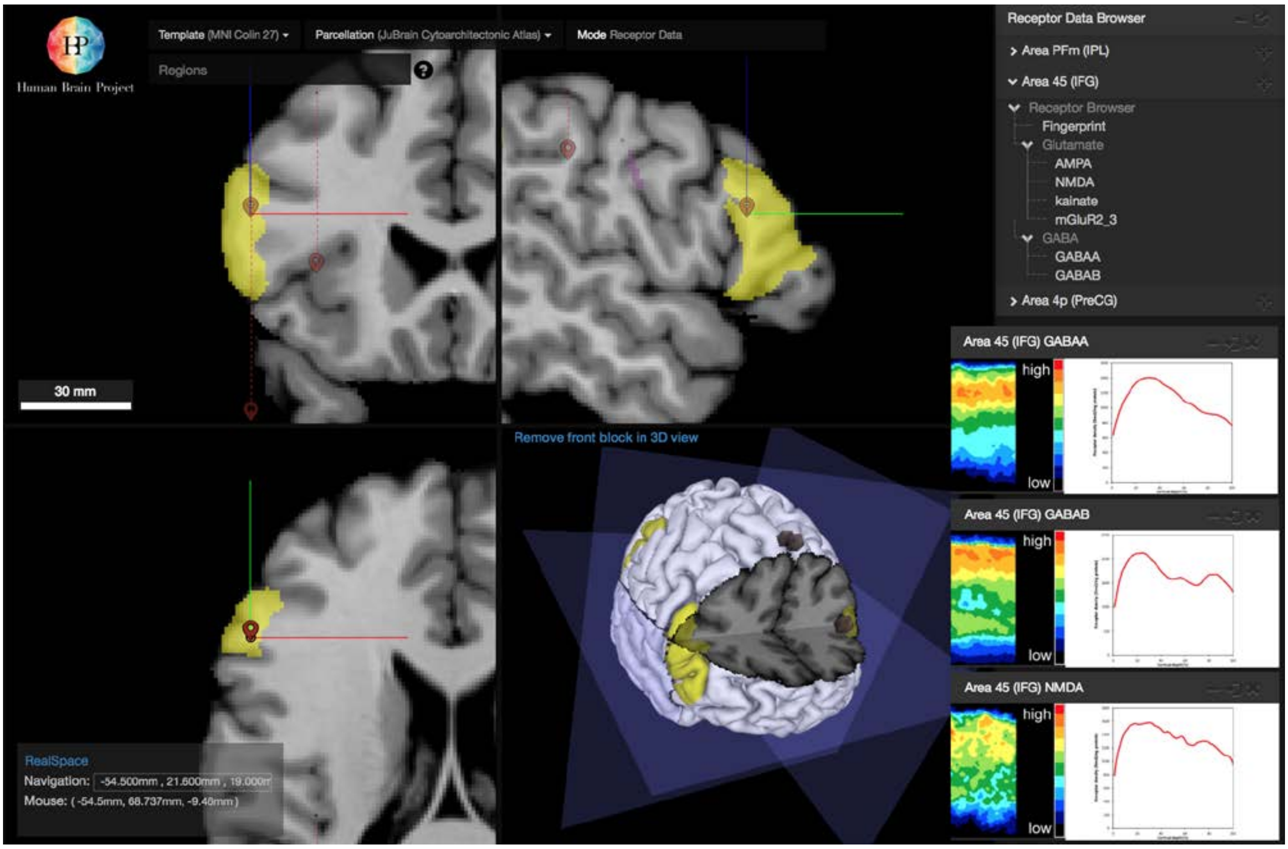
Grant Number:	720270	Grant Title:	Human Brain Project SGA1

Deliverable Title:	D2.7.3 (D12.3 D55) CDP3 Components Report for SGA1 M13-M24
Contractual Number and type:	SGA1 D2.7.3 (D12.3 D55) report
Dissemination Level:	PUBLIC with a CONFIDENTIAL annex
Version / Date:	Submitted date: 23 Apr 2018; ACCEPTED 09 Jul 2018

Abstract:	This deliverable is the annual compound of HBP deliveries and results (outputs and outcomes) from CDP3. The live complete catalogue of HBP deliveries is accessible on-line from the HBP portal.
Keywords:	CDP3, Multi-level Human Brain Atlas



HBP interactive atlas viewer, showing a 3D view of the JuBrain cytoarchitectonic atlas (K. Amunts and colleagues, JUELICH) with a particular area (IFG) selected, and samples of receptor distribution (GABA-B) for this specific area (K. Zilles & colleagues, JUELICH). The receptor data were retrieved by visual exploration of the brain areas, in a specific browsing mode for this modality.

