# *Multiscale human whole brain connectome data set (D1.3 – SGA3)*

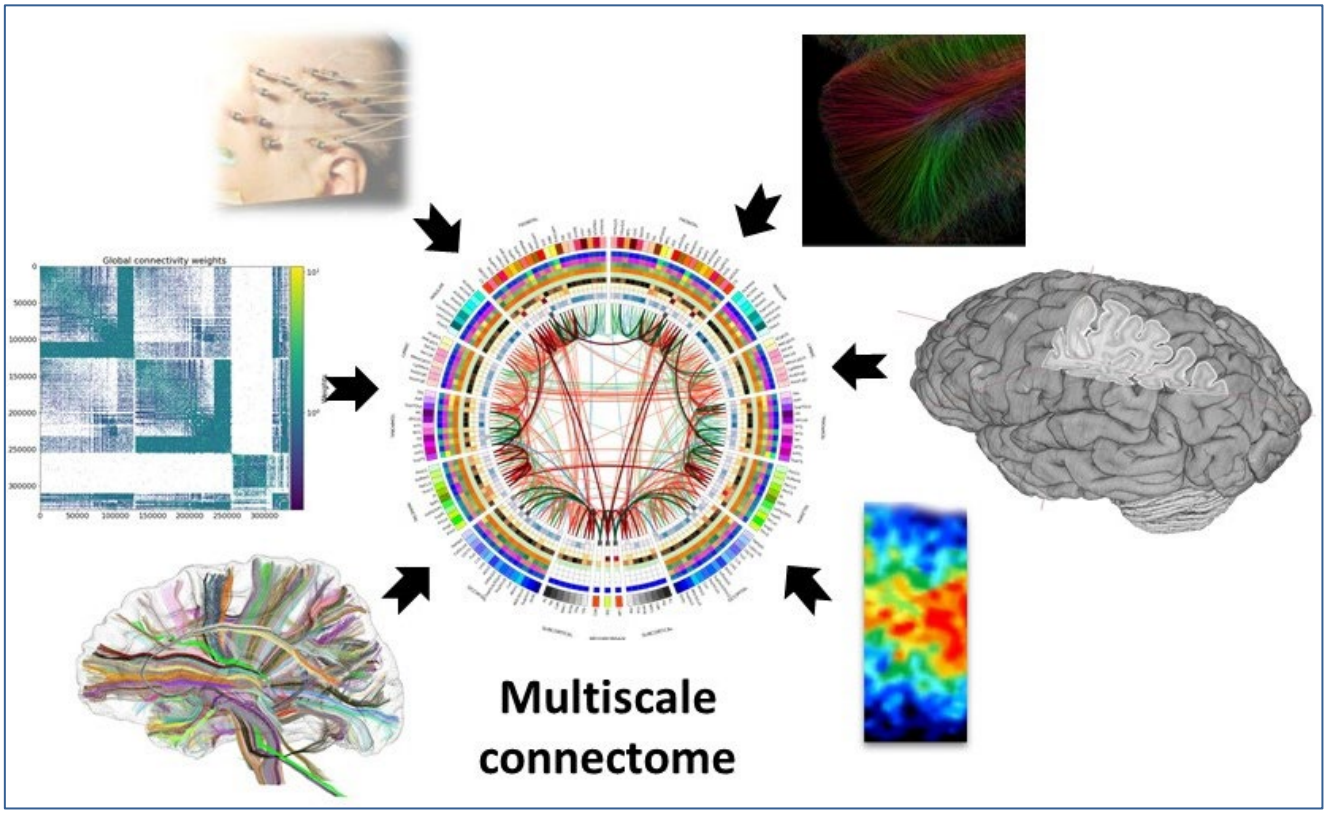


**Figure 1: Multiscale connectome**

**The multiscale connectome embeds macroscopic connectivity based on MRI of 1,000 subjects and iEEG from 300 patients, but also mesoscopic connectivity based on a worldwide unique post-mortem MRI scan at 200 micron resolution (5,000 hours at 11.7T) as well as microscopic cell and receptor densities from the multilevel human brain atlas.**

