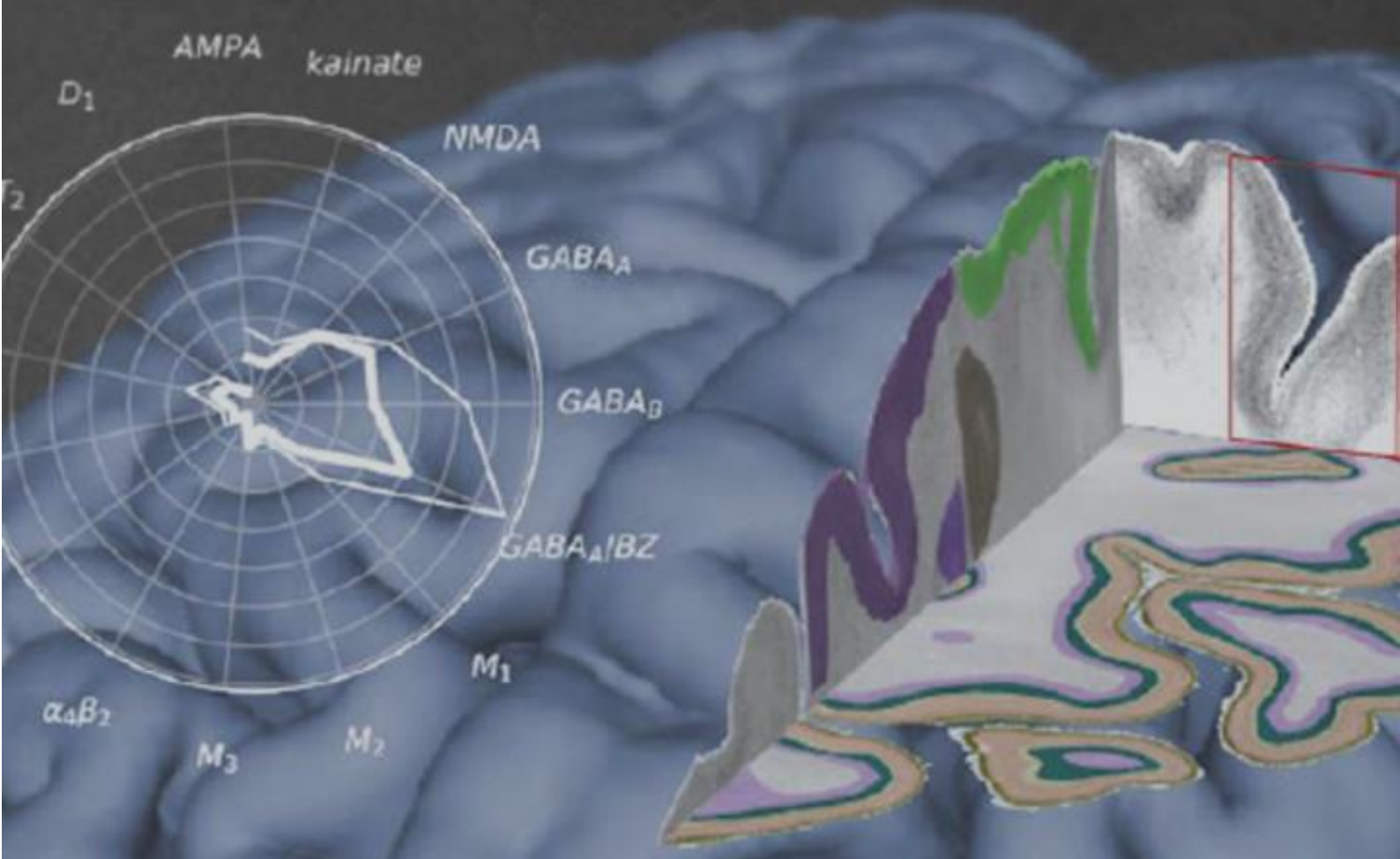
EBRAINS Multilevel Human Brain Atlas

A Market Analysis of the Technology



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Human Brain Project

Innovation & Technology Transfer Node

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Abstract:	The last decades have witnessed an ever-growing development of new brain maps and atlases as the ultimate tools to further discover the brain's anatomy, functions and connections, both with research and clinical purposes. As one of the most important brain research initiatives ever, the Human Brain Project has devoted important efforts to this domain and obtained correspondingly notable results, being the EBRAINS Multilevel Human Brain Atlas the most important one. In this market analysis, we first describe the main features of the EBRAINS Atlas to then review the broad landscape of international brain research and mapping initiatives. This enables the taxonomization of the main existing atlases according to 39 filters grouped into three key domains: content, digital infrastructure and miscellanea. The conclusions of such contextualization of the EBRAINS Atlas among its international competitors are then condensed into a SWOT analysis. Once aware of the EBRAINS Atlas baseline scenario, we explore its exploitation possibilities through the insights of six interviewees: four neurologists, one neurosurgeon and one former surgeon now working as Medical Director in the neurotechnology industry. The information gathered throughout the market analysis is then used to outline exploitation strategies for the EBRAINS Atlas based on different scenarios, according to the resources available. Finally, a list of some of the most important private players in neurotech, potential customers and/or partners for the EBRAINS Atlas, is provided.
Keywords:	HBP, EBRAINS, atlas, market analysis, SWOT, exploitation, stakeholders
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Abstract

