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Abstract:	This report describes the goals of HBP Subproject 2 “Strategic Human Brain Data,” and its role in the HBP. It outlines SP2’s considerable progress and main achievements, and defines plans for the next six months. Because of its role in the HBP, SP2’s collaboration with other SPs and with Partners outside the HBP is central to all its activities.		
Keywords:	Strategic Human Brain Data, Human Brain Atlas, multi-level organisation of the brain, <i>post mortem</i> and <i>in vivo</i> human brain data		



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## 1. Strategic Human Brain Data (SP2): Summary

### 1.1 The Human Brain Project (HBP)

The Human Brain Project (HBP) is a major international scientific research project, involving over 100 academic and corporate entities in more than 20 countries. Funded by the European Commission (EC), the ten-year, EUR 1 billion Project was launched in 2013 with the goal "to build a completely new ICT infrastructure for neuroscience, and for brain-related research in medicine and computing, catalysing a global collaborative effort to understand the human brain and its diseases and ultimately to emulate its computational capabilities."

The fields of neuroscience, medicine and information technology each have important roles to play in addressing this challenge, but the knowledge and data that each is generating have been very fragmented. The HBP is driving integration of these different contributions.

During the Ramp-Up Phase, the HBP will collect strategic data, develop theoretical frameworks, and perform technical work necessary for the development of six Information and Communication Technology (ICT) Platforms during the Operational Phase. The ICT Platforms, offering services to neuroscientists, clinical researchers and technology developers, comprise Neuroinformatics (a data repository, including Brain Atlases and analysis tools); Brain Simulation (building ICT models and multi-scale simulations of brains and brain components); Medical Informatics (bringing together information on brain diseases); Neuromorphic Computing (ICT which mimics the functioning of the brain); and Neurorobotics (allowing testing of brain models and simulations in virtual environments). A High Performance Computing Platform will support these Platforms.

### 1.2 The Role of Strategic Human Brain Data in the HBP

Subproject 2 (SP2) creates knowledge, provides an understanding and generates strategic multi-level data about the human brain that is necessary to understand its multi-level organisation, and to emulate its computing capabilities. These efforts parallel those of the HBP's Strategic Mouse Brain Data Subproject (SP1). SP2 analyses the relationships between different types of data characterising brain organisation, and selects those that are strategically relevant for building models.

We expect to observe significant differences with respect to the mouse data, in particular concerning large cognitive systems, e.g. the circuits responsible for language, symbolic representation and number processing; the architecture of fibres of both grey and white matter; and patterns of cortical segregation. Other levels of organisation—e.g., cellular, sub-cellular and molecular—are expected to be more similar. The relationship of the structural organisation of the human brain with the principle governing cognitive processes will be addressed together with SP3, Cognitive Architecture, in order to identify the principles of mental processes and behaviour in human beings and their anatomical substrates.

Strategic human brain data from SP2, strategic mouse brain data from SP1, and data on cognitive architectures from SP3 will drive the development of, and benefit from, the Neuroinformatics Subproject (SP5). Results of this collaboration will reach the neuroscience community directly via the HBP Brain Atlas. SP2 researchers will inspire the development of hardware to analyse and visualise large amounts of data in SP7, and the development of new medical diagnostic tools and therapies in SP8.

In SP2, we will derive general principles describing the structural organisation of the human brain, allowing predictive reconstruction of human brain models. To reach this goal in the Operational Phase, the aim in the Ramp Up-Phase is to develop the workflows required to generate, analyse and



share these data. We will also ensure that the methods used and data generated meet the highest possible quality standards and HBP requirements.

## 1.3 Purpose of this Document

The report will provide a detailed account of the implementation and validation of methods for mapping the Human Brain, show how they are embedded in the activities of other Subprojects, and demonstrate their relevance for the HBP as a whole.

## 1.4 Structure of this Document

This document is divided into four chapters. The first chapter provides an overview of SP2, highlighting its overall goals, progress, achievements, and collaboration with other SPs and external Partners. This chapter also outlines SP2's plans for the next six months. The subsequent two chapters describe scientific work at the Work Package and Task levels, looking at overall goals, progress, main achievements, interactions with other SPs and external Partners, and plans for the next six months. These chapters include figures and graphs to illustrate the work achieved so far. The last chapter summarises activities for coordinating the Subproject. Finally, the Annexes present information about meetings within SP2, with others SPs and with external Partners, as well as summarising the status of SP2 Milestones (MS), and the Subproject's Scientific Key Performance Indicators (SKPI).

## 1.5 SP2: Overall Goals

Subproject 2 is contributing to a better understanding of the human brain as a highly important, basic question of science, and in terms of providing data for human brain modelling and simulation. Knowledge generated by SP2 will complement existing data, and will represent a relatively small, but relevant fraction of the data required to model the human brain. For example, our knowledge of the connectivity structure of the human brain at the microscopic level is highly limited, which makes it difficult or sometimes impossible to interpret diffusion-based data from analyses of the living human brain at the microscopic scale. At the same time, the volume of the human brain's white matter is more than 50,000 times that of the mouse brain, while the volumes of the whole brains differ only by a factor of 7,500.

In addition, data on the distribution of neurons in the cerebral cortex in the different cortical areas are still limited, and cortical segregation differs significantly between human and mouse brain. Nevertheless, such data are needed to understand the constraints of applying data from the mouse brain to human brain simulation. Another example concerns the morphology of human neurons, which is different from that of mouse neurons. This difference has implications for the physiological properties of neurons and small circuits, and for models. Understanding these scaling rules and differences in complexity is a necessary prerequisite to creating a human brain model, which begins with data obtained from the mouse brain.

For technical, practical and ethical reasons, it is harder to collect data from the human brain than from rodents. Some methods, e.g. retrograde tracing, electron microscopic and optogenetic techniques, cannot be applied to the human brain for technical reasons. Other factors causing practical difficulties include the sheer size of the human brain, the complex folding of the human cerebral cortex, and the impossibility of assembling the large samples that would be needed to account for inter-subject variability, which is higher than it is in mice. Finally, ethical concerns have led to the definition of regulatory standards for the acquisition and processing of brains from human donors, and for imaging experiments on the living human brain, that are generally far more restrictive than those governing experiments on animal brains. As a result, our knowledge of the neurobiological basis of human brain organisation is incomplete. Mouse brain data can be used to generate hypotheses



about the organisation of the human brain, but adequate human data remains critically important for human brain modelling in the Operational Phase of the HBP.

SP2 will combine data from *post mortem* studies with data from non-invasive imaging studies of the living human brain as a bridge to cognitive architectures (SP3). Integrating insights from SP3 will make it possible to derive general cognitive system principles at the level of large networks encompassing different cortical areas. These data will play a critical role in developing the human brain models and modelling tools that the Brain Simulation Platform (SP6) will make available in the Operational Phase, by contributing and strengthening the top-down perspective of modelling.

To achieve this, the project identified the following Milestones (MS) for Month 12:

- Perform a whole brain study of receptor concentrations of 20 receptor types (MS20; Task 2.1.5)
- Establish a method for a fibre tract Atlas based on PLI (MS21, Task 2.1.2)
- Complete a first data set on maturation of major fibre tracts of human infant brains (MS22, Task 2.1.6)
- Make tools for comparison of *post mortem* and *in vivo* imaging data accessible as part of the "Anatomy Toolbox" (MS34, Task 2.1.2)
- Define methods for making existing whole brain cytoarchitectonic maps available through the HBP Human Brain Atlas (MS35, Task 2.2.2)
- Define methods for making existing, quantitative whole human brain receptor expression maps available through the HBP Human Brain Atlas (MS36, Task 2.2.2)
- Define methods for providing diffusion-based data on major and U-shaped tracts in adult human brains (MS37, Task 2.1.2)
- Define methods for making existing whole human brain fibre tract scans available through the HBP Human Brain Atlas (MS38, Task 2.2.2)

## 1.6 SP2: Progress and Main Achievements

The procedures to define and measure progress in developing methods for human brain mapping, as described in D2.3.1, have been implemented successfully. All 8 Milestones and 22 scientific KPIs (SKPIs) for Month 12 have been reached. One Milestone (MS24) for Month 18 has also been partly completed (see Chapter 2.6.2.2). The five new Partners that joined SP2 since Month 6 have been fully integrated, and are contributing to the SP's goals. Progress in each Task is summarised below. For a detailed description, see please see Chapter 2.

### 1.6.1 Work Package 2.1 (*Multi-level organisation of the brain*)

#### 1.6.1.1 T2.1.1 Anatomical and functional organisation of the human brain (Thirion)

We have made three steps towards a statistically valid Brain Atlas inference procedure. To obtain an accurate and reproducible map of functional cortical segregation, we have performed pilot studies to find the most relevant resolution for multi-functional mapping. The pilot studies showed that Ward's clustering performed better than alternative methods with regard to reproducibility and accuracy. However, these two criteria diverge when it comes to the preferred models, with the need for reproducibility leading to more conservative solutions. This defers the practical decision to a higher-level alternative, namely, a trade-off between accuracy and stability.

To ensure that candidates' brain activity patterns do not simply reflect non-informative imaging artefacts, we have introduced a multivariate analysis method that can be evaluated in terms of



prediction accuracy, while providing a segmentation of the discriminative pattern that can be readily interpreted as a set of brain regions.

To overcome inter-subject variability in group-level inference, a novel analysis framework has been introduced. The framework estimates the amount of variance that is fit by a random effects subspace learned in other images. A principal component regression estimator outperforms other regression models and fits a significant proportion (10% to 25%) of the between-subject variability. This proves for the first time that the accumulation of contrasts in each individual can provide the basis for more sensitive group analyses.

### 1.6.1.2 T2.1.2 Connections between brain regions (Mangin, Poupon, Axer, Eickhoff)

Connections between brain regions are studied using both *in vivo* (e.g., diffusion imaging) and *post mortem* techniques (e.g. 3D Polarised Light Imaging, or 3D-PLI). The main parts of the 3D-PLI-analysis workflow have been implemented successfully. The workflow has been conceptualised as a high-throughput automated pipeline, using distributed processing across the JUDGE and JUROPA platforms at the Jülich Supercomputing Centre (JSC). Based on this workflow, 250 brain sections of the hippocampal target region were analysed and transferred into fibre orientation maps (FOMs) with 1.3 and 64 microns resolution in-plane.

Axon diameters and axon density in the human corpus callosum were also measured, based on diffusion imaging. The results were stable across 10 subjects, and were in accordance with *post mortem* measurements. This was possible at 7T using a series of diffusion times, which resolved the signature of trapped water molecules diffusing within axons. We continue our work on the robust delineation of white matter fibre tracts, and will add new computations.

### 1.6.1.3 T2.1.3 Numbers and distribution of neurons and glia in each brain region (Amunts, DeFelipe)

We have performed pilot studies to define conditions for a multimodal approach, combining immunohistochemical and receptorautoradiographic preparations in neighbouring sections of the same *post mortem* brain. A *post mortem* delay of 12 hours still allows for high-quality results, but a delay of 5-2 hours is superior. This approach will generate data such as average concentration of a certain receptor type per layer or neuron type, absolute amount of a neuron type per layer or area etc. In other words, this approach will generate the parameters necessary for modelling and simulation.

### 1.6.1.4 T2.1.4 Morphologies of selected human neurons (Mansvelder)

The coordination of sharing data on neuronal morphologies is well under way. Ten full dendritic morphologies have been uploaded to the SP5 Neuroinformatics Platform database. Also, over 20 full morphologies, including axonal reconstructions and full physiological characterisations, were shared with SP4 and SP6 for modelling and published in a joint publication [1].

### 1.6.1.5 T2.1.5 Distribution of selected receptors in the human brain (Zilles)

We have defined the whole-brain study of receptor concentrations of 20 receptor-binding sites. We have also established the binding protocols, and the measuring and visualisation pipeline. First estimates of transmitter receptors densities in a subset of cortical areas and subcortical nuclei have been made ahead of time. In addition to the language-related and primary sensory and motor regions of the human cerebral cortex, the studies have been extended to multimodal association regions of the parietal cortex.

We have demonstrated that the relationship between the densities of 15 different excitatory, inhibitory and modulatory receptors in eight language-related areas are highly similar, and differ considerably from those of 18 other brain regions not directly involved in language processing [2]. Thus, the fingerprints of all cortical areas underlying a large-scale cognitive domain such as language is a characteristic, functionally relevant feature of this network, and an important prerequisite for the underlying neuronal processes of language functions.



## 1.6.1.6 T2.1.6 The developing human brain (Dehaene)

We have solved a crucial methodical problem in studying brain tissue maturation: the geometrical distortions on diffusion images due to acquisition. To correct the distortions and align all multimodal images per infant, we estimated an elastic transformation between each diffusion image and each quantitative mapping to match with the anatomical scan. Visual inspections have proven this registration approach to be very effective. A classification algorithm has been applied on these registered data to segment brain tissue according to the degree of maturation. The resulting segmentations, based on seven classifications, show a progressive apparition of mature regions at the expense of immature regions. Non-compact and mature compact white matter can be well differentiated, so it could be shown that even at a very young age, some white matter is already mature. The same applies to grey matter [3].

## 1.6.1.7 T2.1.7 Homologies between humans and other primates (Vanduffel, Goebel)

The comparative human-monkey study has started both for the auditory and the visual cortex. For the analysis of the auditory cortex, methods for feature-based analysis have been adapted to the available monkey fMRI data. In a preliminary analysis of the monkey data, we obtained high-resolution tonotopic and tuning width topographic maps of the auditory cortex of monkeys, which responded to natural sounds. We compared these maps with maps in humans.

For the comparative analysis of the visual cortex, we collected preliminary data in humans using the same paradigm and stimuli that were previously used in monkeys. For the correct classification and localisation of visual areas, functional localisers in the form of retinotopic mapping (eccentricity and polar angle) stimuli, including monkey faces or walking bodies, were applied.

## 1.6.1.8 T2.1.8 Revealing activity and function of cortical layers (Goebel, Roelfsema)

We have selected and implemented an fMRI design to isolate feedforward, horizontal and feedback components in the BOLD response at 7T, using COGENT and MATLAB. We have debugged the scripts and tested the randomisation and timing of the stimuli. We have also analysed laminar data obtained from primary visual V1 of awake monkeys to examine the laminar distribution of suppression of the background responses in a figure-ground segregation task. This information will also be useful in interpreting the laminar BOLD MRI data. We also began designing the first architectures for the model of processing in the different layers of the visual cortex.

## 1.6.1.9 T2.1.9 Combining intra-cranial EEG and MRI in humans (Lachaux, Kahane)

We have defined and implemented the localisers, and set up a fast data analysis pipeline to process iEEG data. Thus, the main part of the project can start—namely, the continuous evolution and filling-in of the database to reach the planned numbers. Only the acquisition of micro-recordings has been slightly delayed by a pending ethical approval. The recording process will likely begin in January 2015. Meanwhile, work on improving the quality of data acquisition and finding the best micro-electrodes has proceeded.

## 1.6.2 Work Package 2.2 (*Standardised techniques, tools and data management*)

### 1.6.2.1 T2.2.1 Standardised techniques, tools and data management (Mangin)

After a complex stage of reverse engineering the DISCO prototype, we initiated a first tuning to infant brains, and the results demonstrate the success of the reverse engineering. In addition, we have successfully tuned the pipeline dedicated to the extraction of the cortical sulci on the *post mortem* brains from JUELICH. This represents an important step towards combined analysis of *post mortem* and *in vivo* data, and allows access to cytoarchitectonic maps in neuroimaging studies of the living human brain.



### 1.6.2.2 T2.2.2 Deposition of human brain data in the HBP Brain Atlas and Brainpedia (Amunts)

Deposition of human brain data is coordinated with SP5 (WP5.5.2). EPFL has already integrated the Big Brain data set into the development version of the Unified Portal and HBP Atlas viewer. Results have been presented, and functionalities of the Portal and viewers have been discussed between EPFL and JUELICH. Work has also begun in JUELICH to provide BigBrain surface meshes for integration into the HBP Atlas viewer (outer and inner cortical surfaces to delineate the cerebral cortex). The meshes are derived from pixelwise classifications at ~1mm resolution.

Cytoarchitectonic data (probabilistic areas and Maximum Probability Map, or MPM) from the [JuBrain Atlas](#) have been transformed to a second reference space ([MNI-ICBM152nlin2009casym](#)), in addition to the T1-weighted, single subject template of the MNI. Offering these data sets in different reference spaces will meet the needs of a larger user community in neuroimaging. EPFL and JUELICH have agreed on a target format to integrate these data into the 3D HBP Atlas. In this context, cytoarchitectonic probability maps were updated to generate a new MPM.

From MS36, first receptor data are available for numerous cytoarchitectonically defined cortical and subcortical brain regions (cholinergic M2 receptor, mean receptor densities averaged over all cortical layers or the complete extent of a nucleus, and layer-specific receptor densities as laminar profiles). These data are ready for implementation in the HBP Atlas. In collaboration with J. Bjaalie (SP5), we developed methods to register mouse and rat receptor data to the Waxholm space, and to achieve a 3D registration of the cholinergic M2 receptor (and later, of other receptors as well) in the rat brain. This data set will be ready for HBP release before M18.

### 1.6.2.3 T2.2.3 iEEG database organisation and multi-modal integration as a prototype for an international extension (Lachaux)

The main activities of this Task were to design prototypes that meet all the requirements for a convenient tool to add, navigate and visualise rich multi-modal data; to decide on the programming environment; and to eventually program and debug. Two options have been selected: Python and C# Unity. As the BrainVisa-environment is extremely convenient (this software is also used in T1.2.2), a BrainVisa-compatible module has been implemented to localise intracerebral electrodes (iEEG recordings) onto subjects' individual anatomy in 3D.

### 1.6.3 Work Package 2.3 (Scientific Coordination)

This Work Package focused on organising and fostering communication, reporting, and documentation of SP2's activities. This led to intense exchange and cooperation within SP2 (14 internal meetings), with other SPs (27 cross-SP meetings), and with external Partners (7 external meetings). These meetings were not limited to PIs of SP2, but included other researchers, doctoral students and the administrative staff. Many more informal exchanges took place regularly. SP2 submitted all reports requested for the respective period to the Editorial and Science and Technology Offices on time. The documentation of all activities was done by the SP Coordinator in EMDESK, thus ensuring a complete record of SP2's activities at the scientific and administrative levels.

## 1.7 SP2: Collaborations with other SPs and External Partners

The collaboration of SP2 with other SPs and external Partners has been intense and constructive (see Chapter 4.2.1 Communication and Annex D: Internal Meetings, Annex E: Cross-SP Meetings and Annex F: External Meetings). This is particularly important for SP2 due to its central role within HBP as a data provider for the HBP Brain Atlas in the Neuroinformatics Platform (SP5) and the Simulation Platform (SP6), and as a user of tools developed in SP7: High-Performance Computing. Other SPs are also related to SP2's activities, but to a smaller degree during the Ramp-Up Phase.



SP2's close and intense collaboration with SP5 is realised through WP2.2 in particular. Several rounds of discussion have led to the definition of use cases for uploading data to the HBP Human Brain Atlas. For example, 10 full dendritic morphologies have been uploaded to SP5, and the Big Brain data set has been included as a microstructural reference space (WP2.1). We have also considered the needs of the new Partners when gathering information from SP5 about existing HBP requirements for data formatting and programming languages, in order develop a multimodal data visualisation interface that is compatible with the global Project. Collaboration with SP5 also covers registration of mouse and rat receptor data to the Waxholm Space. The interaction with SP5 strongly benefits from the fact that SP2 Task Leaders Amunts and Zilles are also responsible for Tasks in SP5 (T5.5.2 and T5.1.6).

We have seen increased interaction with SP3, e.g., to receive functional localisers to be used at the end of Ramp-Up and Operational Phase and to implement cognitive tasks on symbols manipulation in infants.

Interactions with SP1 concern the development of methods to combine specific cell labelling with quantitative data on the molecular architecture, which will be submitted to the HBP Brain Atlas. For example, immunohistochemically stained cells were compared with autoradiographic data in collaboration with SP1.

We obtained new results on neuronal morphology that not only represent an important step toward understanding interspecies differences and their consequences for neuronal activity, but that were also used as a starting point for simulation. This collaboration between SP2 and SP6 resulted in a publication in one of the top neuroscience journals [1].

Collaboration with external Partners concerned in particular the Human Connectome Project (HCP). SP2 Partners have been able to use HCP protocols, e.g. for the U-fibre bundle Atlas inference in the Operational Phase. They also received retinotopic stimuli to map various parts of the cortex in collaboration with Marty Sereno. The Center for Magnetic Resonance Research (University of Minneapolis) provided relevant expertise for optimising the MR acquisition protocols and sequences for the collection of 7 Tesla fMRI human data in T2.1.7. Also, human neuron recording protocols concerning morphologies in particular were synchronised with research groups in the UK, Germany and South Africa.

Another important external Partner is the Allen Institute for Brain Science in Seattle, USA. Several high-level physical meetings in SP2 have been organised there to exchange ideas and data. For example, first registration fields have been calculated to transfer the MNI space to the individual *post mortem* brains, which were used by the Allen Institute to perform studies in gene expression. The registration quality has been further improved to achieve higher spatial accuracy. Such efforts are necessary to exchange data between the Allen Institute and the HBP, and to take advantage of the different research strategies, which supplement each other.

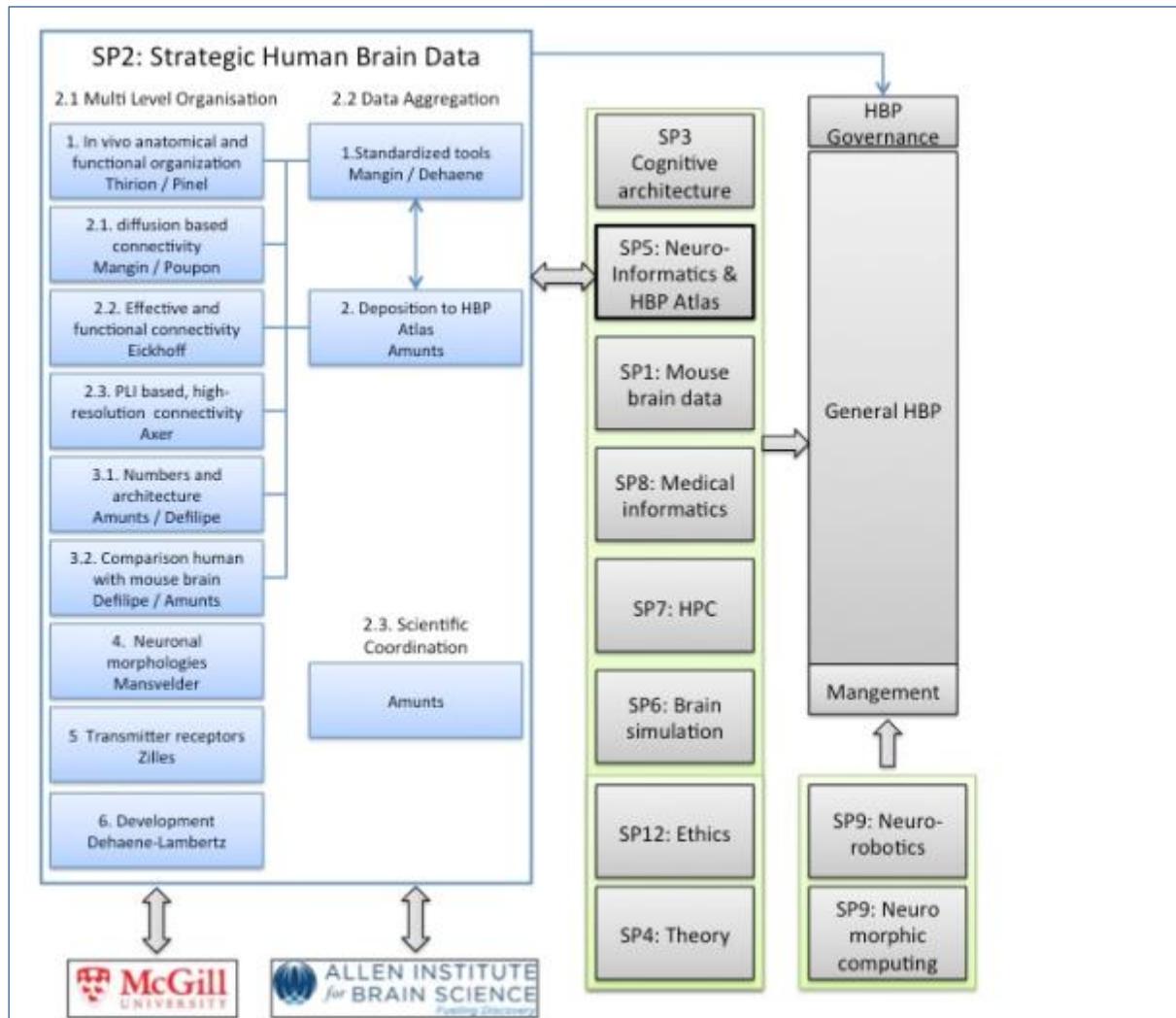


Figure 1: Interaction between SP2 and its Partner Subprojects (from D2.3.1)



## 1.8 SP2: The Next Six Months

In Month 18, the first package of “Strategic human data for the HBP Human Brain Atlas” (D2.3.3) will be delivered as planned. This Deliverable will include:

- Whole human brain volumes and dimensions
- Whole human brain cytoarchitectonic maps
- Absolute numbers and distributions of neurons and glia in human neocortical areas (primary sensory, motor, and at least five higher associative areas (MS23)
- Whole brain labelling of receptors of 20 receptor types
- First estimates of transmitter receptor densities in a subset of cortical areas (primary sensory, motor, and at least five higher associative areas) and subcortical nuclei (thalamus (MS24)
- Whole human brain fibre tract scans
- Diffusion-based data on major and U-shaped tracts in adult human brains; major tracts in infant brains.

