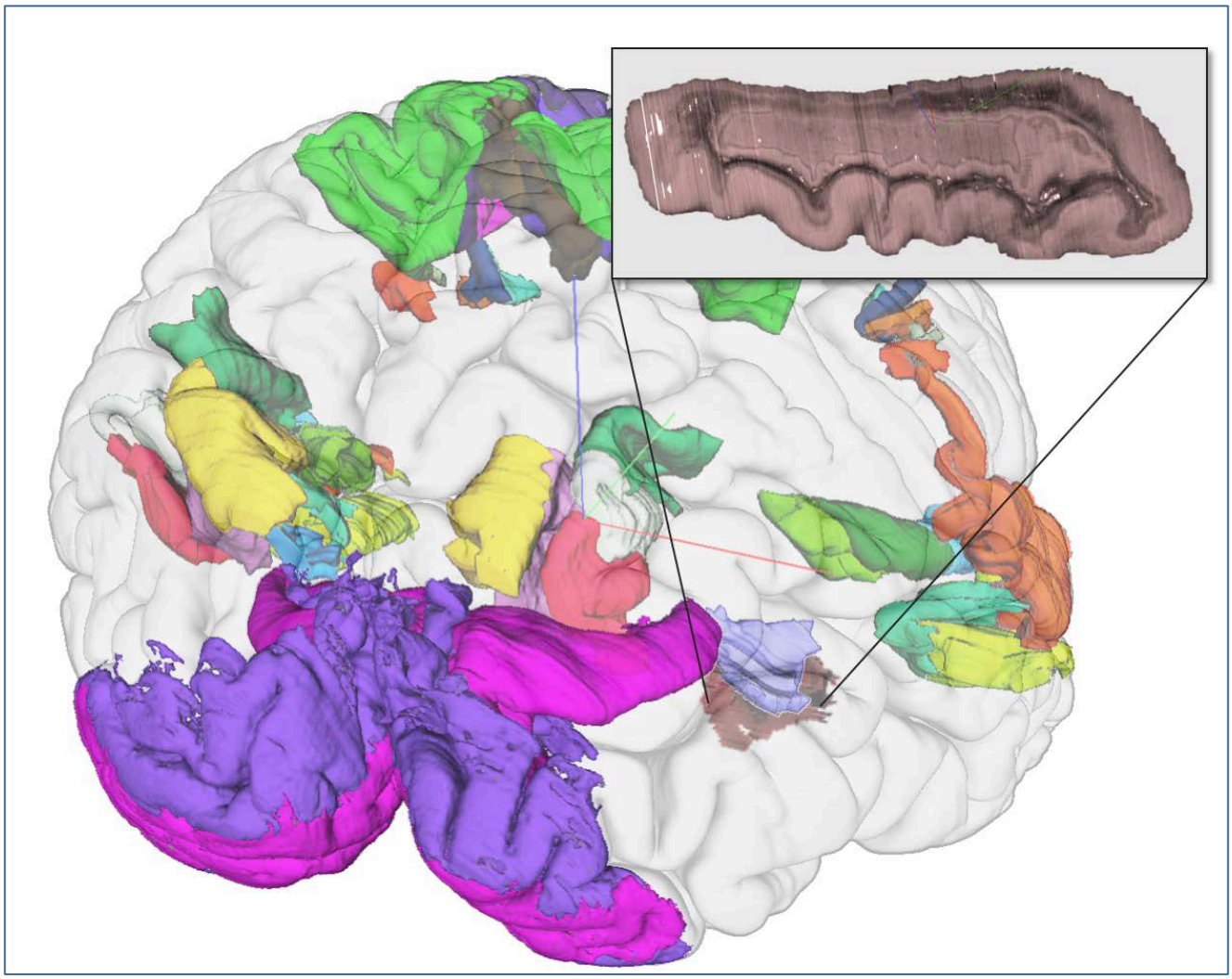
CDP3 Results for SGA2 Year 2 (D2.7.4 – SGA2)



Front Figure: High-resolution 3D maps of cytoarchitectonic areas (Schiffer et al. 2019, P1887) for the BigBrain model (Amunts et al. 2013), together with a linearly aligned 3D PLI reconstruction of a high-resolution sample of the hippocampus from another subject (Axer, WP2.3).

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Abstract:	The aim of Codesign Project 3 (CDP3) in this project phase is to enrich the multilevel human brain atlas that was successfully setup in SGA1, by improving the integration of functional and connectivity data, and extending the interactive functionality of the atlas services to explore and access this data. Priority will be given to the integration of atlas features promoting and advancing trans-disciplinary workflows in the HBP. HBP's multilevel human atlas is distinct from other available maps in that it is defined on different spatial scales and across different modalities, while implementing links between them. The work of CDP3 in the second year of this project period was dominated by a reinforced integration of software and data, and efforts to understand the role of the multilevel atlas for providing and supporting information to build and validate multi-scale brain models. The online atlas now provides high-resolution maps and functionality to explore connectivity matrices, while better tools have been developed to allow interactive alignment to high-resolution models. A catalogue of atlas features to inform modelling has been created, and a prototype API for programmatic access to human atlas information has been developed. These will be the basis for connecting atlas and simulation.
Keywords:	Human Brain Atlas, CDP3, The Virtual Brain, TVB, Connectivity, Web viewer
Target Users/Readers:	Scientists, Companies and other potential users of HBP results.

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History of Changes made to this Deliverable (post Submission)

Date	Change Requested / Change Made / Other Action
26 May 2020	Deliverable submitted to EC
29 Jul 2020	Resubmission with specified changes requested in Review Report Main changes requested: Change 1: The catalogue of atlas features to inform modelling has – asap - to be disseminated to the public (e.g. as an appendix to the deliverable) and made easily accessible (on EBRAINS website)
11 Sep 2020	Revised draft sent by SP/CDP to PCO. Main changes made, with indication where each change was made: Change 1: see Appendix: Catalogue of Atlas Features
11 Sep 2020	Revised version resubmitted to EC by PCO via SyGMa

1. Overview

The aim of Codesign Project 3 (CDP3) is to enrich the multilevel human brain atlas that has been setup in Project phase SGA1, by improving the integration of functional and connectivity data, and extending the interactive functionality of the atlas services to explore and access this data. Priority will be given to the integration of atlas features promoting and advancing trans-disciplinary workflows in the HBP.

HBP's multilevel human atlas is distinct from other available maps in that it is defined on different spatial scales and across different modalities, while implementing links between them. Using reference atlases of the brain defined at the millimetre and the micrometre scale, we aim to integrate experimental data addressing function, connectivity, as well as cellular and molecular architecture to a common reference framework at their appropriate level of resolution.

The work of CDP3 in the second year of this Project period was dominated by a reinforced integration of software and data, and efforts to understand the role of the multilevel atlas for providing and supporting information to build and validate multi-scale brain models. The online atlas now provides high-resolution maps and functionality to explore connectivity matrices, while better tools have been developed to allow interactive alignment to high-resolution models. A catalogue of atlas features to inform modelling has been created, and a prototype API for programmatic access to human atlas information has been developed. A workflow for mapping of atlas features upon model parameters, building and simulating the brain network, and subsequent validation has been developed. Critical components of the workflow have been tested for specific examples using The Virtual Brain (TVB). The workflow from human brain atlas to full brain network modelling and validation against empirical brain imaging data is now complete. These will be the basis for connecting atlas and simulation.