The last decades have witnessed an ever-growing development of new brain maps and atlases as the ultimate tools to further discover the brain's anatomy, functions and connections, both with research and clinical purposes. As one of the most important brain research initiatives ever, the Human Brain Project has devoted important efforts to this domain and obtained correspondingly notable results, being the EBRAINS Multilevel Human Brain Atlas the most important one. In this market analysis, we first describe the main features of the EBRAINS Atlas to then review the broad landscape of international brain research and mapping initiatives. This enables the taxonomization of the main existing atlases according to 39 filters grouped into three key domains: content, digital infrastructure and miscellanea. The conclusions of such contextualization of the EBRAINS Atlas among its international competitors are then condensed into a SWOT analysis. Once aware of the EBRAINS Atlas baseline scenario, we explore its exploitation possibilities through the insights of six interviewees: four neurologists, one neurosurgeon and one former surgeon now working as Medical Director in the neurotechnology industry. The information gathered throughout the market analysis is then used to outline exploitation strategies for the EBRAINS Atlas based on different scenarios, according to the resources available. Finally, a list of some of the most important private players in neurotech, potential customers and/or partners for the EBRAINS Atlas, is provided.

Abbreviations

AIBR:	Allen Institute for Brain Research	IT:	Information Technologies
API:	Application Programming Interface	I#x:	Interviewee number x
AR/VR:	Augmented / Virtual Reality	KG:	Knowledge Graph
CLI:	Command Line Interface	MNI:	Montreal Neurological Institute
DBS:	Deep Brain Stimulation	MRI:	Magnetic Resonance Imaging
fMRI:	Functional MRI	NIF:	Neuroscience Information Framework
FSL:	FMRIB Software Library	NWB:	Neuroscience Without Borders
GUI:	Graphical User Interface	PCW:	Post Conception Weeks
HBP:	Human Brain Project	PET:	Positron Emission Tomography
HCP:	Human Connectome Project	SK:	Software Kit
IBI:	International Brain Initiative	SPM:	Statistical Parametric Mapping
ICBM:	International Consortium for Brain Mapping	ISH:	In-Situ Hybridization

Introduction

What are Brain Atlases?

Working Principle, Templates and Parcellations

Introduction. What are Brain Atlases? Working Principle, Templates and Parcellations

The brain is one of the most complex organs present in nature. In humans, as in all higher vertebrates, it integrates sensory information, directs motor responses and acts as center of learning.

With an approximate weight of 1.5 kg, the human brain integrates billions of cells called neurons[1], which are connected amongst them through synapses. While neurons produce the chemical and electrical messages that underlie cognitive activities (such as basic sensory functions), synapses are responsible for the transmission of those signals between neurons. This transmission process is critical to learning, memory and thought formation, and other cognitive activities.

It is this fundamental role of the brain what gives rise to its study. The outcomes of brain-related research are three-fold. The more we discover the brain and its functions,

- the better the treatments developed for its related disorders;
- the more we improve the computing technologies that try to imitate it (high data storage capacity, high processing speed, low energy consumption);
- and the more we satiate human curiosity for its own brain, mind and behaviour.

But studying the brain has never been easy. With its different regions and multiple functions, the human brain is a perfect example of complex system dynamics. To uncover those dynamics and understand how the human brain works, researchers map its segregation into structurally or functionally distinct regions, as well as the connections between those regions (i.e. the brain's connectome). Then come some of the most complex challenges, such as understanding brain plasticity, consciousness or the relationships between the brain's structure and function.

For the purposes of this market study, brain mapping will be defined as the "*attempt to specify in as much detail as possible the anatomy, connectivity and localization of function in the human brain*" (adapted from (Savoy, 2001)). Furthermore, nowadays brain maps should be regarded as databases, as this is

[1] Among other cell types that also include glial cells, which provide physical and metabolic support to neurons; or nerve fibers, the main nerve tracts in the central nervous system.

the only way to enable "*an integrated, computerized, as well as a comprehensive description of brain structure and function, along with the particulars of acquiring those data*" (Toga & Mazziotta, 2002). Finally, this market analysis will follow a brain atlas definition from (Amunts et al., 2014). This definition's main components include:

- The *template*. "*An exemplary brain scan or an aggregate of brain scans, which are possibly multi-modal and often averaged across multiple subjects*".
- The *space*. In this context, "*simply the coordinate system associated with a specific template*".