A short report will describe each level of data and provide quantitative indicators of the completeness of the data compared to the targeted data set and a projected full data set to be generated by the research community. With MS25, the acquisition of axonal calibration protocol of 10 subjects and diffusion-based scans of major tracts in infants will be completed.

The new Partners that joined SP2 in Month 7 supplement the original work plan with four new Tasks and nine new Milestones. For example, they will deliver human 7 or 9.4T data for laminar fMRI in texture segregation, thus completing MS265. The goal is to identify the functional fingerprint of cortical layers in V1 during a neural phenomenon, which leads to a so-called Figure Ground Segregation (FGS) in vision.



## 2. WP2.1 Multi-level Organisation of the Brain

### 2.1 WP2.1: Overall Goals as Defined in D2.3.1

WP2.1's goals for the implementation and validation of methods for mapping the human brain were defined in the Month 6, D2.3.1. Goals were described in three areas: method development, data acquisition and data integration. The goals were also defined in terms of Milestones (MS), and partially accompanied by Scientific Key Performance Indicators (SKPIs). These are listed in Annex A: Milestones and Annex B: Scientific Key Performance Indicators (SKPIs) respectively.

In Work Package 2.1, the goals for Month 12 were defined in four Milestones:

1. MS20: Whole brain study of receptor concentrations of 20 receptor types defined (Task 2.1.5, Leader K. Zilles, JUELICH)
2. MS21: Method for fibre tract Atlas based on PLI established (Task 2.1.2 M. Axer, JUELICH)
3. MS22: First data set on maturation of major fibre tracts of human infant brains (Task 2.1.6, Leader G. Dehaene-Lambertz, CEA)
4. MS34: Tools for comparison of *post mortem* and *in vivo* imaging data made accessible as part of the "Anatomy toolbox" (Task 2.1.2, S. Eickhoff, UDUS)

All Milestones and SKPIs in WP2.1 have been completed (see Annex A: Milestones and Annex B: Scientific Key Performance Indicators (SKPIs)). In Chapter 2.6, K. Zilles also reports that he has already achieved parts of MS24 "First estimates of transmitter receptor densities in a subset of cortical areas (primary sensory, motor, and at least five higher associative areas) and subcortical nuclei (thalamus)," which is due in Month 18.

The goals are further described at the Task level in separate paragraphs in each of the following chapters. The new Partners in WP2.1, which joined the SP six months ago, are studying the homologies between humans and other primates; revealing the activity and function of cortical layers; and combining intra-cranial EEG and MRI in humans. Their goals are outlined in detail in Chapters 2.8.1, 2.9.1, and 2.10.1.

### 2.2 T2.1.1 Anatomical and Functional Organisation of the Human Brain (Task Leaders B. Thirion, INRIA; P. Pinel, CEA)

#### 2.2.1 T2.1.1: Goals

This Task focuses on the exhaustive anatomical and functional characterisation of individual brains at high resolution. Twelve human adults will be recruited to participate in multiple sessions of Magnetic Resonance Imaging (MRI) and magneto- or electro- encephalography scanning (about 10 per year over several years), thus serving as a resource for the human functional imaging community. The latter will hence be able to submit functional imaging protocols and have them run in increasingly well-described brains. A set of functional MRI localisers and more advanced cognitive protocols will be gathered to cover essential aspects of human brain functions, including retinotopy, visual perception/action, decision and reward circuitry, and human-specific processes such as episodic memory encoding and retrieval circuits, spatial, time, number and language areas. Using these data, functional areas will be delimited, and their inter-individual variability in relation to structural anatomy will be characterised. The acquired data will be related to the state-of-the-art in human brain mapping represented by image-based meta-analyses of the data from the community.



## 2.2.2 T2.1.1: Progress and Main Achievements

### 2.2.2.1 IRB and legal approval

The individual brain charting protocol was submitted to all relevant legal authorities for medical and legal approval, as well as authorisation for data diffusion. The latter is still pending, but we have all necessary authorisations to recruit subjects and acquire data.

### 2.2.2.2 Pilot acquisitions and parameter settings for fMRI acquisitions, setting of volume- and surface-based analysis

We have run a benchmark of different acquisition parameters to choose the best parameters and EPI distortion correction tools.

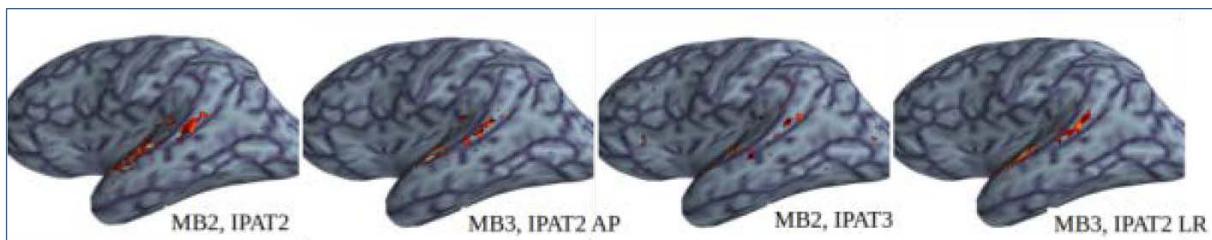


Figure 2:

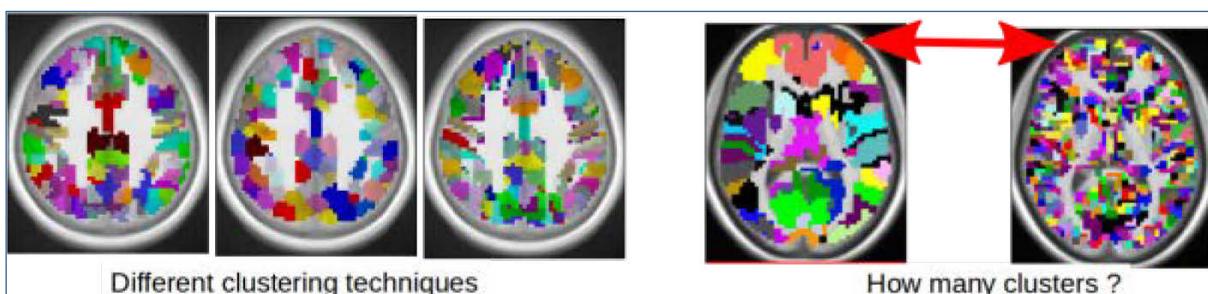
#### Replication of a sentence listening experiment in a single subject

The subject was involved in the same paradigm, while fMRI images were acquired with four different parameter sets. The results display both a high stability and different levels of sensitivity across sequences.

### 2.2.2.3 Meta-analysis

We performed some meta-analyses to relate our findings to those of the functional neuroimaging community outside the HBP:

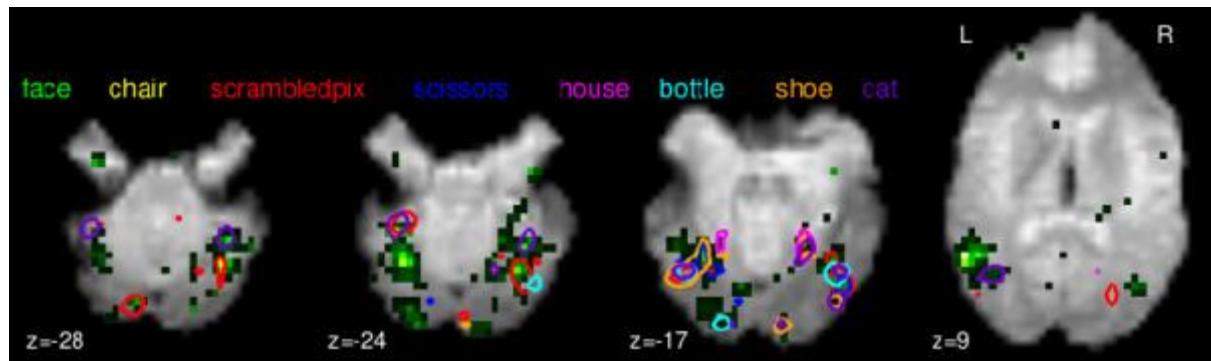
**Unsupervised meta-analysis: selecting the most relevant resolution for population multi-functional mapping.** To analyse and interpret neuroimaging data, it is often necessary to divide the brain into a number of regions, or parcels, with homogenous characteristics that are defined in the brain volume or on the cortical surface. While predefined brain atlases do not adapt to the signal in the individual subjects images, parcellation approaches use brain activity (e.g., activity found in some functional contrasts of interest) and clustering techniques to define regions with some degree of signal homogeneity. In this work, we addressed the question of which clustering technique is appropriate, and how to optimise the corresponding model. We used two main criteria: goodness of fit (accuracy), and reproducibility of the parcellation across bootstrap samples. We studied these criteria on both simulated and two task-based functional Magnetic Resonance Imaging (fMRI) data sets for the Ward, spectral and K-means clustering algorithms. We showed that in general, Ward's clustering performs better than alternative methods with regard to reproducibility and accuracy. We also showed that the two criteria diverge with respect to the preferred models (with reproducibility leading to more conservative solutions), thus deferring the practical decision to a higher-level alternative—namely, the choice of a trade-off between accuracy and stability. [4]



**Figure 3: Methodological challenges in the representation of multi-contrast functional MRI data sets**

What clustering method is best suited to compress the available data, in view of existing spatial accuracy? What complexity should be chosen for the clustering model?

**Supervised analysis: tailoring regularisers to solve reverse inference in the small sample setting.** Learning predictive models from brain imaging data, as in decoding cognitive states from fMRI, is typically an ill-posed problem as it entails estimating many more parameters than available sample points. This estimation problem thus requires regularisation. Total variation regularisation, combined with sparse models, has been shown to yield good predictive performance as well as stable and interpretable maps. However, the corresponding optimisation problem is very challenging: it is non-smooth, non-separable and ill conditioned. For the penalty to fully exercise its structuring effect on the maps, this optimisation problem must be solved to a good tolerance, resulting in a computational challenge. We have therefore explored a wide variety of solvers and exhibited their convergence properties on fMRI data. We introduced a variant of smooth solvers and showed that it is a promising approach in these settings. Our findings show that care must be taken in solving TV-I1 estimation in brain imaging, and in highlighting the successful strategies. [5]



**Figure 4: Tailoring regularisers to solve reverse inference in small sample setting**

Across several experimental conditions, TV-I1 regularisation provides a good mean to obtain discriminative models that also incorporate our priors on the actual organisation of these regions: sparse spatial support, organisation into clusters.

**Validation experiment: Measuring the information shared across functional protocols.** Inter-subject variability is a major hurdle for neuroimaging group-level inference, as it creates complex image patterns that are not captured by standard analysis models, and jeopardises the sensitivity of statistical procedures. A solution to this problem is to model random subjects effects by using the redundant information conveyed by multiple imaging contrasts. In this paper, we introduce a novel analysis framework in which we estimate the amount of variance that is fit by a random effects subspace learned on other images. We show that a principal component regression estimator outperforms other regression models, and that it fits a significant proportion (10% to 25%) of the between-subject variability. This proves for the first time that the accumulation of contrasts in each individual can provide the basis for more sensitive neuroimaging group analyses. [6]

### 2.2.3 T2.1.1 *Interactions with Tasks from other SPs and External Partners*

We increasingly interact with SP3, which will provide functional localisers to be used in the future of our Task (at the end of Ramp-Up Phase and the Operational Phase). We held two meetings with SP3 to define a common program for mapping two brain systems:

- High-resolution, multi-contrast mapping of the parietal cortex, including saccades and numerotopic mapping
- Mapping of the language system by manipulating the syntactic complexity of stimuli, and possibly their interaction with semantics.



We interacted with the Human Connectome Project Consortium (HCP) to make sure that we could reuse their protocol. In addition, we collaborated with Professor Martin Sereno from the HCP, a leading expert in the field of retinotopic mapping, in order to get the retinotopic stimuli used by their group to map occipital, parietal and some parts of the frontal cortex.

## **2.2.4 T2.1.1: Specified Plans for the Next 6 Months**

### **2.2.4.1 Selecting the IBC cohort and acquisitions of the first protocols ("archi protocol")**

Our objective is to perform 3 MRI acquisitions on a group of 12 subjects. The IBC (Individual Brain Charting) consists of acquisitions performed as part of the HBP on a unique set of 12 subjects that will be scanned under a very large number of experimental conditions. The archi protocol is a set of acquisitions on 80 subjects performed in 2010 by SP2 Partners C. Poupon, J.F. Mangin and P. Pinel to study connectivity, anatomy and function. It provides high quality data that are used to build proof-of-concepts of our future contributions. These data will also be shared with the HBP Consortium.

### **2.2.4.2 Conducting a discriminative meta-analysis**

We will systematically conduct classification analyses of the existing fMRI data sets. These classification analyses will result in a multi-label problem, in which each brain scan can be associated with several tags describing the experimental protocol presented to the subjects.

### **2.2.4.3 Revisiting tools for small-sample discriminative analysis of fMRI data sets**

First, we will benchmark the existing estimators on several problems to infer what the best performers are. Second, we will investigate extensions of the expensive, yet accurate, TV-L1 estimators to obtain sharper estimates.

## 2.3 T2.1.2 Connections between brain regions (Task Leaders J. Mangin, C. Poupon, CEA; M. Axer, JUELICH; S. Eickhoff, UDUS)

### 2.3.1 T2.1.2: Goals

Data on the major fibre tracts will be obtained using structural MRI, Diffusor Tensor Imaging (DTI) for living human brains, and high-resolution Polarised Light Imaging (3D-PLI) for *post mortem* brains.

### 2.3.2 T2.1.2: Progress and main achievements

For the first time, a 3D fibre model of an entire rat brain was generated, utilising fibre orientation maps (FOMs) obtained from 3D-PLI with a resolution of  $64 \times 64 \times 70 \mu\text{m}^3$ . This type of data set is well suited for atlas purposes. Consequently, we have started to adapt the developed methods for the high throughput of large (i.e., human) data sets. Thus, we achieved Milestone MS21 “Method for fibre tract atlas based on polarised light imaging.”

We successfully implemented and optimised the main parts of the 3D-PLI workflow in terms of automation, using distributed processing on the supercomputing platforms JUDGE and JUROPA at the Jülich Supercomputing Centre (JSC). UNICORE was employed as grid technology middleware to manage the complex workflow [7]. It includes image operations such as calculation of histograms, segmentation, and removal of artefacts. Based on this workflow, 250 human brain sections covering the hippocampal target region were analysed and transferred to FOMs with 1.3 and 64-micron resolution. Each FOM has a size of about 4 GB. In addition, the precise alignment of consecutive high-resolution FOMs by means of spline transformations was brought into focus.

We have successfully measured *in vivo* the axon diameters and the axon density in the human corpus callosum. The results were stable across 10 subjects and in accordance with *post mortem* measurements. This was achieved at 7T using a series of diffusion times resolving the signature of trapped water molecules diffusing within axons.

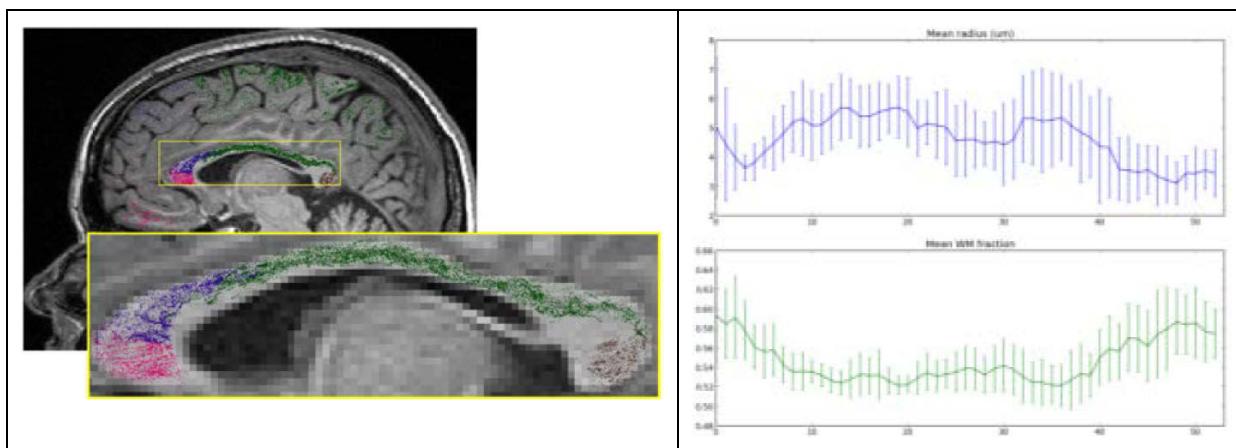
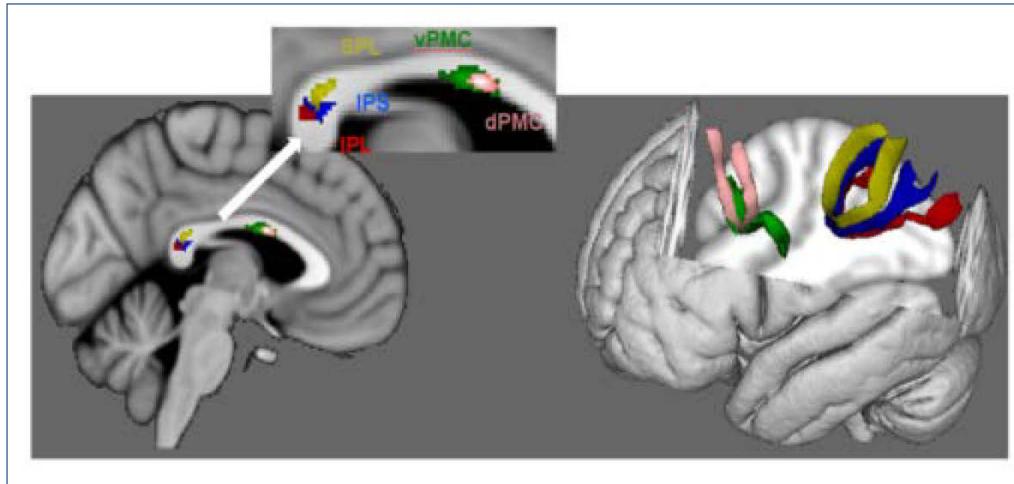


Figure 5: Axon diameters and density in human corpus callosum - 10 subjects at 7T (50mT/m)

Probing the diffusion process of water molecules trapped in axons with a series of diffusion time led to reproducible estimations of the microstructure of a fibre bundle (Lebois, A, ongoing PhD thesis).

In addition, we continued the robust delineation of white-matter fibre tracts between functionally defined regions, which required a change in the approach and new computations. Several projects were started to examine the relationship between different measures of function and structural connectivity.



**Figure 6: DWI-based probabilistic tractography to characterise the geometry of fibre pathways between cortical areas**

Many streamlines (~50,000) were generated for each subject. This defined a spatial probability distribution across subjects. Pathways represent the “core” of this distribution and they are spatially contiguous, but distinct (non-overlapping).

On 23 July 2014, the JUELICH/UDUS Partners made the SPM Anatomy Toolbox v2.0 freely available to the community. This release is a major improvement over previous versions, and includes better 3D reconstruction and spatial normalisation of *post-mortem* brains. It also includes accurate handling of partial volume effects, and ensures continuous, rather than discrete, representation of histological probabilities. These improvements required major rewriting of the software for the comparison of *post mortem* and *in vivo* data, which was performed and extensively tested in-house before release. The respective data are currently being integrated into the HBP Neuroinformatics Platform. Thus, we have achieved MS34 “Tools for comparison of *post mortem* and *in vivo* imaging data made accessible as part of the ‘Anatomy toolbox.’”

### 2.3.3 T2.1.2: *Interactions with Tasks from other SPs and external Partners*

A major challenge for establishing a high-resolution 3D fibre model of the human hippocampus is the development of image analysis methods for geometric alignment and 3D reconstruction. To date, existing approaches for non-rigid image registration do not fully exploit the information in histological images, and thus lack accuracy and robustness, which is a pre-requisite for subsequent fibre tractography. In order to address this issue, we cooperated with K. Rohr from the Biomedical Computer Vision (BMCV) Group at the University of Heidelberg, Germany, as an external Partner. To deal with the enormous size of generated 3D-PLI data, high-performance computing tools are required for both analysis and reconstruction. These requirements are being supported in close collaboration with SP7.

In addition, we have started to prepare a rat brain volume based on 3D-PLI fibre orientation maps at 64 microns isotropic voxel size, and to transfer this volume into the template Waxholm space in collaboration with J. Bjaalie (SP5). This project is meant to provide a first fibre rodent model developed with 3D-PLI tools, to be used for Atlasing development.

At Neurospin, CEA, experiments with a high-resolution, 1000-subject data set from the Human Connectome Project have begun in preparation for the next phase of the HBP, when this set could be used for the U-fibre bundle Atlas inference.



### 2.3.4 T2.1.2: Specified plans for the next six months

A formalin-fixed human temporal lobe was transferred this summer from JUELICH to CEA, Neurospin, where dedicated fine-tuning of high-field MR diffusion sequences will be performed in the coming months. Then, the *post mortem* sample will be sent back to Jülich and fed into the PLI protocol to obtain a joint PLI-DTI data set. These acquisitions will trigger our research program on cross-validation of both imaging modalities to prepare our analyses of the microstructure of white matter pathways. At the same time, Neurospin will initiate the recruitment of 10 subjects for the massive acquisition process planned for this purpose. Five sessions of acquisitions will be proposed to these subjects to obtain enough measurements to assess the microstructure.

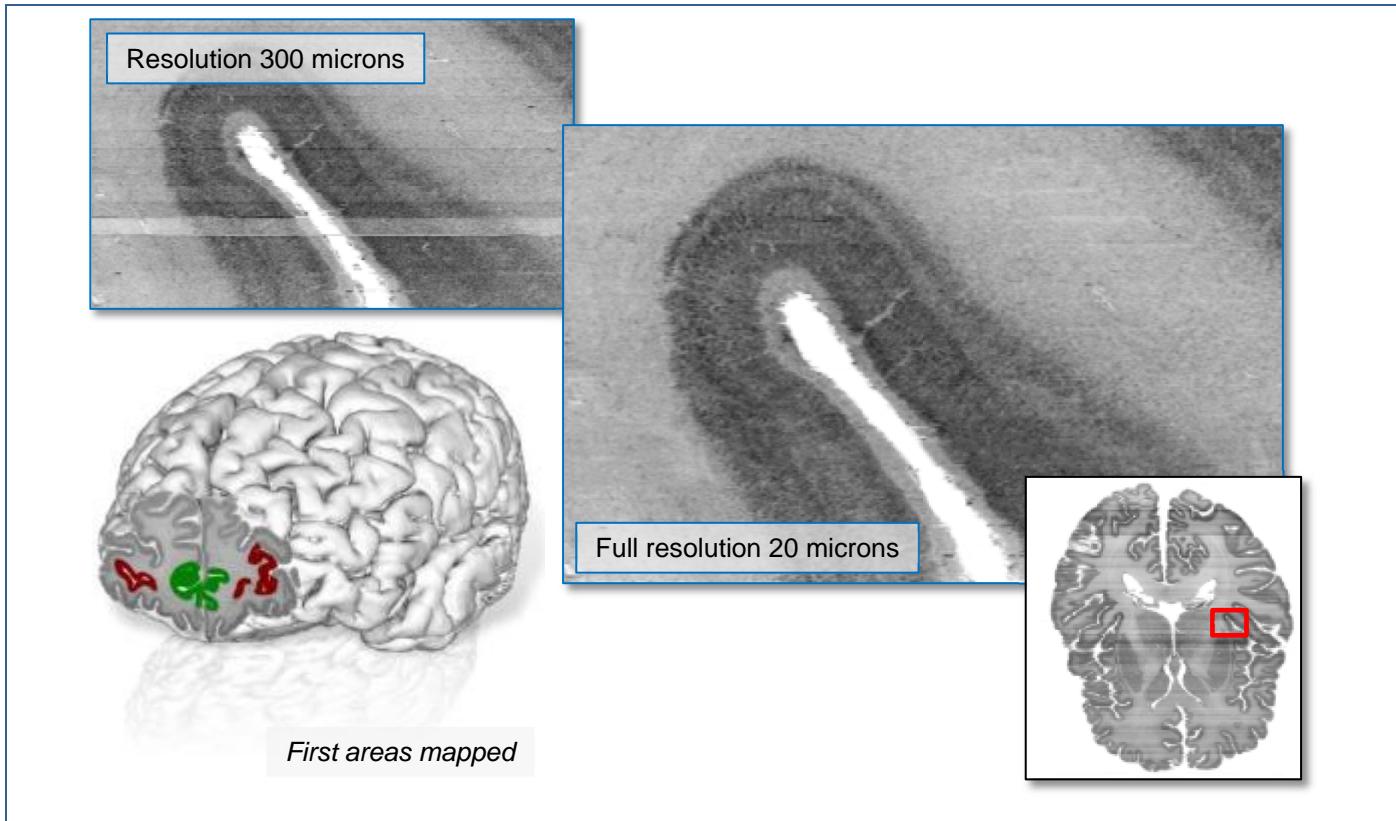
## 2.4 T2.1.3 Numbers and distribution of neurons and glia in each brain region (Task Leaders K. Amunts, UDUS; J. DeFelipe, UPM)

### 2.4.1 T2.1.3: Goals

This Task will generate cell body-stained histological sections covering the complete human brain. Individual sections will be 20 microns thick and will offer in-plane resolutions of 20 microns. Our aim is to reach a resolution of 1 micron. Complete series of sections will be supplemented by series with alternating sections labelled for cellular markers (neurons and glia) to determine the numbers and distributions of neurons and glia in brain regions. These data will help SP6 to populate brain models with neurons and glia. These data will be combined with information coming from quantitative receptor autoradiography, and other markers. This Task is also aiming at ultra-high resolution reference brains of cellular architecture, such as Big Brain, as a prerequisite to the topographically correct 3D mapping of different neuron types and glia.