In SGA3, the work of CDP3 will be an important basis for building a multiscale human connectome.

2. Introduction

In this document, we summarise the work performed in the context of CDP3 "Multilevel human brain atlas". This co-design project mostly connects infrastructure development in SP5 for the human brain atlas (WP5.3, WP5.4) and the TVB (WP5.10) with research, in particular in SP4 for The Virtual Brain (WP4.4 and WP4.5). Following the aims already outlined in the overview, the work in CDP3 is structured around 3 Key Results:

- KRc3.1: Integration of function across scales
- KRc3.2: Extended functionality and data integration for exploring experimental connectivity
- KRc3.3: Integration of atlas with workflow in The Virtual Brain (TVB)

The remainder of this document will be centered around these Key Results.

CDP3 was originally finished in the previous Project phase (SGA1), in the sense that the fundamental requirements for hosting a multiscale atlas had been established, and could be further developed in Work Packages WP5.3 and WP2.6 of the current Project phase (SGA2). As a result of the review of SGA1, it was suggested to continue the CDP due to its successful impact on the Project, and the central role of the atlas. Therefore, a modified CDP3 was started with a delay of several months in SGA2. After focusing on KRc3.1 and setting up the cooperation between the relevant people in the first year, we were now able to address KRc3.2, and made important progress on understanding, structuring and setting up the knowledge exchange between TVB and the HBP atlas (KRc3.3).

3. Key Result KRc3.1 – Integration of function across scales

3.1 Outputs

3.1.1 Overview of Outputs

3.1.1.1 List of Outputs contributing to this KR

- Output 1: Integration of high-resolution maps of cortical layers and cytoarchitectonic areas to the BigBrain model (C2272, C2375, C2376)
- Output 2: Cortical-depth driven nonlinear anchoring method for high-resolution partial volumes (C2434, C2267)
- Output 3: Probabilistic assignment of functional activations to the JuBrain reference atlas (C2370)

3.1.1.2 How Outputs relate to each other and the Key Result

Output 1 provides the first high-resolution structural cortical delineations in the BigBrain. Output 2 provides a prototype tool to align high-resolution cortical volumes of interest from other subjects and modalities with the BigBrain, aiming at an approximate superimposition of individual cortical layers. Taken together, these achievements lay the foundation for multimodal data aggregation across subjects at the laminar level in the human brain.

3.1.2 Output 1: Integration of high-resolution maps of cortical layers and cytoarchitectonic areas to the BigBrain model

The BigBrain model represents the microscopic reference space for the human brain in the HBP atlas. One aim of the multilevel human atlas is to localise different multimodal signals in this reference space at the level of areas and cortical layers. Together with T5.3.1 and T5.3.3, we have now integrated the first 3D maps of cytoarchitectonic areas and cortical layers to the BigBrain model. These are reported in more detail in SGA2 Deliverable D5.8.2 (D35.2 D41), KR5.4. The 3D maps have already been published with their DOI in the Knowledge Graph ahead of paper submission, and are publicly accessible in the interactive atlas viewer.

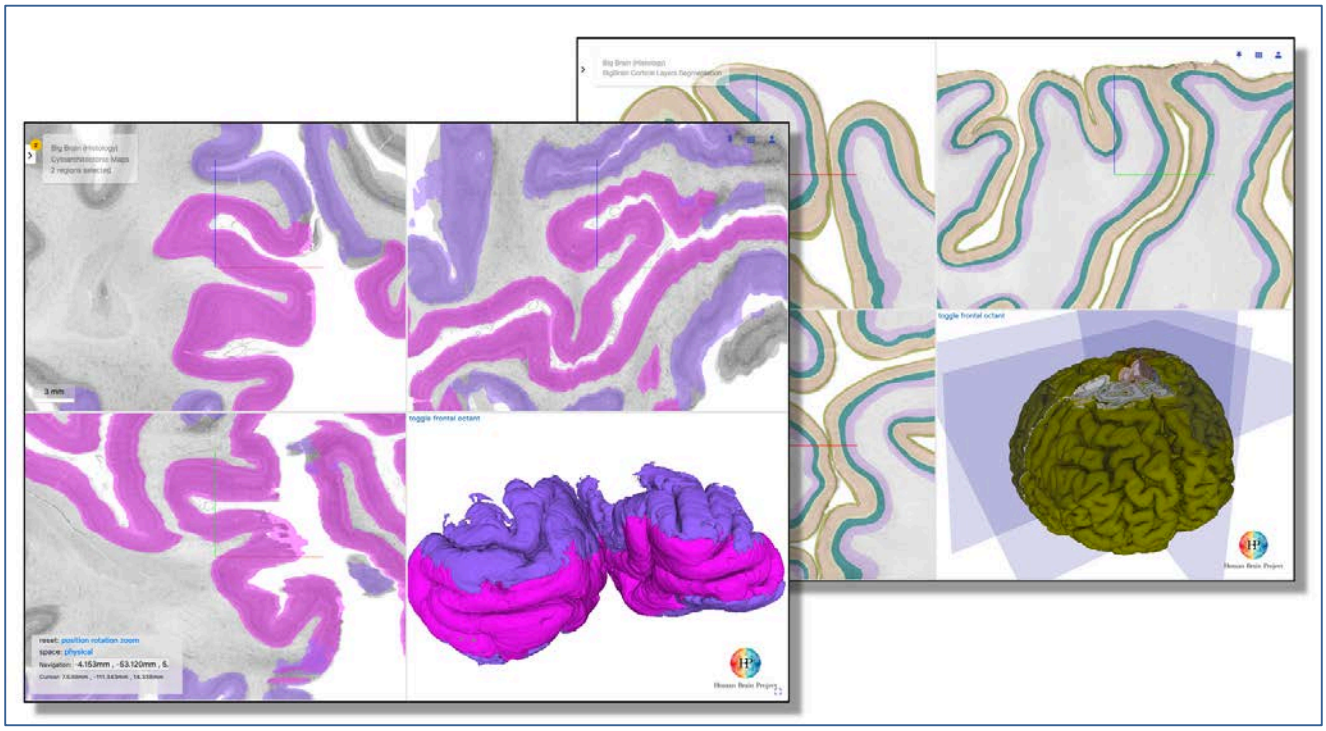

Figure 1: Maps of cytoarchitectonic areas (left) and cortical layers (right) integrated with the atlas

Maps of cytoarchitectonic areas (left) and cortical layers (right) integrated with the atlas, and publicly accessible via the interactive atlas viewer.