Thus, a brain atlas will be understood as a *mapping between a certain content and the atlas template's coordinate system (space)*. Finally, depending on how that space has been obtained, atlases will be classified as deterministic (the coordinate system provided uses a single brain as reference) or probabilistic (several brains have been averaged to provide a probability distribution associated with a set of labels).

Working Principle

To fully understand the concept of brain atlas, let's take a look at Figure 1. Through this comparative illustration, we would like the reader to understand that a brain atlas working principle is analogous to that of the Earth (Toga & Mazziotta, 2002).

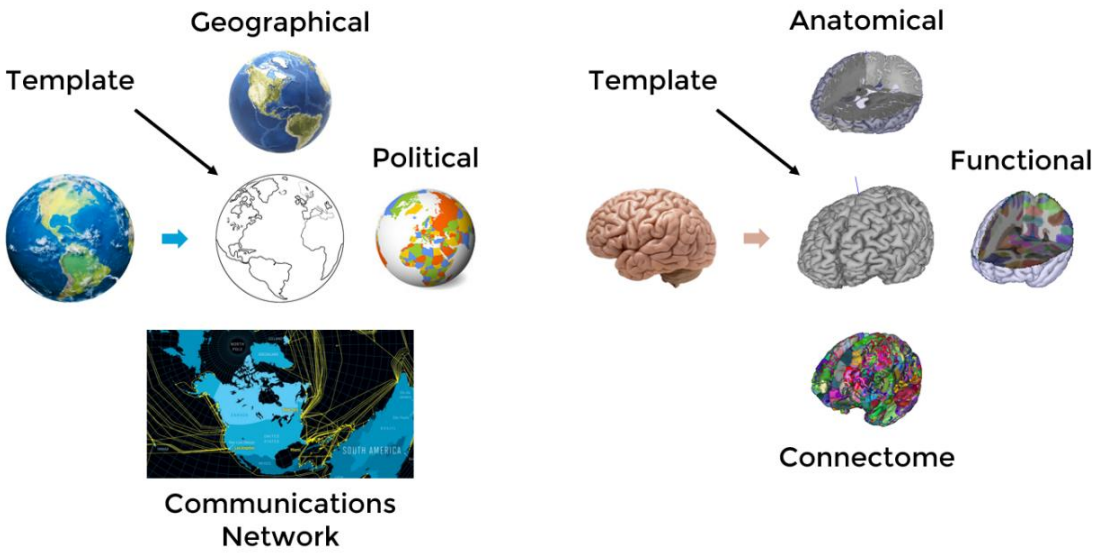

Figure 1. Comparative illustration of the Earth and a brain atlas.

First, we have a reality that we want to characterize. In this case, a human brain and its analogue for this example, the Earth[2]. We want to describe them not only at the physical level, but also regarding what is happening in that physical space (electrical impulses being transmitted, people crossing the Spanish-French border...), and how do some parts of the space relate to others.

In this case, both the human brain and the Earth are really complex themselves and understanding them better requires us to dismantle the problem in smaller pieces. Parcels of each reality that we will study separately. For example, the geographical and political characteristics of the Earth or, analogously in the brain, its anatomy and function.

Once a coherent understanding of those "smaller" problems has been achieved, it is the time to bring all available information together, in order to get the broadest perspective possible of our object of study. For this aim, a common reference space will be needed, where all that available information can be projected. In the case of the Earth, this is not too difficult: apart from physical considerations on what the shape of the planet is (Lowrie & Fichtner, 2020), a clear, single template (such as the one shown in Figure 1) will probably come to our minds.

However, this is not the case for the brain. Every single human brain is different to one another (Valizadeh et al., 2018), as a result of sexual dimorphism, age, ethnicity and other characteristics (Toga & Mazziotta, 2002). What brain should be then used as a template?

Brain Templates

Deepening into the *space* definition, for the purposes of this market analysis a *brain template* (also, *brain* space, *common brain reference space* or, simply, *space*), should be further understood as "*a standardized, or 'stereotaxic'[3], 3D coordinate frame for data analysis and reporting of findings from a neuroimaging experiment*" (Evans et al., 2012).

Modern brain spaces can be traced back to the developments of Jean Talairach, who first introduced a 3D coordinate system to orientate deep-brain surgeries in 1967. His collaboration with Pierre Tournoux, which resulted in a

[2] *A* human brain and not *the* human brain because of the immense existing intersubject variability. There are many different brains, and we can observe and describe only a very small fraction of them, so there is not one clearly defined reality. On the other hand, there is only one Earth.

[3] Stereotaxy, within the domain of brain mapping, "*concerns the coordinate system used to locate structures reliably in different individuals*" (Toga & Mazziotta, 2002).

printed atlas for the same purpose in 1988, was also a key milestone (Evans et al., 2012).

