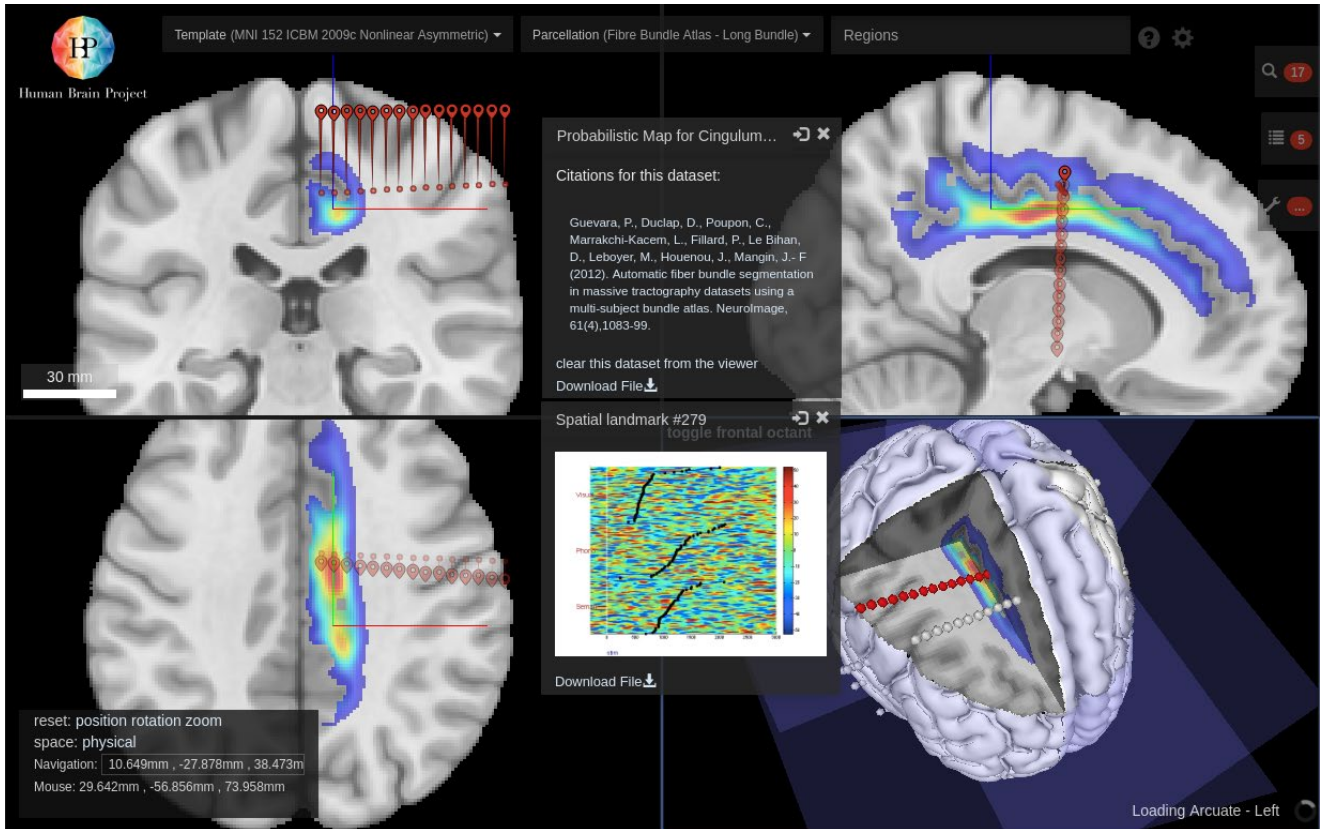# *CDP3 Results for SGA2 Year 1*
(D2.7.3 – SGA2)

Figure 1: iEEG recording sites on top of a probabilistic cytoarchitectonic map displayed in the HBP interactive atlas viewer.