| Project Number: | 945539 | Project Title: | HBP SGA3 |
|---|---|---|---|

| | |
|---|---|
| Document Title: | Multiscale human whole brain connectome data set |
| Document Filename: | D1.3 (D9) SGA3 M30 SUBMITTED 230721.docx |
| Deliverable Number: | SGA3 D1.3 (D9) |
| Deliverable Type: | Data |
| Dissemination Level: | PU = Public |
| Planned Delivery Date: | SGA3 M30 / 30 Sep 2022 |
| Actual Delivery Date: | SGA3 M40 / 21 Jul 2023 |
| Author(s): | Jean-François MANGIN, CEA (P11) |
| Compiled by: | Jean-François MANGIN, CEA (P11) |
| Contributor(s): | Jean-François MANGIN, CEA (P11) contributed to Section 1,2, 3, 4<br>Timo DICKSCHEID, JUELICH (P20) contributed to Section 1, 2, 3, 4<br>Oleksandr POPOVYCH, JUELICH (P20) contributed to Section 2.1.1<br>Cyril POUPON, CEA (P11) contributed to Section 2.2<br>Clément LANGLET, CEA (P11) contributed to Section 2.1.1<br>Denis RIVIÈRE, CEA (P11) contributed to Section 2.1.1<br>Olivier DAVID, AMU (P78), contributed to Section 2.1.2<br>Maciej JEDYNAK, AMU (P78), contributed to Section 2.1.2 |
| WP QC Review: | Giovanna RAMOS QUEDA, AMU (P78), Pilar F. ROMERO, UPM (P68) |
| WP Leader / Deputy Leader Sign Off: | Viktor JIRSA, AMU (P78) |
| T7.4 QC Review: | Martin TELEFONT, Annemieke MICHELS EBRAINS (P1) |
| Description in GA: | Data set will be available comprising multiscale connectome and microscopic resolution 3D brain areas with realistic measurements of 3D cell densities and morphologies, densities and distributions of neurotransmitter receptors, nested connectomes and axonal conduction velocities, and functional brain imaging data, all directly linked to the probabilistic maps that interface to the macroscopic scale, fully annotated and curated, and organised in the same brain reference framework. |
| Abstract: | This deliverable describes the result of the integration of the atlas data across the different scale levels, in order to feed multiscale simulations. This integration provides a variety of structural and functional connectomes to be used by modellers. The connectomes are computed from diffusion and functional MRI or intracranial EEG recording. Connectivity data is provided for more than 1,000 subjects and from an outstanding post-mortem acquisition. A variety of features complement the connectivity information embedded in the connectomes (cell density, conduction axonal delays, synaptic constants and velocities, etc.) |
| Keywords: | *Brain connectivity, Connectome, parcellation, simulation of brain dynamics* |

| Target Users/Readers: | computational neuroscience community, computer scientists, neuroimaging community, neuroinformaticians |
|---|---|

## Table of Contents



## Table of Figures

# 1. Introduction

The key data for simulation of brain dynamics are organised in the form of a connectome, i.e. a connectivity matrix that describes the way nodes making up the brain model communicate. The connectome must further be enriched with information about node properties, i.e. the number of neurons they represent, and about the efficiency of the pairwise communications, i.e. the number of axons connecting two of these nodes. Depending on the scale at which the simulations are performed, the nature of these nodes changes, which strongly affects the models. At the macroscopic scale, the nodes correspond to brain areas, at the mesoscopic scale to populations of neurons, and at the microscopic scale to neurons themselves.

During the early phases of the HBP, modelling efforts were confined to a single scale level, and it was relatively easy to find adequate data in the human brain atlas. During SGA3, the first multi-scale simulations have been implemented, interfacing the single-scale models. In order to feed such simulations, it was imperative to integrate further the data from the atlas across the different scale levels, and thus to bring them together in a common reference system (see Figure 1). This was the objective of this Deliverable with respect to the human brain.

Choosing reference parcellations for human brain simulations nowadays still needs to balance different factors, in particular with regard to the cortex. On one hand, an increase in resolution should be reflected by a stronger emphasis on detailed and anatomically precisely defined parcellation schemes, such as provided by cytoarchitecture. On the other hand, today's simulation models utilise only moderate number of parcels and assume a balanced granularity of parcel sizes. Therefore, the connectome and human brain atlas are designed to support different parcellations, enabling to investigate a transition from purely macroscopic to microstructurally defined parcellations. It has therefore been decided to propose to the modellers alternative reference systems that they can compare. In the future, it is likely that iterations between modelling and data analysis will contribute to the emergence of a universal system. Such comparisons require experiments based on a large number of subjects. This is why macroscopic connectomes have been calculated for a thousand individuals of the database currently considered as the reference, that of the American Human Connectome Project (HCP). For each of the parcellation systems considered, a structural connectome was inferred from diffusion MRI data, and a functional connectome was calculated from functional MRI data. One of the criteria for guiding the modelers' choice of parcellation will be the ability of their models to simulate functional connectivity from structural connectivity.

Macroscopic connectomes calculated on MRI data acquired in vivo have a resolution slightly greater than one millimetre. In order to implement more resolved models, a world record has been achieved to get a diffusion MRI acquisition of mesoscopic resolution, i.e. 200 microns isotropic. This extraordinary mapping of the cerebral connectivity of a post-mortem human brain required 5,000 hours of acquisitions on an 11.7T MRI imager with a gradient of one Tesla per meter. In addition to the gain in resolution, it allows for a gain in reliability because it allows disentanglement of fibre crossings that disturb the interpretation of in vivo data. This outstanding image was used to generate connectomes for each of the parcellations used for the HCP cohort data. In addition, an ultra-high resolution voxel-based connectome at the 200 micron scale was integrated into the atlas to allow in the future the generation of additional connectomes tuned to alternative parcellations desired by EBRAINS users.

The modality used to infer the structural connectome is diffusion MRI, which exploits the random motion of water to probe the geometry of fibre bundles. This modality is not as reliable as invasive tracer-based techniques used with animals. Therefore, the atlas has been enriched with a complementary modality based on intracranial recording using electrodes implanted in patients (iEEG) in the context of epilepsy surgery. As the number of electrodes used for a patient is limited to the regions likely to be at the origin of the seizures, it was necessary to aggregate recordings made in 300 European patients in order to carry out a global mapping of the connectivity of the cortex. As for post-mortem diffusion imaging, this mapping was projected in all the usual parcellation systems. This macroscopic map provides outstanding information inaccessible with MRI, such as the speed of propagation of nerve impulses between two regions, or the preferential direction of transmission when the exchanges are not symmetrical.