The innovations introduced by Talairach and Tournoux are still crucial in today's brain atlasing, namely: 1st) the use of a coordinate system to locate any particular brain region, relative to some anatomical landmarks used as origin of coordinates; 2nd) the possibility of matching two different brains through a spatial (mathematical) transformation; and 3rd) the elaboration of an "*atlas describing a standard brain, with anatomical and cytoarchitectonic labels*" (Brett et al., 2002).

More specifically, Talairach's stereotaxic approach is based on aligning the brain to the line described by the anterior commissure (AC) and posterior commissure (PC)[4], the AC-PC line, which is taken as the Y axis of the brain coordinate space. From this reference, the Z axis is described as the vertical line passing through the interhemispheric fissure and the AC, and the X axis is just the perpendicular line to the intersection of both. This construction allows to locate any point in the brain relative to these axes and "*has become almost universal in functional imaging*" (Brett et al., 2002).

Even though this core principle of brain mapping has remained almost unchanged since its formulation, the precise construction of brain spaces has, however, evolved through history in search for higher resolutions (Evans et al., 2012). Let's now briefly review the most renowned ones: the Talairach space[5] and the Montreal Neurological Institute (MNI) space, as well as the BigBrain, the most precise one up to date (Amunts et al., 2013).

The Talairach-Tournoux atlas[6], or the *Talairach space*, was built from a sectioned (thus, postmortem) 60-year-old female brain. Any strict mapping (projection) of a given brain scan to this template "*involves (...) application of three piece-wise linear scaling factor*" (Evans et al., 2012). However, such technique leads to variable spatial (in)consistency, and its use "*requires great care and understanding of its limitations*" (Nowinski & Thirunavuukarasuu, 2009), uncertainties already pointed out by Talairach and Tournoux in their original publication (Brett et al., 2002).

The paradigm of brain templates that followed the Talairach proposal was created by the Montreal Neurological Institute (Evans et al., 2012), and is based on averaging normal Magnetic Resonance Imaging (MRI) scans (Brett et al., 2002).

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[4] Relatively invariant subcortical landmarks (Brett et al., 2002).
[5] The term space should be regarded here is a synonym of template.
[6] Dear reader, do not let yourself be confused by terminology: the Talairach-Tournoux atlas is itself Talairach-Tounoux's brain template.

The first MNI space ever created, the MNI 305 T1 atlas, pioneered the concept of statistical MRI atlas for brain mapping (Evans et al., 2012). This atlas followed a two-step construction. First, it involved manual scaling of T1-weighted MRI scans (Evans et al., 2012) from 241 young healthy brains (Brett et al., 2002) to the Talairach brain. This resulted in a first-pass averaged space in the form of a T1-weighted MRI volume (Evans et al., 2012). Finally, such volume was used to renormalize another 305 normal MRI scans, by an automated linear normalization (Brett et al., 2002), to yield the definite MNI 305 T1 template.

It is remarkable that this MNI 305 atlas, which has served as the basis for the subsequent generations of MNI brain spaces, is itself "*an approximation of the original Talairach space*" (Evans et al., 2012). But also that, if differences between the two approaches are neglected, this can lead to space misinterpretation and "*significant errors, especially for coordinates in the temporal lobe*" (Brett et al., 2002).

The successive generations of MNI mappings were aimed at increasing the resolution of the resulting space. This was achieved through both averaging repeated scans of a single individual (MNI Colin 27 T1 atlas) and registration of a cohort of MRI scans, in both cases to a preexisting MNI template. With this procedure, the MNI developments have reached a maximum resolution of 0.5x0.5x0.5 mm^3 (MNI Non Linear 2009b) (*The McConnell Brain Imaging Centre: ICBM 152 N Lin 2009*, n.d.).

It should be noted that MNI spaces are the ones preferred by several software toolboxes related to brain mapping, such as Lead-DBS (based on MNI Non Linear 2009b), focused in facilitating Deep Brain Stimulation (DBS) electrode reconstructions and computer simulations (Lead-DBS, n.d.); the Statistical Parametric Mapping (SPM) software package (based on MNI 152 6th-generation), designed for the analysis of brain imaging data sequences (Ashburner, 2012); or the FMRIB Software Library (FSL) package (which integrates the MNI 152 6th-generation, also), a library of analysis tools for MRI brain imaging data (Jenkinson et al., 2012).

Even though the highest MNI resolution may be alright for nowadays clinical mapping applications, as this market analysis will show, there is a much higher resolution template already in place: the BigBrain space, which precision goes down to the micrometer scale (Amunts et al., 2013), thus filling a previously existing gap and complementing the millimeter scale templates. We will further explore it in Part 1 of this market analysis, when describing the EBRAINS Multilevel Human Brain Atlas content.

Once brain spaces have been explained, the reader is ready to understand what brain parcellation is, and so to end this introductory chapter.