3.1.3 Output 2: Cortical-depth driven nonlinear anchoring method for high-resolution partial volumes (C2434, C2267)

A common problem in high-resolution brain atlasing is spatial anchoring of high-resolution volumes of interest (VOIs) from specific imaging experiments into the detailed anatomical context of a high-resolution reference model like BigBrain (Amunts *et al.*, 2013), to allow integration of partial volumetric data at the level of cortical areas, individual cortical layers or subcortical structures. Downloading and interacting with reference templates of whole human brains at microscopic resolution is out of reach for many neuroscientists due to the sheer size of such data, as well as the lack of practical tools. In T5.3.3, we developed a first version of a web-based interactive volumetric alignment tool - VoluBA - which allows anchoring of such VOIs to very large reference volumes (C2269, C2372). Users can interactively adjust the orientation, position, scale and shearing parameters of the VOI to match the BigBrain space. The resulting transformation parameters can be downloaded for submission to HBP data curation, and the aligned image volume can be directly opened in EBRAINS' interactive atlas viewer to view the VOI in full anatomical context and in relation to atlas regions. To improve alignment of cortical VOIs to cortical layers, we further developed prototype functionality for nonlinear alignment (C2434, C2267, C2433), which exploits Bok's

equivolumetric model of cortical depth. The software (not curated) assumes an additional grey/white matter segmentation of the VOI, and can improve the alignment of layers in different subjects significantly. The new functionality is currently employed for alignment of high-resolution fMRI to the BigBrain space.

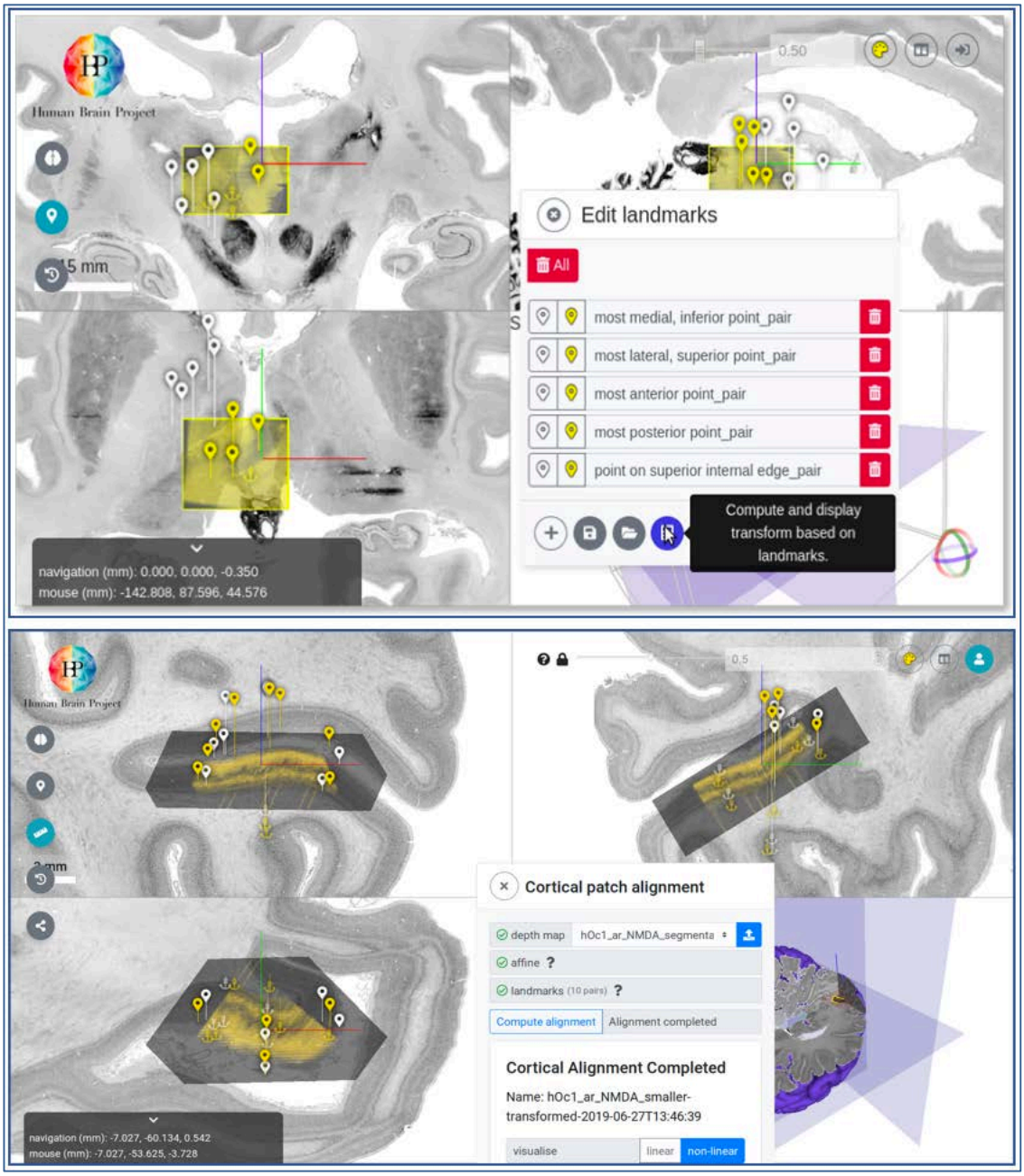

Figure 2: VoluBA online tool for interactive anchoring of volumes of interest (VOIs) to the BigBrain model

Top: Affine anchoring using landmark pairs. Bottom: New prototype functionality for nonlinear alignment of a cortical VOI based on the equivolumetric model of cortical depth, which allows much better superimposition of the layer structures across subjects.

Table 1: Output 2 Links

Component	Link to	URL
C2267, C2434	Online service	https://voluba.apps.hbp.eu
	Software repository	https://github.com/HumanBrainProject/cortical-voluba
	User documentation	https://voluba-user-doc.apps-dev.hbp.eu/
	Technical documentation	https://voluba-user-doc.apps-dev.hbp.eu/

3.1.4 Output 3: Probabilistic assignment of functional activations to the JuBrain atlas (C2370)

In a cooperation between T2.6.1 and T5.3.1, we have computed probabilistic assignments of fMRI activations (starting with IBC study, Thirion, C365) to the JuBrain probabilistic cytoarchitectonic atlas. The computation corresponds to the principle implemented in the SPM anatomy toolbox[1], and for a given activation map yields one probabilistic assignment value (percentage) per area in the atlas, with high values indicating a high activation in the corresponding region. These values will be stored as part of the metadata of the fMRI datasets, and can be used to retrieve fMRI by brain region when exploring the atlas. We are currently working with the curation teams (C2401) and developers of the interactive atlas viewer to add this probabilistic assignment to the metadata schemes of the Knowledge Graph, and use it for retrieval via the region query mechanisms in the atlas viewer (C2370). The first curated data and viewer functionality are scheduled for release in April 2020.

Table 2: Output 3 Links

Component	Link to	URL
C2370	Online service	http://jubrain.humanbrainproject.eu
	User Documentation	https://interactive-viewer-user-documentation.apps-dev.hbp.eu/

3.2 Validation and Impact

3.2.1 Actual and Potential Use of Output(s)

The first two Outputs represent a basis for region- and layer-specific anchoring of data to the high-resolution BigBrain template space. Output 1 now enables to navigate brain regions and layers in the BigBrain, and provides the firsts links between the macro- and microscale human brain atlases. While a manuscript on the methodology for deep learning aided 3D mapping is still in preparation, the first visual area maps are of final quality and have been verified by neuroanatomists. They are accessible via the public version of the interactive atlas viewer. User numbers for the viewer are reported in SGA2 Deliverable D5.8.2 (D35.2 D41) under KR5.6. Output 2 has to date been used by researchers at CEA and JUELICH for first alignments of cortical patches to this space. It is of significant importance for the work of the curation teams and HLSTs on advanced spatial data integration in SGA2. It is potentially useful for any neuroscience lab acquiring high-resolution VOIs, and as such to many histological labs. Both outputs together will now be used to align and correlate sublaminar fMRI measurements in the BigBrain space. First results are expected towards the end of SGA2.