Finally, information from the microscopic scale has been inferred from the 3D histological image of the big brain, such as the density of neurons in each region of the architectural parcellation. Other post-mortem acquisitions also allowed us to obtain the density of a large number of neuroreceptors in certain of these regions. The spatial heterogeneity of these different parameters is one of the keys to the realism of the brain dynamics models.

# 2. The multiscale connectome

## 2.1 Macroscopic connectome

### *2.1.1 MRI-based connectomes*

#### 2.1.1.1 Constellation-based nested connectomes

The macroscopic structural connectome of a brain is obtained for a parcellation of the grey matter, which includes the cell bodies of the neurons. The matrix is filled up by the connections between these parcels established by the bundles organising the neuron axons. For the past twenty years, it has been possible to access a macroscopic version of this connectome from diffusion MRI, which allows scientists to map the brain fibre bundles in vivo. It is now common to map millions of bundle trajectories for each brain. Hence, studies that require the comparison of thousands of brains require significant computational resources. A wide variety of parcellations can be used, depending on the questions investigated. In the context of WP1, two alternatives have been considered as priorities. The first one relies on cytoarchitecture, materialised through the Julich-Brain cytoarchitectonic atlas, and the second one, the Desikan-Killiany morphological atlas, stems from one of the leading software of the community (freesurfer). Both are adapted to the morphology of the cortex of each subject using a registration operation. But, since there is no absolute link between morphology and fibre organisation, this approach is suboptimal. Therefore, in order to improve the stability of the connectome across subjects, the Constellation algorithm developed during SGA1 was applied to subdivide the macroscopic regions of the Desikan-Killiany atlas and the remaining gap maps of the Julich-Brain using diffusion-based connectivity (see Figure 2 and Figure 3)

Thanks to the resources of Fenix, a team from Neurospin, CEA, has analysed the organisation of the fibres of 1,004 individuals of the American Human Connectome Project database, which provides outstanding diffusion MRI data (www.humanconnectome.org). This analysis, based on the Constellation software, has yielded a cortex parcellation where each parcel corresponds to a region whose connectivity to the rest of the brain is stable throughout the population (see Figure 2). Machine learning tools were used to adapt this average parcellation to the organisation of the fibres of each individual, to obtain very stable connectomes from one individual to another (see Figure 3). Each region of the average parcellation has a particular signature that corresponds to its connectivity with the rest of the brain. Competition between these signatures enables cortical surfaces to be subdivided according to individual connectivity. These individual parcellations were then used to create a functional connectome that describes probable communications between these parcels from functional MRI images. For each of the 1,004 individuals, the structural and functional connectomes have been made available to the modelling community [Langlet et al., 2022]. They will also give rise to heritability studies.

#### 2.1.1.2 Connectomes based on the Julich-Brain cytoarchitectonic atlas

Cytoarchitecture is a priori the best candidate to define an optimal reference parcellation, closely related to the architecture of the cortex. Unfortunately, cytoarchitectonic mapping is only possible in post-mortem brains by histology, and therefore not easy to adjust precisely to the specificities of individuals imaged in vivo. To address this problem, the Julich-Brain cytoarchitectonic atlas provides probabilistic maps capturing the variance of brain regions across at least ten postmortem brains. To enable an assessment between individual in-vivo-parcellations and probabilistic atlases, our strategy

is to provide alternative parcellations for modelling. Regarding the Julich-Brain cytoarchitectonic atlas, an additional difficulty results from the existence of “gap maps”, some associative regions of the cortex whose detailed mapping is not yet finalised because it is particularly difficult. While the size of these gap maps shrinks with each release of the atlas, these regions still occupy a larger surface area than the architectonic areas, which leads to an imbalance of the computed connectome that affects the simulation of brain dynamics. To overcome this problem, the Constellation algorithm mentioned in the previous chapter was used to subdivide these gaps maps in a way consistent with the connectivity. We selected the adequate number of clusters so that the mean area of the subregions would be close to 300mm2, two times the mean area of the already mapped Julich-Brain regions. We obtained an enhanced atlas called the Constellation-augmented Julich-Brain (see Figure 3). Finally, we projected this atlas to the 1,004 individual subjects of the HCP database and computed their reduced connectome for structural and functional connectivity, as for the previous parcellation [Langlet et al., 2022].