Brain Parcellation / Segmentation

Medical imaging applications often require three-dimensional datasets to be segmented, parceled, as a starting point that enables further and finer analysis of the data. Segmentation of medical images is based on categorizing the voxels[7] of an image data into object classes. Such classes could inform about intensity distribution, spatial location, shape or neighborhood of the categorized information (Goldszal & Pham, 2000).

In brain mapping, in particular, such categorization usually consists in the specification of neuroanatomical regions to localize brain activation. On one side, said specification of neuroanatomical regions relies on already existing brain spaces (Evans et al., 2012) that have been previously segmented and labeled, in what is often called "*atlas-guided segmentation*" (Goldszal & Pham, 2000). On the other side, information about brain activation comes from brain scans (e.g. MRI scans). Once a scan is registered to a presegmented and prelabeled space, it acquires both the structural information and labels of that space (Goldszal & Pham, 2000), and thus segmentation of such brain scan is completed.

Parcellation criteria are varied. Neuroanatomical domains used for this aim range from cytoarchitecture, myeloarchitecture and gross anatomy; to fMRI, chemoarchitecture, vascular territories, anatomic connectivity, functional connectivity, anatomic-functional connectivity, (multi)receptor architecture and/or multiplicity of them; among others and as listed in (Amunts & Zilles, 2015).

Some examples of renowned volumetric parcellation schemes, as briefly reviewed by (Evans et al., 2012), include:

- The MNI spaces, which generated regional probability maps using data from their own database.
- The Talairach Daemon, "*a region-labeling tool for stereotaxic space,* [based on MNI probability maps and] *used in the BrainMap database* (...) [which] *data was subsequently included in the Pickatlas*, (...) *an extension to SPM*".
- The Harvard-Oxford, a probabilistic atlas in MNI 152 space that includes several T1-weighted cortical and subcortical regions. It is distributed with the FSL software package.

[7] The basic units of information of the dataset (codified as pixels when the dataset is visualized as an image).

- FreeSurfer, "*an open source software suite for processing and analyzing (human) brain MRI images*" (*FreeSurfer*, n.d.). Freesurfer integrates its own brain template, the Aseg atlas, built from "*four groups of 10 subjects each: (1) young, (2) middle aged, (3) healthy older adults* [and] *(4) older adults with AD (Alzheimer's Disease)*" (*FreeSurfer Wiki*, n.d.).
- The Automatic Anatomic Labeling (AAL) atlas, which segmented MNI Colin 27, non-linearly warped to MNI 152 space, into 45 volumes per hemisphere, also including a cerebellar parcellation.
- Cytoarchitectonic maps developed by Jülich non-linearly warped to MNI space. This is the only of the cited parcellation schemes based on microscopic / cytoarchitectonic features (the rest refer to macroscopical landmarks). It is included in EBRAINS (EBRAINS KG Dataset - Julich-Brain Atlas cytoarchitectonic maps (v2.9), n.d.) , as well as in the SPM software package (Eickhoff et al., 2005).

Part 1

Current Position of the EBRAINS Multilevel Human Brain Atlas

Part 1. Current Position of the EBRAINS Multilevel Human Brain Atlas

Once the reader understands the basics of brain atlases, templates and parcellations, we can now introduce the EBRAINS Multilevel Human Brain Atlas (hereafter, the EBRAINS Atlas / HBP Atlas). In particular, we will explore its content, digital infrastructure and other aspects relevant to this market analysis.

Before getting started, it shall be useful to have a broad image of the EBRAINS Atlas. In the content section, the brain templates and maps directly accessible via the EBRAINS Atlas' siibra-toolsuite will be explored. The siibra-toolsuite includes the web-based interactive viewer *siibra-explorer*, the python client *siibra-python* and the HTTP application programming interface (API) *siibra-api*. Secondly, that content only accessible via the EBRAINS Knowledge Graph (KG) Database will be described. Following the EBRAINS KG and the EBRAINS Atlas' siibra-explorer and siibra-api will be further explained. Finally, we will discuss other complementary aspects (miscellanea).

EBRAINS Atlas Content

We will present the EBRAINS Atlas content in two levels. *Integrated Content* will refer to all templates and maps directly accessible via the EBRAINS Atlas' siibra-toolsuite. On the other hand, *External Content* will refer to the EBRAINS KG data that cannot still be retrieved through the siibra-toolsuite. It shall be noted that most of the EBRAINS Atlas content is publicly available in the EBRAINS KG. Also, that all EBRAINS Atlas content is (planned to) be retrievable from the EBRAINS KG into the atlas' API for its programmatic treatment.