Targeted users/readers	Researchers, Policy Makers
Contributing Work-Package(s):	SGA1 WPs 2.6, 5.3, 5.4, 2.2, 2.5
Initially Planned Delivery Date:	SGA1 M24 / 31 03 2018 (Date for submission to EC, as set out in DoA)

Authors:	Timo DICKSCHEID, JUELICH (P20) Katrin AMUNTS, JUELICH (P20)
Compiling Editors:	
Contributors:	Jean-Francois MANGIN, CEA
SciTechCoord Review:	EPFL (P1): Jeff MULLER, Martin TELEFONT, Marie-Elisabeth COLIN UHEI (P47): Martina SCHMALHOLZ, Sabine SCHNEIDER
Editorial Review:	EPFL (P1): Annemieke MICHELS

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1. Introduction

The aim of this document is to provide an overview of progress in the HBP that has been endorsed and driven during SGA1 by Codesign Project 3 (CDP3) "Multi-Level Human Brain Atlas". CDP3 is motivated by the fact that the development of a multilevel human atlas will require significant coordination across SPs, bringing together the development of front end technologies in SP5, the contribution of strategic datasets and methods from SP2 and SP3, the opinions of modellers in SP4 and SP6, and the expertise of infrastructure providers in SP7. The CDP identified the following products to focus on:

1) The development of web-based 2D and 3D image viewers for data at different scales, with sizes that may extend the capacity of the client's working memory by orders **(P1, P2)**. These are a basic requirement for users to display and navigate atlas data at multiple levels without installing complex expert software.
2) The collection and curation of a range of strategic atlas templates and parcellations, together with related quantitative and qualitative data that allows to demonstrate the usefulness of a multilevel atlas **(P3, P4)**
3) First prototypes of web-based interactive registration tools, that allow users and data curators to spatially anchor new volumetric data to existing atlases at high resolutions **(P5)**, thus removing the need of a complex and often infeasible data and software installation in each contributing lab.
4) A set of initial interactive tools for working with atlases and related data **(P6),** as a first showcase of what a multimodal atlas can do, and as a trigger to attract users and get more feedback on future implementations.
5) A conceptual extension of the metadata schemes and knowledge graph, to address the complex aspects of human intervariability **(P7).**
6) Provision of experimental data constraints to constrain and validate simulations of whole-brain models **(P8)**.

CDP3 made very good progress on the critical products P2, P3, P5 and P6, although the work was heavily affected by the changes in the SP5 workplan and consequent delayed recruitment. At the HBP summit in Glasgow, we were able to give users hands-on access to pre-release versions of a volumetric 3D atlas viewer for large datasets (P2), a web-based spatial registration tool for large image volumes (P5), and an interactive tool for differential analysis of Allen gene expressions with respect to areas selected from the JuBrain atlas (P6). These were based on releases of the Big Brain and JuBrain atlas templates. The new toolsets have also been demonstrated to the wider public in a hands-on session of SfN2017.

During the summit in Glasgow, CDP3 selected two flagship Use Cases for the remainder of SGA1: i) the implementation of interactive tools to work with area-specific gene expressions and receptor distributions, and ii) a proof-of-principle implementation of P8.

At the time of writing, i) has been achieved. Regarding ii), SP2 has extracted functional and structural connectivity matrices from HBP experimental data and exchanged them with modellers in SP4. After a proof-of-concept verification in SP5, intense discussions between the SPs have resulted in a technical description of requirements to make this workflow a service of the NIP. These requirements can be found in the appendix of this document. A proof-of-principle implementation has been started.

2. Results

This is the list of Key Results, the outputs and outcomes from CDP3 – Multilevel human brain atlas. Each Key Result is presented together with the list of the corresponding HBP Components which constitute/contribute to this element, and a table is provided for each newly released (brand new or new version) Component. Key Results can also be a major integration of existing HBP or external Components or the achievement of an CDPs objective or related major Use Case.

2.1 Online exploration of very large brain volumes in 3D

SP2 and SP3 are generating and gathering a unique portfolio of high-quality human brain templates, maps and multilevel data. To actually generate an impact for the wider community, these data have to be provided in a simple, user-friendly yet mostly useful fashion to users through the web interfaces and APIs of the Neuroinformatics Platform. CDP3 has fostered a close cooperation of researchers in SP2 with developers in WP5.4 to design a first version of a web-based 3D atlas viewer that is capable of displaying a large volume like the Big Brain across the web, including oblique slicing, a whole brain overview, surface meshes and maps. Based on this development, we provided releases of dedicated viewers for strategic atlas templates:

- The Big Brain: http://bigbrain.humanbrainproject.org
- The JuBrain atlas: http://jubrain.humanbrainproject.org
- The Waxholm rodent atlas: http://waxholm.humanbrainproject.org
- The Allen Mouse Brain Atlas: http://amba.humanbrainproject.org

To our knowledge, there is no other web-based tool that allows to navigate different Terabyte-sized brain atlas volumes on the web that combines fluent zooming into high resolutions and oblique slicing with a 3D overview that gives appropriate neuroanatomical context. The 3D viewer is designed with an API that allows to precisely control its behaviour and use it as a component in other HBP web applications. In this way, we built an important prerequisite for a more unified viewer architecture in HBP. Its direct integration into an interactive atlas viewer is the first proof of this principle. A rich interactive atlas viewer application, which embeds this viewer and allows interaction with different templates, parcellations, and region-specific data, will be released in the beginning of April 2018 (Figure 1).