### 2.4.2 T2.1.3: Progress and main achievements

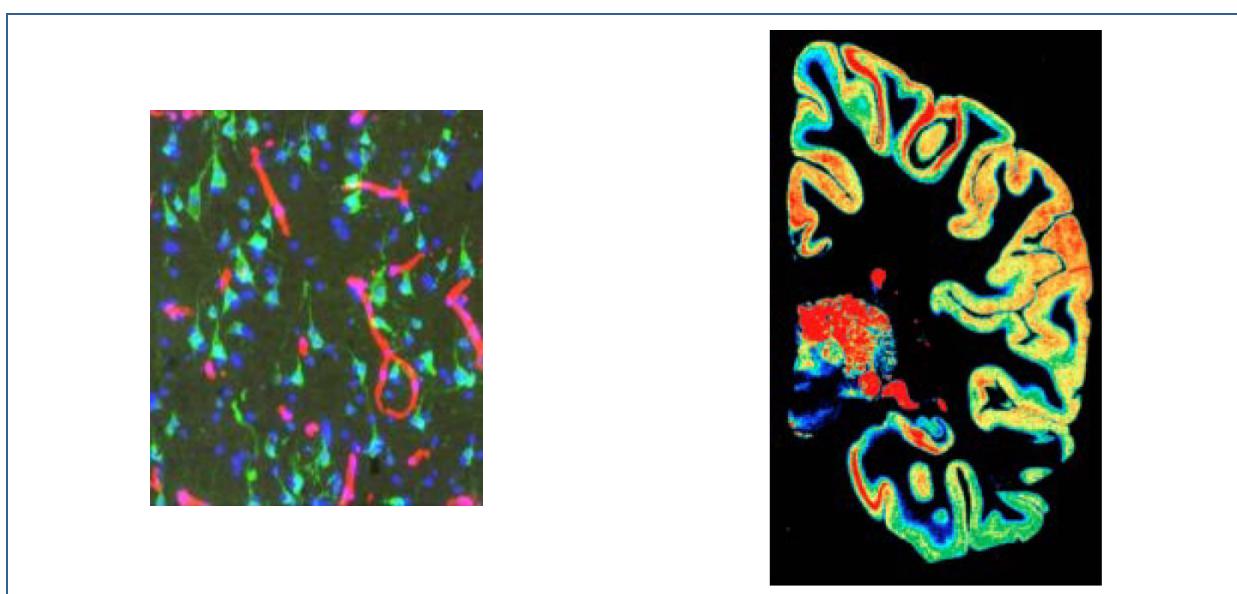
The work on the cellular organisation of the human brain is progressing. In addition to the first Big Brain data set, we have achieved a new high-resolution data set of another *post mortem* brain. The Big Brain data sets are going to be labelled - first tissue segmentations have been provided and areas mapped as prerequisites for cell counting.



**Figure 7: Second Big Brain Data**

This is a first 3D reconstruction at 20 microns - isotropic. First areas, including Fp1 and Fp2 of the frontal pole were labelled [8].

Frozen human brain sections have been delivered from JUELICH to UPM, where they were labelled with different immunomarkers (NeuN, DAPI, collagen-IV, parvalbumin) as a pilot test for cell counting preparations.



**Figure 8: Multi-immunolabelling (confocal stack, DeFelipe) and quantitative receptor autoradiography in neighbouring sections of a human brain (Amunts, Zilles)**



The confocal microscopy stack shows individual neurons within a small region of interest in the cerebral cortex (left).

The receptor autoradiogram shows a whole human brain hemisphere; the concentration in fmol/mg protein of the muscarinic M2 receptor is color-coded: red corresponds to high concentrations, blue tones to low ones.

We have tested the 3D segmentation algorithm generated in SP1's T1.2.3 to characterise the density and principle patterns of spatial distribution of neurons and glia (DAPI nuclei of NeuN-positive and NeuN-negative neurons in different human brain regions). This methodology will be used to examine possible correlations between the density of cells and variations in receptor maps generated in the laboratory of Katrin Amunts (UDUS, JUELICH). We have processed material from autopsy brains with different *post mortem* periods and fixation procedures to optimise and standardise procedures, and to establish how these factors might affect results from binding and immunocytochemical experiments. Furthermore, we have analysed the density of cells in brain sections immunostained for parvalbumin (a major type of GABAergic neuron) in different cortical regions from three individuals. These regions were the following Brodmann's cytoarchitectonic subdivisions: primary visual area 17; secondary motor area 6; associative lateral temporal areas 20 and 21; orbital frontal areas 11 and 12; dorsolateral frontal areas 9, 10 and 46; and anterior limbic cingulate areas 24 and 32 of each individual. This information will be integrated into the HBP Brain Atlas.

#### 2.4.3 T2.1.3: Interactions with Tasks from other SPs and external Partners

We collaborated with Prof. Alan Evans from the MNI in Montreal, who has been a Partner for many years in the Big Brain project. This collaboration enabled us to improve the quality of the 3D reconstruction of the Big Brain data set, and to label the different tissue compartments (e.g., grey and white matter, CSF). Collaboration between SP1 and SP2 has a direct impact on multimodal characterisation of data, and methods developed in SP1 for mouse brain tissue are being applied to human brain tissue. We collaborated with SP5 (T5.5.2) when EPFL made the Big Brain data available in the development version of the HBP Atlas viewer. We will integrate more cellular and receptor organisation data into the HBP Atlas in the near future.

#### 2.4.4 T2.1.3: Specified plans for the next six months

In the next six months, we will provide data on the absolute numbers and distributions of neurons and glia in a sample of neocortical areas (primary sensory, motor, and at least five higher associative areas). We will also generate first data on the relationship of such cellular measures to those of the molecular architecture. We plan to create a first high-resolution data set based on slices of *post mortem* brains, and parallel MR-imaging of the fixed brain. We will increase the number of structures labelled in the Big Brain data sets, and this work will be performed in cooperation with the international neuroscience community. To this end, a workshop is being planned for the beginning of 2015.

### 2.5 T2.1.4: Morphologies of selected human neurons (Task Leader H. Mansvelder, VU)

#### 2.5.1 T2.1.4: Goals

The goal of this Task is to coordinate data sharing with researchers worldwide, who are recording and reconstructing human neurons from brain parts excised during neurosurgery. This coordination will make it possible to standardise the methods used to reconstruct neurons, and to match human and mouse neurons based on their physiological properties. This standardisation and matching will maximise the value of reconstructed cells and help identify candidates for reconstruction (human cells that match well-established cell-types in the mouse brain). The results will feed the data-analysis efforts in SP5 (Neuroinformatics Platform) and the modelling efforts in SP4 (Theoretical Neuroscience).



## 2.5.2 T2.1.4: Progress and main achievements

In the past six months, 10 full dendritic morphologies have been uploaded to the Neuroinformatics Platform database. Also, over 20 full morphologies, including axonal reconstructions and full physiological characterisations, were shared with I. Segev from SP4/SP6 for modelling. In collaboration with Partners in SP4, a paper on these studies has been published [1]. Initial contacts with the Allen Institute in Seattle and the Neurosurgery department of the Seattle Children's Hospital were established.

## 2.5.3 T2.1.4: Interactions with Tasks from other SPs and external Partners

On 24-25 March 2014, the HBP coordinated a meeting of 35 researchers from all over the world to discuss progress on human neuron recordings. This meeting was succeeded in the following months by intense discussions on strategies and protocols to harmonise research efforts. On 26 June, H. Mansvelder met with UK researchers specialising in recording human neurons to advise them on protocols and priorities. In addition, human neuron recording protocols were synchronised between research groups in the UK, Germany and South Africa.



## 2.2.4.4 T2.1.4: Specified plans for the next six months

A visit from the Head of Allen Institute in Seattle, C. Koch, and the Neurosurgery department of the Seattle Children's Hospital is planned to harmonise research strategies and methodologies for human neuron recordings. Collaborations and interactions with I. Segev (HUJI) from SP4/SP6 and M. Telefont (EPFL) from SP5 will continue, and first steps towards a human cortical model will be made.

## 2.6 T2.1.5 Distribution of selected receptors in the human brain (Task Leader K. Zilles, JUELICH)

### 2.6.1 T2.1.5: Goals

The aim of this Task is to implement and validate methods for mapping the human brain based on the analysis of multiple transmitter receptor distributions using quantitative *in vitro* receptor autoradiography in human, rat and mouse brain. Six human hemispheres will be scanned *in situ* using Magnetic Resonance Imaging, deep-frozen with rat and mouse brains, and further processed for analysis receptor expression. First complete human hemispheres and rodent brains have been serially sectioned. Alternating sections were already processed for receptor autoradiography or stained for visualisation of cell bodies or myelin. The different receptor binding sites for the transmitters glutamate, GABA, acetylcholine, noradrenaline, serotonin, dopamine, and adenosine will be labelled

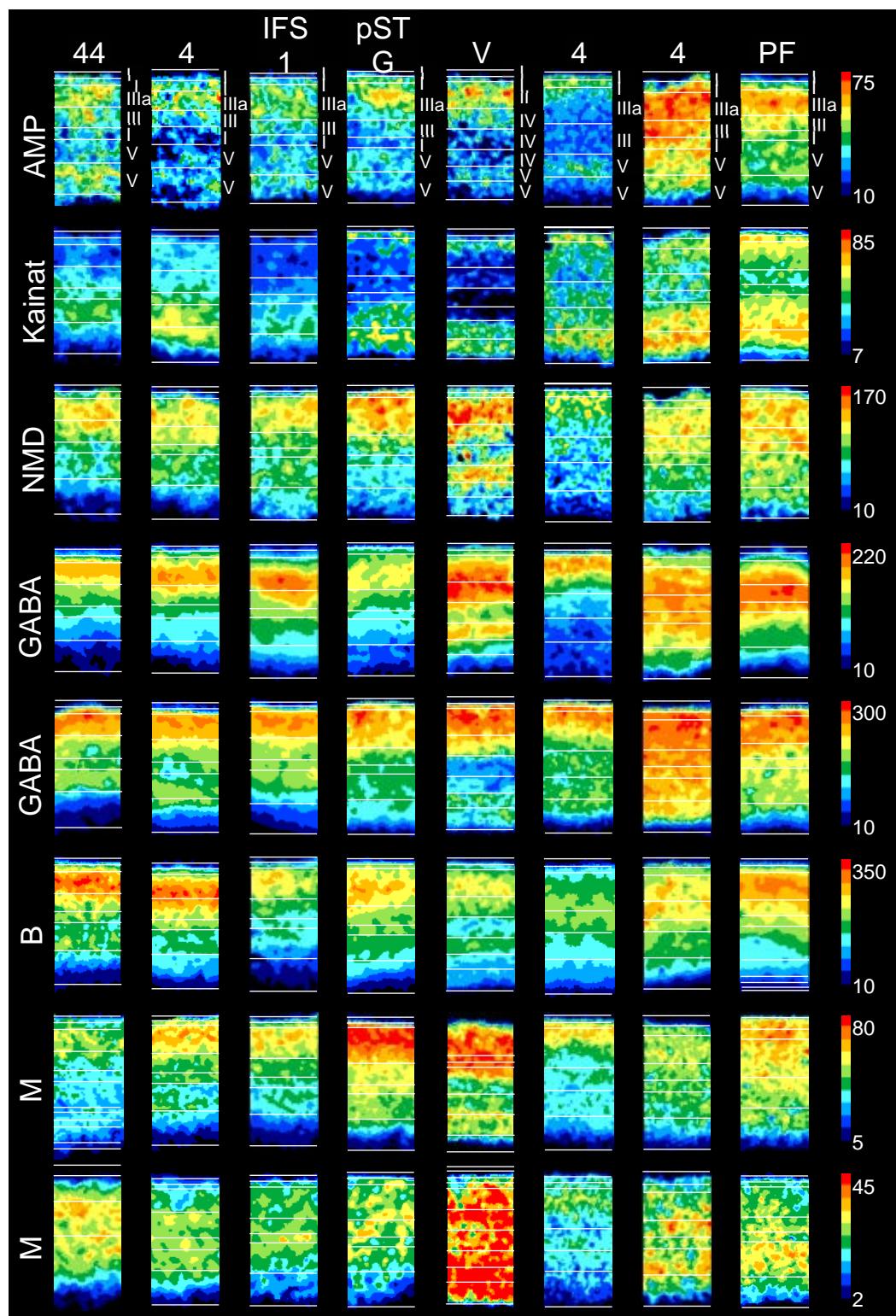


in each hemisphere. The measurements of the regional and laminar receptor densities in cytoarchitectonically defined regions throughout the complete hemispheres of rodent brains will be performed using a standardised pipeline (see D2.3.1 for more details).

## *2.6.2 T2.1.5: Progress and main achievements*

### **2.6.2.1 Milestones achieved according to plan**

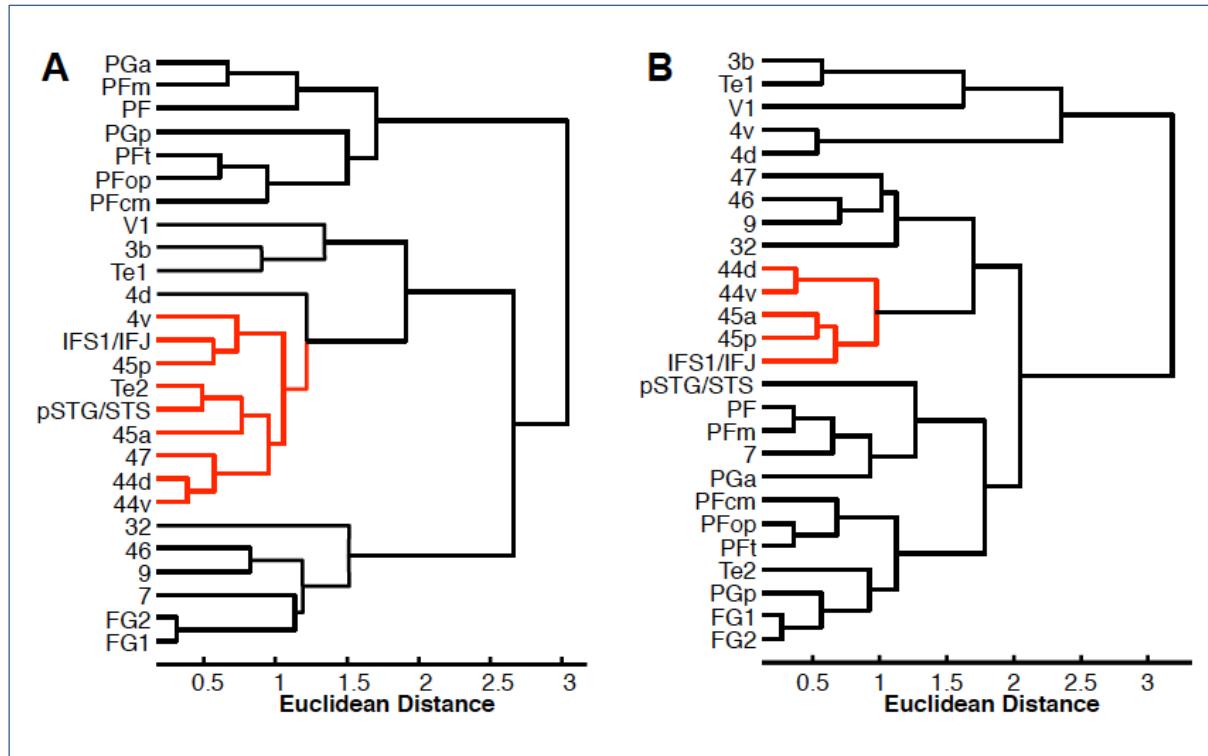
Milestone MS20, "Whole brain study of receptor concentrations of 20 receptor binding sites defined," was completely achieved during this period. The binding protocols and the measuring and visualisation pipeline have been established. Thousands of images displaying the multiple receptor distribution patterns in human, rat and mouse brains are available. Now, the time-consuming measuring period can start (see MS24 below).



**Figure 9: Laminar distribution of receptors in selected cortical areas**

Colour-coded receptor autoradiographs visualising the laminar distribution of glutamate (AMPA, kainate, NMDA); GABA ( $GABA_A$ ,  $GABA_B$ ,  $GABA_A$  associated benzodiazepine (BZ) binding sites); acetylcholine ( $M_1$ ,  $M_2$ ,  $M_3$ , nicotinic  $a_4/b_2$ ); norepinephrine ( $a_1$ ,  $a_2$ ); serotonin ( $5-HT_{1A}$ ,  $5-HT_2$ ); and dopamine ( $D_1$ ) receptors in 8 of the 26 examined brain areas (44d, 45, IFS1/IFJ areas of Broca's speech region; pSTG/STS language-related region in the temporal lobe; V1 primary visual cortex; 4d dorsal part of the primary motor cortex (hand region); 47 prefrontal area; PFm area of the inferior parietal association cortex). Color-coding indicates receptor densities in fmol/mg protein. [2]

Milestone MS36 “Methods defined for making existing, quantitative whole human brain receptor expression maps available through the HBP Human Brain Atlas” was achieved insofar as first receptor data are available for numerous cytoarchitectonically defined cortical and subcortical brain regions (cholinergic M2 receptor; mean receptor densities averaged over all cortical layers, or the complete extent of a nucleus; layer-specific receptor densities as laminar profiles). The data are ready for implementation in the HBP Atlas.



**Figure 10: Hierarchical cluster tree analysis of the fingerprints of 15 receptors in 26 cortical regions of the human brain in the left (A) and right (B) hemisphere**

Whereas the mouth representation of the motor cortex (4v), areas of Broca's region (IFS1/IFJ, 45a, 45p, 44d, 44v), prefrontal area 47, and notably the temporal areas Te2 and pSTG/STS cluster together in the left hemisphere, in the right hemisphere only the areas of the Broca's speech region show similar receptor fingerprints [2].

#### 2.6.2.2 Milestone partly ahead of the timetable of the proposed plan

Parts of MS24, “First estimates of transmitter receptor densities in a subset of cortical areas (primary sensory, motor, and at least 5 higher associative areas) and subcortical nuclei (thalamus)” were achieved ahead of schedule. In addition to the language-related regions and primary sensory and motor regions of the human cerebral cortex, we extended our studies to multimodal association regions of the parietal cortex. Mean receptor densities as well as laminar profiles vertical to the cortical surface were measured. Since neurotransmitter receptors are key molecules of information processing, we hypothesised that cortical areas that are part of the same functional language network may show highly similar multi-receptor expression patterns (“receptor fingerprints”), whereas those that are not part of this network should have different fingerprints. We demonstrated that the relationship between the densities of 15 different excitatory, inhibitory and modulatory receptors in eight language-related areas are highly similar, and differ considerably from those of 18 other brain regions not directly involved in language processing. Thus, the fingerprints of all cortical areas underlying a large-scale cognitive domain such as language are characteristic, functionally relevant features of this network, and important prerequisites for the underlying neuronal processes of language functions.



According to the plan, we will gather receptor data on subcortical nuclei (basal ganglia and some thalamic nuclei) by the end of Month 18.

### **2.6.3 T2.1.5: Interactions with Tasks from other SPs and external Partners**

We initiated collaboration with J. Bjaalie (SP5) to register mouse and rat receptor data to the Waxholm space, and to achieve a 3D registration of the cholinergic M2 receptor (and later of other receptors) in the rat brain. We collaborated with J. DeFelipe (SP1) to compare immunohistochemically stained receptors with autoradiographic data in the human brain. There is constant intensive collaboration with Task 2.2.2 (K. Amunts).

### **2.6.4 T2.1.5: Specified plans for the next six months**

We will complete receptor measurements in more cytoarchitectonically defined cortical areas, as well as in selected subcortical nuclei. We will make measurements on glutamate receptors AMPA, NMDA, kainate, and metabotropic GluR2/3; GABA receptors GABAA (both agonistic and antagonistic binding sites), GABAB and benzodiazepine-binding sites of GABAA; acetylcholine receptors; muscarinic M1, M2 (both agonistic and antagonistic binding sites), M3, and nicotinic D4; serotonin receptors 5-HT1A and 5-HT2A; noradrenaline receptors antagonistic binding sites); and adenosine receptors A1 and A2A. No changes to the work plan are necessary. This Task is ahead of schedule.

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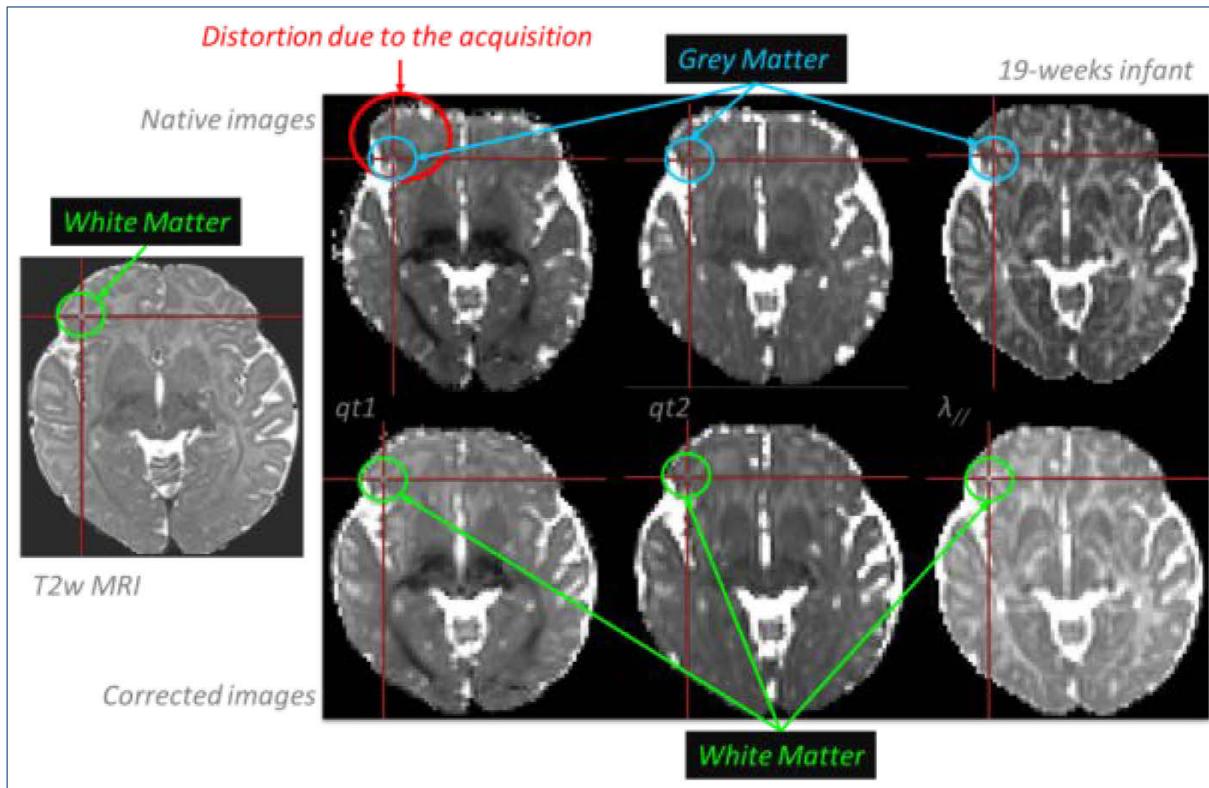
## **2.7 T2.1.6 The Developing Human Brain (Task Leader G. Dehaene, CEA)**

### **2.7.1 T2.1.6: Goals**

Part of this Task aims to study the maturation of white and grey matter during the first post-natal months in infants. We have acquired different MR scans on infants aged 4 to 19 weeks (corrected age) to get different tissue contrasts: T2w anatomical images, diffusion images and quantitative T1 and T2 mappings. Thanks to a classification algorithm, brain tissues can be segmented without anatomical *a priori* information, according to the degree of maturation of each brain.