Integrated Content will also be subclassified following a three-level scheme. We will discuss each accessible template and, subsequently before moving on to the next one, the brain maps available within that brain space. Third, we will refer to the content accessible through the EBRAINS Atlas' siibra-explorer plug-ins. Graphically, our analysis will follow the scheme presented in Figure 2:

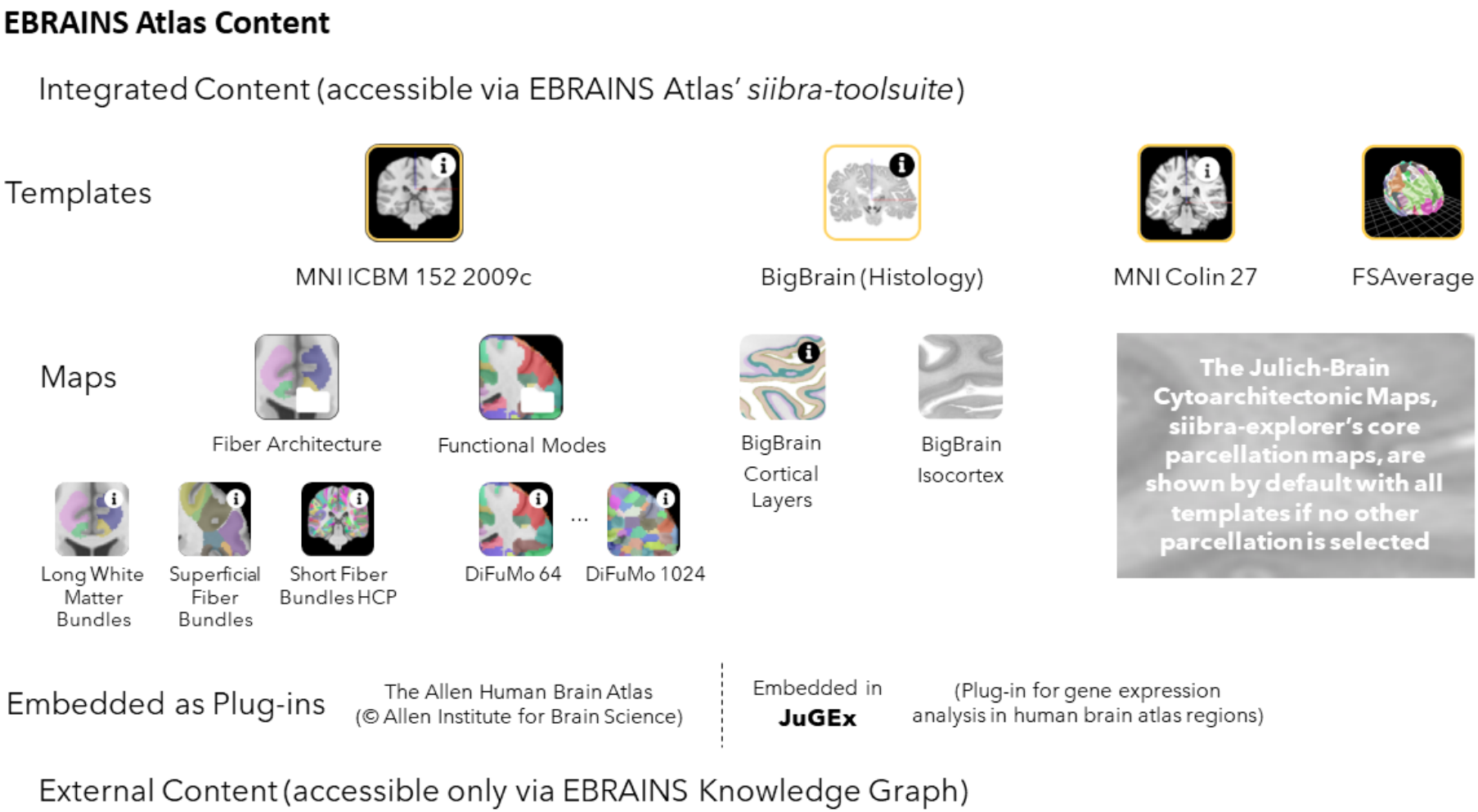

Figure 2. The EBRAINS Atlas content classification, showing the templates and brain maps already accessible via the EBRAINS interactive atlas viewer (siibra-explorer) (May 2022).

Integrated Content (templates & maps accessible via EBRAINS Atlas' siibra-toolsuite)

The EBRAINS Atlas' siibra-toolsuite integrates four different brain templates: the MNI ICBM 152 2009c Non-Linear Asymmetric, the BigBrain, the MNI Colin 27 and the FSAverage surface.

For all templates, the EBRAINS interactive atlas viewer (the siibra-explorer) displays, by default, the Julich-Brain Cytoarchitectonic Atlas. This space contains a three-dimensional cytoarchitectonic (microstructural) whole-brain parcellation of cortical areas and subcortical nuclei. Resulting from the slice of 20um thick histological sections from 23 postmortem brains, the Julich-Brain probabilistic nature enables to account for variations between individuals. It is remarkable that unmapped cortical regions were filled by gap maps: artifacts that enable to compute the parcellation of the entire cortical surface by filling unmapped regions, voids (Amunts et al., 2020).