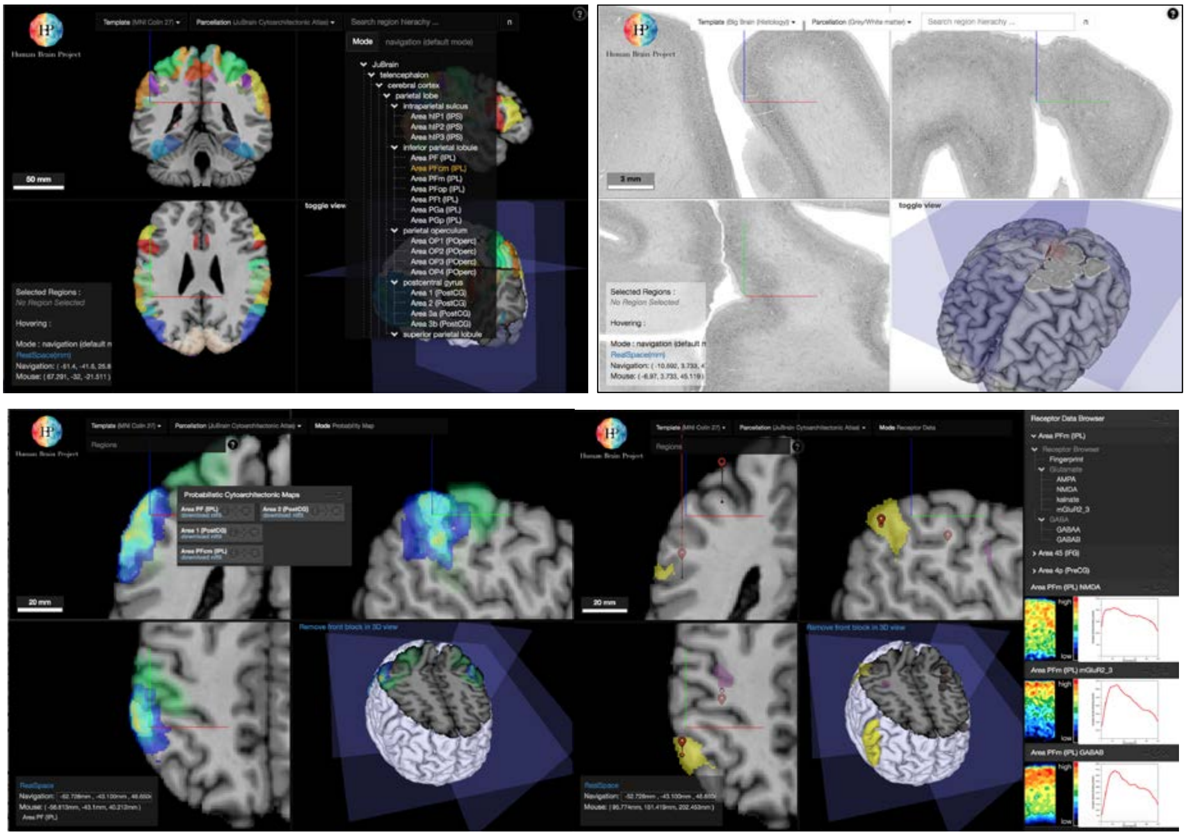

Figure 1: Screenshots of the interactive atlas viewer

Screenshots of the interactive atlas viewer in different data browsing modes. Upper left: interactive browsing of parcellations and brain regions (default mode; here: JuBrain cytoarchitectonic atlas). Upper right: High resolution detail with oblique slicing and an intuitive anatomical overview in one application (here: BigBrain template, ~1 TByte). Lower left: Probability map browsing mode, with the possibility to directly download individual maps as Nifti files. Lower right: Area specific receptor data browsing mode, with the possibility to download individual receptor distribution maps and profiles. Style and background colours automatically adapt appropriately to the selected atlas, i.e. the light microscopy images of the Big Brain are rendered with their natural white background, whereas MRI templates have a dark background.

2.1.1 Achieved Impact

The viewer was presented to prospective users in different hands-on sessions, including the HBP summit in Glasgow, a workshop of SfN 2017 in Washington (annual meeting of the Society for Neuroscience; more than 30.000 attendees), and the DutchBrain outreach event in Amsterdam. The feedback was overall very positive: users appreciate the intuitive and simple interface, and are surprised about the performance when navigating the large Big Brain volume online, even when using WiFi connections. We made initial contacts with scientists from neuroanatomical labs, who showed their interest in anchoring high-resolution volumes from their lab studies to the Big Brain, to be able to present their data online and to provide appropriate anatomical context.

2.1.2 Component Dependencies

Component ID	Component Name	HBP Internal	Comment
1503	Web-based big data viewer to navigate the Big Brain in three planes at different resolutions	Yes	Provides functionality to interactive exploration of overlays of Terabyte-sized brain volumes on the web in 3D.
2909	Extension of web-based 3D viewer to select and display a parcellation as a semitransparent overlay	Yes	Provides functionality to select and switch between different brain templates and parcellations, while exploring large 3D volumetric atlas data.

2.2 Interactive region-based analysis of different modalities

On CDP3 request, the interactive atlas viewer already provides capabilities to develop custom plugins for modality-specific functionalities that can interact with selected atlas regions. CDP3 co-designed this plugin architecture, and implemented a first set of interactive tools that use this principle (Component 800):

1) Interactive retrieval of region-specific receptor densities from the JuBrain cytoarchitectonic atlas (see title page illustration and Figure 1).
2) Differential analysis of gene expressions, retrieved from the Allen Human Brain Atlas, according to two areas defined in the JuBrain cytoarchitectonic atlas (Figure 2)
3) Interactive retrieval of electrophysiological recordings by their recording sites, using a prototype of spatial search (Figure 1).

Regarding 2), WP2.6 reimplemented the “Jugex” matlab tool (Bludau et al., 2018) as a python application, and embedded it into the plugin architecture of the HBP interactive atlas viewer (cf. Architecture diagram in Figure 4).