### **2.7.2 T2.1.6: Progress and main achievements**

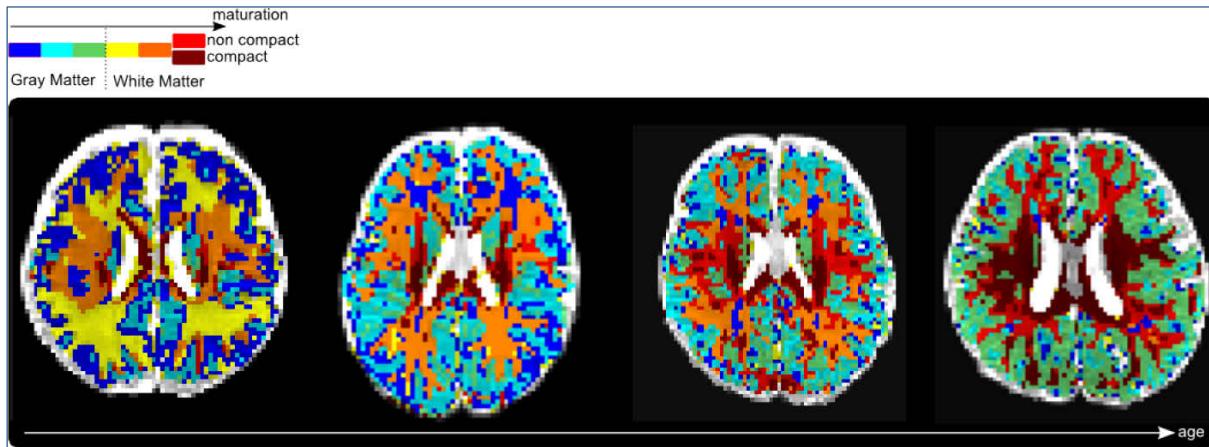
A crucial preliminary step in the study of brain tissue maturation is to align all multimodal data for each subject. Due to the acquisition, geometrical distortions often appear on diffusion images as well as on quantitative mapping. To overcome this issue, a phase map should be acquired and then used to correct data. The resulting maps could then be easily registered with anatomical scans. Unfortunately, phase map acquisition requires time, which is limited in studies of infants. Nevertheless, to correct the distortions and align all multimodal images per infant, an elastic transformation has been estimated between each diffusion image and each quantitative mapping to match the anatomical scan. Visual inspections show that this registration approach is particularly suitable for overcoming the distortion issue with these data (see Figure 11). [9] Thus, MS22 "First data set on maturation of major fibre tracts of human infant brains" has been achieved.



**Figure 11: Registration approach for the correction of geometrical distortion on diffusion images**

The top row displays native quantitative T1 ( $qt_1$ ) and T2 ( $qt_2$ ) mapping and one of the acquired diffusion images ( $\lambda_{//}$ ) with intrinsic geometrical distortions (see red circle). On these images, the cross points to grey matter (see blue circles) whereas it points to white matter on the anatomical data shown on the left side of the figure (see green circle). The bottom row displays same quantitative mapping and diffusion image after distortion correction. The cross points to white matter (see green circles).

We then applied a classification algorithm based on Gaussian Mixture Modelling to the registered data to segment brain tissues according to their maturation degree, without any *a priori* information (except the number of classes). Multiple tests have been performed to determine the appropriate number of classes to fix, and to select the images for classification to obtain understandable results. Segmentations resulting from classification based on seven classes are displayed in Figure 12. The progressive apparition of mature regions at the expense of the immature regions is shown on this figure, and the non-compact mature white matter can be easily differentiated from the compact mature white matter. This figure also shows that even at a very young age, some white matter is already mature. The same observation has been made concerning the grey matter (not shown here) [3] [10].



**Figure 12: Brain tissue classification obtained on infants of different ages**

Immature tissues represent the majority of brain tissue in the youngest infant (on left), and progressively decrease with age in favour of mature tissue.

### 2.7.3 T2.1.6: *Interactions with Tasks from other SPs and external Partners*

Once maturation is better quantified during the first months of life, we plan to collaborate with SP8 (G. Decco, V. Jirsa) to study how temporal delays in some networks due to immaturity affect the neurodynamical models of the brain they have proposed. We will implement cognitive tasks on symbol manipulation in collaboration with SP3.

### 2.7.4 T2.1.6: *Specified plans for the next six months*

The brain tissues segmentation resulting from the classification algorithm seems to be coherent, and suggests that brain tissue maturation can be studied using this approach. Results are currently analysed individually to follow the maturation progression across ages, and to compare these observations with those in the literature.

In parallel with this work, different tests are being performed to align all anatomical images using the DISCO algorithm (T2.2.1). When the inter-individual registration is validated, a cortical parcellation defined in an infant template brain [11] could be propagated in the whole database, enabling maturation study at the scale of the defined regions of interest.

## 2.8 T2.1.7 Homologies between Humans and other Primates (Task Leaders W. Vanduffel, KUL; R. Goebel, UM)

### 2.8.1 T2.1.7: *Goals*

The overall goals of this Task are to:

- Develop and optimise methods to compare multimodal high-resolution functional imaging data from different primate species
- Acquire sub-millimetre visual and auditory event-related fMRI data in humans using natural sounds/images (experimental paradigms and stimuli for these acquisitions will be identical to those that were used for the collection of monkey data)
- Develop and use multiple complementary analytical methods to study functional correspondences between monkeys and humans with spatially constrained (feature-based modelling) and unconstrained methods (interspecies activity correlation).

- Establish functional correspondence between detailed functional topographies of early and higher level visual and auditory cortical areas in humans and monkeys. The emphasis is on relating maps of relevant acoustic and visual stimulus features derived from fMRI responses to natural sounds and images.

### 2.8.2 T2.1.7: Progress and main achievements

The KUL (Vanduffel) and UM (Goebel, Formisano) groups have started comparative human-monkey studies both for the auditory and visual cortex.

#### 2.8.2.1 Homologies in auditory brain systems - Feature-based modelling of responses to natural sounds

To study the auditory cortex, the KUL Partners have adapted methods for feature-based analysis, previously developed by the UM Partners, for analysing available monkey fMRI data. With a preliminary analysis of the monkey data, we have obtained high-resolution tonotopic and tuning width topographic maps of the auditory cortex of monkeys responding to natural sounds (see Figure 13). These maps are being compared to existing maps in humans (1.5 mm resolution) and to higher resolution human maps (<1mm) that will be collected within the project (see 2.8.4).

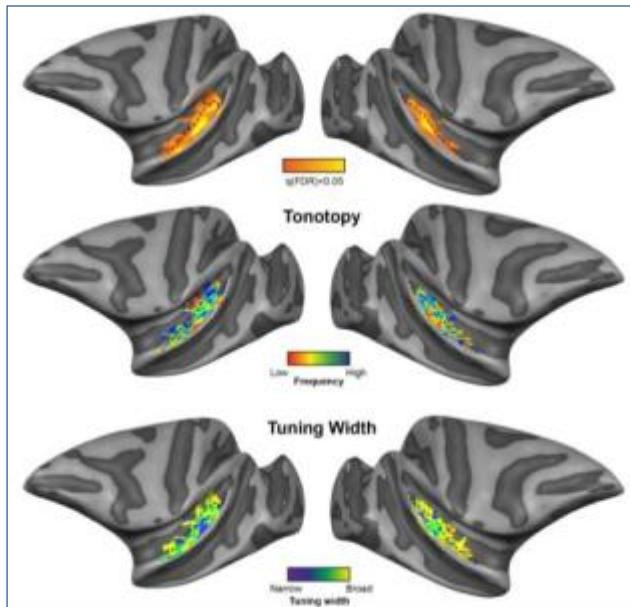


Figure 13: Results of feature-based modelling of monkey auditory fMRI data.

Top row: Overall activation to natural sounds in monkey auditory cortex. Middle and Bottom row: Tonotopic and tuning width (frequency selectivity) maps obtained from feature-based modelling of the responses to natural sounds.

#### 2.8.2.2 Homologues in visual brain systems - Data-driven analysis of analogous visual networks in monkeys and humans

For the comparison of monkey and human visual cortex, the Partners at KUL (Vanduffel, Zhu) and at UM (Goebel, Budnik) have collected high-resolution (1.5 mm voxel size) brain imaging data from several human participants (7 Tesla fMRI) at UM. They have adapted the same paradigm and stimuli previously applied to the corresponding monkey data at KUL. Images carefully controlled for visual features like contrast, luminance, size of human and monkey body parts, heads/faces, and objects of everyday use or abstract were presented to participants (Figure 14). In order to classify and localise visual areas correctly, functional localisers in the form of retinotopic mapping (eccentricity and polar angle) stimuli, including monkey faces or walking human bodies, were applied. These data will be used for further specialised analysis (ISAC) to directly compare human and monkey brain area activity

in response to specific visual stimuli. Figure 15 shows first imaging data analysed with Brain Voyager tools. The activation has been found in the expected brain areas in accordance with pre-existing monkey data obtained at KUL. More subject data, including implementation of further paradigm adjustments, are being analysed now.

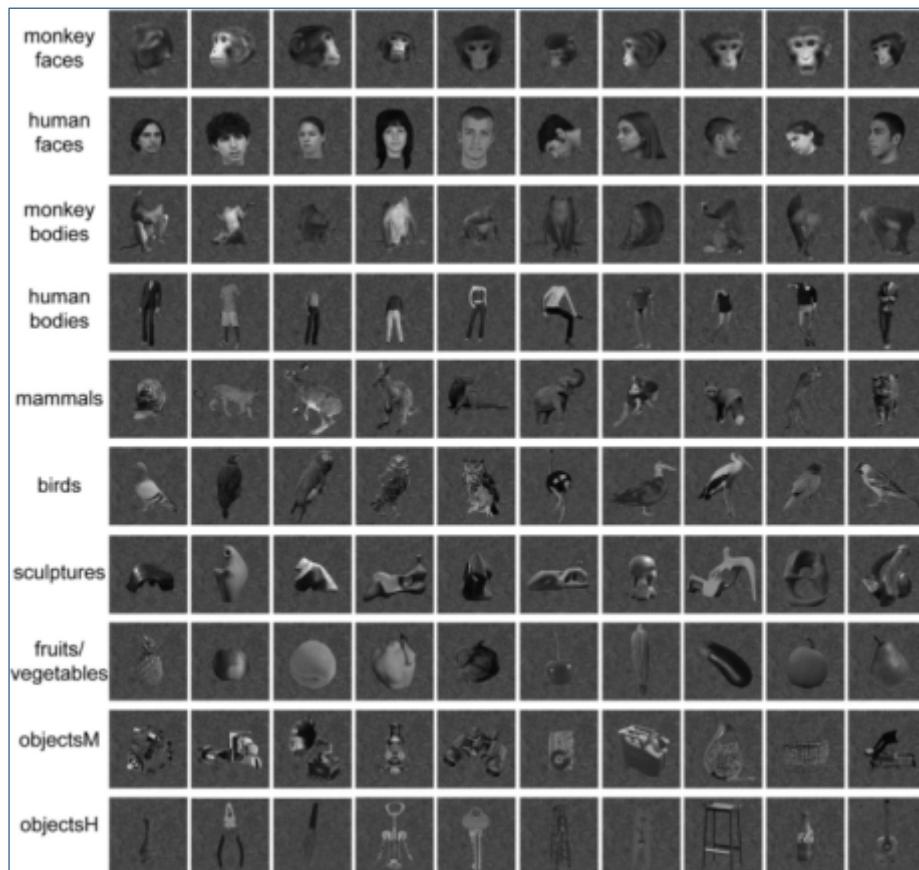


Figure 14: Species-specific stimuli for the comparative human-monkey study of the visual cortex

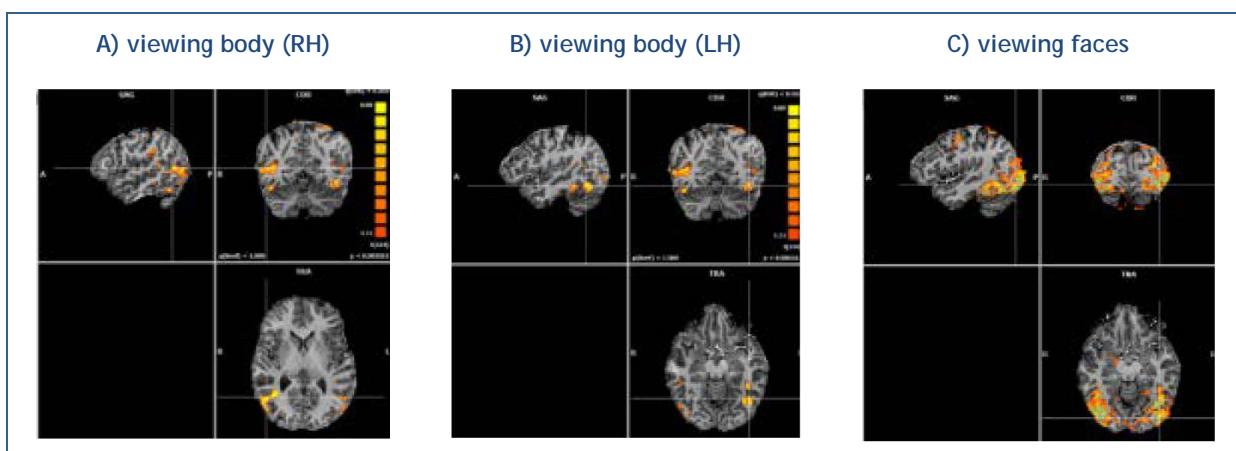


Figure 15: Results of high resolution 7T brain imaging in humans

Body-specific visual activation: A) 3D view on right hemisphere (RH); B) 3D view on left hemisphere (LH); C) human face processing (yellow-red) overlapped with monkey face activation (green).



## 2.8.3 T2.1.7: *Interactions with Tasks from other SPs and external Partners*

In the first six months, most of the work in this Task required extensive collaboration among the different research groups (KUL, UM). K. Ugurbil from the Center for Magnetic Resonance Research at the University of Minneapolis, who is part of the Human Connectome Project (HCP), is our external Partner. He provided relevant expertise for optimising the MR acquisition protocols and sequences for the collection of 7 Tesla fMRI human data.

## 2.8.4 T2.1.7: *Specified plans for the next six months*

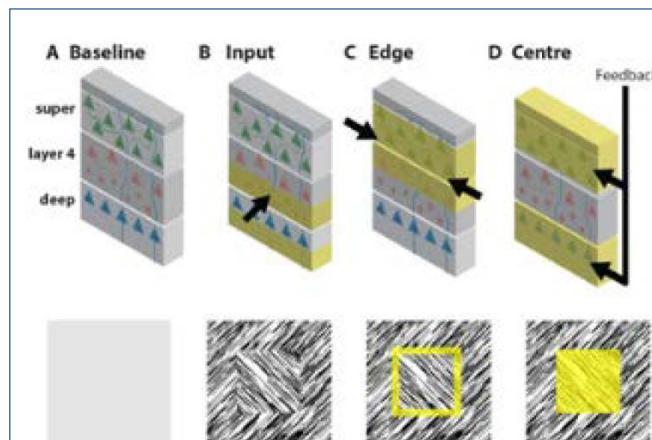
In the next six months, our focus will be on the following three activities:

- Completing the feature-based analysis monkey data (auditory): The current analysis only considered frequency as an acoustic feature, so we plan to use a more complete model of the sounds (stimuli) that includes an explicit representation of temporal and spectral modulation.
- Completing the acquisition of visual fMRI data in humans (7 Tesla).
- Starting the data-driven analysis monkey/human (auditory, visual data): As specified in the proposal, the approach of inter-species activity correlations (ISAC) will be used to perform a spatially unconstrained comparison of human and monkey maps.

## 2.9 T2.1.8 Revealing the activity and function of cortical layers (Task Leaders R. Goebel, UM; P. Roelfsema, KNAW)

### 2.9.1 T2.1.8: *Goals*

The overall goal of this Task is to understand the roles of different cortical layers in sensory processing. We will use high-field imaging to measure activity in a texture segregation task (see Figure 16). We will use existing data in non-human primates as a benchmark for the validation of laminar fMRI in humans. There are two processes involved in texture-segregation that impose conflicting constraints on the interactions between neurons. The first is an early boundary detection process (Figure 16A) that depends on inhibitory interactions between neurons tuned to the same orientation. The second is a process that enhances neuronal activity in the centre of the representation of a texture figure (Figure 16B) and relies on excitatory feedback from neurons in higher visual areas. We will build a model for texture segregation in which these apparently conflicting constraints are resolved by differential involvement of the cortical layers, in accordance with our new neurophysiological findings. The data will be used to inform neuro-computational models of laminar processing.



**Figure 16: Role of layers in figure-ground segregation**

(A) Upper row: cortical column. Lower row: texture stimulus that induces figure-ground segregation in perception. (B) The registration of features starts in layers 4 and 6, which receive the input from the LGN. (C) Boundaries are detected in the superficial layers by horizontal interactions. (D) After an additional delay, the interior of the figure representation is enhanced by feedback from higher visual areas.

### 2.9.2 T2.1.8: Progress and main achievements

Both Partners have agreed on an fMRI design to isolate feedforward, horizontal and feedback components in the BOLD response at 7T, thus completing sKPI\_31. We have implemented this design using COGENT and MATLAB, debugged these scripts and tested the randomisation and timing of the stimuli. We are now exchanging these scripts with the Goebel group to adjust the code and optimise the task design. We are piloting the experiment on ourselves to determine the necessary difficulty level of the task, so we can carry out the first scanning sessions in the coming month. We have also been analysing laminar data obtained from V1 of awake monkeys to examine the laminar distribution of suppression of the background responses in a figure-ground segregation task. This information will also be useful for interpreting the laminar BOLD MRI data. The NIN Partner has also begun designing the first architectures for the model of processing in the different layers of the visual cortex.

### 2.9.3 T2.1.8: Interactions with Tasks from other SPs and external Partners

In the first six months, most of this Task's work required extensive interaction and collaboration among the different participating research groups (NIN, UM). Our modelling approach links to the modelling work in WP4.4 "Principles of Brain Computation" led by W. Maass (SP4, Task 4.4.1), with whom the NIN has an on-going collaboration.

### 2.9.4 T2.1.8: Specified plans for the next six months

We will explore the role of feedback connections in models of neuronal plasticity. The new hypothesis is that feedback connections label those features in low-level areas that are relevant to solve a task. We will test the hypothesis that the pattern of these feedback connections can be learned through the models experience in a task. We will also compare the roles of feedback connections to those of feedforward connections. A new model that can explain how feedback connections are formed would be an important breakthrough.



## 2.10 T2.1.9 Combining intra-cranial EEG and MRI in humans (Task Leaders J.P. Lachaux, UCBL; P. Kahane, UJF)

### 2.10.1 *T2.1.9: Goals*

The overall goal of this Task is to provide a unique and extensive multi-modal/multi-scale database of human brain data, both functional and structural, from single-unit recordings to DTI. Specifically, we will collect and analyse intracranial EEG (iEEG) data from 30 patients each performing eight functional localisers; for example, eight short and classic paradigms designed to activate large-scale neural networks involved in language processing, verbal and visuo-spatial working memory, visual attention, motor behaviour, high-level visual and auditory perception. The data set will amount to more than 4,000 cortical recording sites, each recorded during eight tasks and during rest. In addition, 20 of the patients will be recorded in fMRI in those tasks after electrode explanation. We will also combine simultaneous iEEG and fMRI recordings from 20 patients, in tasks selected in each patient from among the eight localisers based on the responsiveness of iEEG electrode sites. We will provide anatomical connectivity maps in those patients, based on two independent techniques: DTI and cortico-cortical evoked potentials (potentials evoked in iEEG sites by electrical pulses sent in other iEEG sites, in which latency and amplitude measures characterise the type of connectivity between iEEG sites). Finally, we will perform single-/multi-unit recordings with microwires simultaneously with standard mesoscopic iEEG recordings in 10 epileptic patients. Each patient will be recorded during the eight functional localisers. All Milestones have been set to Month 30.

### 2.10.2 *T2.1.9: Progress and main achievements*

The pace of the project is essentially dependent upon the progressive accumulation of data as new patients are recorded in the hospitals. This involved a few preliminary steps, such as defining and implementing the localisers, and setting up a fast data analysis pipeline to process iEEG data. Now that these steps have been completed, the project has gone into stationary mode, marked by a steady evolution and filling-in of the database. The exception is the acquisition of micro-recordings (single units in humans), which is dependent upon ethical approval, but we are confident that the recordings will start in January 2015. All procedures have been carried out on our side to ensure that we get approval rapidly, but we are still waiting of a formal agreement. In the meantime, we are improving the quality of data acquisition and finding the best micro-electrodes for our project. To date, we have acquired iEEG data in 15 patients during the localisers. We have simultaneously recorded four in iEEG and fMRI, and we have acquired structural connectivity data from four (DTI/cortico-cortical evoked potentials, CCEP). Numbers are evolving on a monthly basis. So far, there has been no change to our objectives.

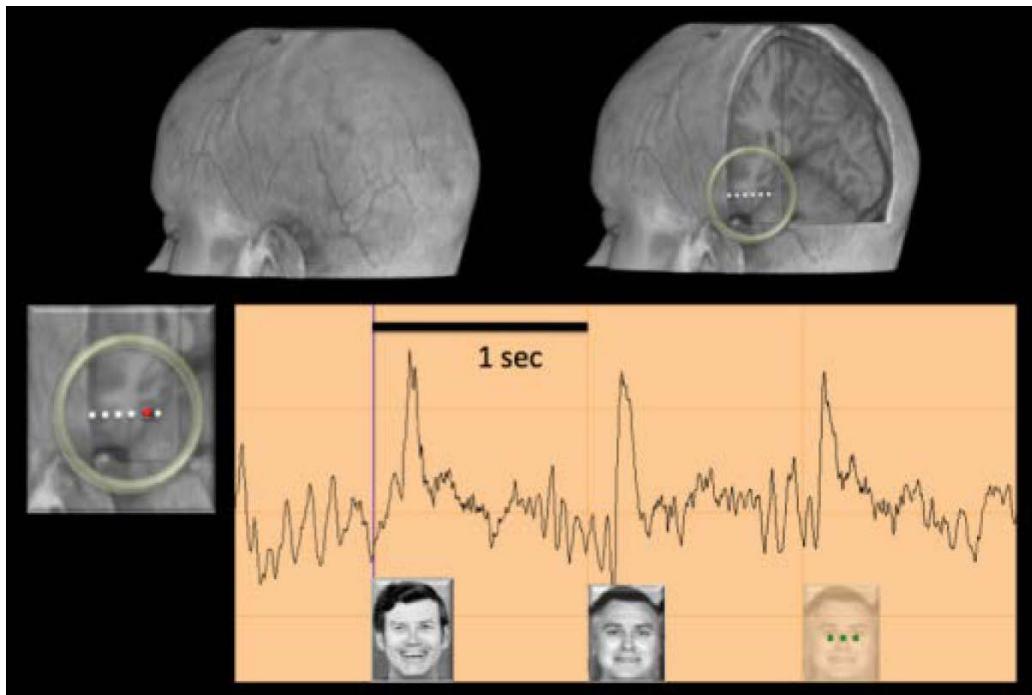


Figure 17: Principles of intracranial EEG recordings

Electrodes (circled) are inserted directly onto the patient's brain to record neural activity in multiple, adjacent, sites (white dots). The signal-to-noise ratio of the recordings is so good that the neural response to visual stimuli, for instance (here, faces) can be readily seen in the raw signals.

#### 2.10.3 T2.1.9: *Interactions with Tasks from other SPs and external Partners*

Until now, interactions have primarily been with T2.2.3, which manages the organisation/manipulation of this database and which is led by our local Consortium (Grenoble/Lyon). During the HBP Summit of 29 September 2014 in Heidelberg, we also held discussions with T2.1.1. Our intracranial EEG/fMRI localisers will now be added to the set of localisers that will be performed in 12 subjects and recorded over the coming years.

#### 2.10.4 T2.1.9: *Specified plans for the next six months*

In the next six months, we will continue building up the database with data from new patients. We will benefit from the help of a post-doc fully dedicated to micro-recordings (data acquisition/de-noising/data analysis), who will start in November 2014. We will also welcome an engineer dedicated to improving the pipeline of CCEP acquisition and analysis.



## 3. WP2.2 Data Aggregation, Analysis and Dissemination

### 3.1 WP2.2: Overall Goals as defined in D2.3.1

The goals of this Work Package concern 1) the standardisation of techniques and tools and management of the data they produce, and 2) the deposition of different types of data: a) data characterising anatomical and functional segregation, b) connection data from *in vivo* and *post mortem* studies, c) *post mortem*-data on cellular and receptor architecture and neuronal morphologies, and d) data from infant brains.

In WP2.2, the goals for Month 12 were defined in four Milestones:

1. MS35: Methods defined for making existing whole brain cytoarchitectonic maps available through the HBP Human Brain Atlas (Task 2.2.2. Task Leader K. Amunts, UDUS)
2. MS36: Methods defined for making existing, quantitative whole human brain receptor expression maps available through the HBP Human Brain Atlas (Task 2.2.2. Task Leader K. Amunts, UDUS)
3. MS37: Methods defined for providing diffusion-based data on major and U-shaped tracts in adult human brains (Task 2.2.1 Task Leader J. Mangin, CEA)
4. MS38: Methods defined for making existing whole human brain fibre tract scans available through the HBP Human Brain Atlas (Task 2.2.1 by Task Leader J. Mangin, CEA)

All four Milestones have been achieved. The new Partners, who joined WP2.2 at Month 6, are working on an iEEG database organisation and multimodal integration as a prototype for an international extension. Their goals are outlined in Chapter 3.4.

### 3.2 T2.2.1 Standardised techniques, tools and data management (Task Leader J.F. Mangin, CEA)

#### 3.2.1 T2.2.1: Goals

Existing, standard brain alignment methods are not optimal in the context of heterogeneous data, which should be supplemented with a standard reference space (*post mortem*, infants, adults). This is particularly true of the cerebral cortex, with its highly individual folding. Firstly, we will use the cortical folding patterns as a proxy of architecture to drive alignment. This will advance our understanding of the architectural value of the different sulci. Several algorithmic tunings of a constraint-based diffeomorphic alignment method called DISCO will be performed for each alignment situation. The ultimate goal will be to drive each Atlas to the space(s) of the MNI individual Atlas. After the Ramp-Up Phase, DISCO will be provided as a service to the community through the HBP Unified Portal. Secondly, we will address and supply different anatomical reference spaces (see below).