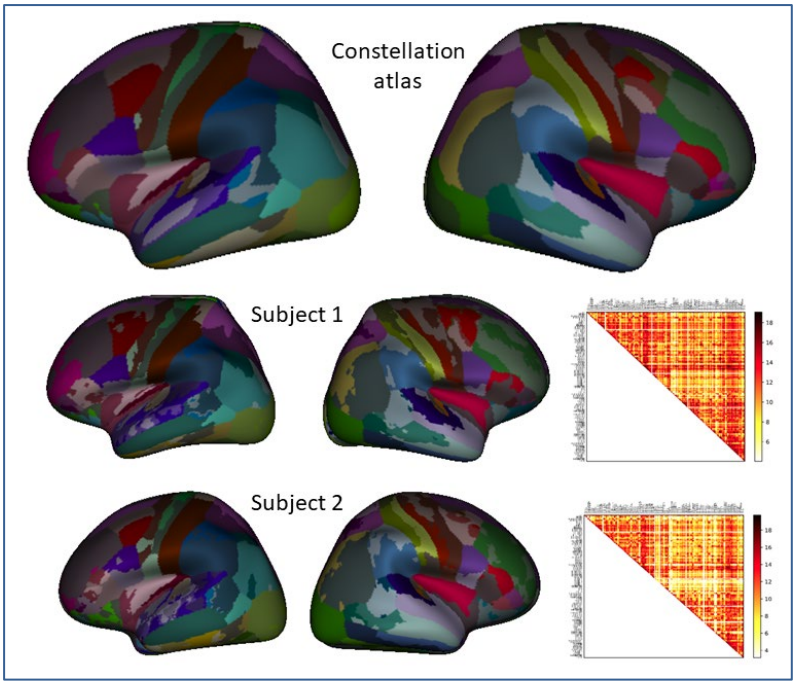


**Figure 2: Connectivity-based subdivisions of the Desikan-Killiany atlas**

**Connectivity-based subdivisions of the Desikan-Killiany atlas leading to the nested Constellation atlas with higher resolution endowed with high stability across subjects.**

### 2.1.1.3 Other parcellations

In addition to the parcellations provided for 1,004 subjects of the HCP dataset, structural and functional connectomes based on 19 different state-of-the-art cortical parcellations have been computed for 200 subjects of the HCP young adult dataset [Jung et al., 2022]. Furthermore, to provide the opportunity to test the reproducibility of any result relative to age, this has also been done for 261 older subjects of the 1000BRAINS cohort of healthy adults [Domhof et al., 2022].

It should be noted that a highly visible North American research program based on the Human Connectome Project attempts to use functional MRI and machine learning approaches to adapt to individuals an alternative parcellation supposed to match the architectonic parcellation [Glasser et al., Nature, 2016]. While this work is not consensual, it would be a very valuable additional alternative that will be integrated into EBRAINS as soon as it will be public, which is not the case yet.

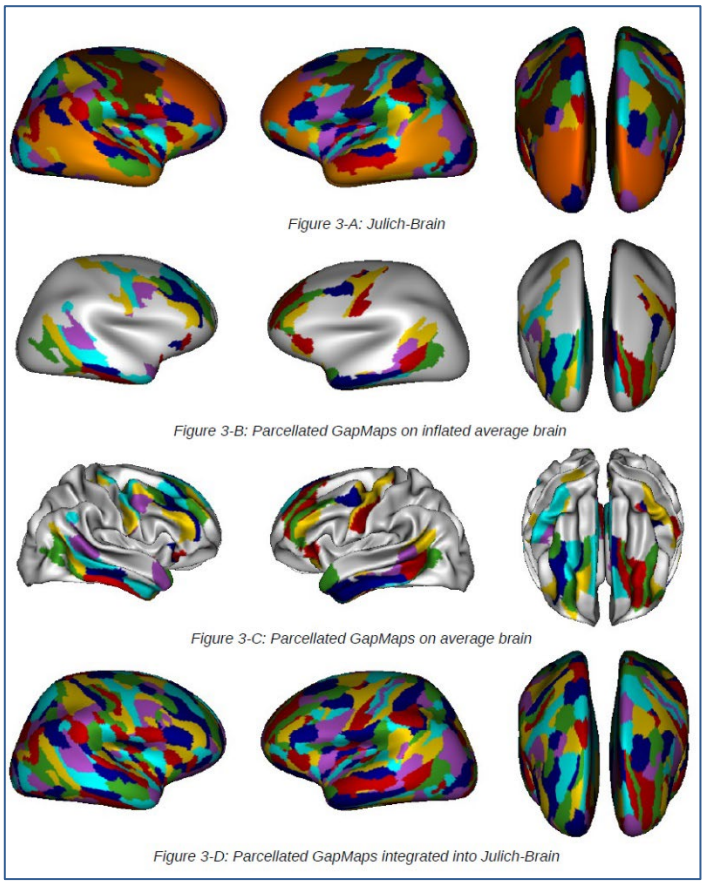


**Figure 3: Parcellation of GapMaps and Integration in Julich Brain**

### *2.1.2 iEEG-based connectomes*

The in vivo techniques of mapping connectivity mentioned above provide information about structural scaffold of the brain, they do not, however, inform how does it serve as an infrastructure for signal propagation in the brain. Similarly, studies involving functional MRI allow us to investigate this subject in a limited manner, because they rely on covariance of activity registered in individual parcels, rather than on explicit communication between them. An exemplary illustration of this limitation is directionality of connections that cannot be assessed explicitly with either of the above techniques. In order to furnish our multi-scale atlas with information related to signal propagation, we enrich it with anatomo-functional connectivity derived from intracranial-EEG recordings in human epileptic patients.

To this end we generated a human brain atlas from the F-TRACT (https://f-tract.eu) cohort, considering nearly 600 adult subjects. This atlas contains a collection of connectivity features, including conduction axonal delays, synaptic constants and velocities obtained with the dynamic causal modelling (DCM) method described in [Lemaréchal et al. BRAIN, 2021 – P3210] (see Figure 2). Furthermore, this atlas has been generated in four versions, yielded by application of two independent conditions. The first condition determines whether only early responses are considered. Applying it focuses the atlas onto direct connections. In the alternative version late responses are also considered. The second condition removes or not those data that might be related to epilepsy-originating abnormalities. We projected this atlas onto a number of parcellations, including the Julich parcellation, thereby allowing for referring it to other components of the multi-scale atlas (see Figure 4).