These interactive tools are the first examples of extending the atlas viewer with interactive, modality specific plugins. They showcase the value of multimodal data linked in one atlas, and accessible through visual 3D exploration of the brain. The prototype application that will have its first release in the beginning of April 2018 will be the first of its kind regarding the multimodal richness of data that can be explored. The implementation of Web-JuGEx is a scaffold to combine many HBP infrastructure aspects:

- Curated data stored on the NIP storage system (in this case: curated JuBrain probability maps)
- Interface to external repositories (in this case: The Allen Human Brain Atlas API)
- Modality-specific analysis functions, abstracted in a Python library that can be accessed independently, connected to the interactive atlas viewers as a plugin

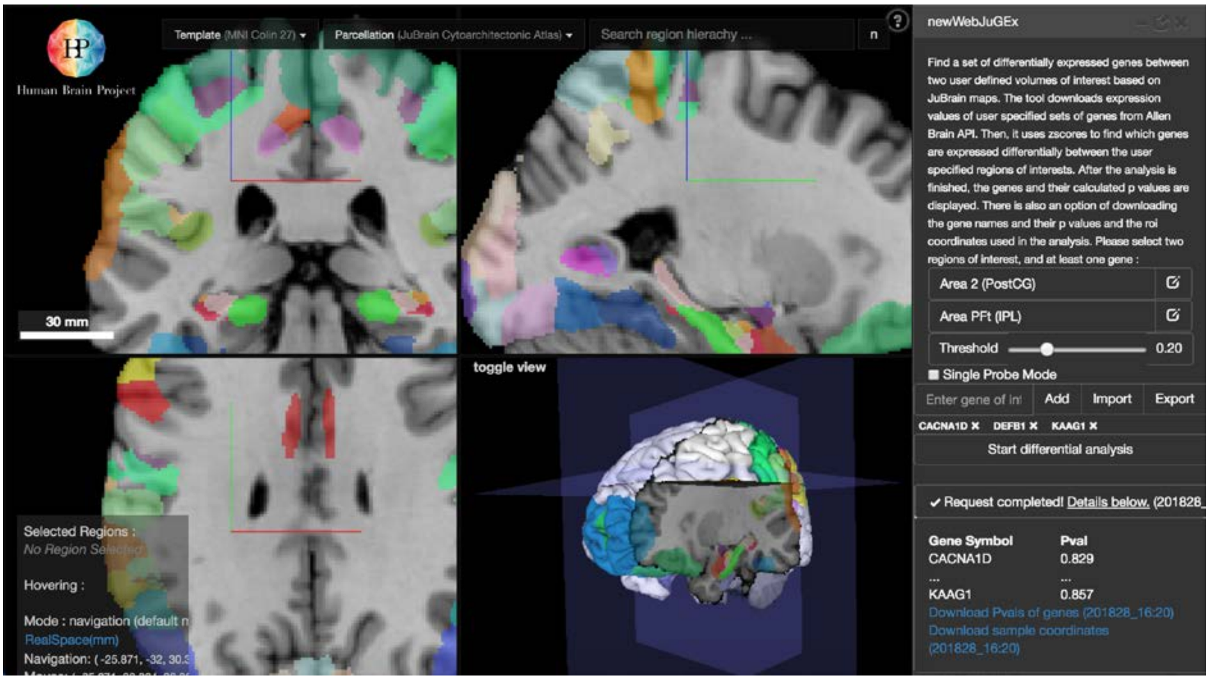

Figure 2: "Web-JuGEx"

"Web-JuGEx" embedded as an interactive tool into the interactive atlas viewer, exploiting the atlas viewer's plugin architecture.

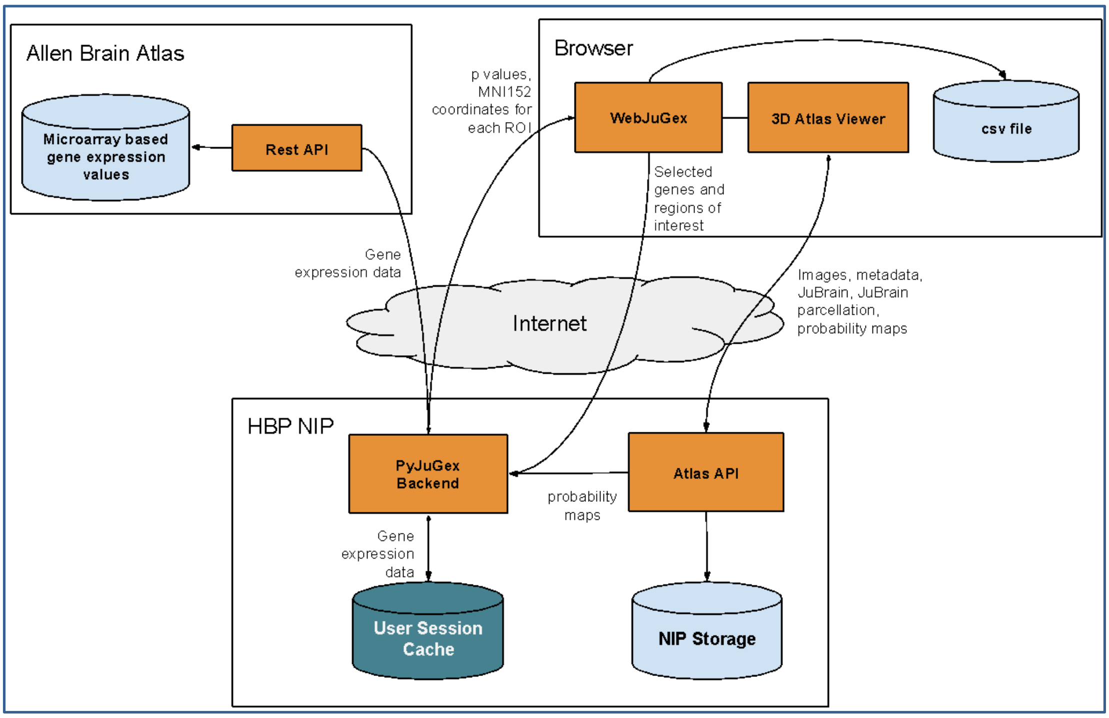

Figure 3: Architecture of "Web-JUGEX"