These characteristics make it a suitable reference template to compare functional activation, networks, genetic expression patterns or anatomical structure studies, among others, in the same stereotaxic space. This is actually the case for JuGEx, the plugin embedded in the EBRAINS Atlas' siibra-explorer, which results from the combination of the Allen Brain Atlas genetic expression data and the Julich-Brain space. JuGEx will be explored later in this market analysis.

In the case of the BigBrain, this template is itself one of the 23 postmortem brains used in the construction of the Julich-Brain. This is why the atlas displayed by default is the individual cytoarchitectonic parcellation of the BigBrain itself. This parcellation, however, does not include cytoarchitectonic maps of all brain regions (it is not yet fully mapped). Spaces to be completed have been automatically filled drawing on expert annotations or interpolations of such.

With this brief introduction to the maps shown by default for all templates accessible via EBRAINS Atlas' siibra-explorer, let's now dive into each of them.

MNI ICBM 152 2009c Non-Linear Asymmetric space. This template is based in the previous MNI 152 (also known as ICMB 152), a template which itself is based in the already explained MNI 305.

The MNI 152, developed within the International Consortium for Brain Mapping (ICBM), was created through the individually linear registration of approximately 450 MRI volume images to the MNI 305 space. These scans derived from a normative young adult population, "*were acquired at a higher resolution that the MNI 305 data and exhibited improved contrast*". The resulting template, the MNI 152, exhibits better contrast and definition "*of the top of the brain and the bottom of the cerebellum due to the increased*

coverage during acquisition". The quality of the MNI 152 brain space led it to be incorporated into popular brain software packages, such us SPM, FSL AIR, LORETA, VARETA or BRAINWAVE (Evans et al., 2012).

Building on the success of MNI 152, the MNI ICBM 152 2009 (also known as the 40th Generation MNI 152) was developed.

The MNI ICBM 152 2009 is an "*unbiased* [8] *non-linear average of the MNI152 database*". It incorporates both high-spatial resolution and signal-to-noise ratio, while not being subject to the particularities of any single brain. The construction procedure "*involved 40 iterations of a process where, at each iteration, individual native MRIs were non-linearly fitted to the average template from the previous iteration, beginning with the MNI152 template*" (Evans et al., 2012).

The MNI ICBM 152 2009 is available in six different variants, each describing the exact same anatomy, but through different sampling or pre-processing of the data. The 2009c Non-Linear Asymmetric, the template accessible via the EBRAINS Atlas' 3D viewer, displays a maximum resolution of 1x1x1mm^3. It incorporates T1-weighted, T2-weighted and PD-weighted[9] scans, as well as tissue probability maps, brain mask, eye mask and face mask (*ICBM 152 Nonlinear atlases (2009) – NIST*, n.d.).

With the MNI ICBM 152 2009c, the EBRAINS Atlas covers the millimeter resolution scale.

The EBRAINS Atlas' 3D viewer accessible maps projected into the ICBM 152 2009c space can be grouped into two categories: the fiber tracts maps and the functional modules maps.

The **fiber tracts maps** include the Long Bundle Map, the Short Bundle Map and the HCP[10] Short Fiber Bundles map.

The **Long Bundle Map** "*contains the maximum probability map*[11] *of deep white matter fiber bundles (atlas of deep white matter fiber bundles, version 2018)* (...). *These bundles were identified by fiber clustering, from the tractography datasets of 78 subjects in Neurospin's ARCHI database. The maximum probability corresponds to the voxels with the highest number of putative fibers going through*" (*EBRAINS KG Dataset - MPM of deep white matter fibre bundles*, n.d.).

[8] Understood as free of assumptions about the structure of interest (Pakkenberg et al., 2019).
[9] Proton Density -weighted.
[10] Human Connectome Project. One of the world's avantgarde initiatives for mapping the human brain's connectome.
[11] Also, MPM.

It is remarkable that this dataset was automatically segmented, from a massive tractography dataset, through a robust method proposed in (P. Guevara et al., 2012). This publication was co-authored by Jean François Mangin, custodian of the Long Bundle Map dataset in EBRAINS KG.

The **Short Bundle Map** "*contains the maximum probability map of superficial white matter fiber bundles* (...). *These bundles were identified using a hybrid approach, incorporating anatomical information (from cortical regions of interest) and fiber shape (fiber clustering), from the tractography datasets of 78 subjects in the Neurospin's ARCHI database. The maximum probability corresponds to the voxels with the highest number of putative fibers going through*" (*EBRAINS KG Dataset - MPM of superficial white matter fibre bundles*, n.d.).

It should be noted that, while the Long Bundle Map (P. Guevara et al., 2012) did not receive any HBP funding[12], the Short Bundle Map (M. Guevara et al., 2017) did receive partial support by HBP funding. This distinction between (non-) HBP funded datasets will be key if we want to assess HBP's and EBRAINS' capacity to integrate brain maps which development has been completely independent from HBP.