Recently the F-TRACT data were explored in a study conducted by an international collaboration led by prof. Andrew Zalesky from Australia. The results of this project are available in an open access bioRxiv preprint [Seguin et al., 2023 – P4022].

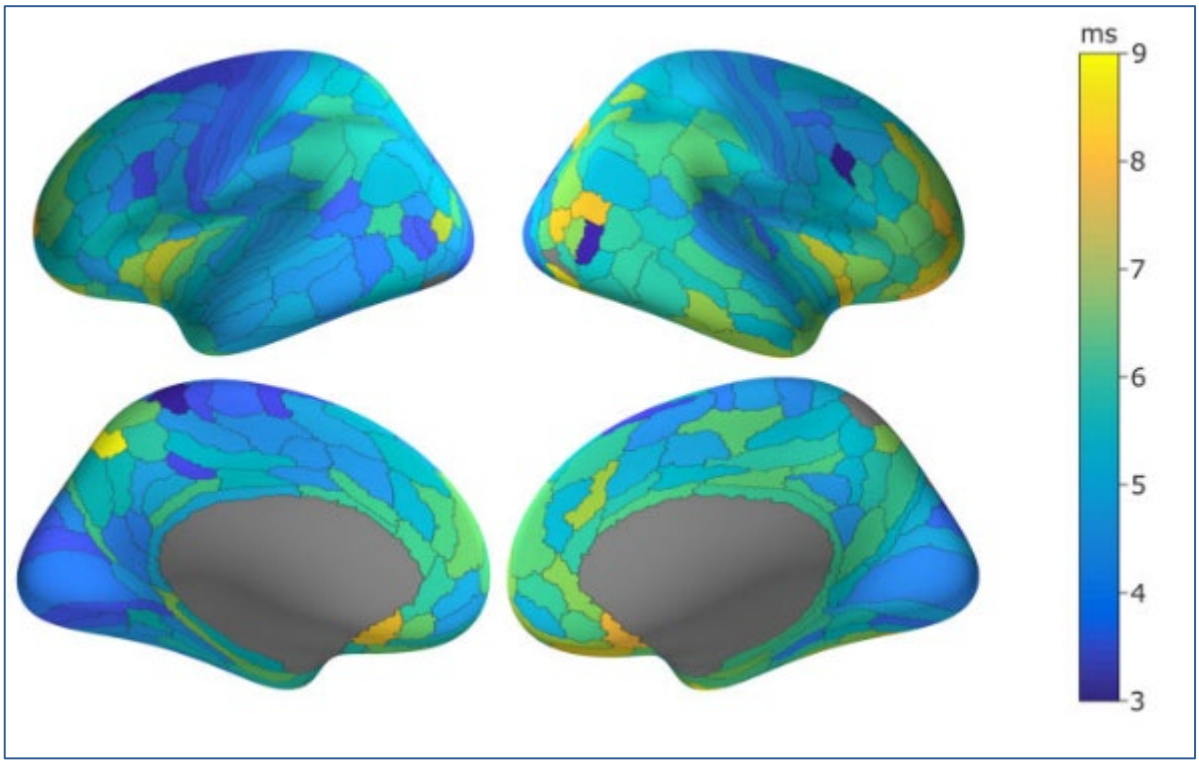


**Figure 4: A spatial map of excitatory time constant in the HCP parcellation**

**A spatial map of excitatory time constant in the HCP parcellation Obtained from the DCM method. Adapted from (Lemaréchal et al. BRAIN, 2021 – https://doi.org/10.1093/brain/awab362 – P3210)**

## 2.2 Mesoscopic connectome

A human brain specimen was scanned ex vivo using a preclinical ultra high field (UHF) magnetic resonance imaging (MRI) system at 11.7T to obtain a mesoscopic anatomical and diffusion MRI dataset. A 500um isotropic resolution block-face image was acquired on a 3T clinical MRI before cutting the brain to separate its two hemispheres. Each hemisphere was then cut into blocks of 20cm x 4.2cm x 4.2cm each. Up to 4 scans were performed over 4 overlapping sub-field of views (5.6cm x 4.2cm x 4.2cm) to cover each entire block, providing high resolution anatomical MRI data at 100um and 150um isotropic resolution, and multiple-shell diffusion MRI data at 200um isotropic resolution along 25/60/90 diffusion directions with b=1,500/4,500/8,000s/mm² (see Figure 5). In order to reconstruct the whole encephalon from the set of individual scans covering different 5.6cm x 4.2cm x 4.2cm field of views, a dedicated preprocessing pipeline was developed to perform various file conversions (Bruker native format, DICOM format, NIFTI format), to correct images from Rician noise corruption, to correct from intensity inhomogeneities, to compute diffeomorphic transformations for all the individual scans to the block-face frame, to perform spatial (for anatomy) and spatial+q-space (for diffusion) reinterpolation, and ultimately to create 3 datasets [Poupon et al., 2021] https://search.kg.ebrains.eu/instances/1be7069f-fd40-4f15-b3b3-80904d95e360:

- a high resolution 100um anatomical UHF MRI dataset
- a high resolution 150um anatomical UHF MRI dataset
- a high resolution 200um multiple-shell diffusion UHF MRI dataset

These 3 datasets are the input of a series of processing steps to deliver:

- a 3D map of segmented deep grey structures at the mesoscopic scale
- a 3D map of segmented laminar structures within the cortex at the mesoscopic scale
- a 3D map of long and short white matter fibre bundles at the mesoscopic scale