Architecture of "Web-JUGEX", a tool for differential analysis of gene expressions from the Allen Atlas according to regions defined in the JuBrain atlas, which is embedded as an interactive plugin into the new HBP interactive atlas viewer.

2.2.1 Achieved Impact

Together with the plain volumetric viewer (KR1), an early version of the interactive viewer and the Web-JUGEX tool were presented to prospective users during the HBP summit in Glasgow, during a workshop of SfN 2017 in Washington and during the DutchBrain outreach event in Amsterdam. Furthermore, selected HBP internal neuroscientists have now worked with WebJugex in more detail. Compared to the original Jugex implementation in Matlab, they appreciated that 1) they do not have to download and handle their own copy of the atlas in the form of several hundreds of Nifti files, 2) they do not have to be concerned about compatibility of the template spaces with the resulting risk of invalid results, and 3) they have a more intuitive way of selecting brain areas interactively in 3D. Running the procedure is now free (e.g. it does not require any software license) and immediate (e.g. it does not require any software installation or significant data download).

2.2.2 Component Dependencies

Component ID	Component Name	HBP Internal	Comment
2909	Extension of web-based 3D viewer for selecting and displaying a parcellation as a semitransparent overlay	Yes	Provides functionality to select and switch between different brain templates and parcellations while exploring large 3D volumetric atlas data.
800	Integration of papaya prototype with JuBrain atlas and receptor measurements into NIP back end	Yes	The receptor query prototype realised in the papaya framework has been replaced by a more unified solution of receptor queries directly in the HBP interactive atlas viewer.
2254	Query and analysis tool for Allen human gene expressions grouped by atlas regions	Yes	This is a SGA2 component that we started to develop ahead of the workplan motivated by CDP3. It has reached the prototype stage in SGA1 and is embedded in the interactive atlas viewer (89-2) using its novel plugin architecture, to co-design the viewer and showcase its extensibility.

2.3 A workflow for integrating user data to the atlases

CDP3 has coordinated efforts to build web-based tools to anchor new data to high-resolution atlases through simple web interfaces, using atlas data that are already available online. Although it is still in the prototype stage, we presented these registration tools to users during the HBP summit in Glasgow, during a workshop of SfN 2017 in Washington and during the DutchBrain outreach event in Amsterdam. The interactive registration tool has been used by several neuroscientists in Jülich to anchor high-resolution datasets to the Big Brain (in particular, they aligned high-resolution volumes of interest from Polarized light imaging as well as subcortical 3D cell distributions, see Figure 4). It was the first time they could interactively carry out such a 3D interactive process at high resolution. Feedback was collected which will be considered for further developments. The developments are reported in detail in the SP5 deliverable report, as Key Result 5.4 and 5.5.