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SciTechCoord Review:	Martin TELEFONT, EPFL (P1)		
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Description in GA:	CDP3 SGA2 Results Overview Deliverable: Overview of Key Results achieved in M1 to M12, tailored for presentation to the relevant audiences (research/industry/public)		
Abstract:	The aim of Codesign Project 3 (CDP3) is to enrich the multilevel human brain atlas that has been set up 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 these data. 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. In the first half of SGA2, we have worked on advanced concepts to integrate functional and connectivity data in the atlas, and analysed the needs of the TVB modelling engine that can be served by the atlas.		
Keywords:	Human Brain Atlas, CDP3, TVB, Web viewer, iEEG, HiBoP, TVB, Spatial Search		
Target Users/Readers:	Neuroanatomists, Computationals neuroscientists, People interested in Neuroinformatics		

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1. Overview

The aim of Codesign Project 3 (CDP3) is to enrich the multilevel human brain atlas that has been set up 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 these 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 models of the brain, defined at the milli- and micrometre scale, the HBP curation teams anchor experimental data, covering function, connectivity, as well as cellular and molecular architecture, to their appropriate level of resolution.

Last year, the CDP3 work was dominated by a strong shift of focus. Previously, we built the fundamental requirements for hosting a multi-scale 3D atlas online. Now, we work on its application for providing and supporting information to build and validate the multi-scale brain models. We started by integrating 3D atlas views with "The Virtual Brain (TVB)". The Virtual Brain provides a computational framework for simulating network dynamics using biologically realistic large-scale brain activity. Here, HBP's human brain atlas can provide a high-quality reference framework in which data and model elements can be described. We worked on advanced concepts to integrate functional and connectivity data in the atlas, and analysed the needs of the TVB modelling engine that can be served by the atlas.

In the upcoming year, we plan a range of software releases to open new functionalities for a broader audience.

2. Introduction

In this document, we summarise the work performed by CDP3 until the end of the first year of SGA2. Following the aims outlined in the overview, the work in CDP3 is centred around 3 Key Results (KRs):

- 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)

This document will be centered around these Key Results.

CDP3 was originally terminated at the end of the previous project phase (SGA1), in the sense that the fundamental requirements for hosting a multi-scale atlas had been established, and that this could be further developed by work packages WP5.3 and WP2.6 of the current project phase (SGA2). However, as a result of the SGA1 review, it was suggested to continue CDP3 because of its successful impact on the project, and because of the central role of the atlas. For this reason, the modified CDP3 started in SGA2 with a delay of several months. The consequence is that this report only covers a period of about 8 months. During this period, our focus was on KRc3.1, and on setting up the cooperation between the relevant people working on the TVB and the HBP atlas services (KRc3.3).

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

3.1   Outputs

3.1.1   Overview of Outputs

- Prototype software interface between HiBoP and the HBP interactive atlas viewer
- First high-resolution 3D maps of visual areas for integration of sublaminar fMRI signals into the BigBrain

3.1.2   Prototype software interface between HiBoP and the HBP interactive atlas viewer

HiBoP is expert software, used by clinicians and neuroscientists to manage, visualise and analyse intracranial EEG data. It was developed by the team of Jean-Philippe LACHAUX (INSERM), SGA2 Task T2.6.1 (C2246). The software is installed and runs on a client PC. It provides advanced display and handling of electrode locations, activity signals, and patient brain information.
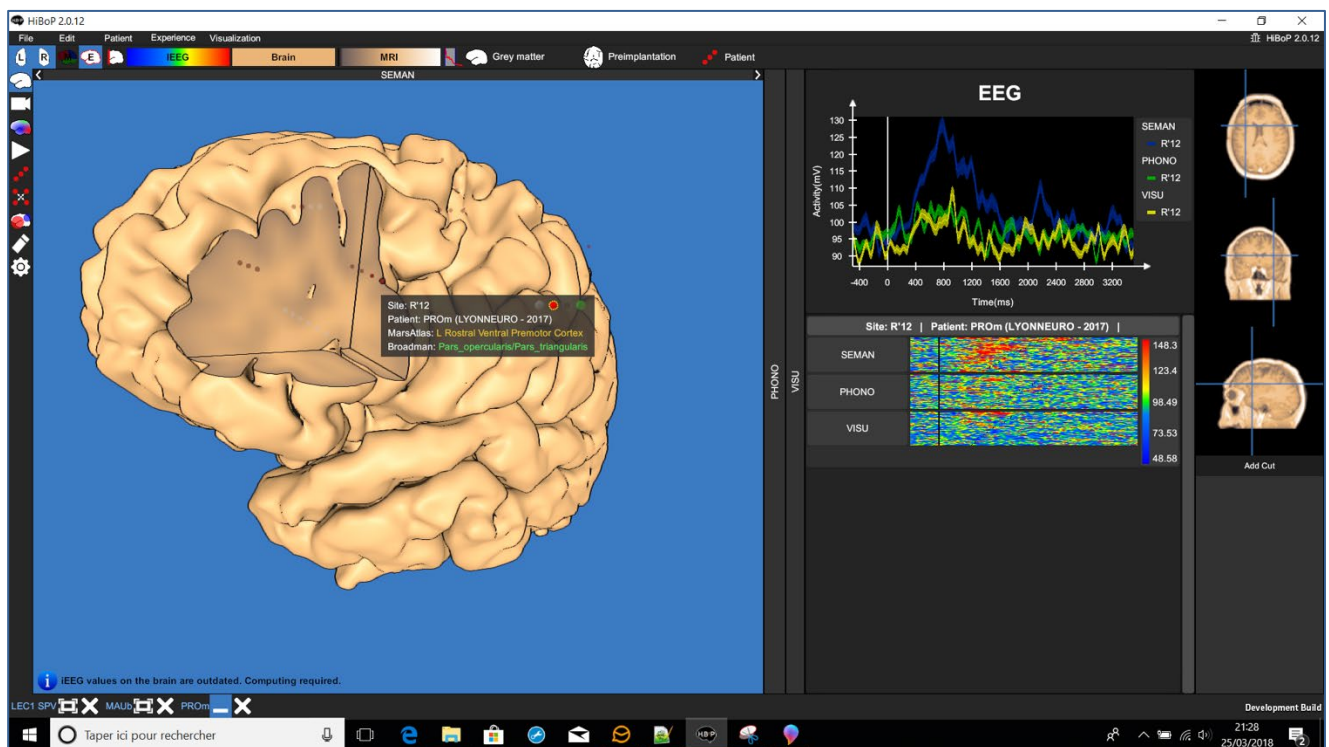