Output 3 represents a feasible workflow for Tier 2 curation of human functional MRI data, and follows the principles of the de facto standard – the SPM anatomy toolbox - that is used by many researchers in neuroimaging.

3.2.2 Publications

None in this phase of the Project.

[1] Eickhoff SB, Paus T, Caspers S, Grosbras MH, Evans A, Zilles K, Amunts K Assignment of functional activations to probabilistic cytoarchitectonic areas revisited. NeuroImage 36(3), 511-521, 2007

4. Key Result KRc3.2: Extended functionality and data integration for exploring experimental connectivity

4.1 Outputs

4.1.1 Overview of Outputs

4.1.1.1 List of Outputs contributing to this KR

- Output 1: Connectivity browser for the interactive atlas viewer
- Output 2: Initial alignment of multilevel connectivity in the hippocampus to the BigBrain model

4.1.1.2 How Outputs relate to each other and the Key Result

The two Outputs are largely independent. While the first addresses exploration of whole-brain connectivity in the form of matrices, the second is a first successful step towards anchoring microstructural connectivity measurements to the BigBrain. We aim to establish a link between the two in SGA3, by "connecting" regional quantitative characterisations of microstructural connectivity to brain regions and thereby to endpoints of major pathways.

4.1.2 Output 1: Connectivity browser for the interactive atlas viewer

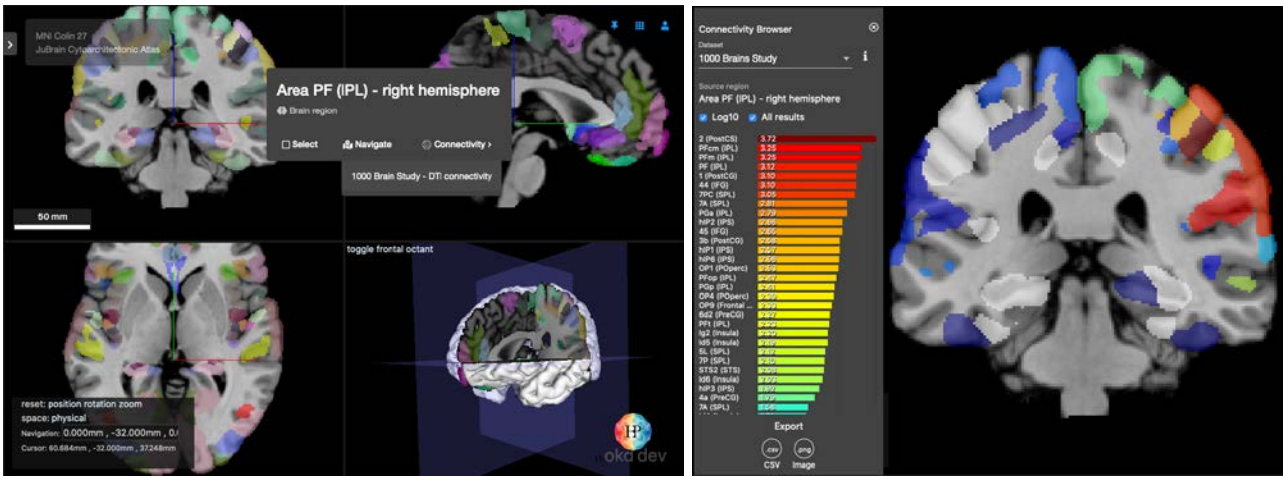

Figure 3: Connectivity matrix for the interactive atlas viewer

Left: Selection of connectivity source for a particular brain region.
Right: Connectivity browser will colour brain regions by connection strength, and provide an interactive list of the connections.

In a collaboration between T5.4.3 (C2802, C2370) and T2.6.4 (C2260), The interactive atlas viewer has been extended by a connectivity browser mode. On selection of brain area, the atlas viewer considers available connectivity matrices which are defined for the given parcellation, and if applicable allows to select such matrix and explore connections strengths from the selected regions. When entering the connectivity browser mode, the displayed map will be coloured by connection strength, and a side panel presents a sorted interactive list of connectivity strengths. Items in the list, which correspond to other brain regions, can be selected as the next considered source region,

and (optionally) navigated to. By iteratively selecting highly connected brain regions, users can literally navigate through the brain along major pathways. The connectivity matrix is also available for download, and described with basic metadata from the Knowledge Graph.

4.1.3 Output 2: Initial alignment of multilevel connectivity in the hippocampus to the BigBrain model

In cooperation with WP2.3 (C2386, of SGA2 Deliverable D2.7.2 (D14.2 D36)), we have performed a linear alignment of a combined post-mortem MRI, blockface and 3D PLI measurement of a human hippocampus sample to the BigBrain space. This alignment is an important case study for regional alignment of high-resolution connectivity data from different sources to a common space, and for advanced Tier 2 curation tasks. It demonstrates the value of the BigBrain model and atlas infrastructure to assess volumes of interest in a whole brain anatomical context at microscopic resolutions. To this end, the atlas viewer (C2371, C2260, C2370) has been extended by new functionalities to deal with multiple image layers, including sliders to adjust opacity of overlays. The alignment has been performed using the VoluBA tool developed in T5.3.3 (C2372, C2269, software not curated yet). Note that new nonlinear alignment functionality (see KRc3.1, Output 2 above) could not be applied here, as it is only applicable in the cortex.