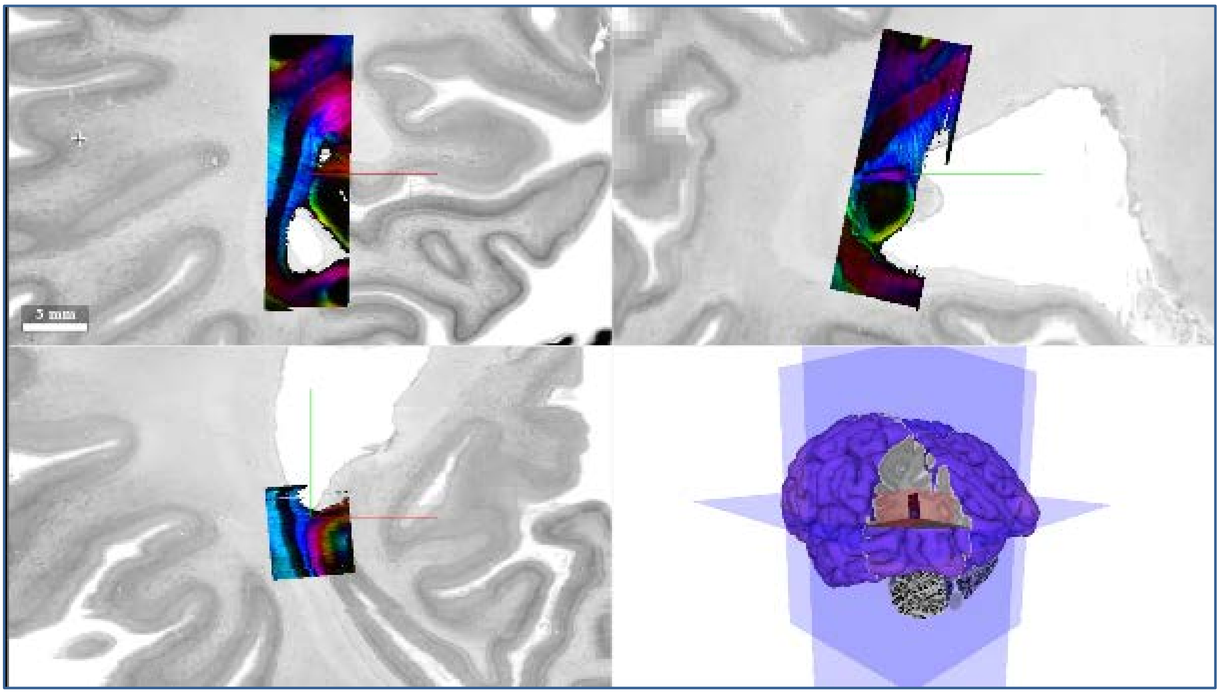

Figure 4: A high-resolution 3D volume of interest from Polarized Light Imaging

A high-resolution 3D volume of an area of interest using Polarized Light Imaging, reflecting the fibre architecture of this area, anchored to the Big Brain template, which reflects the cytoarchitecture. The anchoring step was performed online, using the new 3D spatial registration tool developed in WP5.3. The whole process did not require downloading of the Big Brain dataset, moreover, it works in a standard web browser without additional software installation.

2.4 Modelling and model validation using human quantitative data

CDP3 has initiated a fruitful collaboration between neuroanatomists, neuroinformaticians and theoreticians from SP2, SP5 and SP4 on the use of experimental human data for modelling. SP2 (CEA) provided connectivity matrices from different connectivity data sources, grouped by different cortical parcellations, to SP4, that will use them to constrain their resting-state models (Figure 5). A report formalises the requirements for a software service in more detail, this would allow modellers to configure and generate such data on their own, using HBP's *in-vivo* data and parcellations (cf. Annex: Modelling and model validation using human quantitative data). SP2 and SP5 started the implementation of such a service, and introduced it into the SGA2 Work Plan (Component 2260).

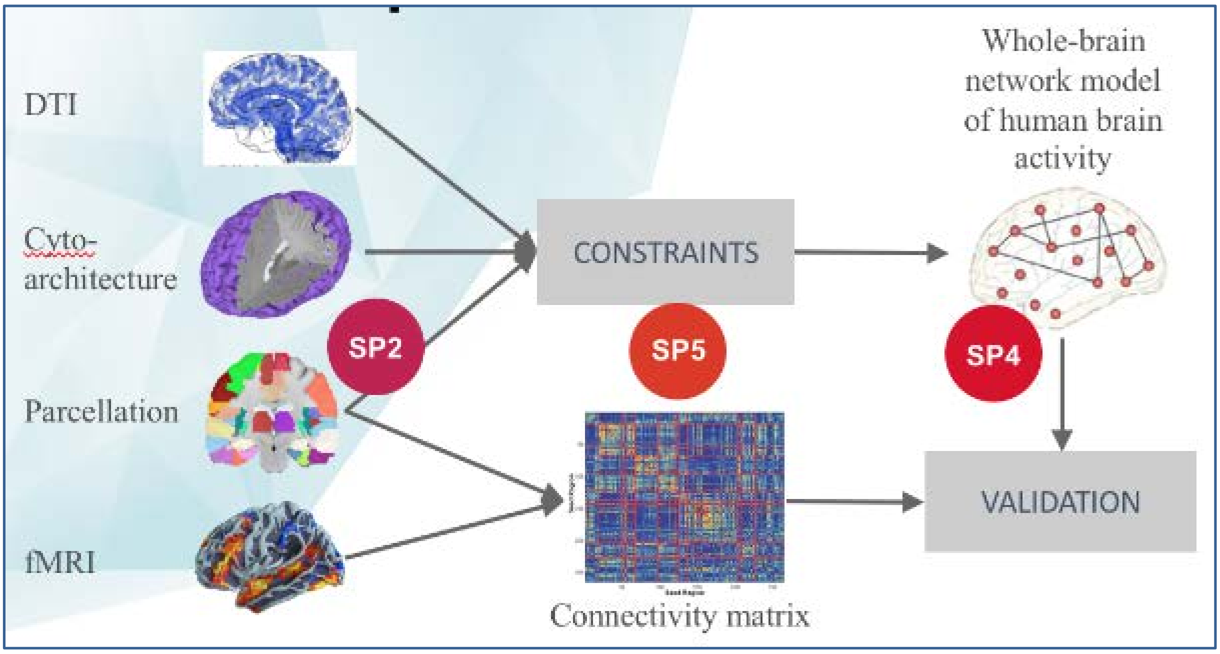

Figure 5: Dataflow used for whole-brain modelling

Dataflow for generating constraints and validation of connectivity matrices used for whole-brain modelling of human brain activity in SP4, illustrating the cooperation between SP2, SP4 and SP5 in the development of a NIP software service connected to the HBP human atlas.

2.4.1 Achieved Impact

The data provided to SP4 were valuable for its modelling tasks, they are already considered for publication. We are developing an interactive tool in the SP5 atlas that allows more users. With SP2 (WP2.5, WP2.6), SP5 (WP5.3) and SP4 (WP4.4), we have analysed the requirements for an atlas-related software service that helps modellers to constrain and validate whole-brain network models based on real experimental data. The feasibility and usefulness of the approach have been verified with a range of connectivity matrices generated from SP2 experimental data. We now have a requirements documentation that will be the basis for software development in SGA2.