Figure 2: Screenshot of the HiBoP Software (C2246, SGA2 T2.6.1).

The HBP interactive atlas viewer (C2802, SGA2 Task T5.4.3), on the other hand, is a browser-based application for navigating multi-scale reference atlases in 3D. It allows identifying brain regions, finding region-related multi-modal data, and exploring brain anatomy. We started working on a compatibility layer between the two. This layer will allow users of the online atlas to easily open iEEG data that they discover in the atlas viewer, for advanced inspection and analysis in HiBoP. Vice versa, for users of HiBoP, it will be possible to open an electrode location of interest directly in the atlas viewer to better assess its location in the brain, identify the related brain region, and compare it with other data linked to that region.

To conceptualise its interface, HiBoP developers visited Forschungszentrum JUELICH (FZJ) in September 2018 and worked extensively with the developers of the interactive atlas viewer. As a result of this meeting, first proofs-of-principle were developed: i) a HiBoP prototype which demonstrates a one-way transition from HiBoP to the interactive atlas viewer, and ii) an interactive atlas prototype which displays spatial landmarks and metadata of iEEG data related to HiBoP. The latter prototype can launch the atlas viewer with a comparable brain orientation, and display contact point coordinates in 3D (see Figure 2).

3.1.3 First high-resolution 3D maps of visual areas for integration of sublaminar fMRI signals to the BigBrain