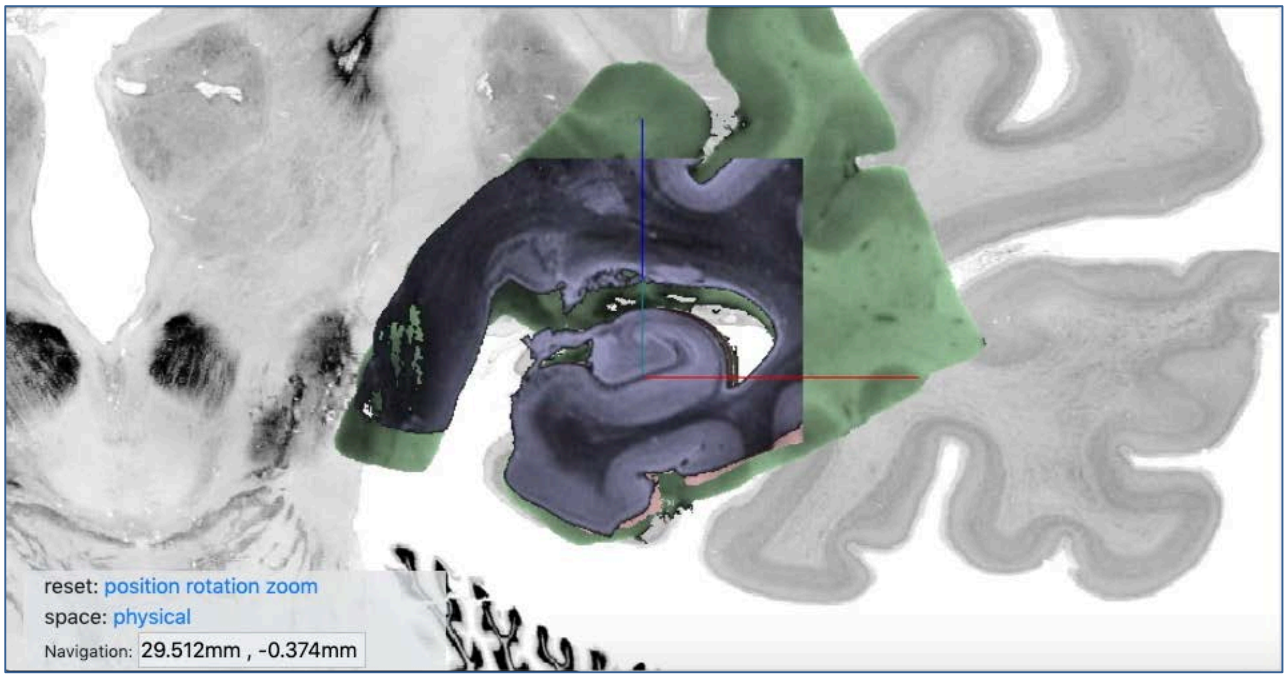

Figure 4: Linear anchoring to the BigBrain reference model of multi-level connectivity in the hippocampus

A volume of interest taken from the same tissue sample, but imaged under different high-resolution modalities (post mortem MRI, blockface, 3D PLI) has been aligned to the BigBrain model.

Table 3: Output 1 and 2 Links

Component	Link to	URL
C2269	Online service	https://voluba.apps.hbp.eu/#/
	User Documentation	https://voluba-user-doc.apps-dev.hbp.eu/
C2372	Software Repository	https://voluba.apps.hbp.eu/#/
	User Documentation	https://voluba-user-doc.apps-dev.hbp.eu/
C2371 C2260 C2370	Online service	https://atlases.ebrains.eu/viewer/ https://interactive-viewer.apps.hbp.eu
	User Documentation	https://interactive-viewer-user-documentation.apps-dev.hbp.eu/

4.2 Validation and Impact

4.2.1 Actual and Potential Use of Output(s)

Output 1 has been presented to users for the first time during the HBP summit in Athens in February 2020, both in a plenary presentation as well as in practical demonstrations at the EBRAINS atlas boot. It received a very good feedback, and our intention to provide more connectivity sources as well as a way to customise connectivity matrices was well received especially by researchers performing whole-brain simulation. We also received valuable feedback; for example, we will add dynamical highlighting of regions in the 3D view when hovering the connectivity browser list. The connectivity browser is the first explicit way of interacting with connectivity information in the HBP atlas and therefore an important step towards a real multimodal user experience. It will be released in the public version of the viewer before the end of SGA2. Output 2 is a case study. Its important impact is so far the interaction between curation teams in SP5 and experimental researchers in SP2 on such a multimodal, high-resolution data integration problem. However, the anchored dataset is now under curation and will be released to the public before the end of SGA2.

4.2.2 Publications

None in this phase of the Project.

5. Key Result KRc3.3: Integration of atlas with workflow in The Virtual Brain (TVB)

5.1 Outputs

5.1.1 Overview of Outputs

5.1.1.1 List of Outputs contributing to this KR

- Output 1: Document outlining suitable atlas data for informing a TVB simulation
- Output 2: Prototype of a REST API and Python client for structured programmatic retrieval of human atlas information and data (C3140)
- Output 3: Document outlining workflow of validation framework for multiscale simulation

5.1.1.2 How Outputs relate to each other and the Key Result

Output 1 is the basis for reviewing atlas contents, identifying missing items, and prioritising those in the continuous human data curation processes and reference atlas updates. Output 2 is the first version of an interface that TVB can access for realising Output 3 - atlas data retrieval and validation. Output 3 outlines the workflow using the atlas contents (accessed through Output 2) in TVB and demonstrates the detectability of brain atlas effects in functional imaging data.

5.1.2 Output 1: Document outlining suitable atlas data for informing a TVB simulation

CDP3 has initiated a range of physical and online meetings between the human data curation team (T5.3.1), researchers and developers working on the TVB (WP 4.5), and developers of the human

atlas infrastructure services (T5.4.3 and voucher 55 IHAVTVB). These working meetings addressed the identification of suitable datasets from the atlas to inform simulation, including gaps and missing data for consideration in future data acquisitions and atlas developments, and technical obstacles of accessing and using these data. A visible result of these meetings is a document of suitable atlas data for TVB models, that will now serve as a basis for ongoing cooperation between atlas and TVB development.

Table 4: Output 1 Links

Component	Link to	URL
n/a	Online report	https://wiki.humanbrainproject.eu/bin/view/Collabs/atlas-tvb-mapping/

5.1.3 Output 2: Prototype of a REST API and Python client for structured programmatic retrieval of human atlas information and data (C3140)

In order to allow easy programmatic access to HPB's human atlas, a prototype REST API has been developed which implements common queries to parcellations, template spaces and region-specific data (C3140). This API is the basis for a lightweight Python client which is well suited for data scientists and modellers who want to access HBP human atlas directly from their experiments. The design and implementation of queries in the API is directly based on functions of the interactive atlas viewer, that will be replaced by the new API in one of the upcoming versions. This way, user actions in the atlas viewer will directly correspond to a set of http calls, as well as to a short Python code snippet. This will allow us to provide easy transitions from visually oriented and explorative use of the atlas in the interactive viewer, to larger scale and batch oriented access from an external script of software. Such transition has recently been implemented for the new version of the JuGEx plugin (C2254, cf. KR5.7 in SGA2 Deliverable D5.8.2 (D35.2 D41)), where a particular analysis in the viewer can be exported to a corresponding piece of Python code which runs in a private Jupyter notebook of the HBP Collaboratory. The prototype API will now be reviewed and validated by TVB developers, with the goal of accessing relevant atlas contents as listed under Output 1. Software is not curated yet.

Table 5: Output 2 Links

Component	Link to	URL
C3140	Software Repository	https://github.com/HumanBrainProject/ebrains-atlascore
	Technical Documentation	https://ebrains-atlascore.apps.hbp.eu/v2/api-docs
	User Documentation	https://ebrains-atlascore.apps.hbp.eu/swagger-ui.html

5.1.4 Output 3: Document outlining workflow of validation framework for multiscale simulation

Output 1 establishes a list of suitable atlas data to inform TVB models. Output 2 establishes a prototype for structured programmatic retrieval of atlas data. Output 3 establishes proof of concept that the integration of the atlas data and TVB has the capacity to provide meaningful results, in particular that the regional variation provided by the atlas data is detectable (in principle) in functional brain imaging data. For Output 3, we developed an uninterrupted workflow (see Figure 5) comprising the mapping of atlas data upon parameters in detailed mathematical models of morphologically-reconstructed human neurons; the translation of the microscopic data features and their variability across scales (via point neuron models, mean field models) to macroscopic brain region representations in full brain networks (to be performed in SGA3); the model inversion via data fitting and parameter sampling.