2.4.2 Component Dependencies

Component ID	Component Name	HBP Internal	Comment
2260	A Connectivity matrix export tool of the human atlas	Yes	Service to be implemented in SGA2, that realises the proof of principle achieved in CDP3.
340	Human connectivity matrix from atlas parcels	Yes	This task will compute pairwise structural connectivity information for connectome nodes defined from post-mortem, diffusion (T 2.5.1) or functional data. Hence this task will provide the connectivity matrix used to serve the connectome-oriented requests to the HBP atlas.
999	Macroscopic model of spontaneous human brain activity	Yes	This model is the current Use Case for applying experimental data from the atlas.

3. Component Details

The following is a list of the newly released internal Components for this deliverable.

3.1 Web-based big data viewer to navigate the Big Brain in three planes at different resolutions

This component is also listed in the SP5 deliverable.

Field Name	Field Content	Additional Information
ID	1503	
Component Type	software	
Contact	CHERVAKOV, Pavel	
Component Description	Web-based viewer for high-resolution Big Brain data with capabilities for interactively panning and zooming the image data in three different planes.	
Latest Release	0.5, 2018 Apr 10	
TRL	TRL 5	
Location	uploaded to an approved HBP data repository location (see confidential Annex 5)	
Format	NA	
Curation Status	NA	
Validation - QC	Pass	CHERVAKOV, Pavel
Validation – Users	Yes	The software was demonstrated to users inside and outside HBP in the context of the Glasgow Summit and several community events (e.g. as part of Katrin Amunts' pre-conference tutorial session at SfN 2017). A demo is planned for OHBM 2018 in Singapore.

Validation – Publications	No	
Privacy Constraints	NA	See guidance below
Sharing	sharing class	See guidance below
License	GPFL v3 planned for release	See guidance below
Component Access URL	The software is deployed online for different reference atlases: http://bigbrain.humanbrainproject.org, http://jubrain.humanbrainproject.org, http://waxholm.humanbrainproject.org, http://amba.humanbrainproject.org	See guidance below
Technical documentation URL	https://collab.humanbrainproject.eu/#/collab/2689/nav/39750	See guidance below
Usage documentation URL	https://collab.humanbrainproject.eu/#/collab/2689/nav/39750	See guidance below
Component Dissemination Material URL	NA	See guidance below

3.2 Extension of the web-based 3D viewer to select and display a parcellation as a semitransparent overlay

This component is also listed in the SP5 deliverable.

Field Name	Field Content	Additional Information
ID	2909	
Component Type	software	
Contact	GUI, Xiaoyun	

Component Description	In this extended version, the user will be able to choose a parcellation from a list, which is then displayed as a semi-transparent overlay on top of the original contrast. We assume the parcellation to be given as a labelled (integer) volume dataset	
Latest Release	2018 March 05	
TRL	TRL 4	Prototype Component
Location	uploaded to an approved HBP data repository location, see confidential annex 5	
Format	NA	
Curation Status	NA	
Validation - QC	Pass	Manual testing passed (GUI, Xiayun)
Validation – Users	Yes	The software is deployed as a test installation for initial verification by selected HBP researchers. The software has been demonstrated to users inside and outside HBP in the context of the Glasgow Summit and several community events (e.g. as part of Katrin Amunts' pre-conference tutorial session at SfN 2017). A demo is planned for OHBM 2018 in Singapore.
Validation – Publications	No	
Privacy Constraints	NA	
Sharing	sharing class	
License	GPFL v3 planned for release	
Component Access URL	uploaded to an approved HBP data repository location, see confidential annex 5	

Technical documentation URL	uploaded to an approved HBP data repository location, see confidential annex 5	
Usage documentation URL	uploaded to an approved HBP data repository location, see confidential annex 5	
Component Dissemination Material URL	NA	

3.3 Query and analysis tool for Allen human gene expressions grouped by atlas regions

Field Name	Field Content	Additional Information
ID	2254, 800	
Component Type	software	
Contact	BHATTACHARYA, Haimasree	
Component Description	Python toolset for computing differential analysis of gene expressions from the Allen Human Brain Atlas, grouped by areas selected from an HBP atlas. This is a SGA2 component that we started to develop ahead of the workplan motivated by CDP3. It has reached the prototype stage in SGA1 and is embedded as a visual tool to the interactive atlas viewer (89-2) using its novel plugin architecture, to co-design the viewer and showcase its extensibility.	
Latest Release	0.6	April 10, 218
TRL	TRL 4	Prototype Component
Location	data hosted by other non-HBP 3rd party	
Format	NA	

Curation Status	NA	
Validation - QC	Pass	Manual testing passed (BHATTACHARYA, Haimasree)
Validation – Users	Yes	The software is deployed as a test installation for initial verification by selected HBP researchers. The software was demonstrated to users inside and outside HBP in the context of the Glasgow Summit and several community events (e.g. as part of Katrin Amunts' pre-conference tutorial session at SfN 2017). A demo is planned for OHBM 2018 in Singapore.
Validation – Publications	Yes	Integration of transcriptomic and cytoarchitectonic data implicates a role for MAOA and TAC1 in the limbic-cortical network. S. Bludau, T. W. Mühleisen, S. B. Eickhoff, M. J. Hawrylycz, S. Cichon, K. Amunts. Brain Structure and Function, 2018, *in press* This is the publication for the methods itself. The implementation is independent as of new, but being tested by the authors of this paper.
Privacy Constraints	NA	
Sharing	NA	
License	GPFL v3 planned for release 1.0, currently copyright	
Component Access URL	https://github.com/haimasree/Jugex	