For integration of sublaminar resolution fMRI signals into the BigBrain reference model, access to delineations of cortical areas and measures of normalised cortical depth are necessary. We have worked with SGA2 Task T2.1.4 (C2272) and SGA2 Task T2.6.4 (C2376) to produce first versions of high-resolution, dense 3D maps of areas hOc1 and hOc2 in both hemispheres of the BigBrain (Figure 3). This required precise labelling of these areas in a series of hundreds of histological sections. It was performed with help of a Deep Learning-based workflow that learns from a set of only a few expert annotations. The principle is described in more detail in SP2 compound Deliverable, D2.7.1 (D14.1, D16). The first maps of areas V1 and V2 in the atlas will be publicly available from May 2019.
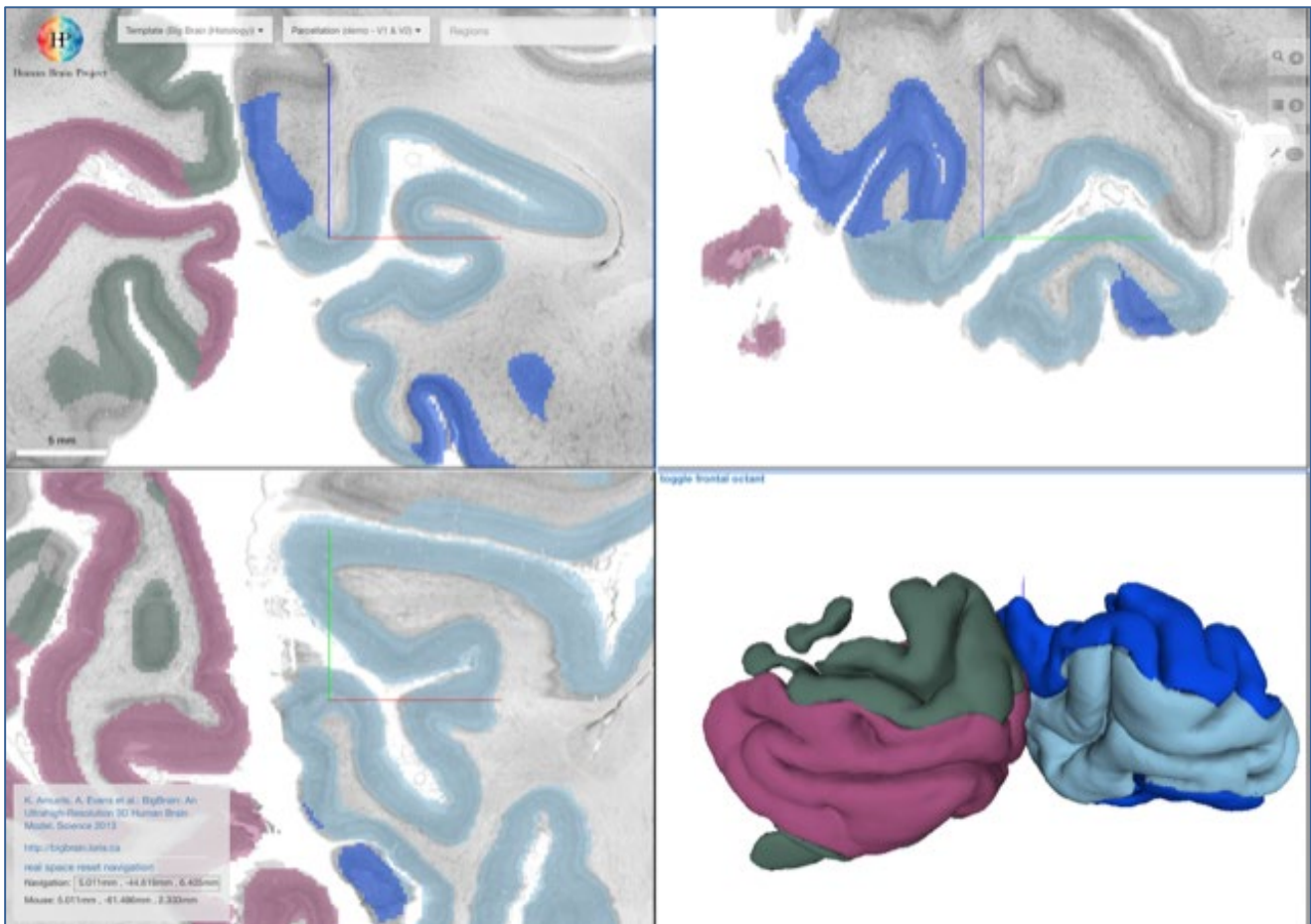

Figure 3: Preliminary high-resolution 3D maps of areas hOc1 and hOc2 defined in the BigBrain template.

3.2 Validation and Impact

The proof-of-principle interface between the HiBoP expert software and the atlas viewer demonstrates the benefit of localising recordings in a comprehensive atlas. Beyond a simple projection of a parcellation onto the subject, the HBP atlas allows comparison of locations with different organisational principles like cytoarchitectonic areas and fibre bundles, and in particular allows a probabilistic assessment of localisation, illustrated on the front page of this Deliverable (Figure 1).

The new high-resolution maps of visual areas in the BigBrain allow comparison of sublaminar functional activity with other data anchored to the BigBrain. They also allow making inferences on connectivity of the visuo-motor system at the laminar and areal level. Since the mapping procedure conceptually matches the method used to determine our probabilistic cytoarchitectonic maps, and provides areas of the same taxonomy, this strategy will generate a bridge between the macro-scale used in neuroimaging and the microscopic scale.