#### 3.2.2 T2.2.1: Progress and main achievements

After the DISCO prototype (provided by its designer—DISCO software results from PhD work) was reverse engineered, a first tuning to infant brains was initiated. First results prove the success of the reverse engineering. Thanks to optimal manual grey/white classification provided by a team from Stanford, the pipeline dedicated to the extraction of the cortical sulci has now been successfully tuned on the *post mortem* brains from Jülich.



An advanced diffusion MRI protocol combining several diffusion times was set up and tested on 10 human subjects. This protocol provides the information required to perform a tractography of the main fibre bundles, and to assess the number of axons in each bundle. Thus, we have achieved MS37, "Methods defined for providing diffusion-based data on major and U-shaped tracts in adult human brains."

Raw, diffusion-based acquisitions based on DICOM format can be completed with the spatial transformation required to align the data with one of the reference spaces proposed in the Human Brain Atlas. This is achieved by aligning diffusion acquisitions with T1-weighted acquisitions and spatial normalisation. Thus, we have achieved MS38, "Methods defined for making existing whole brain fibre tract scans available through the HBP Human Brain Atlas."

### **3.2.3 T2.2.1: Interactions with Tasks from other SPs and external Partners**

Several rounds of discussion with the SP5 Partners have led to the definition of use cases for uploading data to the HBP Atlas referential.

### **3.2.4 T2.2.1: Specified plans for the next six months**

A systematic study involving Jülich's individual cytoarchitectonic maps will lead to the selection of sulci to be imposed during the different alignments. The DISCO framework will be embedded in a toolbox, allowing various modulations related to the choice of the sulci driving the deformations.

## **3.3 T2.2.2 Deposition of Human Brain Data in the HBP Brain Atlas and Brainpedia (Task Leader: Katrin Amunts, UDUS)**

### **3.3.1 T2.2.2: Goals**

The probabilistic cytoarchitectonic JuBrain Atlas is well known, and is widely used for the anatomical interpretation of structural and functional MRI, PET and MEG studies. The current version of the Atlas is defined in the stereotaxic MNI-Colin27 reference space. However, this reference space—defined by a single subject—differs from the mean MNI reference spaces most commonly used for group analysis in functional MRI studies. Therefore, a new version of the probabilistic cytoarchitectonic JuBrain Atlas will be developed that is defined in the latest version of the asymmetric nonlinear MNI-ICBM152-2009c reference space.

The present reference brains only provide a macroscopic spatial framework at a macroscopical level in the range of mm, and are therefore, inadequate for integrating fine structural information of cortical layers, microcircuits and cell assemblies. Big Brain-1 provides the first ultra-high resolution model of the human brain at 20 microns isotropic resolution.

The ultimate goal will be to define a common reference space covering BigBrain-1 and the stereotaxic nonlinear MNI reference spaces that allow the integration of different data modalities at any spatial resolution.

### **3.3.2 T2.2.2: Progress and main achievements**

The BigBrain-1 data set has been integrated in a first test implementation of the HBP Unified Portal. First anatomical areas have been identified in series of histological sections, and 3D-reconstructed. A quality check is currently being carried out. A low-resolution version of the 3D data set was linearly and nonlinearly transformed into the MNI-Colin27 and asymmetric nonlinear MNI-ICBM152-2009c reference space.

To build the new version of the JuBrain Atlas, the other *post mortem* brains were linearly and nonlinearly transformed into the asymmetric nonlinear MNI-ICBM152-2009c reference space. A first

Atlas has been created. However, the atlas still requires improvements in anatomical accuracy. Thus, we have achieved MS35, "Methods defined for making existing whole brain cytoarchitectonic maps available through the HBP Human Brain Atlas."

To represent receptor expression maps in a standard reference space, we have developed the first 3D-receptor map of a rat brain. The rat brain is smaller than the human brain; furthermore it is histologically sectioned as a whole (not in slabs), and is not folded. These features makes it model in 3D than the human brain. The different grey-level distributions of the different receptor types are a major challenge; grey-value based tools will not be sufficient to achieve alignment, which will require the use of other techniques (e.g. mutual information). A necessary prerequisite to performing such 3D reconstruction is a high-quality registration of the receptor autoradiograms to the corresponding blockface images of the brain. The tools can be directly applied for the mouse brain, but need refinement and modification for human brain data [12]. Thus, we have achieved MS36, "Methods defined for making existing, quantitative whole human brain receptor expression maps available through the HBP Human Brain Atlas" (see also Chapter 2.6.2).

### 3.3.3 T2.2.2: Interactions with SP5 and external Partners

Discussions with the SP5 Partners have defined a roadmap for the implementation of user interaction scenarios for the BigBrain-1 data set that has already been integrated in a test implementation of the HBP Unified Portal. These include, for example, selection of absolute spatial coordinates with a double-click. Arbitrarily oriented virtual cutting planes can be defined within the volume and shown up to the highest possible resolution of 20 microns. To facilitate better orientation based on anatomically distinct structures, e.g. sulci and gyri, a 3D thumbnail view of the full BigBrain-1 data set with highlighted cutting planes will be created. For this, we will provide SP5 with a suitable low-resolution triangulated surface model.

During an international meeting on Atlasing at the OHBM 2013 in Seattle, members of the HBP (Amunts, Eickhoff, Dehaene, Dehaene-Lambertz, Vanduffel, Hill, Zilles, Thirion, Poline, Bjaalie) identified the constraints of a multi-modal human Brain Atlas as prerequisites to integrating data on different spatial and temporal scales [13].

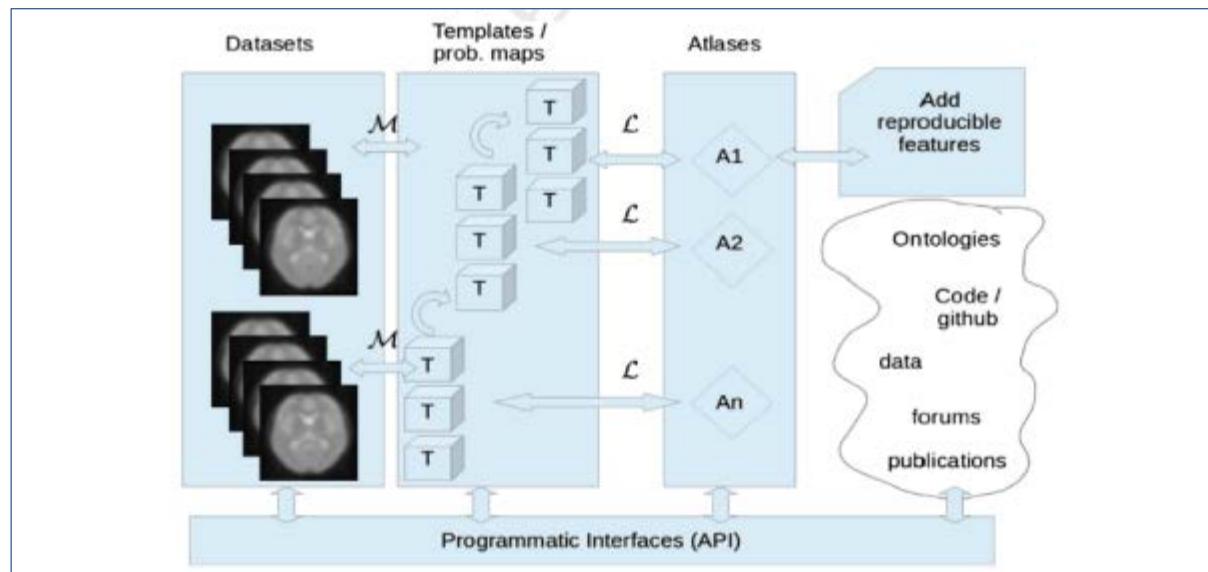


Figure 18: Schematic summary of the relationship between data sets (illustrated by fMRI scans but including all types of features on brain organisation), interoperable templates (providing the spatial framework for the analysis and representation of a particular feature) and Atlases (as mapping between a template and the probability distribution for a set of features/labels)



We differentiate between template or a probabilistic map (T), to which data are registered through a mapping (M), and labelling schemes (L) that take a template as input and a labelled volume (or surface) as output. An Atlas (A) in this framework is a labelled template. Atlases would grow with new reproducible features, and ways to interact with data. Template or Atlases would benefit from open-science projects in the neuroinformatics domain, and from web-based discussions within the brain imaging community [13].

### 3.3.4 T2.2.2: Specified plans for the next six months

Contour labels of miscellaneous anatomical areas will be acquired in histological series sections of the BigBrain-1 data set, and 3D reconstructed. The reconstructions will be uploaded and integrated into the HBP Unified Portal, provided by SP5..

The complete probabilistic cytoarchitectonic JuBrain Atlas will be transformed to the asymmetric nonlinear MNI-ICBM152-2009c reference space at a resolution of 1x1x1 mm. After an accurate quality check, the new Atlas will be uploaded to the Unified Portal.

*Post mortem* brains that have not yet been classified in grey and white matter with sufficient quality will be processed by an optimised data classification pipeline, so that they can be further processed by T2.2.1 (Standardised techniques, tools and data management).

## 3.4 T2.2.3 iEEG Database organisation and multimodal integration as a prototype for an international extension (Task Leader J.P. Lachaux, UCBL)

### 3.4.1 T2.2.3: Goals

The goal of this Task is to provide two software tools. The first will organise the massive multi-modal, multi-scale database built in T2.1.9, and facilitate the navigation, data selection and input of new multi-format data into that database. The second will enable convenient multi-modal visualisation—on 3D brain reconstructions—of dynamic iEEG and single/multi-unit data, fMRI data, and multivariate anatomical and functional connectivity patterns. Milestones have been set to Month 24.

### 3.4.2 T2.2.3: Progress and main achievements

The project involves three main steps. The first is the design of prototypes that meet all the requirements for adding, navigating and visualising rich multi-modal data. This design is essentially a “wish-list” from investigators who are experienced in manipulating such data. The second step is to decide on the programming environment that is best suited to implement the design. Two important factors must be taken into account at this stage: 1) the time-constraints of the project, since the software must be operational and fully debugged by Month 30, and 2) durability—the software should be robust in the face of operating system evolution once its main developers, hired solely for the duration of the HBP, are gone. Until now, most Task achievements concern those two steps. The final step, of course, is the actual programming and debugging phase.

During this initial period, we narrowed down the panel of options to two possibilities (Python/C# Unity). In particular, we tried to maximise the links with the existing environment, BrainVisa, which is extremely convenient for manipulating and organising multimodal data. It is also convenient for performing a number of crucial anatomical data-processing steps, such as 3D mesh reconstruction from anatomical MRI. We have implemented a BrainVisa-compatible module to precisely localise the location of intracerebral electrodes (iEEG recordings) onto subjects' individual anatomy in 3D. This is an essential preliminary step for all data visualisation involving iEEG. We have also designed a first version of our multimodal data visualisation interface (guidelines/constraints) on paper, in preparation for the upcoming recruitment of two engineers this fall.

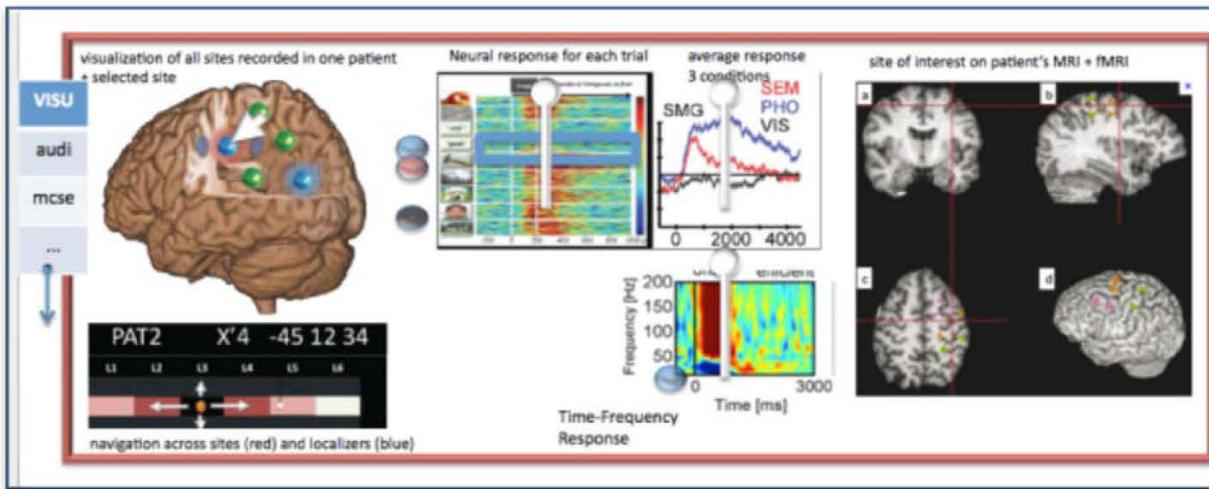


Figure 19: Schematic display showing all recorded sites on the anatomy for one patient

The display allows navigation across sites and cognitive tasks to show the neural response for every trial, as well as the average response for each condition (including Time-Frequency Response). The location of the site of interest can be visualised simultaneously on the patient's MRI with a projection of fMRI data.

### 3.4.3 T2.2.3: *Interactions with Tasks from other SPs and external Partners*

The main interaction was with T2.1.9, to obtain the data included in the T2.1.9 database. We have also gathered information from SP5 about HBP requirements for data format and programming language. This information will enable us develop a multimodal data visualisation interface that is compatible with the HBP.

### 3.4.4 T2.2.3: *Specified plans for the next six months*

In the next six months, we will completely specify the organisation of the database and the specifications of the multi-modal visualisation/manipulation software. We will choose the programming environment for that project, and build the first components for 3D visualisation of iEEG data (either at the individual level or for groups) with high anatomical and dynamic precision. Two software engineers, hired specifically for that Task, will work on the project.



## 4. WP2.3 Scientific Coordination and Support

### 4.1 WP2.3: Overall Goals

The main goal of WP2.3 is to support, coordinate and monitor all HBP research in SP2. This involves the planning and realisation of the research, the definition of indicators to measure progress, and documentation. It also includes the organisation of meetings and other kinds of communication within the SP, as well as with other SPs and external Partners. A third important goal is to report the progress of work at all levels of the SP to HBP Central Management. The SP Coordinator ensures the documentation of all activities.

The SP Leader manages scientific coordination, represents the SP on the Board of Directors, and contributes actively to supporting the HBP as a whole. At the same time, the SP Leader ensures that all PIs in the SP are aware of and implement the decisions of the Board and Executive Committee.

### 4.2 WP2.3: Main Activities

SP2 has completed a series of important and highly visible publications (see Annex C: References). All KPIs have been completed. However, from the perspective of the SP, they do not represent a meaningful monitoring and controlling tool, since they generally do not reflect scientifically relevant aspects of progress. This is different for Milestones and scientific publications, which still represent the most relevant performance indicators in neuroscience. All activities described were prepared, organised and executed by the Coordinator, and closely supervised by the SP Leader. This facilitated scientific progress, timely and complete reporting, and fruitful communication between scientists within HBP and beyond.

#### 4.2.1 Communication

Since Month 6, intense and diverse communications have developed within the SP, with other SPs, and with external Partners. There were the routinely scheduled meetings, such as the general SP2 meetings (2), the JUELICH/UDUS-scientific-meetings (4), the JUELICH/UDUS coordinators' meeting (3) and the German Partner Meetings (5). Many more meetings were initiated and realised by PIs to meet specific objectives within SP2 (14 internal meetings - see Annex D: Internal Meetings). Most meetings were with other SPs (27 cross-SP meetings - see Annex E: Cross-SP Meetings), namely SP1, 3, 5, 6 and 7. This reflects SP2's role in the generation of strategic human brain data and in reconciling human data with mouse data from SP1 and data on cognitive architectures from SP3; Meetings were also held with relevant external Partners, including the Allen Institute, the US Initiative Human Connectome Project, and the Center for Magnetic Resonance Research (University of Minneapolis)(see Annex F: External Meetings). As can be seen in the sections of this report on "Interactions with other SPs and external Partners," there were also many informal interactions, facilitating necessary collaboration.

In addition to lively communication between the scientific Partners, regular communication between the administrative staff played an important role in the successful coordination and operation of SP2. This administrative communication was carried out through defined meetings, such as the JUELICH/UDUS coordinators meetings, the participation of the STO in SP2 meetings, regular information on SP2 issues, and personal and contact with the SP2 Coordinator.

To support the PI's meetings with other SPs, regular interactions were organised between the SP2 Coordinator and her colleagues in SP1, SP3, SP4, SP5, SP6 and SP7.

Daily interactions took place between the SP2 Coordinator and HBP Central Administration concerning meetings, reporting, financial issues, dissemination, etc. These made it possible to establish a reliable and constructive relationship, which provides a foundation for SP2's successful organisation and



performance. The SP Leader has taken part in all Board Meetings, and has contributed vital input to all discussions concerning the future scientific and administrative development of the HBP. During SP-internal meetings, the SP Leader has reported proceedings to the PIs in SP2, either directly or with support from the Coordinator.

### 4.2.2 Reporting

During the last six months, the third and fourth Quarterly Reports and this second Deliverable have been completed. The Periodic Report was also prepared. The latter three reports had the same deadline (30 September).

The reports are based on physical meetings, conference calls, Skype meetings and email communications. The physical SP2 meeting in June revealed many new results, so that SP2 submitted the third Quarterly report not only at the SP level, but also at the Task level, and documented all results in EMDESK. The fourth Quarterly report is documented by the scientific presentations at the physical SP2 meeting in Heidelberg.

The outline of the M12 Deliverable was developed with the HBP Editorial Office and the Science and Technology Office (STO) to illustrate the special role and goals of SP2 in the HBP. The SP leader ensured that all reports were submitted by their deadlines, and that they met defined quantitative and qualitative requirements. She also monitored financial reporting. The SP Leader has edited and reviewed the scientific parts of reports in particular, and has finalised all documents.

### 4.2.3 Documentation

An important activity of the Coordinator is to keep records of all activities, thus accomplishing internal monitoring and quality control. This included supporting PIs by keeping them informed of deadlines and procedures, and giving them important background information. An important objective was to keep as many administrative activities as possible away from the PIs, and to only involve them in scientific issues. As requested by the HBP, the Coordinator documented all activities in EMDESK, namely meetings, reports, publications and dissemination as well as basic information on the Partner institutions involved. The Coordinator also monitored documentation of the financial situation, which has to be done by the financial department of each Partner institution.

## 4.3 WP2.3: Activities in the Next Six Months

Three meetings are still planned for 2014. The fourth (conference call) and fifth general SP2 meetings (at JUELICH) will be held to discuss the progress in work and prepare for the first EU Review. In addition, a physical cross-SP meeting between SP2 and SP5 will take place at JUELICH. It will provide a framework for solving concrete technical and methodical problems in achieving both the SPs' aims, and will intensify the collaboration between them.

In the short-term, the Coordinator will prepare all Partners for an appropriate presentation of SP2 at the first EU Review in January 2015. This includes discussions of the main areas to be presented, the PIs to be involved and the staging, as well as close communication with HBP Central Management about the requirements and the conditions on-site.

The documentation focus will be on completing all requested aspects of the Periodic Report in EMDESK, namely scientific progress, Milestones, publications, KPIs, meetings, and other dissemination activities. The next two Quarterly Reports for Month 15 and 18 have to be completed and the third Deliverable for Month 18 prepared.

## 4.4 SP2 Meetings



#### ***4.4.1 Internal meetings***

Please see Annex D: Internal Meetings

#### ***4.4.2 Cross-SP Meetings***

Please see Annex E: Cross-SP Meetings

#### ***4.4.3 External Meetings***

Please see Annex F: External Meetings



## Annex A: Milestones

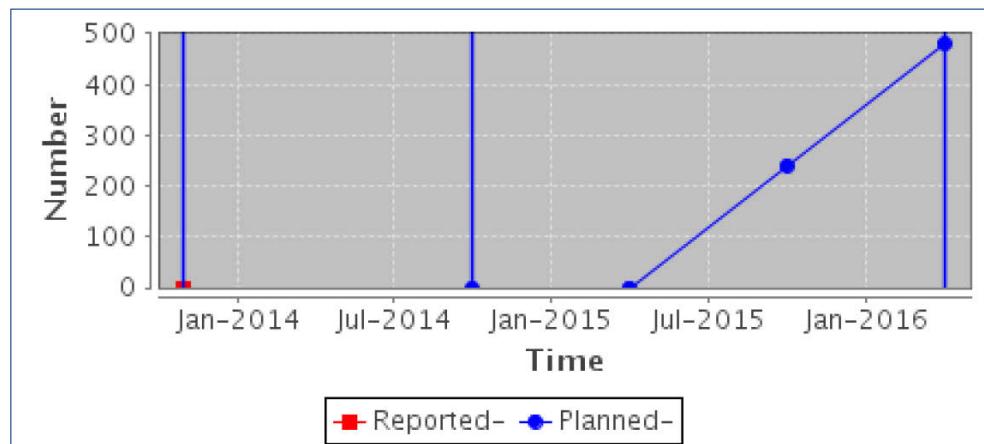
No.	Milestone Name	WP	Month Due	Month Achieved	See Page
M16	Optimisation of a diffusion-weighted acquisition protocol to perform calibration of axonal density and diameter using Neurospin 7T scanner.	2.1	6	6	
M17	Massive mapping of ten subjects to study individual variations defined and ethically approved.	2.1	6	12	
M18	Method for polarised light imaging established.	2.1	6	6	
M19	Study of maturation of selected fibre tracts in human infant brains defined.	2.1	6	6	
M33	Set-up of informatics and management for HBP human brain imaging data.	2.2	6	6	
M20	Whole brain study of receptor concentrations of 20 receptor types defined.	2.1	12	12	
M21	Method for fibre tract Atlas based on polarised light imaging established.	2.1	12	12	
M22	First data set on maturation of major fibre tracts of human infant brains.	2.1	12	12	
M34	Tools for comparison of <i>post mortem</i> and <i>in vivo</i> imaging data made accessible as part of the "Anatomy toolbox".	2.2	12	12	
M35	Methods defined for making existing whole human brain cytoarchitectonic maps available through the HBP Human Brain Atlas.	2.2	12	12	
M36	Methods defined for making existing, quantitative whole human brain receptor expression maps available through the HBP Human Brain Atlas.	2.2	12	12	
M37	Methods defined for providing diffusion-based data on major and U-shaped tracts in adult human brains.	2.2	12	12	
M38	Methods defined for making existing whole human brain fibre tract scans available through the HBP Human Brain Atlas.	2.2	12	12	

## Annex B: Scientific Key Performance Indicators (SKPIs)

### 4.5 WP2.1 Multilevel organisation of the human brain

#### 4.5.1 T2.1.1 Anatomical and functional organization of the human brain

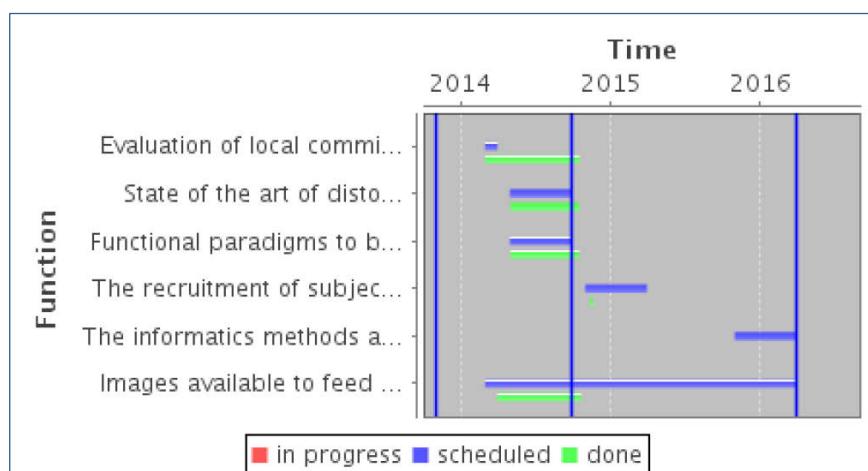
SP2\_SKPI\_01 Number of images of functional contrast of interest available for atlas inference  
Responsible: a.lindner@fz-juelich.de



SP2\_SKPI\_25 Anatomical and functional organisation of human brain

Responsible: a.lindner@fz-juelich.de

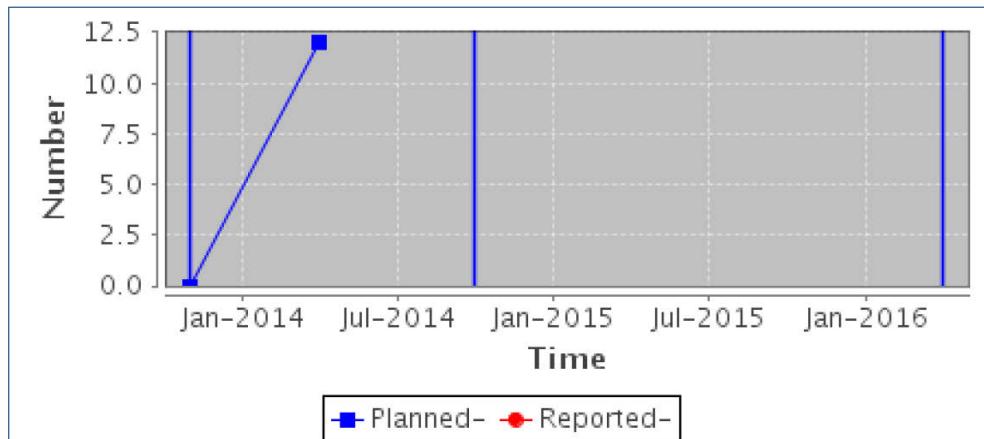
- Evaluation of local committee for IRB approval completed. Planned: 2014/02/28 - 2014/03/31
- State of the art of distortion correction techniques for the data acquisition parameters. Planned: 2014/04/30 - 2014/09/30
- Functional paradigms to be used have been tested. Planned: 2014/04/30 - 2014/09/30
- The recruitment of subjects has started after the IRB approval being accomplished. Planned: 2014/10/31 - 2015/03/31
- The informatics methods and tools will be evaluated and the analysis pipeline installed. Planned: 2015/10/31 - 2016/03/31
- Images available to feed the atlas. Planned: 2014/02/28 - 2016/03/31