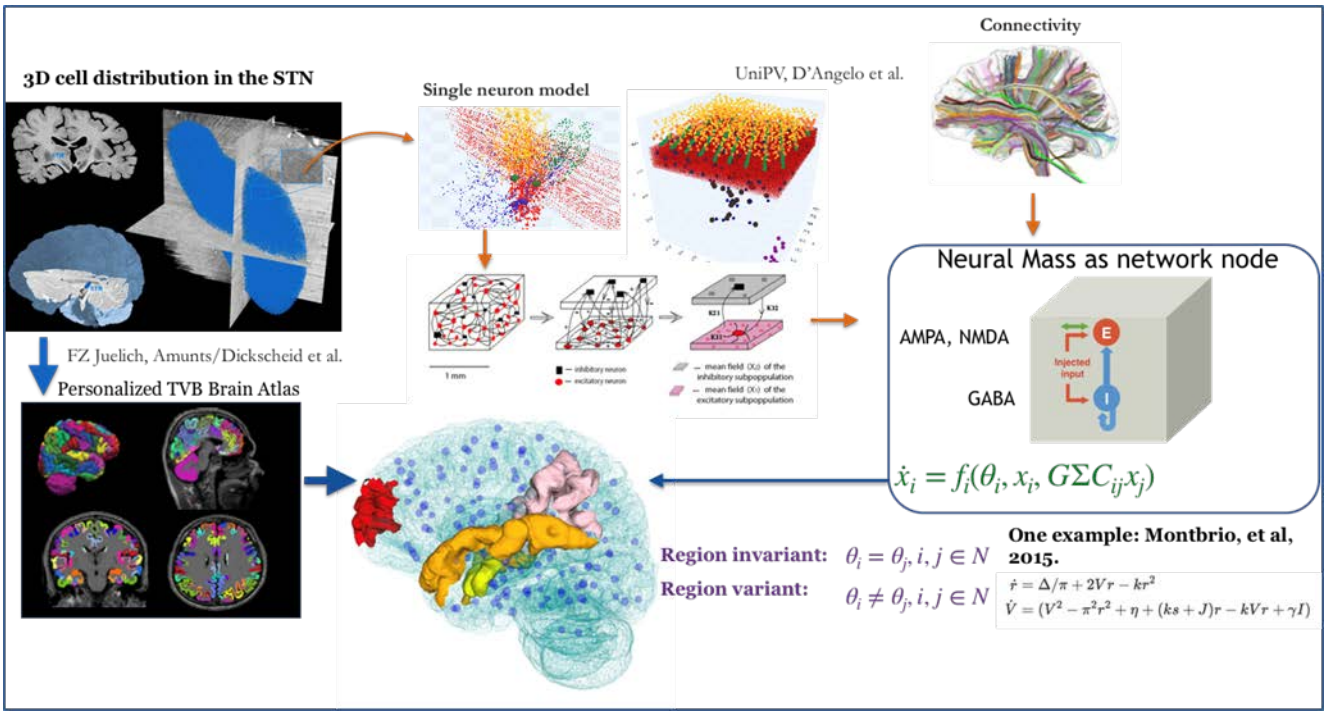

Figure 5: Workflow mapping atlas data upon TVB models

Suitable atlas data are mapped upon parameters in microscopic neuron models and mapped upon neural masses in TVB.

For CDP3 in SGA2, we examined the three workflow components:

1) Establish a suitable listing of regionally variant functional data features, in particular characteristic amplitude and power spectra, from iEEG signals, which demonstrates systematic functional regional variations.
2) Demonstrate that regional variance is, in principle, capable to express itself on the level of non-invasive human brain imaging data (Bold fMRI).
3) Demonstrate the increased predictive power in Bayesian inference through the use of atlas data.

These workflow components are discussed in the following. Two methodological manuscripts have been submitted which are related to this work:

- Hashemi *et al*, The Bayesian Virtual Epileptic Patient (BVEP): a probabilistic framework designed to infer the spatial map of epileptogenicity in a personalized large-scale brain model of epilepsy spread, NeuroImage (under review)
- Hashemi *et al,* On the influence of prior information evaluated by fully Bayesian criteria in a personalized virtual brain model, 2020 (under review).

1) Establish a suitable listing of regionally variant functional data features

We identified region-variant functional data features, in particular characteristic amplitude and power spectra, extracted from iEEG signals demonstrating systematic functional regional variations. These functional data features are known to be informative in model inversion approaches (Moran *et al*. 2011 NeuroImage 55 (2011) 1694–1708) and are illustrated in Figure 6 for three different regions. A completed listing is in preparation and foreseen to be completed in April 2020.

2) Demonstrate that regional variance is detectable in non-invasive human brain imaging data.

The Virtual Brain (TVB) provides a computational framework for modelling human neuroimaging data, by integrating neural mass models with biologically realistic connectivity. We evaluated a range of neural mass models and finally converged to the use of the mean-field model by Montbrio *et al*. 2018, which represents a good balance between microscopic neuronal detail and translational capacity to the macroscopic neural mass representation. We integrated the Montbrio *et al* model into TVB. We initially implemented identical Montbrio *et al* parameters for all brain regions. As a first symmetry breaking, we computed the effect of network structure by progressively increasing