Technical documentation URL	https://github.com/haimasree/Jugex	
Usage documentation URL	https://github.com/haimasree/Jugex	
Component Dissemination Material URL	n/a	

3.4 Human connectivity matrix from atlas parcels

Component 340 is also described in the SP2 deliverable report for WP 2.5

Field Name	Field Content	Additional Information
ID	340	
Component Type	Data	
Contact	MANGIN, Jean-Francois	
Component Description	Diffusion MRI-based connectivity matrices computed for the 78 Archi subjects (group-based and individual) for 3 different parcellations (AAL, Freesurfer Desikan, BrainVISA constellation tuned to connectivity)	
Latest Release	1.0, June 2017	delivered to the SP4 Barcelona group (G. Deco)
TRL	TRL4	
Location	data hosted by SP providing dataset	
Format	gii, csv, npy	
Curation Status	Tier 1	
Validation - QC	Pass	RIVIERE, Denis / ZAMORA-LOPEZ, Gorka - Data exchange and QC for compatibility with SP4 objectives
Validation – Users	Yes	SP4 Barcelona group
Validation – Publications	No	
Privacy Constraints	Human research	
Sharing	partner	Group-based matrix public

License	Attribution-NonCommercial-ShareAlike 4.0 International (CC BY-NC-SA 4.0)	
Component Access URL	see URLs to unpublished components	
Technical Documentation	https://doi.org/10.1016/j.media.2016.01.003	
Usage Documentation	NA	
Component Dissemination Material URL	https://doi.org/10.1016/j.media.2016.01.003	Lefranc S et al. (2016) Groupwise connectivity-based parcellation of the whole human cortical surface using watershed-driven dimension reduction. Medical Image Analysis 30:11-29

3.5 Macroscopic model of spontaneous human brain activity

Field Name	Field Content	Additional Information
ID	999	Macroscopic model of spontaneous human brain activity (model)
Component Type	Model	
Contact	DECO, Gustavo	
Component Description	We construct a model to simulate whole brain activity at rest, at the scale of interconnected brain regions. The model is constrained using an empirically determined structural connectivity matrix (the network) via imaging and tractography. Local activity of the brain regions will be represented by models to simulate the activity of one brain region or neural population. There are many such population models available but each of these choices may lead to a different outcome of the network model. That is, the brain activity simulated by the model depends on how the model is built. Comparison of the model outcome to empirically observed resting-state fMRI will be crucial to determine the correctness of the choices taken to build the model	
Latest Release	V1	The model has been published using a generic, noisy form of the Hopf bifurcation (Stuart-Landau model) to simulate the local dynamics of the brain regions, see publication in "Validation - Users"

TRL	4	
Location	Model is published and model description available in the Model Catalog of the Collaboratory.	
Format	Matlab Code	
Curation Status	NA	
Validation - QC	Passed	The model could reproduce not only static functional connectivity empirically observed from fMRI, but it can also captures the statistics of the temporal fluctuations of the whole-brain dynamics at rest.
Validation – Users	NA	
Validation – Publications	Yes	Gustavo Deco1,2,3,4, Morten L. Kringelbach5,6, Viktor K. Jirsa7& Petra Ritter8,9 (2018) "The dynamics of resting uctuations in the brain: metastability and its dynamical cortical core" Scientific Reports 7:3095
Privacy Constraints	No privacy constraint	
Sharing	Public Authenticated	
License	NA	
Component Access URL	https://project-lifecycle.herokuapp.com/component/999/	
Technical documentation URL	NA	See publication

Usage documentation URL	NA	See publication
Component Dissemination Material URL	NA	

4. Conclusion and Outlook

CDP3 has pushed forward several strategic developments in SP5, bringing in data, tools, experience and requirements mostly from SP2, SP3, SP4. We contributed to many platform-centric cross SP events to improve the mutual understanding of atlas requirements for the NIP and HPAC Platforms. Thanks to these contributions, SGA1 delivers a good basis to make the HBP human atlas a unique and useful tool inside and outside HBP.

We decided to discontinue CDP3 in SGA2, because major aspects are now successfully implemented in the SGA2 Work Plan, and good communication channels between SPs are now in place. WP5.1, WP5.3 and WP5.4 will cover all aspects of continued infrastructure development for viewers and web-based interactive tools, whereas WP2.6 covers the co-design aspects with other Platforms, SP2/3, and modellers. CDP3 established a community inside HBP which meets several times a year. This community will be maintained from within WP2.7 by continuous organisation of workshops centred around the atlas. A notable future event in this context is the HBP school “The HBP Human Brain Atlas: Neuroscientific basis, tools and applications”, that will take place in autumn 2018 in Maastricht, Jülich and Düsseldorf.

During various CDP3 meetings, it became clear that SGA1 is too early to practically address the different factors of human variability in the atlas. The main reasons are a lack of data that covers all aspects of variability, and the limited resources in the SGA1 SP5 Work Plan. A decision was made during the CDP3 parallel session at the Florence summit, to postpone this product to a later stage of the HBP. However, a request has been made to SP12 to develop and circulate an initial table of required semantic attributes, that would be needed in the knowledge graph’s metadata schemes. We suggest to reintroduce this topic in the SGA3 Work Plan.