#### 4.5.2 T2.1.2 Connections between brain regions

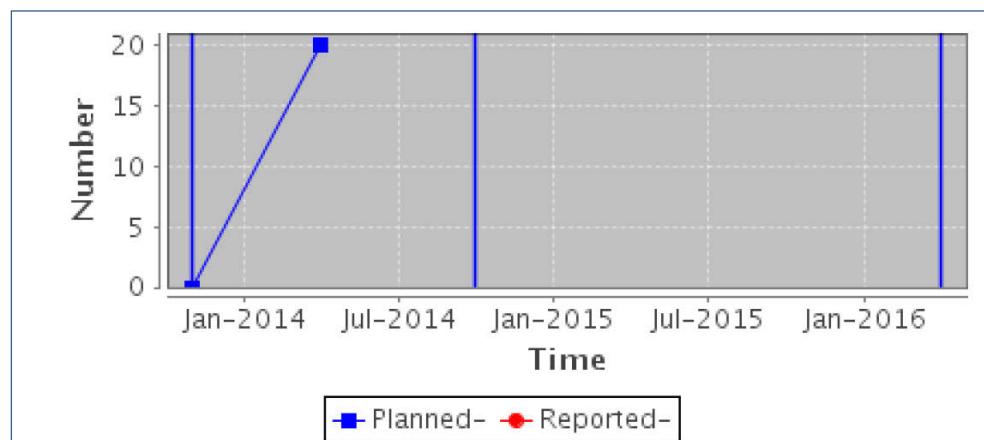
SP2\_SKPI\_02 Number of subjects used to infer the atlas

Responsible: a.lindner@fz-juelich.de



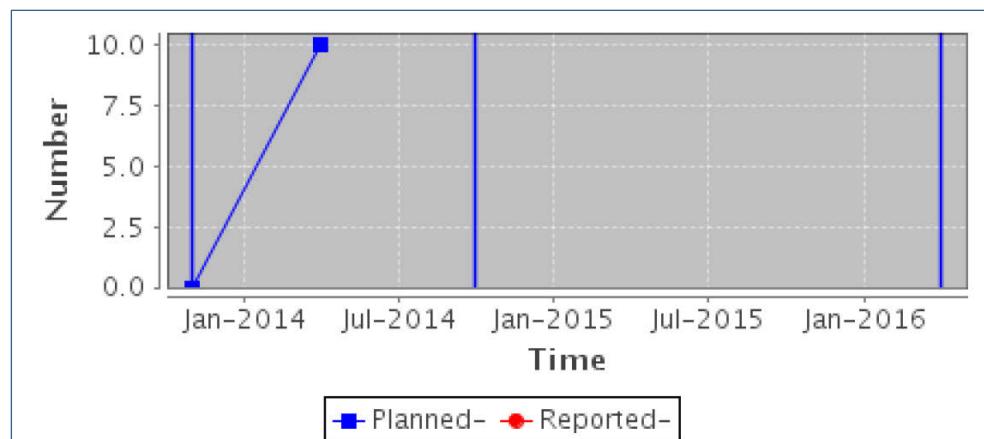
SP2\_SKPI\_03 Number of reproducible bundles in the atlas

Responsible: a.lindner@fz-juelich.de



SP2\_SKPI\_04 Number of axon diameter dedicated acquisition sessions

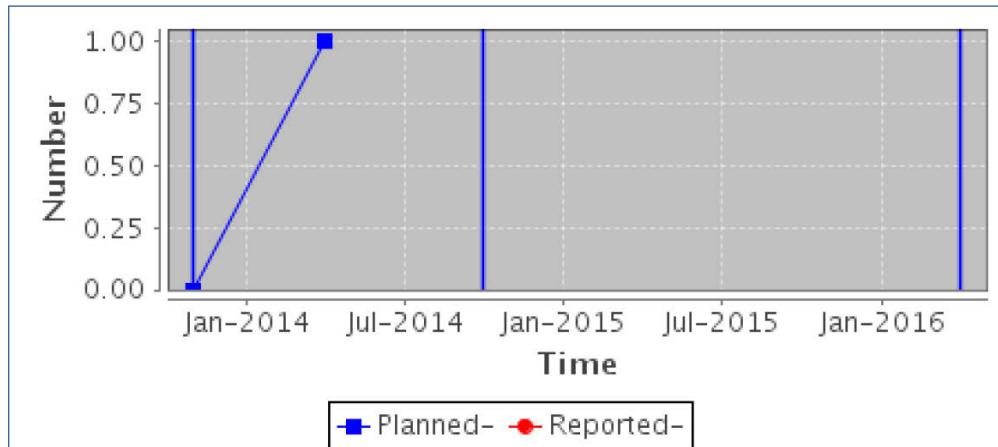
Responsible: a.lindner@fz-juelich.de





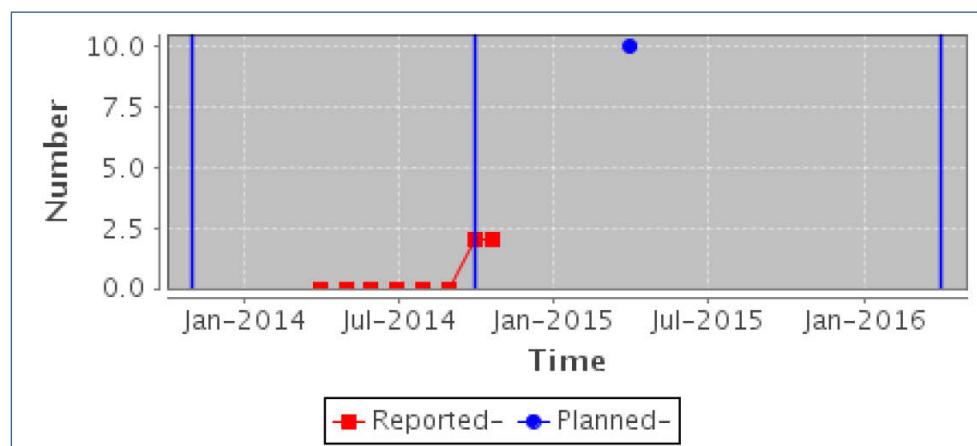
## SP2\_SKPI\_05 Number of atlas bundles with estimation of axon diameters

Responsible: a.lindner@fz-juelich.de



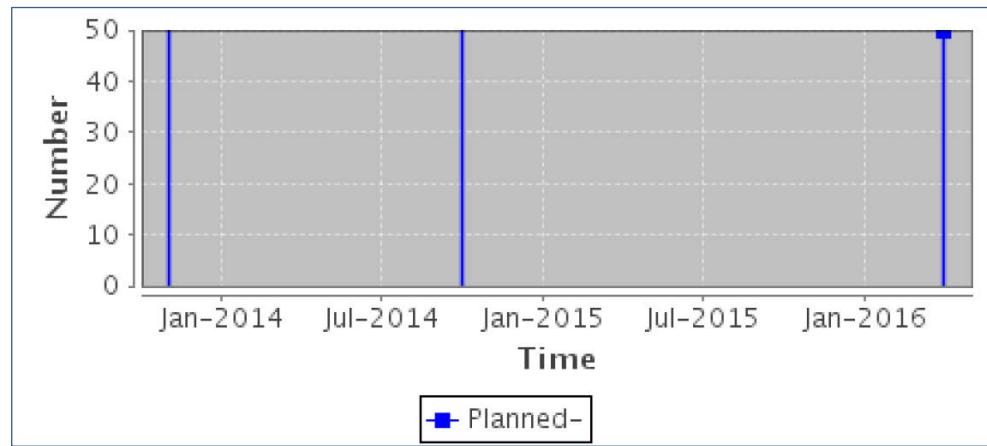
## SP2\_SKPI\_06 Number of tracts mapped in the course of the pipeline development

Responsible: a.lindner@fz-juelich.de



## SP2\_SKPI\_07 Number of tracts mapped and quantitatively characterised

Responsible: a.lindner@fz-juelich.de

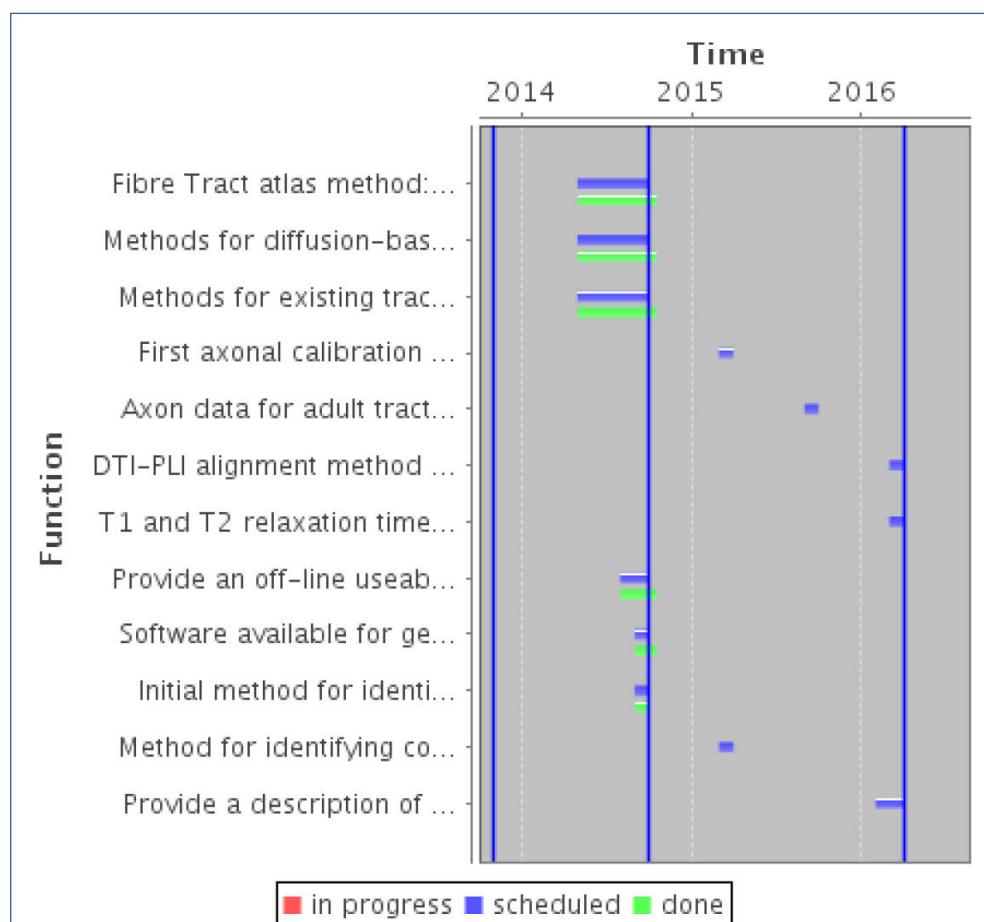


## SP2\_SKPI\_26 Connections between brain regions

Responsible: a.lindner@fz-juelich.de



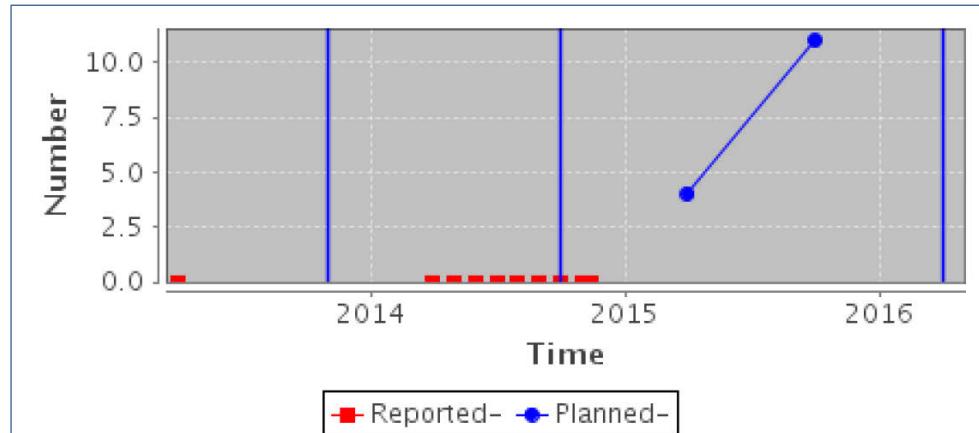
- Fibre Tract atlas method: Using DISCO to align subjects before inference. Planned: 2014/04/30 - 2014/09/30
- Methods for diffusion-based data completed. Planned: 2014/04/30 - 2014/09/30
- Methods for existing tracts scans completed. Planned: 2014/04/30 - 2014/09/30
- First axonal calibration and diffusion-based fibre scans. Planned: 2015/02/28 - 2015/03/31
- Axon data for adult tracts. Planned: 2015/08/31 - 2015/09/30
- DTI-PLI alignment method evaluated and running. Planned: 2016/02/29 - 2016/03/31
- T1 and T2 relaxation time for major tracts. Planned: 2016/02/29 - 2016/03/31
- Provide an off-line useable software for the integration of post-mortem cytoarchitecture and function. Planned: 2014/07/31 - 2014/09/30
- Software available for general use. Planned: 2014/08/31 - 2014/09/30
- Initial method for identifying core fibres connecting functional regions implemented. Planned: 2014/08/31 - 2014/09/30
- Method for identifying core fibre connections is optimised and tested in a first set of regions. Planned: 2015/02/28 - 2015/03/31
- Provide a description of major adult tracts. Planned: 2016/01/31 - 2016/03/31



#### 4.5.3 T2.1.3 Numbers and distributions of neurons and glia in the human brain

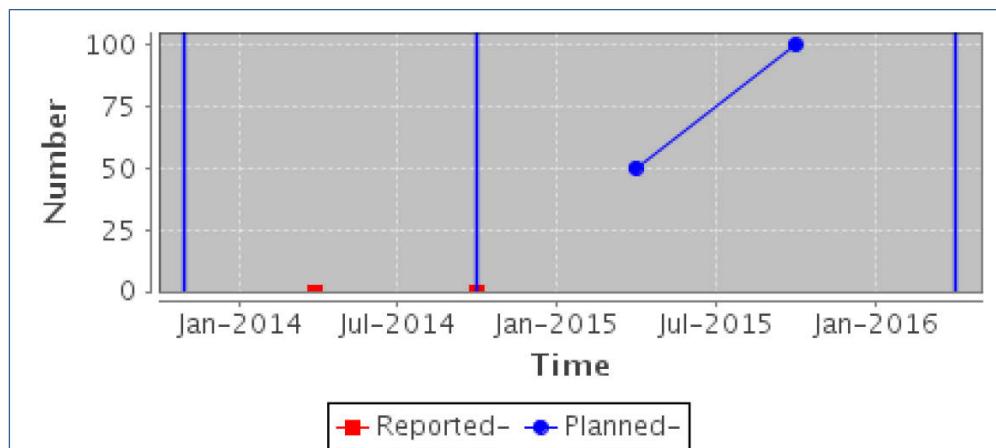
SP2\_SKPI\_08 Number of cellular maps in different brain regions

Responsible: a.lindner@fz-juelich.de



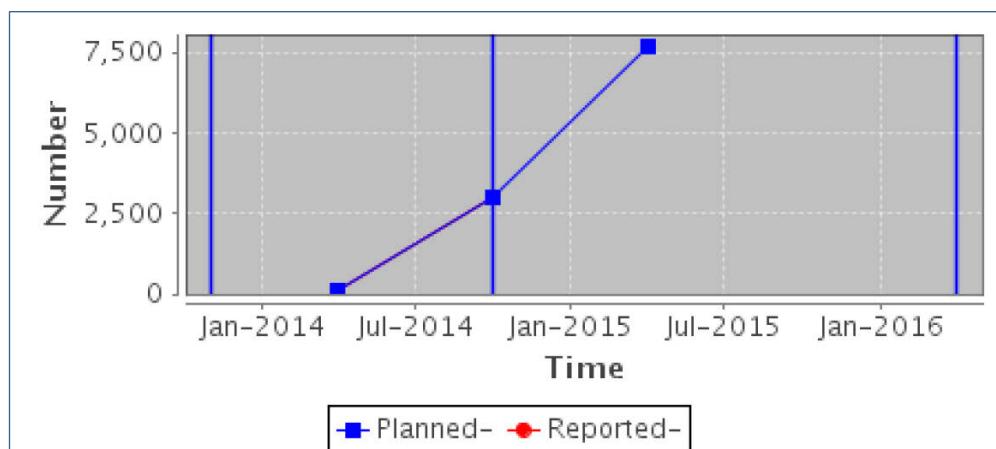
SP2\_SKPI\_09 Number of maps of individual identified neurons

Responsible: a.lindner@fz-juelich.de



SP2\_SKPI\_10 Number of high-resolution scans

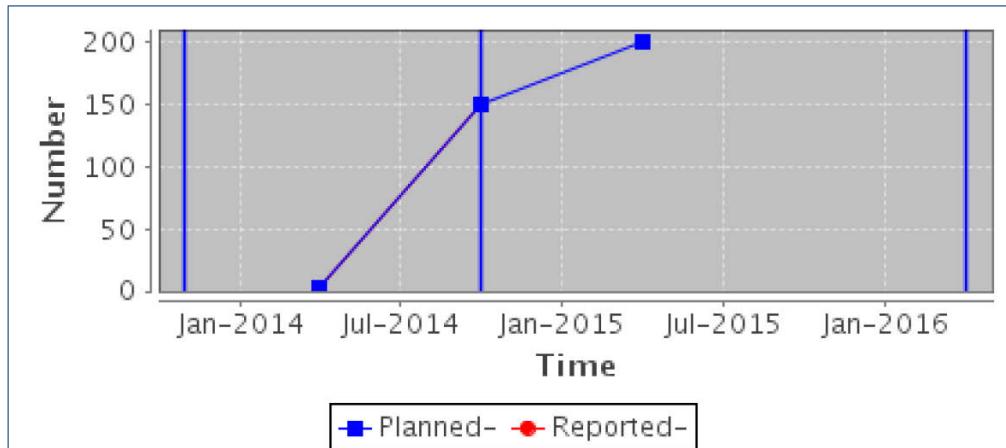
Responsible: a.lindner@fz-juelich.de





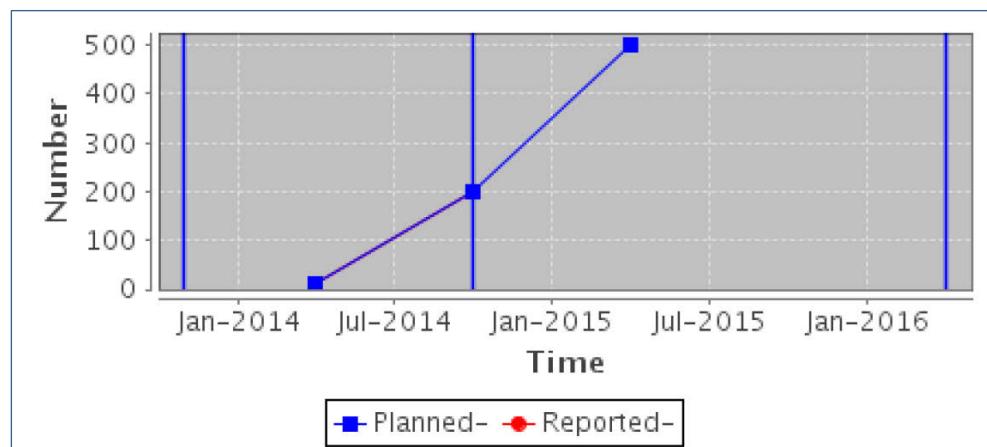
SP2\_SKPI\_11 Number of 200 strongly damaged 3D 20um thin scans reconstructed

Responsible: a.lindner@fz-juelich.de



SP2\_SKPI\_12 Number of 500-1000 lightly damaged 3D 20um thin scans reconstructed

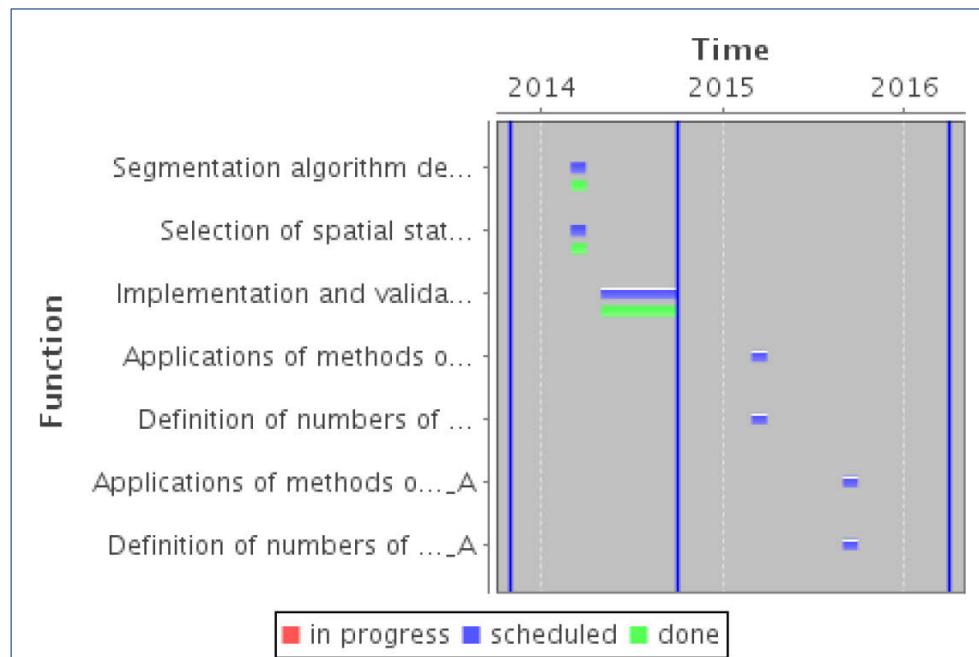
Responsible: a.lindner@fz-juelich.de



SP2\_SKPI\_27 Numbers and distributions of neurons and glia in each brain region

Responsible: a.lindner@fz-juelich.de

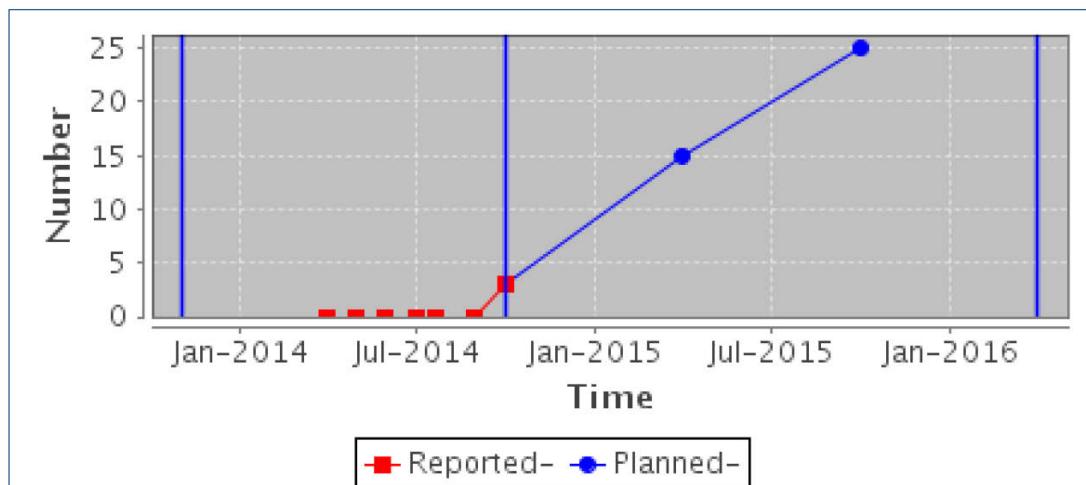
- Segmentation algorithm development. Planned: 2014/02/28 - 2014/03/31
- Selection of spatial statistical techniques. Planned: 2014/02/28 - 2014/03/31
- Implementation and validation of methods. Planned: 2014/04/30 - 2014/09/30
- Applications of methods on the brain regions. Planned: 2015/02/28 - 2015/03/31
- Definition of numbers of neurons and glia in the above regions. Planned: 2015/02/28 - 2015/03/31
- Applications of methods on the brain regions: orbital frontal. Planned: 2015/08/31 - 2015/09/30
- Definition of numbers of neurons and glia in the above regions. Planned: 2015/08/31 - 2015/09/30



#### 4.5.4 T2.1.4 Morphologies of human neurons in different brain regions

SP2\_SKPI\_13 Number of neurons in a reference data set of temporal cortex pyramidal neurons from peri-mortem reco

