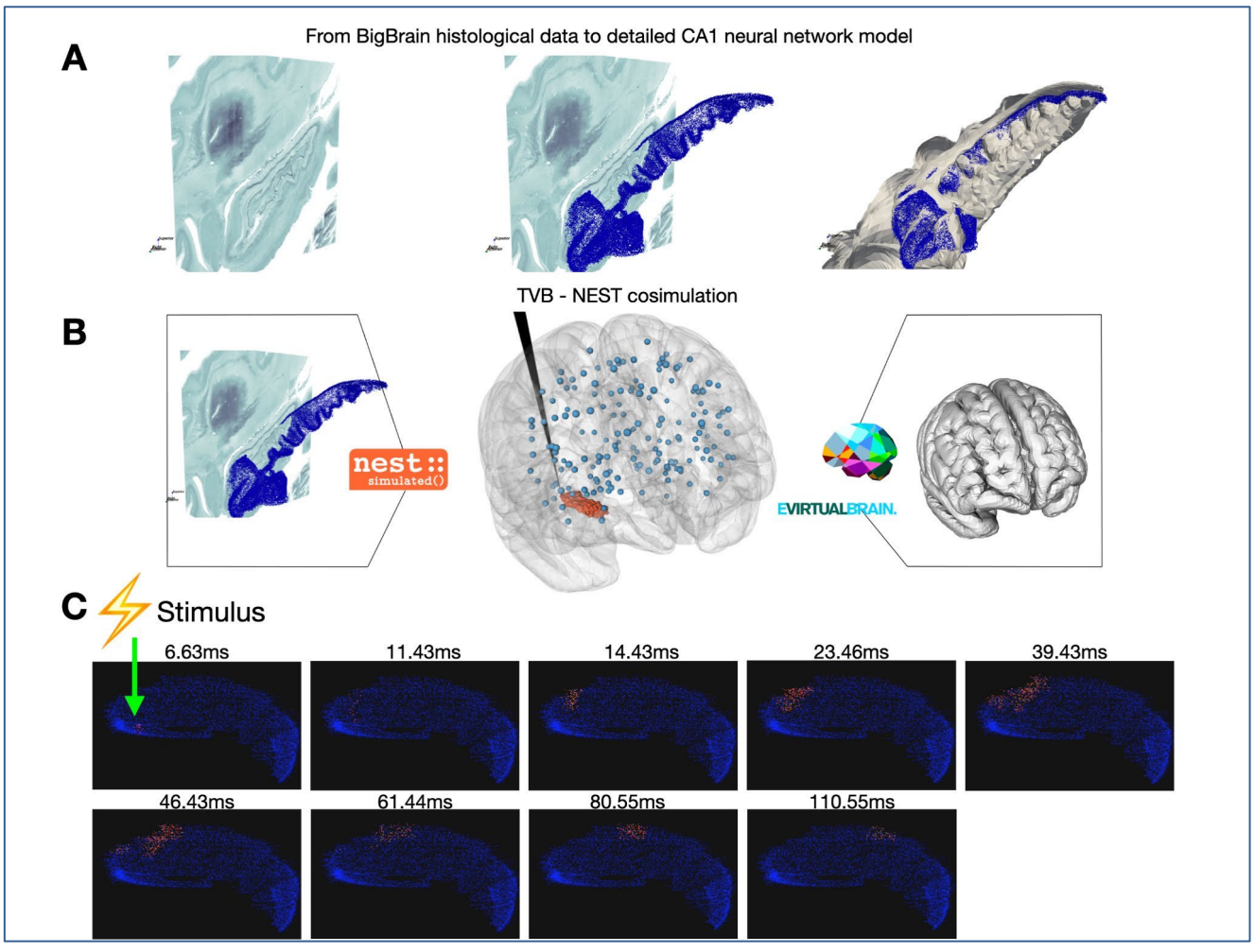

Figure 8: TVB-NEST co-simulation

The co-simulation connects the NEST neuronal model to the high-resolution whole-brain model implemented in TVB.

3.3 Progress from M21

The M21 Deliverable D1.2 (D8) constituted all the steps to construct the high-resolution model and perform inference on the neural mass level.

The progress from M21 to M42 is following

1) Applying the high-resolution model for realistic seizure simulations
2) Developing and testing novel intervention strategies via targeted stimulation
3) Inference on high-resolution virtual brain models

3.4 How to access the Showcase

Showcase 2 is implemented as a series of interactive Jupyter notebooks covering the individual logical steps and can be accessed in a dedicated public EBRAINS Collab. The Collab can be found at: https://wiki.ebrains.eu/bin/view/Collabs/sga3-d1-5-showcase-2

3.5 References

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4. Looking Forward

The workflow on causal relationship between brain's structure and function demonstrated in Showcase 1 has become a benchmark in terms of individual predictive capacity for other large national and international projects. This includes the Virtual Brain Twin for personalized treatment of Psychiatric Disorders (starting in 2024; https://www.ebrains.eu/news-and-events/virtual-brain-twins-ebrains-proposal-awarded-funding-by-horizon-europe), and the French Digital Health project with applications in neurodegenerative disorders (specifically subproject Brain Health Trajectories started in September 2023; https://anr.fr/fr/france-2030/programmes-et-equipements-prioritaires-de-recherche-pepr/sante-numerique/).

Similarly, the Showcase 2 presents a benchmark for high-resolution patient specific brain models to be used for diagnostic stimulation in diseases such as epilepsy and Alzheimer's Disease, and therapeutic stimulation for disorders such as epilepsy, depression and Parkinson's Diseases (several future projects are in the final stage of review).

The real leapfrog in terms of virtual brain's capacity to represent real digital twin brains (Amunts et al. The coming decade of digital brain research — A vision for neuroscience at the intersection of technology and computing), however, will be achieved with the integration of tools and workflows from both showcases. A first application in this direction would be a model that implements multiscale neuromodulatory aspects and more detailed representation of the cortex and subcortical regions, with the model inversion workflows, all of which have been implemented in the above two showcases. This strategy has been foreseen in EBRAINS.