3.2.1   Actual Use of Output(s) / Exploitation

The new 3D maps for the BigBrain are still under quality control and data curation, but Task T2.6.4 already shared them with researchers in SGA2 Task T2.5.6 (C2322), who confirmed the usefulness for integrating high-resolution fMRI signals and clarifying anatomical details for the electrode placement strategies. The proof-of-principle software interface is not yet in practical use, it is the basis for ongoing development and a release in the next year.

3.2.2   Potential Use of Output(s)

The 3D maps of areas hOc1 and hOc2 in the BigBrain will soon be released in the Knowledge Graph, and provided through the HBP atlas viewer. From then, they can be used by the public to study the anatomy of these areas, and superimpose them with any data anchored to the BigBrain dataset. This will be particularly useful when combined with the upcoming release of a volumetric anchoring tool for the BigBrain (SGA2 Task T5.3.3, C2434).

3.2.3   Publications

None yet

3.2.4   Measures to Increase Impact of Output(s): Dissemination

None

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

We have not yet generated any outputs for this Key Result in the period covered by this Deliverable.

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

5.1   Outputs

5.1.1   Overview of Outputs

1)   Generation of the workflow for modelling and validating the multi-scale brain models with personalised and region-specific information.

2)   Analysis of resources available in the HBP and in literature.

5.1.2   Description of Output 1

Generation of workflow:

To link multi-scale data to network modelling, in particular to The Virtual Brain, in the same reference framework, a workflow is required that can be executed with the means and resources available in the HBP. The developed workflow is shown in Figure 4 and is as follows:

Multi-scale, multi-modal, connectome-based whole-brain data sets will be constructed using DMRI-based tractography, 3D-PLI-based axonal architecture, multi-scale nested and overlapping connectome nodes (definitions will vary across regions and include cell types, cell 3D distribution, receptors, and in the future neuromodulators, transcriptomes, synaptic densities, region specific as well as physiological patterns from iEEG, fMRI, EEG, MEG and simultaneous EEG-fMRI) and connectivity-based parcellations. The microstructure of the bundles making up the connections will be described in terms of axon density and diameter, and myelin fraction, and when possible directionality. Evaluation of the connectome will be performed against functional parcellations (task-based, functional connectivity, iEEG responses to direct cortical stimulations, seizure propagation). Data features will be mapped upon model parameters and parameter regimes will be constructed, that define the model's dynamic range. Model inversion sampling network data features (effective/functional connectivity, propagation) will fit model parameters, assess model evidence and quantify relevance and predictive value. Tools to quantify and account for variability will be developed and evaluated for functional relevance (model identifiability).
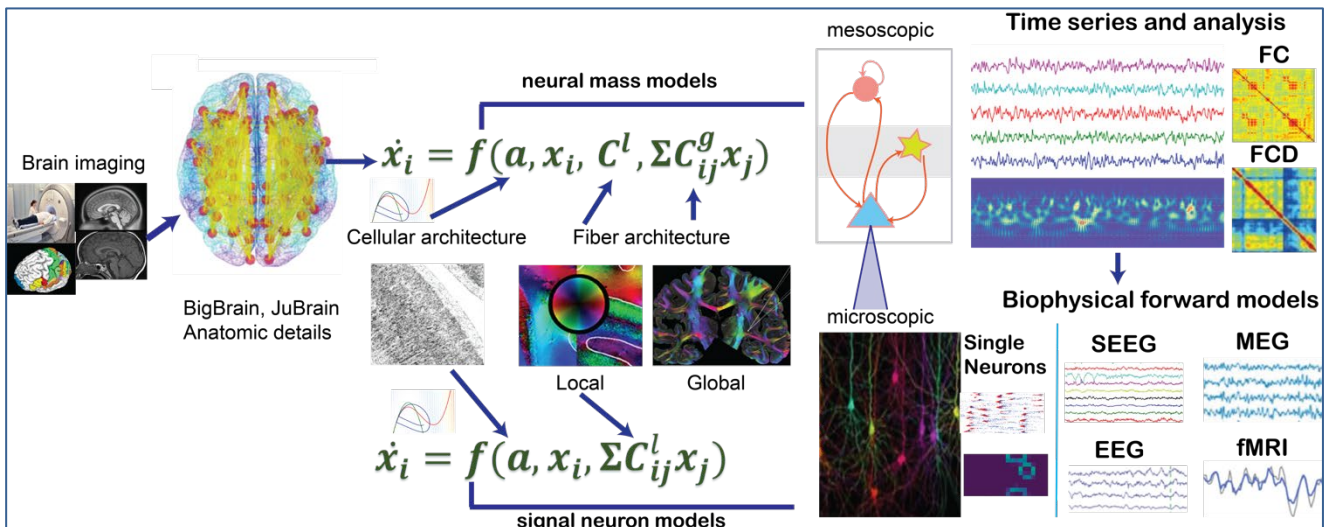

Figure 4: The workflow for modelling and validating the multi-scale brain models with personalised and region-specialised information.