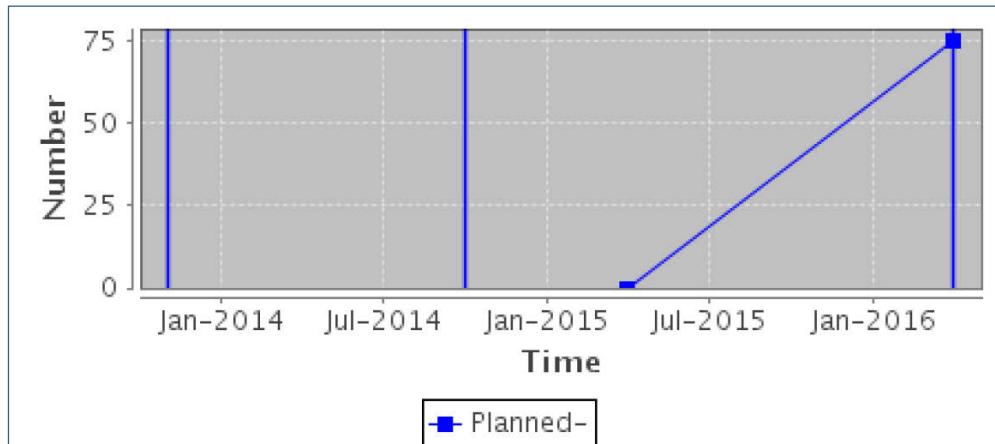
Responsible: a.lindner@fz-juelich.de





SP2\_SKPI\_14 Number of neurons in data sets of temporal cortex pyramidal neurons from three methods compared

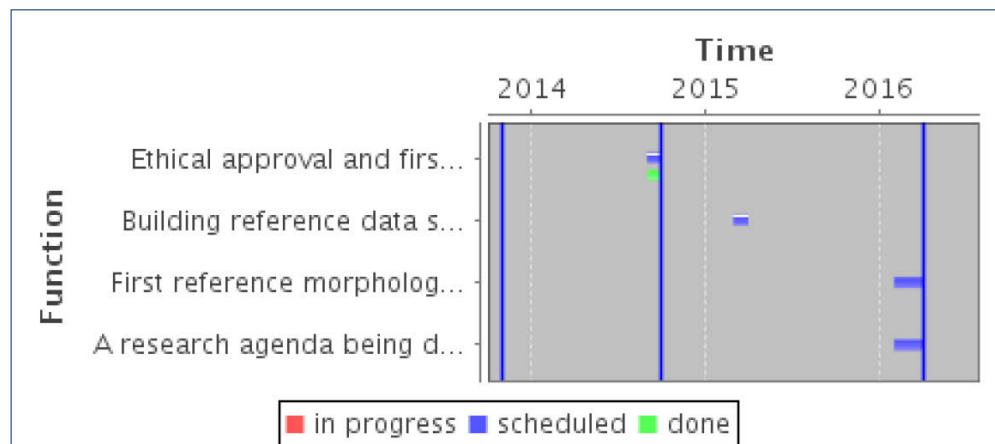
Responsible: a.lindner@fz-juelich.de



SP2\_SKPI\_28 Morphologies of selected human neurons

Responsible: a.lindner@fz-juelich.de

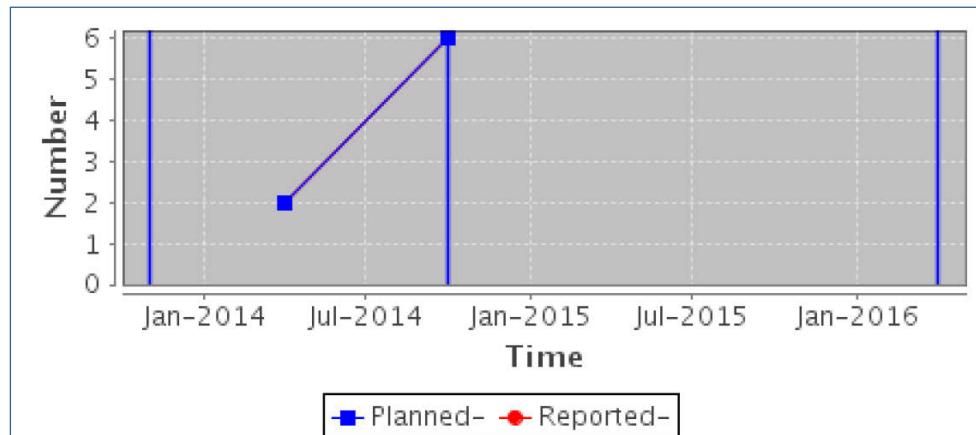
- Ethical approval and first recordings in peri-mortem brain. Planned: 2014/08/31 - 2014/09/30
- Building reference data set on temporal cortex pyramidal neuron morphologies from peri-mortem brain. Planned: 2015/02/28 - 2015/03/31
- First reference morphologies data sets of temporal cortical pyramidal neurons compared among three m. Planned: 2016/01/31 - 2016/03/31
- A research agenda being designed in collaboration with groups worldwide. Planned: 2016/01/31 - 2016/03/31



#### 4.5.5 T2.1.5 Distribution of receptors in the human cerebral cortex

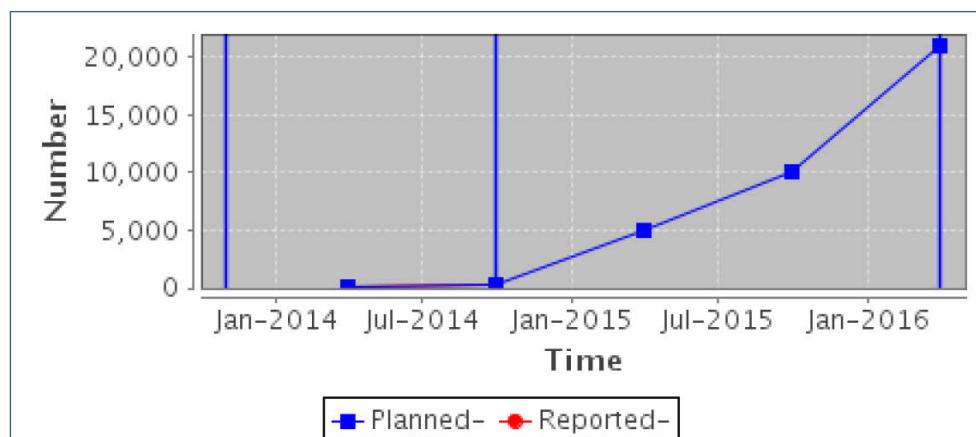
SP2\_SKPI\_15 No of hemispheres sectioned, incubated and exposed to film

Responsible: a.lindner@fz-juelich.de



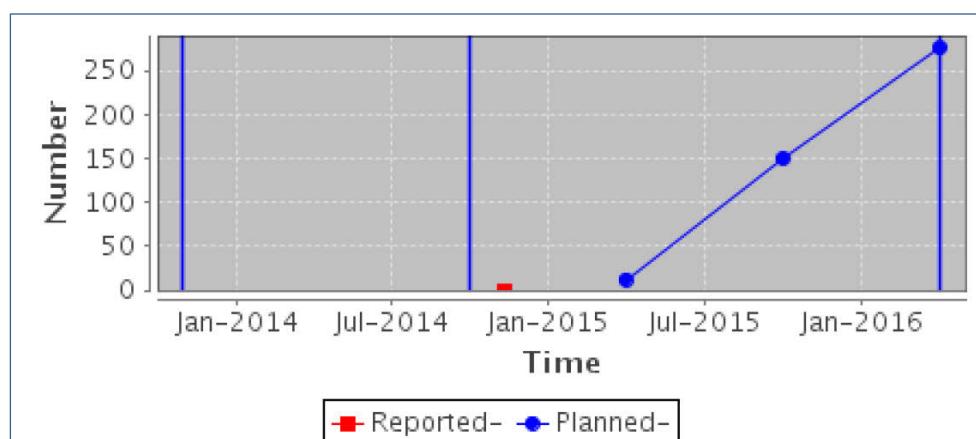
SP2\_SKPI\_16 No of autoradiographs digitised

Responsible: a.lindner@fz-juelich.de



SP2\_SKPI\_17 No of mean receptor densities measured

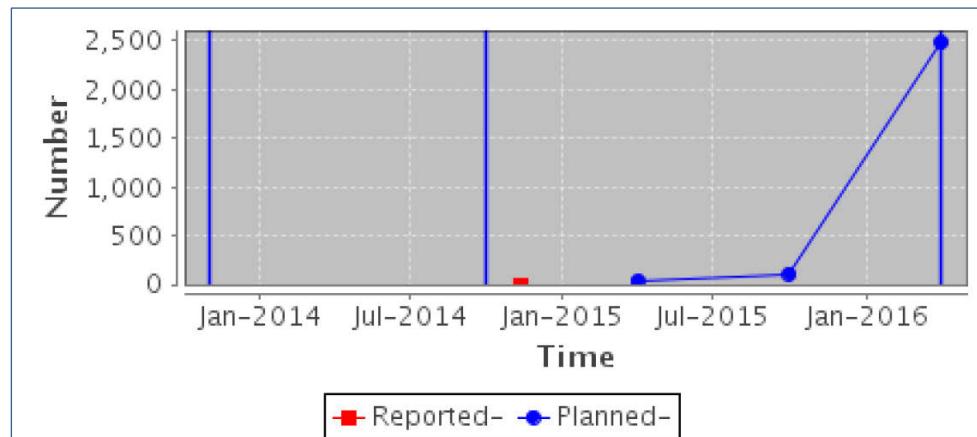
Responsible: a.lindner@fz-juelich.de





## SP2\_SKPI\_18 No of laminar profiles of receptor densities measured

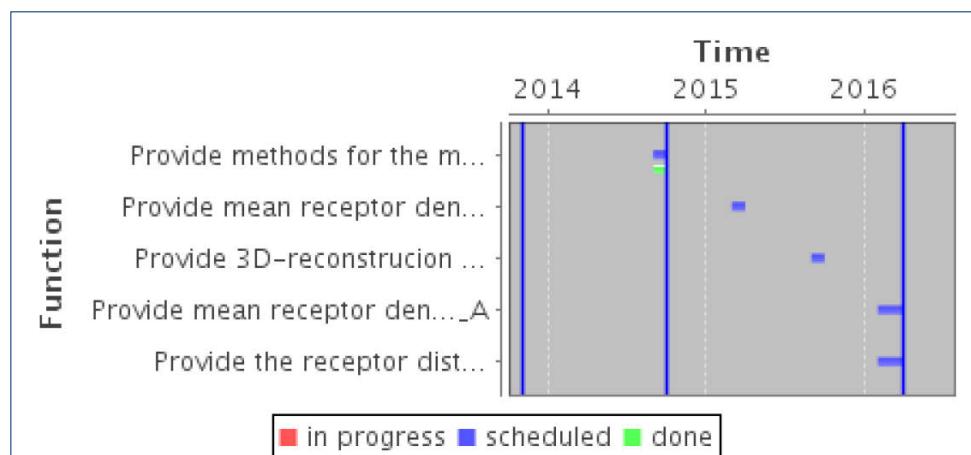
Responsible: a.lindner@fz-juelich.de



## SP2\_SKPI\_29 Distribution of selected receptors in the human brain

Responsible: a.lindner@fz-juelich.de

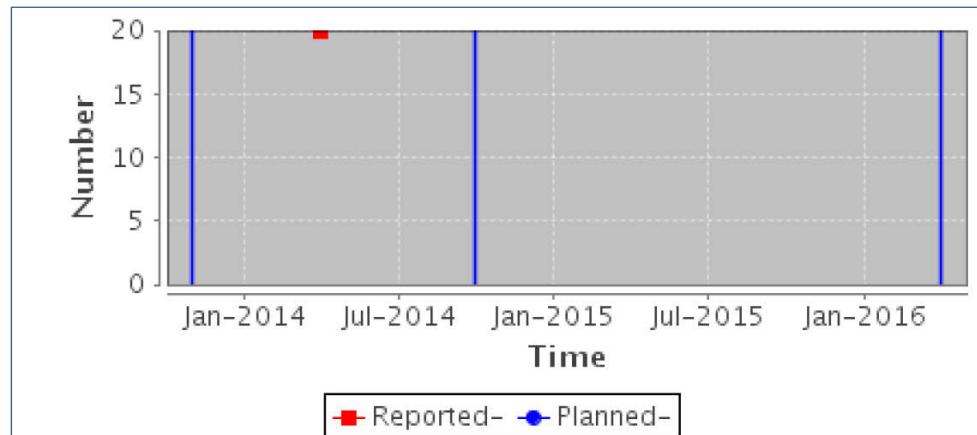
- Provide methods for the measurement of mean receptor density and laminar receptor profiles.  
Planned: 2014/08/31 - 2014/09/30
- Provide mean receptor density and laminar profiles of the muscarinic M2 receptor in primary sensory.  
Planned: 2015/02/28 - 2015/03/31
- Provide 3D-reconstruction of 2 human hemispheres.  
Planned: 2015/08/31 - 2015/09/30
- Provide mean receptor densities and laminar profiles for all 23 receptor binding sites.  
Planned: 2016/01/31 - 2016/03/31
- Provide the receptor distribution map warped to the reference brain of the human brain atlas.  
Planned: 2016/01/31 - 2016/03/31



### T2.1.6 The developing human brain

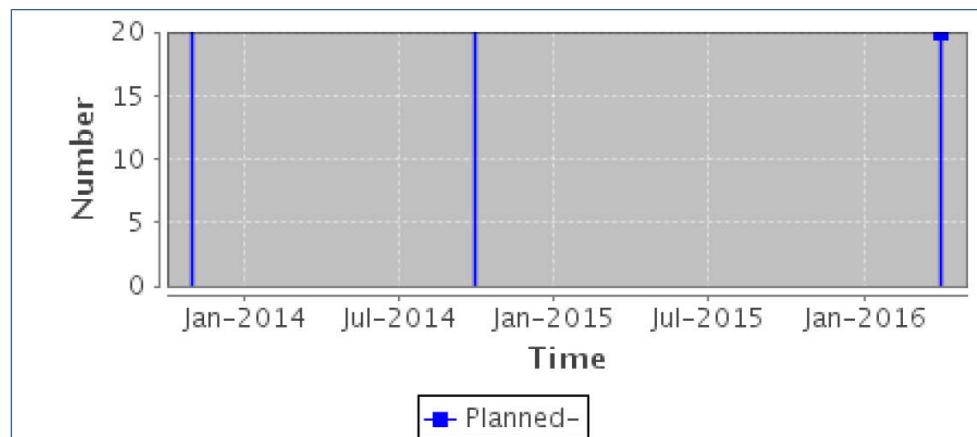
SP2\_SKPI\_19 Number of infants tested to infer the atlases

Responsible: a.lindner@fz-juelich.de



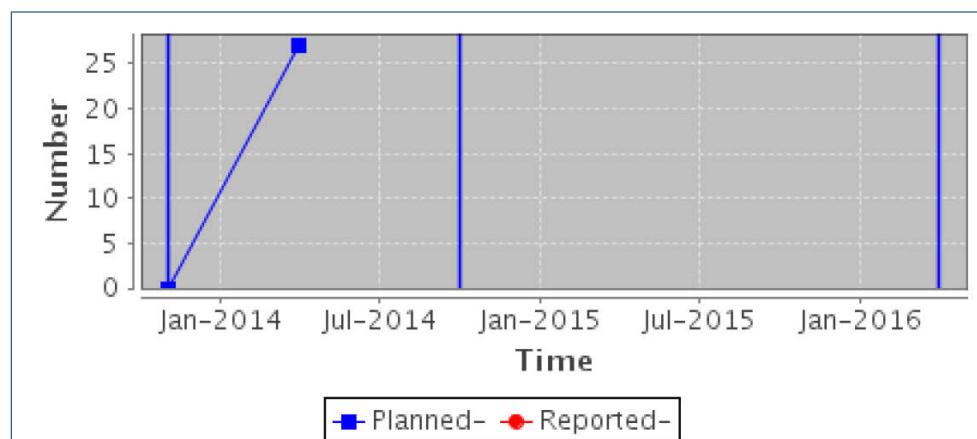
SP2\_SKPI\_20 Number of infants tested for the atlases

Responsible: a.lindner@fz-juelich.de



SP2\_SKPI\_21 Number of T2w anatomical images in infants

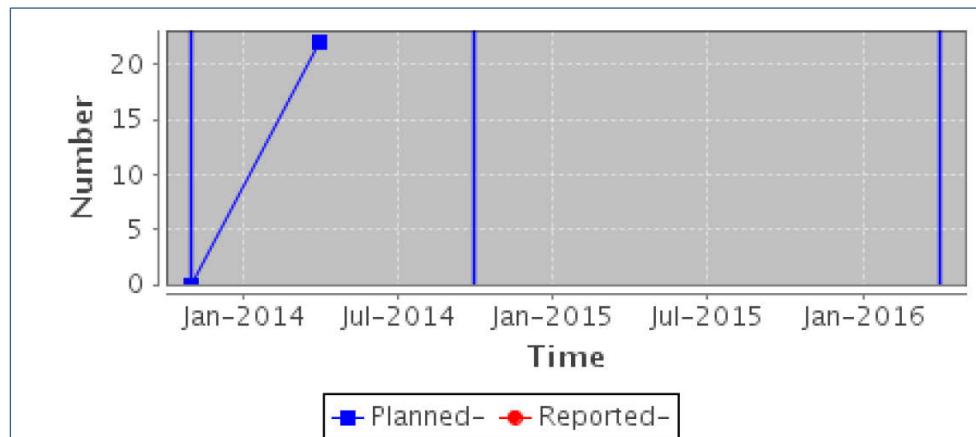
Responsible: a.lindner@fz-juelich.de





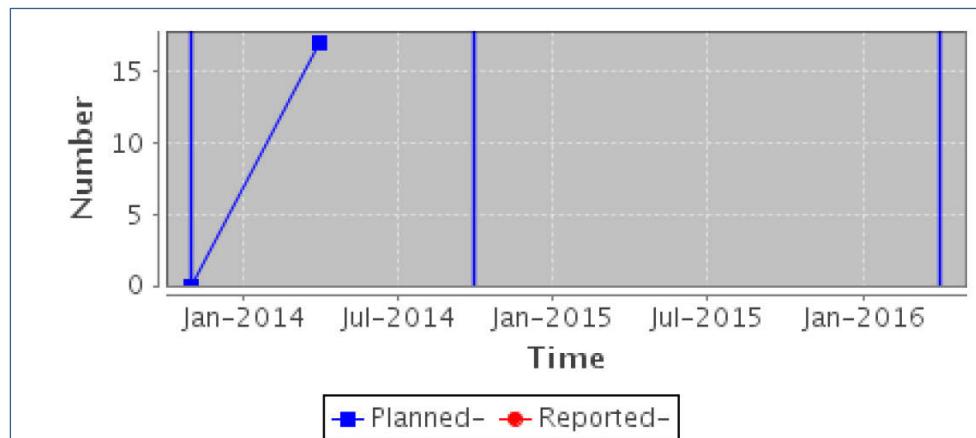
## SP2\_SKPI\_22 Number of diffusion images in infants

Responsible: a.lindner@fz-juelich.de



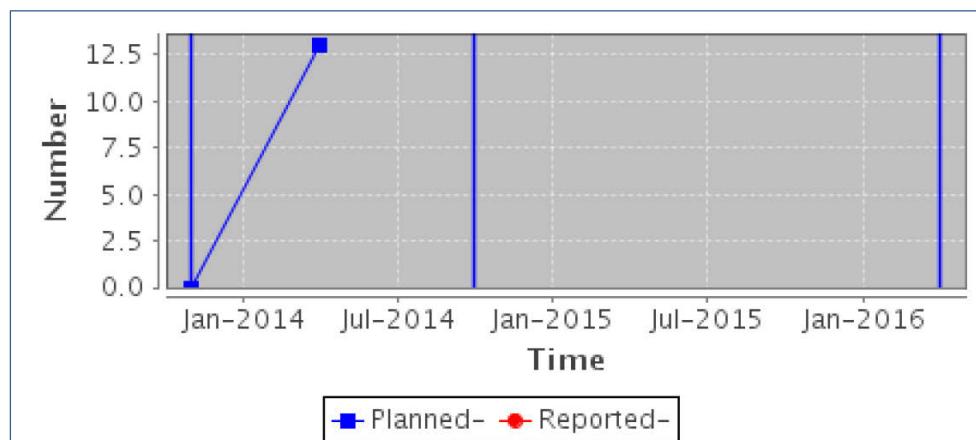
## SP2\_SKPI\_23 Number of T1 and T2 mappings in infants

Responsible: a.lindner@fz-juelich.de



## SP2\_SKPI\_24 Number of young adults tested

Responsible: a.lindner@fz-juelich.de

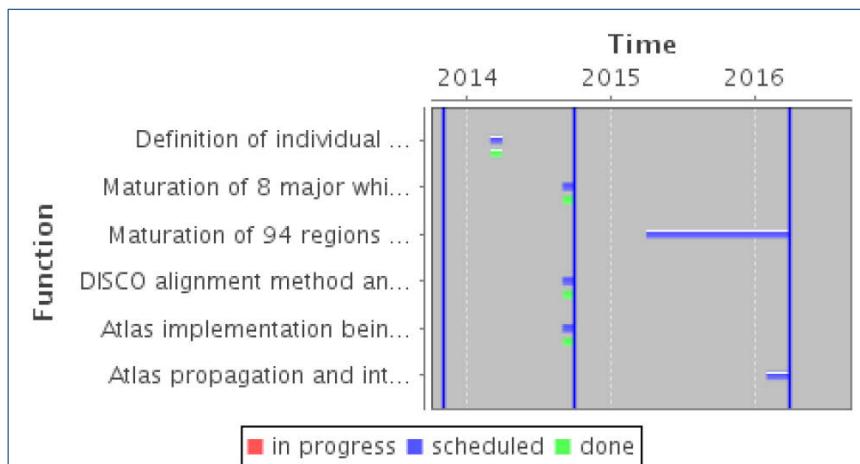




## SP2\_SKPI\_30 The Developing Human Brain

Responsible: a.lindner@fz-juelich.de

- Definition of individual bundles and the cortical template from infant and adult data. Planned: 2014/02/28 - 2014/03/31
- Maturation of 8 major white matter infant tracts. Planned: 2014/08/31 - 2014/09/30
- Maturation of 94 regions defined on our infant template in relation with Tzourio-Mazoyer et al- atlas. Planned: 2015/03/31 - 2016/03/31
- DISCO alignment method and elastic registration tested in infants. Planned: 2014/08/31 - 2014/09/30
- Atlas implementation being performed. Planned: 2014/08/31 - 2014/09/30
- Atlas propagation and integration tests completed. Planned: 2016/01/31 - 2016/03/31

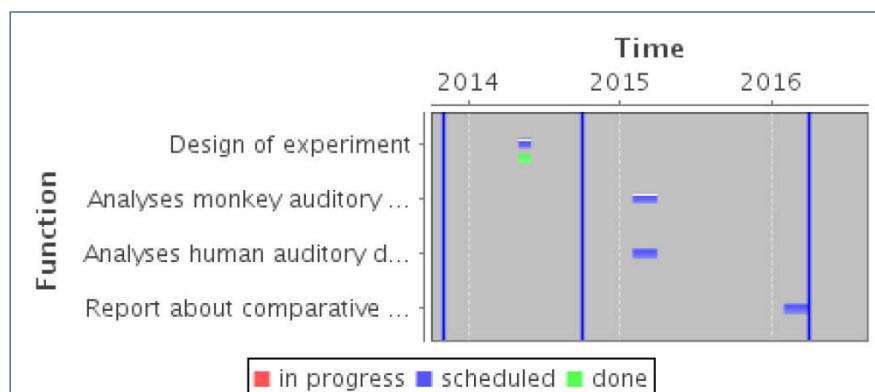


### 4.5.6 T2.1.7 Homologies between humans and other primates

#### SP2\_SKPI\_32 Human auditory fMRI experiment, Formisano/Vanduffel

Responsible: a.lindner@fz-juelich.de

- Design of experiment. Planned: 2014/04/30 - 2014/05/31
- Analyses monkey auditory data. Planned: 2015/01/31 - 2015/03/31
- Analyses human auditory data. Planned: 2015/01/31 - 2015/03/31
- Report about comparative auditory experiment. Planned: 2016/01/31 - 2016/03/31

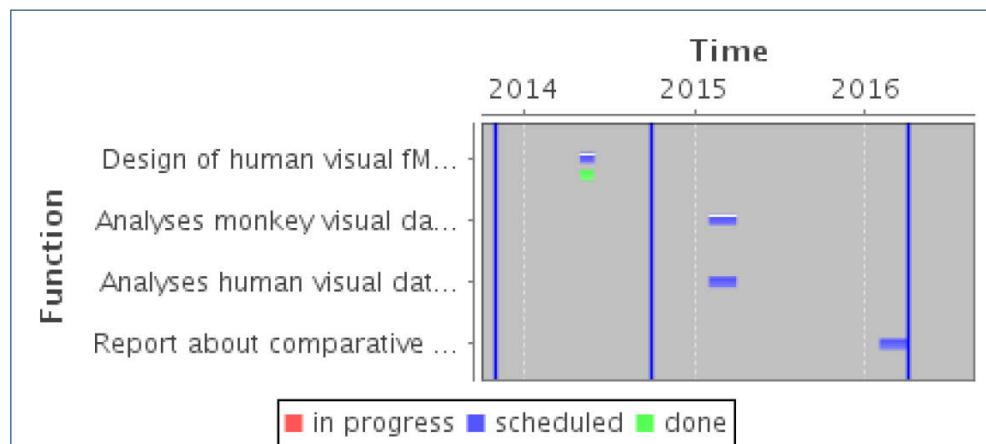




## SP2\_SKPI\_33 Human visual fMRI experiment, Goebel/Vanduffel

Responsible: a.lindner@fz-juelich.de

- Design of human visual fMRI experiment. Planned: 2014/04/30 - 2014/05/31
- Analyses monkey visual data. Planned: 2015/01/31 - 2015/03/31
- Analyses human visual data. Planned: 2015/01/31 - 2015/03/31
- Report about comparative visual experiment. Planned: 2016/01/31 - 2016/03/31