- a set of connectivity matrices between cortex areas and deep grey structures corresponding to the various cortex parcellations available from the HBP atlas

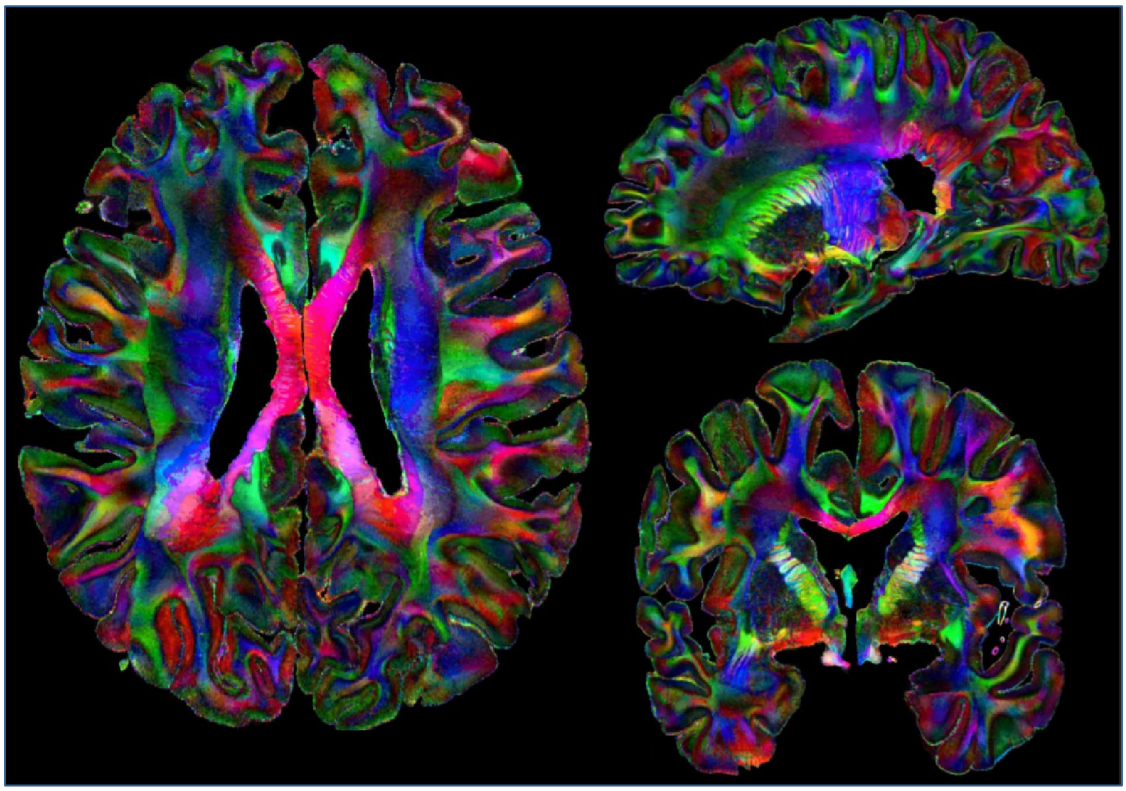

Figure 5: Chenonceau: a 200 micron isotropic connectivity map from 11.7T dMRI

## 2.3 Regional cell densities

The connectome nodes given in the different parcellations can be enriched with realistic measurements of cell densities. Different forms of cell density measures are available in EBRAINS and can be retrieved easily using the siibra-python library [Dickscheid et al., 2023] (Figure 6). A documented code example is included in the siibra-python documentation at https://siibra-python.readthedocs.io/en/latest/examples/03_data_features/007_comparative_assessment.html.

- **BigBrain cortical staining intensity profiles.** Cortical staining profiles of the BigBrain 3D volume have been released as an EBRAINS dataset [Wagstyl et al., 2022] and integrated as a regional data feature in the siibra toolsuite (Figure 6, centre row). Since the BigBrain dataset is a 3D reconstruction from cell body-stained histological sections, the intensities reflect cell densities.
- **Detailed layer-specific distributions of segmented cell bodies in selected cortical brain regions.** To obtain precise measures of neuronal cell distributions in the human brain, we sampled cortical image patches of 1 micron resolution from cell body-stained histological section in 12 distinct cytoarchitectonic regions of the BigBrain model. In total, 120 images were sampled. In each image, cortical layers were annotated by human experts and reviewed in a 4-eye principle. Individual instances of cell bodies were automatically identified using a recently established Deep Learning approach [Upschulte et al. 2022 – P3252]. These data have been published on EBRAINS as a separate dataset per brain region [Dickscheid et al., 2021] and integrated as a regional data feature in the siibra toolsuite (Figure 6, bottom row). At the time of writing, measurements in 30 more brain regions have been collected and will be accessible through the same mechanism.

In addition to these regional feature types, siibra-python allows to sample from the full resolution BigBrain volume at arbitrary 3D locations, allowing to measure average intensities at arbitrary cortical and subcortical locations. Regional sampling positions may, for example, be drawn from a brain parcellation given in MNI space. siibra-python then provides on-the-fly warping of coordinates between MNI and BigBrain space to retrieve the staining intensities. This mechanism is documented

as a code example in the siibra-python documentation (https://siibra-python.readthedocs.io/en/latest/examples/02_maps_and_templates/004_access_bigbrain.html#sphx-glr-examples-02-maps-and-templates-004-access-bigbrain-py).