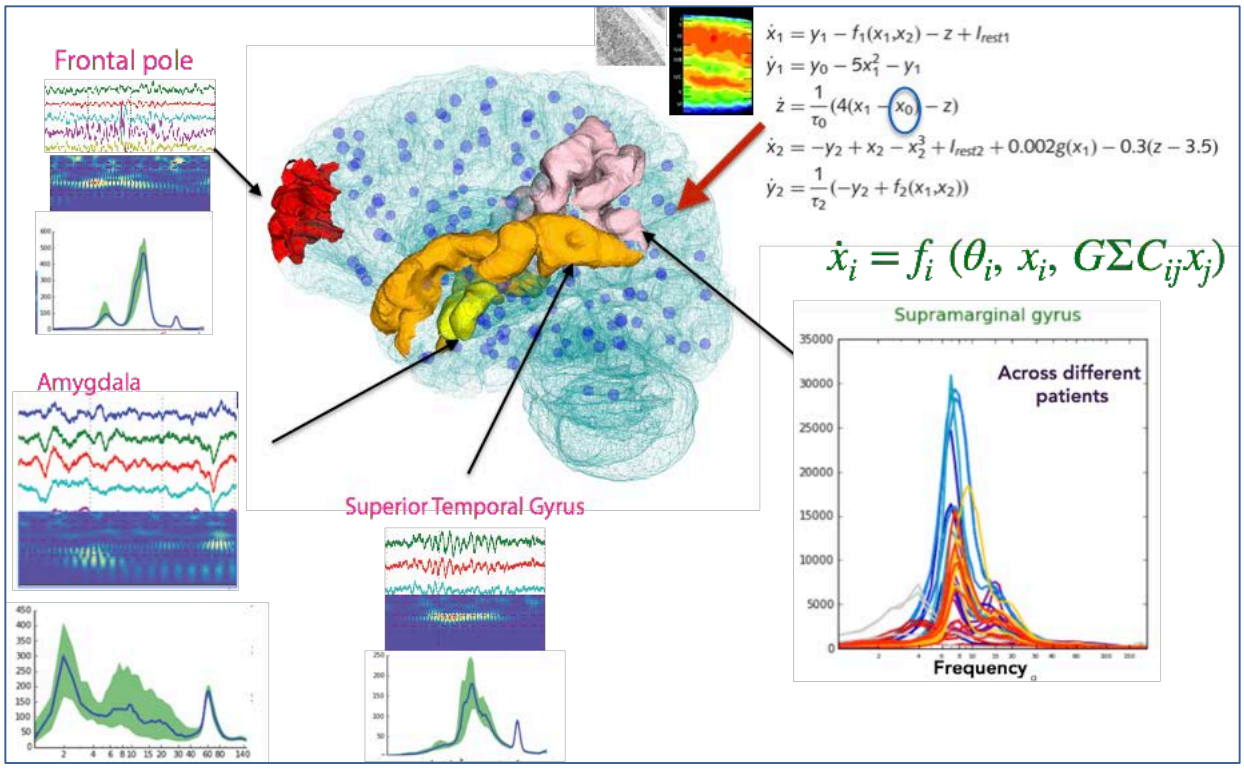

Figure 6: Regionally variant functional data features visualised in the atlas

Amplitude and power spectra in iEEG signals characteristically vary across brain regions.

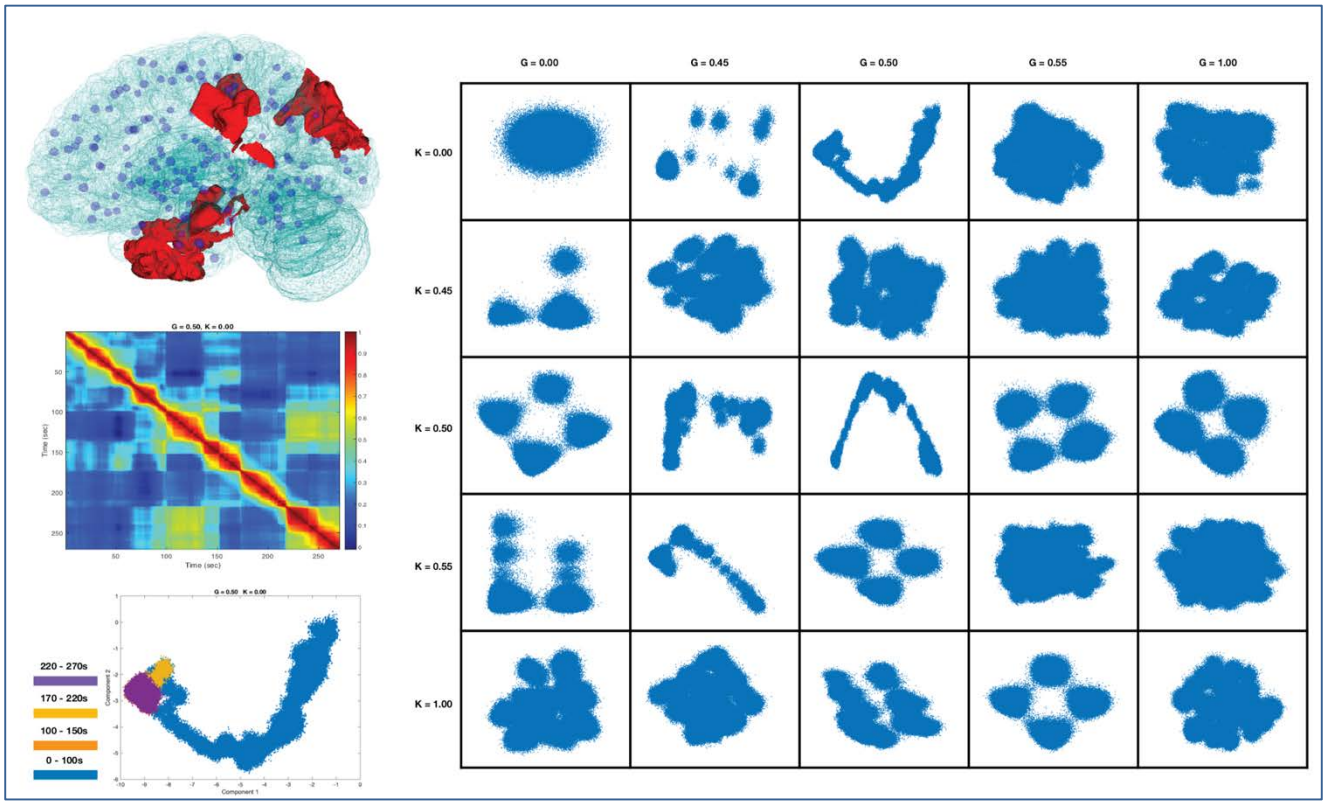

Figure 7: Breaking of network symmetries through regional variance K and connection topology G

Simulations of the network with progressively increasing global coupling strength (G) and regional asymmetry parameter K generate characteristic manifolds.

the global coupling strength G. As G increases, it changes the simulated network dynamics from a fully symmetric distribution (G=0) to characteristic manifolds of the distributed data (see Figure 7, rows for increasing G). Information about regional asymmetry from the atlas data is built into the model via the parameter K. Simulations of the network with regional asymmetry also provide characteristic manifold changes (see Figure 7, columns for increasing K).

3) Demonstrate the increased predictive power in model inference through the use of atlas data.

Although personalised anatomical information has been previously used as prior knowledge on the validation process of brain network modelling, the actual sensitivity to such subject-specific information is still unknown and an important foundation for the here described model inference workflow. In WP4.5 in SGA2 we introduced fully Bayesian information criteria validated by efficient cross-validation on the subject-specific information to accurately determine the most likely network parameter distribution. For proof of concept, we used the Bayesian Virtual Epileptic Patient (BVEP) model, which relies on previous work in SGA1 on the fusion of structural data of epilepsy patients, used to infer the spatial map of epileptogenicity across different brain areas. To show the influence atlas data as a prior upon the model inversion process in TVB, we measured the BVEP predictive accuracy with informative priors (atlas data) and contrasted it with uninformative priors (identical network nodes). We show in Figure 8 that integrating the prior knowledge in the fully Bayesian information criteria allows us to correctly assess different hypotheses about both structural and functional components of whole-brain network models that differ across individuals.