Analysis of the resources available in the HBP and in literature.

To evaluate the feasibility of this CDP3 workflow, an analysis of the competences, resources and previous work in the HBP was performed, including the state of the art in literature. A critical example is the 3D mouse cell atlas (https://bbp.epfl.ch/nexus/cell-atlas in Ero *et al.*, 2018, Frontiers in neuroinformatics), which provides the densities and positions of all excitatory and inhibitory neurons in each of the whole mouse brain regions defined in the atlas. This work has been performed by the group of Marc-Oliver GEWALTIG in SP10. The cell composition information is necessary for the creation of mathematical representations in the modelling of the multi-scale region specialised brain models. Another example is the availability of human data, illustrated in the biophysical and anatomical studies on human neuronal cells by Huibert D. MANSVELDER (Deitcher, *et al.*, Cerebral Cortex 2017). He performed a comprehensive analysis on the morphological and biophysical features of L2 and L3 pyramidal neurons in human temporal cortex. Eyal *et al.*, Frontiers in cellular Neuroscience 2018, have presented detailed models of these pyramidal neurons to simulate the spikes based on experimental anatomical and physiological data. A lot of data are still missing and strategies in the above workflow to complete missing data have to be developed. A possible approach could be the mapping of mouse brain data to the human brain, responding to both criteria, feasibility and availability in the HBP.

The analysis of the available resources in the HBP to complete the proposed workflow is ongoing. For this purpose, we had a workshop in Marseille on 28-29 March 2019.

5.1.3   Actual Use of Output(s) / Exploitation

5.1.4   Potential Use of Output(s)

Both outputs serve as the necessary basis for the next steps linking TVB with the BigBrain and enable us now to initiate these steps.

5.1.5   Publications

None yet

5.1.6   Measures to Increase Impact of Output(s): Dissemination

None

6. Conclusion and Outlook

We progressed on a more comprehensive integration of functional data into the human brain atlas, by implementing a proof-of-principle interface between the HiBoP expert software for iEEG data and the interactive atlas viewer, which is the basis for ongoing developments. We planned a release in the second year of SGA2. Using this software interface, users can switch between advanced iEEG data analyses in the desktop application, and detailed assessment of locations and anatomical contexts in the atlas.

The first high-resolution 3D maps of two cytoarchitectonic areas in the BigBrain have been computed and integrated into the atlas viewer. They are based on highly precise delineations in many hundreds of serial tissue sections, supported by a new Deep Learning tool developed in SP2. These maps have been provided to researchers in SP2 for the first feasibility studies, and they will be published, after further QC and data curation, before M18. They are an important step towards bridging scales, as they have a direct correspondence to probabilistic maps in the cytoarchitectonic atlas, which are defined on the millimetre scale, and well established in the neuroimaging community.

To progress in the improved integration of connectivity data in the atlas (KRc3.2), we prioritise the integration of 3D-PLI data into the BigBrain. The group of Markus AXER (JUELICH) has measured, analysed and performed a 3D reconstruction of a part of a human hemisphere (230 sections in total; Schmitz *et al.*, 2018; C2386) which will now be aligned to the BigBrain template space by the curation teams. The voxel size of this dataset is 64 mm x 64 mm x 70 mm. The entire data set includes blockface images, raw data (stacks of 18 images), transmittance maps, retardation maps and fibre orientation maps.

We developed the workflow to integrate BigBrain information and TVB knowledge for the specialised brain-region large-scale models. We analysed the resources available in the HBP and in the literature. Establishing the HBP atlas services as tool for multi-scale modelling, and adjusting formats, ontologies and APIs, requires a good understanding of these domains. We spent significant efforts on this, including a one-week working meeting between AMU (TVB) and JUELICH (human atlas services) held in February 2019. To define a concrete roadmap for the next years, an in-person meeting between many involved researchers was held on 28-29 March 2019.