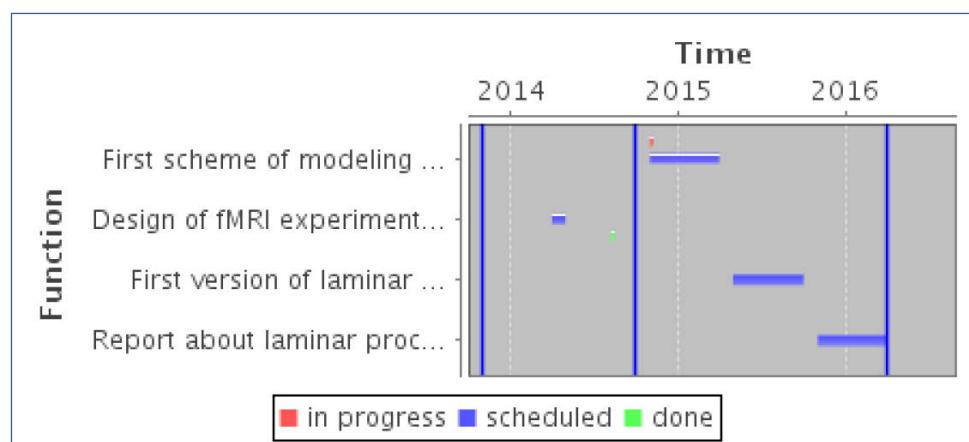


## 4.5.7 T2.1.8 Revealing the activity and function of cortical layers

### SP2\_SKPI\_31 Revealing the activity and function of cortical layers

Responsible: a.lindner@fz-juelich.de

- Design of fMRI experiment in collaboration with Goebel. Planned: 2014/04/01 - 2014/04/30
- First scheme of modeling approach. Planned: 2014/10/31 - 2015/03/31
- First version of laminar model. Planned: 2015/04/30 - 2015/09/30
- Report about laminar processing in the model. Planned: 2015/10/31 - 2016/03/31

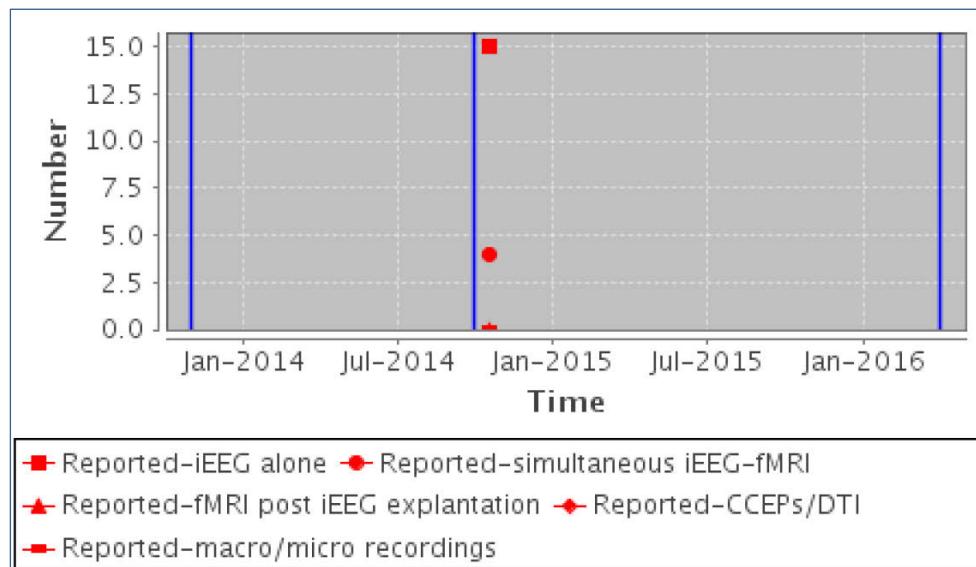




## 4.5.8 T2.1.9 Combining intra-cranial EEG and MRI in Humans

SP2\_SKPI\_36 Number of patient recordings

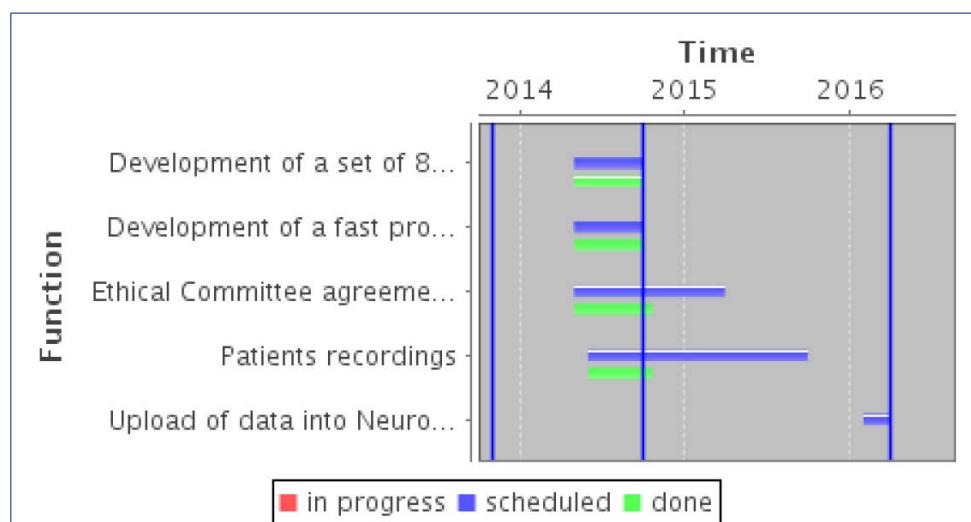
Responsible: a.lindner@fz-juelich.de



SP2\_SKPI\_34 Collect and analyse iEEG data from 30 patients using functional localisers

Responsible: a.lindner@fz-juelich.de

- Development of a set of 8 functional localizers. Planned: 2014/04/30 - 2014/09/30
- Development of a fast procedure iEEG signals induced by localizers. Planned: 2014/04/30 - 2014/09/30
- Ethical Committee agreement for macro/micro-recordings. Planned: 2014/04/30 - 2015/03/31
- Patients' recordings. Planned: 2014/05/31 - 2015/09/30
- Upload of data into Neuroinformatics Platform. Planned: 2016/01/31 - 2016/03/31



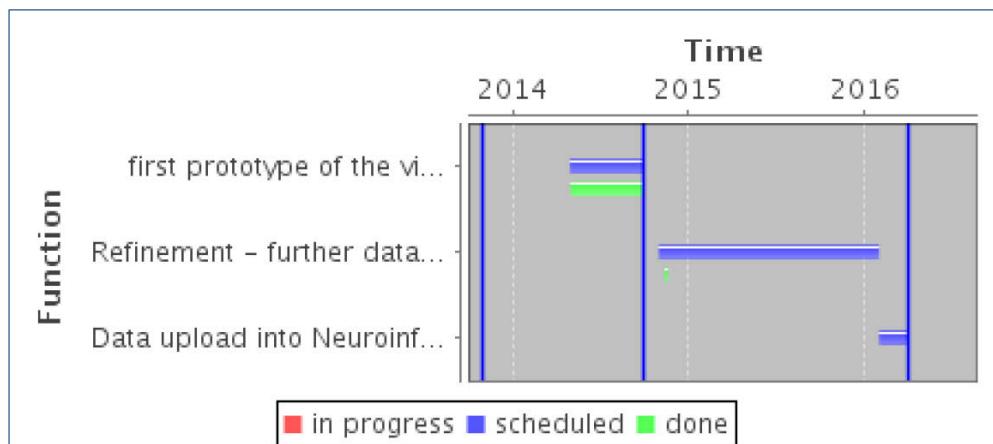
## 4.6 WP2.2: Data aggregation, analysis and dissemination

### 4.6.1 T2.2.3 iEEG Database organisation and multi-modal integration as a prototype for an international extension

SP2\_SKPI\_35 Software data visualisation

Responsible: a.lindner@fz-juelich.de

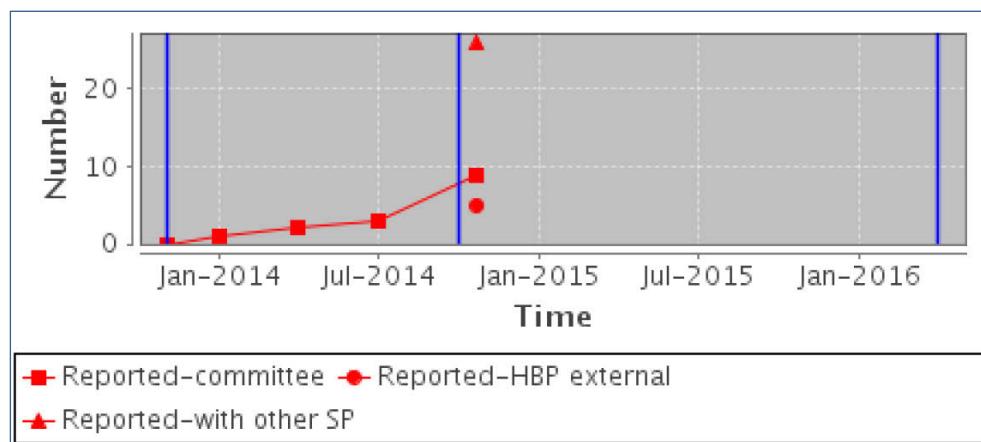
- First prototype of the visualization of iEEG data (population of patients). Planned: 2014/04/30 - 2014/09/30
- Refinement - further data sets. Planned: 2014/10/31 - 2016/01/31
- Data upload into Neuroinformatics Platform. Planned: 2016/01/31 - 2016/03/31



## 4.7 WP2.3 Strategic human brain data: scientific coordination

SP2\_SKPI\_37 SP2 Meetings

Responsible: a.lindner@fz-juelich.de





## Annex C: References

- [1] Eyal, G., Mansvelder, H.D., de Kock, C.P., Segev, I. Dendrites impact the encoding capabilities of the axon. *J Neurosci.* 34 (24), 8063-8071 doi: 10.1523/J Neurosci.5431-13.2014.
- [2] Zilles, K., Bacha-Trams, M., Palomero-Gallagher, N., Amunts, K., Friederici, A. Common molecular basis of the sentence comprehension network revealed by neurotransmitter receptor fingerprints, *Cortex* 63C, 79-89 (2014). doi: 10.1016/j.cortex.2014.07.007.
- [3] Kulikova (Buzmakova) S., Hertz-Pannier, L., Dehaene-Lambertz, G., Buzmakov, A., Poupon, C., Dubois, J. Multi-parametric evaluation of the white matter maturation. *Brain Structure & Function* (in press).
- [4] Thirion, B., Varoquaux, G., Dohmatob, E., Poline, J.B. Which fMRI clustering gives good brain parcellations? *Front Neurosci.* 8:167 (2014). doi: 10.3389/fnins.2014.00167.
- [5] Dohmatob, E., Gramfort, A., Thirion, B. and Varoquaux, G. Benchmarking solvers for TV-I1 least-squares and logistic regression in brain imaging. In: *Pattern Recognition in Neuroimaging (PRNI)*, Tübingen, Germany, April 2014. IEEE
- [6] Thirion, B., Varoquaux, G., Grisel, O., Poupon, C., Pinel, P. Principal Component Regression predicts functional responses across individuals. In: *17th International Conference Medical Image Computing and Computer-Assisted Intervention - MICCAI 2014*, Boston, USA, Proceedings, Part II pp 741-748 Springer
- [7] Amunts, K., Bücker, O., Axer, M. Towards a multiscale, high-resolution model of the brain. In: *BrainComp 2013, LNCS 8603*; L. Grandinetti et al., (Eds.), Springer International Publishing Switzerland, 2014.
- [8] Mohlberg, H., Tweddell, B., Lepage, C., Evans, A., Amunts, K. A new framework for processing BigBrain 2 on massively parallel supercomputers. *20<sup>th</sup> Annual Meeting of the Organization for Human Brain Mapping*, Hamburg, 2014 (Poster)
- [9] Dubois, J., Kulikova, S., Hertz-Pannier, L., Mangin, J.F., Dehaene-Lambertz, G., Poupon, C. Correction strategy for diffusion-weighted images corrupted with motion: Application to the evaluation of infants' white matter. *Magn Reson Imaging.* 2014 Oct; 32(8): 981-92. doi: 10.1016/j.mri.2014.05.007.
- [10] Dubois, J., Dehaene-Lambertz, G., Kulikova, S., Poupon, C., Hüppi, P.S., Hertz-Pannier, L. The early development of brain white matter: a review of imaging studies in fetuses, newborns and infants. *Neuroscience* 2014, 276: 48-71. (*Special issue "Secrets of the CNS White Matter"*) doi: 10.1016/j.neuroscience.2013.12.044.
- [11] Kabdebon, C., Leroy, F., Simmonet, H., Perrot, M., Dubois, J., Dehaene-Lambertz, G. Anatomical correlations of the international 10-20 sensor placement system in infants. *Neuroimage.* 2014 Oct 1;99: 342-56. doi: 10.1016/j.neuroimage.2014.05.046.
- [12] Schober, M., Schloemer, P., Huetz, T., Cremer, M., Mohlberg, H., Amunts, K., Axer, M. Three-dimensional reconstruction of histological blockface images using ID-encoded markers, In: *Annual Meeting of the Organization for Human Brain Mapping (OHBM)*, 2014, Hamburg, Germany
- [13] Amunts, K., Hawrylycz, M.J., Van Essen, D.C., Van Horn, J.D., Harel, N., Poline, J.B., De Martino, F., Bjaalie, J.G., Dehaene-Lambertz, G., Dehaene, S., Valdes-Sosa, P., Thirion, B., Zilles, K., Hill, S.L., Abrams, M.B., Tass, P.A., Vanduffel, W., Evans, A.C., Eickhoff, S.B. Interoperable Atlases of the human brain, *NeuroImage*, 99, 525-532 (2014). doi: 10.1016/j.neuroimage.2014.06.010.



## Annex D: Internal Meetings

Date	Description	Location	Participants	Organiser
5.3.14	1st general SP2-meeting	Conference Call	CEA: J.F. Mangin, G. Dehaene, JUELICH: K. Amunts, M. Aixer UDUS: S. Eickhoff, A. Lindner UHEI-STO: S. Rehberger-Schneider UPM: P. Flores Romero VU: H. Mansvelder	SP2 Coordinator
8.4.14	SP2 Subgroup Meeting UCBL/UJF: First meeting to organise collaboration	UCBL	UCBL: O. Bertrand, P. David, J.P. Lachaux, P. Ryvlin UJF: P. Kahane, J. Bastin	SP2 Partners in Tasks 2.1.9/2.2.3
14.4.14	The IBC medical protocol	INRIA, Paris	INRIA: B. Thirion and working group	SP2 Task Leader B. Thirion
13.5.14	SP2 Subgroup Meeting UCBL/UJF: Macro/micro-recordings	Conference Call	UCBL: JP Lachaux, Bastin UJF: P Kahane, David	SP2 Partners in Tasks 2.1.9/2.2.3
28.5.14	SP2 Subgroup Meeting KNAW/UM: Stimulus design for human laminar project	NIN, Amsterdam	KNAW: Matthew Self, Pieter Roelfsema UM: Ursula Budnik	SP2 Partners in T2.1.7 and T2.1.8
4.6.14	SP2 Subgroup Meeting JUELICH/UDUS	INM1, Jülich	JUELICH: K. Amunts, M. Aixer, K. Zilles, H. Mohlberg UDUS: S. Eickhoff, A. Lindner	SP2 Leader
10.6.14	SP2 Subgroup Meeting UCBL/UJF: Multimodal visualisation	Conference Call	UCBL: JP Lachaux Bhattacharjee, David, UJF: Kahane, Bidet-Caulet,	SP2 Partners in Tasks 2.1.9/2.2.3



Date	Description	Location	Participants	Organiser
16/17.6.14	2 <sup>nd</sup> general SP2-meeting+ Guests from SP5 and STO	INM1, Jülich	CEA: J.F. Mangin; G. Dehaene; J. Lehenberg; C.P. oupon, INRIA: Thirion, Bertrand JUELICH: Amunts, Katrin; M. Aixer; D. Bzdok; S. Könen; S. Mohlberg; N. Palomero-Gallagher; N. Schubert; K. Zilles MU: E. Formisano; U. Budnik LENS: F. Pavone UDUS: S. Eickhoff; A. Lindner VU: H. Mansvelder GUESTS SP5: K. Elsig; J. Muller; X. Vasques (all EPFL) STO: S.R. Schneider, UHEI	SP2 Coordinator
24.6.14	SP2 Subgroup Meeting JUELICH/UDUS	INM1, Jülich	JUELICH: K. Amunts, M. Aixer, K. Zilles, H. Mohlberg, UDUS: S. Eickhoff, A. Lindner	SP2 Leader
23.7.14	SP2 Subgroup Meeting JUELICH/UDUS	INM1, Jülich	JUELICH: K. Amunts, M. Aixer, K. Zilles, H. Mohlberg, UDUS: S. Eickhoff, A. Lindner	SP2 Leader
1.9.14	SP2 Subgroup Meeting JUELICH/UDUS	INM1, Juelich	JUELICH: K. Amunts, M. Aixer, UDUS: A. Lindner	SP2 Leader
18.9.14	Preparation of Heidelberg Summit	Conference Call	UCBL: JP Lachaux, O. Bertrand, P. Ryvlin, David UJF: P. Kahane, Vidal, Bidet-Caulet	SP2 Partners in Tasks 2.1.9/2.2.3
29.9.14	3rd general SP2-meeting	HBP Summit, Heidelberg	CEA: J.F. Mangin INRIA: B. Thirion, T. Ruest JUELICH: M. Aixer, H. Mohlberg UCBL: O. Bertrand UDUS: S. Eickhoff, A. Lindner UM: R. Goebel, U. Budnik	SP2 Coordinator



## Annex E: Cross-SP Meetings

Date	Description	Location	SP / Participants	Organiser
10/11.1.14	Cross Meeting SP2/SP3: Cooperation for connection of body-representing regions in health and schizophrenia	EPFL, Lausanne	SP2: S. Eickhoff (UDUS), SP3: O. Blanke (EPFL)	SP2/SP3 Partners
15.1.14	Cross Meeting SP2/SP5/SP7: Coordination and administration	FZJ Jülich	SP2: A. Lindner, UDUS SP5: M. Reske, JUELICH SP7: B. Orth, A. Dolam, G. Dresia, J. Stier, all JUELICH	JUELICH Administrator
24.3.14	Cross Meeting with SP2/SP5/SP7: coordination and administration	FZJ Jülich	SP2: A. Lindner, UDUS SP5: M. Reske, JUELICH SP7: B. Orth, A. Dolam, G. Dresia, J. Stier, all JUELICH	JUELICH Administrator
27.3.14	BoD-meeting	Conference Call	SP2: K. Amunts, JUELICH/UDUS, J. Mangin, CEA	HBP Administrator
14.4.14	German Partners Meeting	Conference Call	SP2: K. Amunts, JUELICH/UDUS, A. Lindner, UDUS Others: see protocol	UHEI
17.4.14	BoD-meeting to discuss FPA-draft	Conference Call	SP2: K. Amunts, JUELICH/UDUS, J. Mangin, CEA	HBP Administrator
28.4.14	Cross Meeting SP2/SP5/SP7 coordination and administration	FZJ Jülich	SP2: A. Lindner, UDUS SP5: M. Reske, JUELICH SP7: B. Orth, A. Dolam, G. Dresia, J. Stier, all JUELICH	JUELICH Administrator
12.5.14	German Partners Meeting	Conference Call	SP2: K. Amunts, JUELICH/UDUS, A. Lindner, UDUS Others: see protocol	UHEI
	Cross Meeting SP2/SP5: Uploading morphology-data	EPFL	SP2: H. Mansvelder SP5: M. Telefont	SP2 Partners
14.5.14	Cross Meeting SP2/ SP5: Brain Atlas	Conference Call	SP2: K. Amunts, JUELICH/UDUS, M. Axer, H. Mohlberg, JUELICH, S. Eickhoff, UDUS SP5: T. Papillo, J. Muller, X. Vasques (all EPFL)	SP2 Partners
4.6.14	Cross-Meeting SP1/SP2	Conference Call	SP2: K. Amunts, JUELICH SP1: S. Grant, UEDIN	SP2/SP1 Partners
11/12.6.14	Cross meeting SP2/SP3: Cognitive Tasks for infants	CEA, Paris	SP2: G. Dehaene, CEA SP3: HBP-partners	SP2/SP3 Partners
13.6.14	BoD-meeting	Conference Call	SP2: K. Amunts, JUELICH/UDUS J. Mangin, CEA	HBP Administrator



Date	Description	Location	SP / Participants	Organiser
23.6.14	Cross Meeting SP2/SP3: The archi study - scientific results and perspectives for IBC	INRIA, Paris	SP2: B. Thirion, INRIA and working-group, C. Poupon, CEA SP3: S. Dehaene, CEA	SP2/SP3 Partners
24.6.14	Cross Meeting SP1/SP2: Cooperation in Task 2.1.3	Conference Call	SP1: J. FeFelipe SP2: K. Amunts, JUELICH/UDUS	SP2
14.7.14	German Partners Meeting	Conference Call	SP2: K. Amunts JUELICH/UDUS, A. Lindner, UDUS Others: see protocol	UHEI
24.7.14	Cross Meeting SP1/SP2/SP7: Cooperation JUELICH/LENS/ CINECA	LENS, Florence	SP1: F. Pavone, LENS SP2: K. Amunts, JUELICH/UDUS SP7: Th. Lippert, JUELICH	SP1/SP2/SP7 Task Leaders
	Cross Meeting SP2/SP4/SP6: Share morphology data for modelling	Amsterdam	SP2: H. Mansvelder SP4: I. Segev	SP2/SP4 Partners
25.8.14	German Partners Meeting	Conference Call	SP2: A. Lindner, UDUS, H. Mohlberg, JUELICH Others: see protocol	UHEI
1.9.14	Cross Meeting SP2/SP3: Acquisition parameters for IBC	INRIA, Paris	SP2: B. Thirion, INRIA and working-group SP3: C. Pallier, S. Dehaene	SP2/SP3 Partners
19.9.14	Cross Meeting SP1/SP2/SP7: Cooperation JUELICH/LENS/ CINECA	Conference Call	SP1: F. Pavone SP2: K. Amunts, JUELICH/UDUS SP7: Th. Lippert	SP1/SP2/SP7 Task Leaders
28.9.14	Pre-board-meeting	HBP Summit, Heidelberg	SP2: K. Amunts, JUELICH/UDUS; J.F. Mangin, CEA	HBP Administrator
28.9.14	German Partner Meeting	HBP Summit, Heidelberg	SP2: K. Amunts, JUELICH/UDUS; M. Axer, H. Mohlberg, JUELICH, S. Eickhoff, UDUS, A. Lindner, UDUS	UHEI
30.9.14	Cross Meeting SP1/SP2	HBP Summit, Heidelberg	SP2: K. Amunts, JUELICH/UDUS; R. Goebel, UM; J. DeFelipe	SP1/SP2 Leaders
30.9.14	Cross Meeting SP2/SP3	HBP Summit, Heidelberg	SP2: J.F. Mangin, CEA, K. Amunts, JUELICH/UDUS, M. Axer, JUELICH, H. Mohlberg, JUELICH, S. Eickhoff, UDUS, U. Budnik, UM,	SP2/SP3 Coordinators
30.9.14	Cross Meeting SP2/SP5/SP8	HBP Summit, Heidelberg	SP2: J.F. Mangin, CEA, K. Amunts, JUELICH/UDUS, M. Axer, JUELICH, H. Mohlberg, JUELICH, S. Eickhoff, UDUS, U. Budnik, UM, R. Goebel, UM;	SP5/SP2 Coordinators
1.10.14	Cross-SP-meeting SP1/SP2/SP5/SP6	HBP Summit, Heidelberg	SP2: J.F. Mangin, CEA, K. Amunts, JUELICH/UDUS, M. Axer, JUELICH, H. Mohlberg, JUELICH, S. Eickhoff, UDUS, U. Budnik, UM, R. Goebel, UM	SP5/SP2 Coordinators



## Annex F: External Meetings

Date	Description	Location	Participants	Organiser
10.2.14	Potential for collaboration	Maastricht	JUELICH: K. Amunts UM: R. Goebel	SP2 Leader
24/25.3. 14	Conference: Human Neurons and neuronal networks	Amsterdam	SP2: H. Mansvelder, VU 35 international researchers	SP2 Partners
24.3.14	Exchange of data and images	Juelich	SP2: K. Amunts, UDUS/JUELICH Allen-Institute: C. Koch	SP2 Partners
12.5.14	Development of functional localizers	UCBL	SP2: JP Lachaux, P. Kahane, Bastin, Perrone-Bertolotti	SP2 Partners
May 2014	Re-using protocol of Human Connectome Project (HCP)	Conference Call	SP2: B. Thirion, INRIA HCP-researcher	SP2 Partners
June 2014	Receive HCP-retinotopic stimuli to map occipital, parietal, parts of frontal cortex	Conference Call	SP2: B. Thirion, INRIA HCP: M. Sereno	SP2 Partners
26.6.14	Protocols and priorities in recordings from human neurons	Amsterdam	SP2: H. Mansvelder, Researchers from UK	SP2 Partners
June 2014	Discussion on sharing data	Conference Call	SP2: H. Mansvelder, VU Allen-Institute: C. Koch	SP2 Partners