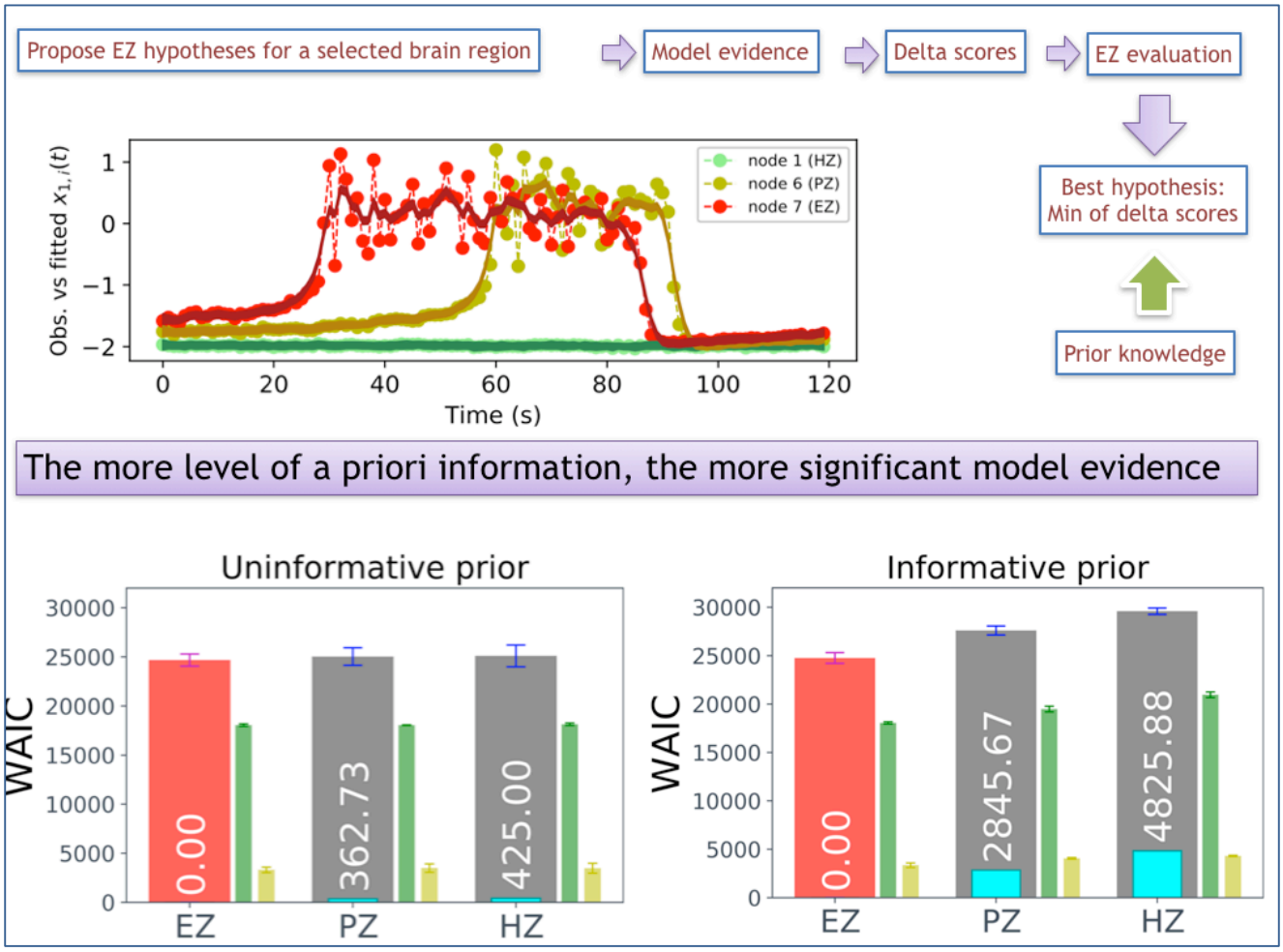

Figure 8: Demonstration of increased predictive capacity in model inference through the use of atlas data

Epileptogenicity hypothesis testing using classical and Bayesian information criteria, WAIC over 4 estimations for each of Epileptogenic Zone (EZ), Propagation Zone (PZ), and Healthy Zone (HZ) hypothesis, while the correct hypothesis corresponds to EZ (shown in red).

5.2 Validation and Impact

5.2.1 Actual and Potential Use of Output(s)

Output 1 through 3 are early versions of work that will be significantly intensified in the next Project phase. Output 1 can be considered as the documentation of the common understanding of partner UMA and JUELICH about the data-related links between human atlas and TVB. The API (Output 2) has been used by developers of the interactive atlas viewer, and already been partially included as an interface in their development versions. We expect the API to become part of the production version of the atlas viewer in early SGA3. The Python client (Output 2) has been used by the developer of the JuGEx plugin. A first evaluation of the API by modellers from SP4 is planned in M24. Output 3 establishes the workflow of end-to-end modelling using TVB integrated with the human atlas. This workflow is adapted from the already existing VEP workflow on epileptic patients, currently used in modified form in the clinical trial EPINOV. Output 3 contains three building blocks (functional data features; manifold organisation for resting data; influence of anatomical data upon model inversion performance) that will be largely expanded upon in the next Project phase. Combined in one workflow, they bear the promise that the integration of the human atlas with TVB improves the predictive power individual brain models.

5.2.2 Publications

None in this phase of the Project.

6. Conclusion and Outlook

CDP3 has established best practices and first showcases of organising functional data at different scales in the multilevel human brain atlas. Tier 2 curation performs probabilistic assignment of whole brain activation maps to the JuBrain atlas and thereby index activations under different tasks by brain areas. For spatial anchoring of high-resolution fMRI to the atlas, a prototype function for nonlinear image registration has been implemented for the new VoluBA tool, which uses Bok's equivolumetric model to match cortical VOIs to the BigBrain model, which now includes high-resolution maps of cortical layers and cytoarchitectonics areas. Public releases of data that were anchored using this principle will follow in SGA3, as the workflow is currently under evaluation, and the preparation of suitable datasets is nontrivial. We are planning to pre-align slabs of high-resolution fMRI based on whole-brain scans, and then perform the proposed scheme for individual cortical blocks of the data.

For connectivity data, we set up similar principles. At the whole-brain level, we have released a new browser for connectivity matrices as part of the interactive atlas viewer, which allows to navigate the JuBrain atlas along major pathways based on connection strengths. Some suitable connectivity matrices are already available in the Knowledge Graph, and additional ones will follow soon. SGA3 will address customisation of connectivity matrices by parameters like gender and age, requiring a more fine-grained curation of DTI tractograms from the different cohorts available to the Project. For high-resolution connectivity data, we also rely on the VoluBA tool and volumes of interest coming from high-resolution DTI and 3D PLI data. A first showcase has been addressed using a multimodal sample of the hippocampus from WP2.3.

The atlas services have now been extended by RESTful API and corresponding Python client to allow programmatic access. While still at the prototype stage, this API and client are now under evaluation for providing data to the TVB simulation. Intense communication between atlas developers and TVB researchers has culminated in a first document that defines suitable datasets and required formats to provide multiscale data for simulation. Kickstarted by this work, informing multiscale models from the multilevel human brain atlas will be a key aim of the upcoming Project period.

CDP3 proposes workflows to explore and register the links of data features of the Big Brain and the neural mass models in TVB to achieve a systematic understanding of how details of the macroscopic

level of brain areas and the microscopic levels of cortical layers can better inform the mathematical TVB models. The scientific challenges will be addressed by WP1 in SGA3. CDP3 provides proof of concepts in three aspects: 1) identification of regionally variant functional data features from iEEG signals; 2) demonstration of identifiability of network symmetry breaking in human brain imaging signals; 3) demonstration of increased predictive capacity of TVB using anatomically correct regionally variant priors in a Bayesian model inversion framework. These three workflow components are important building blocks for the organisation of the internal logic and functioning in WP1 in SGA3. They will be integrated into a full model building and validation workflow in support of the development of the showcases using EBRAINS.

Appendix: Catalogue of Atlas Features

The catalogue of Atlas features informing modelling can be found at the publicly open Collab page: https://wiki.ebrains.eu/bin/view/Collabs/atlas-tvb-mapping