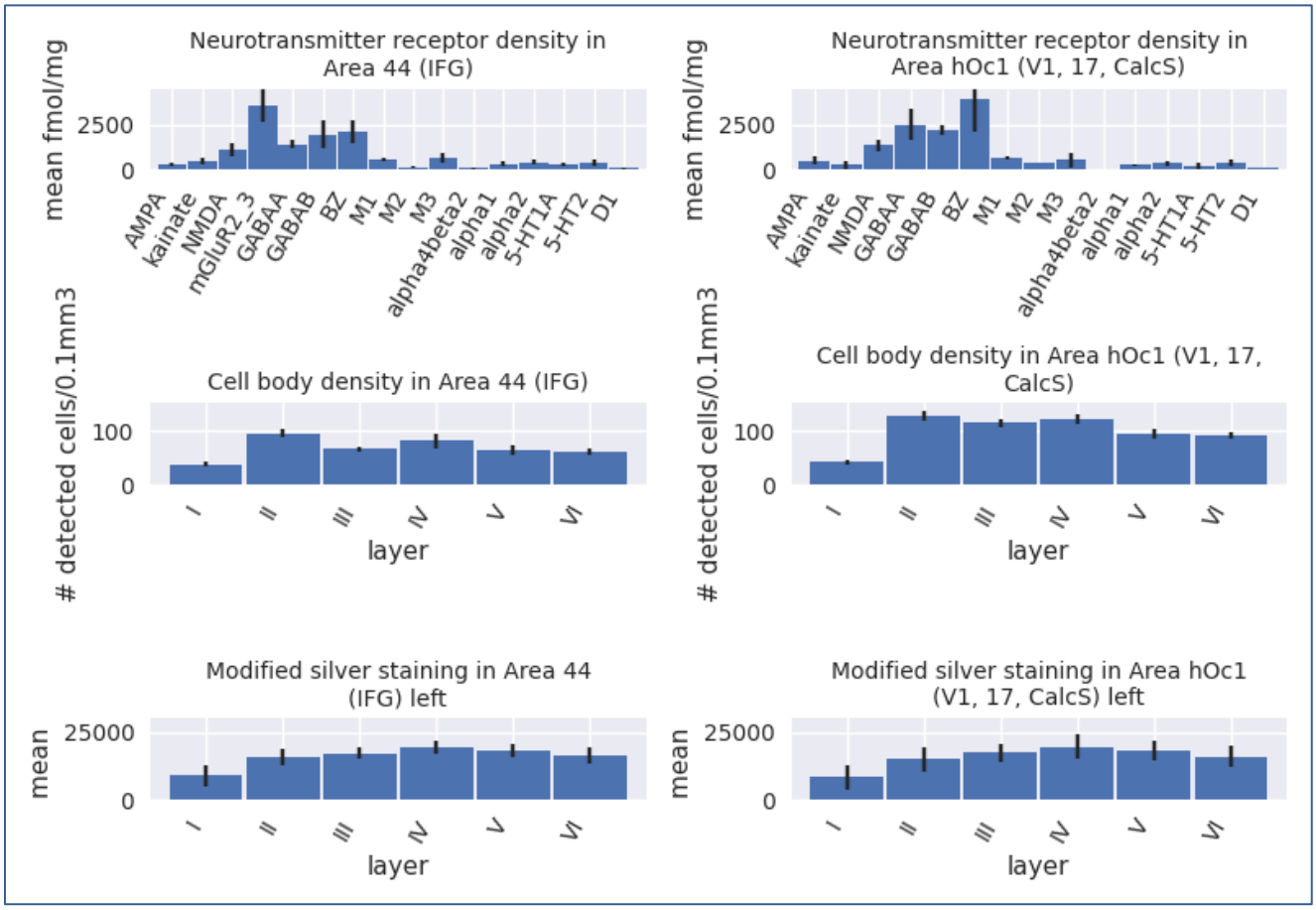


**Figure 6: Plots of BigBrain intensity profiles**

**Plots of BigBrain intensity profiles segmented cell densities and receptor densities delivered by siibra-python, as documented in the siibra-python documentation (https://siibra-python.readthedocs.io/en/latest/examples/03_data_features/007_comparative_assessment.html) (here from two exemplary brain regions 44 and hOc1.**

# 3. Looking Forward

The possibility of accessing a wide variety of connectomes in the same subjects will enable modellers to test and validate different alternatives. The results of these experiments will be used to select the most effective strategies, based on their ability to predict the functional dynamics derived from functional MRI data. Guidelines will be proposed to EBRAINS users, and further efforts to enrich connectomes will focus on the most effective approaches.

# 4. References

## 4.1 Datasets

Langlet, C., Rivière, D., & Mangin, J.-F. (2022). Nested parcellations connectome delivered for one large dataset using Constellation algorithm (v1.1) [Data set]. EBRAINS. https://doi.org/10.25493/5RCR-GS

Poupon, C., Destrieux, C., Beaujoin, J., Yebga Hot, R., & Popov, A. (2023). CHENONCEAU: a ultra high resolution post mortem anatomical and diffusion ultra-high field MRI atlas (v1) [Data set]. EBRAINS. https://search.kg.ebrains.eu/instances/1be7069f-fd40-4f15-b3b3-80904d95e360

Jung, K., Eickhoff, S. B., & Popovych, O. V. (2022). Parcellation-based structural and resting-state functional whole-brain connectomes of 1000BRAINS cohort (v1.1) [Data set]. EBRAINS. https://doi.org/10.25493/8XY5-BH7

Domhof, J. W. M., Jung, K., Eickhoff, S. B., & Popovych, O. V. (2022). Parcellation-based structural and resting-state functional brain connectomes of a healthy cohort (v1.1) [Data set]. EBRAINS. https://doi.org/10.25493/NVS8-XS5

Dickscheid, T., Bludau, S., Paquola, C., Schiffer, C., Upschulte, E., & Amunts, K. (2021):

- Layer-Specific Distributions of Segmented Cells in Area 4a (PreCG) of BigBrain [Data set]. EBRAINS. https://doi.org/10.25493/PV5Q-SFR
- Layer-Specific Distributions of Segmented Cells in Area 7P (SPL) of BigBrain [Data set]. EBRAINS. https://doi.org/10.25493/35K1-BTX
- Layer-Specific Distributions of Segmented Cells in Area 44 (IFG) of BigBrain [Data set]. EBRAINS. https://doi.org/10.25493/THE9-VQU
- Layer-Specific Distributions of Segmented Cells in Area FG1 (FusG) of BigBrain [Data set]. EBRAINS. https://doi.org/10.25493/E1FY-2C4
- Layer-Specific Distributions of Segmented Cells in Area FG3 (FusG) of BigBrain [Data set]. EBRAINS. https://doi.org/10.25493/DA0M-GM
- Layer-Specific Distributions of Segmented Cells in Area FG4 (FusG) of BigBrain [Data set]. EBRAINS. https://doi.org/10.25493/YVWP-9AQ
- Layer-Specific Distributions of Segmented Cells in Area FP1 (Fpole) of BigBrain [Data set]. EBRAINS. https://doi.org/10.25493/YFG8-3R7
- Layer-Specific Distributions of Segmented Cells in Area HOc1 (V1, 17, CalcS) of BigBrain [Data set]. EBRAINS. https://doi.org/10.25493/EVPC-MVH
- Layer-Specific Distributions of Segmented Cells in Area HOc2 (V2, 18) of BigBrain [Data set]. EBRAINS. https://doi.org/10.25493/TMFG-6FQ
- Layer-Specific Distributions of Segmented Cells in Area HOc3d (Cuneus) of BigBrain [Data set]. EBRAINS. https://doi.org/10.25493/F781-V5J
- Layer-Specific Distributions of Segmented Cells in Area HOc4d (Cuneus) of BigBrain [Data set]. EBRAINS. https://doi.org/10.25493/ZXQX-JKP
- Layer-Specific Distributions of Segmented Cells in Area HOc5 (LOC) of BigBrain [Data set]. EBRAINS. https://doi.org/10.25493/J4HZ-14X

Jedynak M and David O., iEEG atlases:

https://search.kg.ebrains.eu/?category=Dataset&q=seeg#f37c9d90-3e3e-4b57-81c0-59e4cc681b63

https://search.kg.ebrains.eu/?category=Dataset&q=seeg#72090f52-b539-4b3a-ac28-7c2ec0270940

https://search.kg.ebrains.eu/?category=Dataset&q=seeg#be548003-bfa4-4623-98aa-71b486f07ec4

https://search.kg.ebrains.eu/?category=Dataset&q=seeg#1570d4e5-8cc5-44b2-bfaa-f91274fe0bf3

Wagstyl, K., Larocque, S., Cucurull, G., Lepage, C., Cohen, J. P., Bludau, S., Palomero-Gallagher, N., Lewis, L. B., Funck, T., Spitzer, H., Dickscheid, T., Fletcher, P. C., Romero, A., Zilles, K., Amunts, K., Bengio, Y., & Evans, A. C. (2022). Cortical intensity profiles sampled across BigBrain isocortex (v1.0) [Data set]. EBRAINS. https://doi.org/10.25493/18ED-DS3

## 4.2 Software

Dickscheid, T., Xiayun Gui, Simsek, A. N., Marcenko, V., Köhnen, L., Bludau, S. & Amunts, K. siibra-python - Software interface for interacting with brain atlases. (2023). doi:10.5281/ZENODO.7885728

## 4.3 Publications

**P4022** - Caio Seguin, Maciej Jedynak, Olivier David, Sina Mansour L, Olaf Sporns, et al.. Communication dynamics in the human connectome shape the cortex-wide propagation of direct electrical stimulation. (2023) BioRxiv 2022.07.05.498875; https://doi.org/10.1101/2022.07.05.498875

Glasser, M. F., Coalson, T. S., Robinson, E. C., Hacker, C. D., Harwell, J., Yacoub, E., ... & Van Essen, D. C. (2016). A multi-modal parcellation of human cerebral cortex. Nature, 536(7615), 171-178.

**P3210 -** Lemaréchal, J.-D. et al. A brain atlas of axonal and synaptic delays based on modelling of cortico-cortical evoked potentials. Brain 145, 1653–1667 (2021). https://doi.org/10.1093/brain/awab362

**P3252** - Upschulte, Eric, Stefan Harmeling, Katrin Amunts, und Timo Dickscheid. „Contour Proposal Networks for Biomedical Instance Segmentation“. Medical Image Analysis 77 (April 2022): 102371. https://doi.org/10.1016/j.media.2022.102371.