That is may erroneously seem the case of the **HCP Short Fiber Bundles Map**, the third and last brain map accessible via the EBRAINS Atlas' 3D viewer and projected into the ICBM 152 2009c space. And I say erroneously because, even though this map has been inferred from the diffusion MRI dataset of the Human Connectome Project, its creation was funded by HBP SGA2 (Avila et al., 2019).

In short, the HCP Short Fiber Bundles Map is the "*largest atlas to date of reproducible short fiber bundles (less than 8cm) of the human brain*". Built following a sulcus-based alignment, this map includes a "*nonlinear ICBM T1-weighted MRI average in order to drive all the subject's tractograms (the set of dMRI-based virtual fibers) to the standard ICBM space*" (*EBRAINS Dataset - Atlas of short fiber bundles inferred from the HCP dMRI dataset*, n.d.).

Then, following a two-level clustering (intra- and intersubject) on the tractograms, the most reproducible bundles across subjects are defined. Subsequent parcellation with the Freesurfer software package enables to label each bundle following to the nomenclature of the *Desikan-Killiany Atlas*[13] (Desikan et al., 2006). Finally, probabilistic maps of each bundle are delivered in the ICBM space, as well as "*an aggregated map providing a parcellation of superficial*

[12] The project had not even started at the time the Long Bundle Map was published.
[13] Together with the Destrieux atlas (Destrieux et al., 2010), the two brain spaces provided by the Freesurfer software package for cortical parcellation of the human brain (*CorticalParcellation - Free Surfer Wiki*, n.d.).

white matter defined from a maximum probability principle" (*EBRAINS Dataset - Atlas of short fiber bundles inferred from the HCP dMRI dataset*, n.d.).

It is important to highlight that this map represents an extraordinary proof of HBP's and EBRAINS' capacity to 1st) take advantage from already existing atlases, and 2nd) contribute with its own added value. In fact, the HCP Short Fiber Bundles Map represents itself a good strategy for the scaling-up of the EBRAINS Atlas: to provide an added value on already existing atlases, generated outside HBP.

It is also remarkable that this added value will be retained until 1st) an improved version of this map is developed, or 2nd) the map itself is also integrated into another platform, let it be a GUI or a database[14]. Thus, exclusivity-based exploitation strategies could be applied to this particular map only as long as HBP / EBRAINS guarantees that this information is only accessible through the EBRAINS Atlas' 3D viewer or the EBRAINS KG Database. However, considering that the HCP Short Fiber Bundles Map is licensed under a CC-BY-NC license[15], it seems difficult to guarantee such exclusive exploitation.

The second group of maps projected into the ICBM 152 2009c space, the **functional modules maps** category, includes the DiFuMo (Dictionary of Functional Modules) in its 64, 128, 256, 512 and 1024 dimensions format. Each of these formats corresponds to a parcellation of the brain into the corresponding number (64, 128, 256, 512, 1024; hereafter, x) of elementary structures, carried out by sparse dictionary learning[16].

All different formats of this atlas contain two main components: an image of the corresponding x spatial components in MNI space, and the anatomical names of the corresponding x regions. As stated in the atlas description provided by the EBRAINS Atlas' 3D viewer, the DiFuMo "*is meant to serve as an atlas to extract functional signals (e.g. to create image-derived phenotypes). These modes are optimized to represent well raw BOLD[17] time series, over a with[18] range of experimental conditions*".

It should be noted that neither DiFuMo description provided by the EBRAINS Atlas' 3D viewer, nor its EBRAINS KG dataset files – e.g., (*EBRAINS KG Dataset - DiFuMo atlas (64 dim)*, n.d.), link the atlas to any publication. For this reason, it could be presumed that DiFuMo has been funded by HBP. Further search using WOS uncovered (Dadi et al., 2020), the publication where the DiFuMo atlas is

[14] This has usually been the case for brain templates (e.g. take the MNI space case), because the more spreaded they are, the more probable it is they will become the standard brain space.
[15] Creative Commons Attribution-NonCommercial 4.0 International (Creative Commons, n.d.).
[16] Dictionary learning is a machine learning method used for the discovery of features in raw data (Bengio et al., 2013).
[17] Blood Oxygen Level-Dependent (Monti, 2011).
[18] Typo we understand as "wide".

presented to the academic community[19]. Indeed, the DiFuMo atlas has been partially funded by HBP SGA2[20] (Dadi et al., 2020).

As a closing remark to this brief analysis of the MNI space maps accessible via the EBRAINS Atlas' 3D viewer, it should be noted that all atlases are closely related to the activity of HBP or EBRAINS. Thus, one could rapidly conclude that external atlasing initiatives do not find it enough attractive to bring their maps into the EBRAINS Atlas. If the cause of this observation lies on the side of the EBRAINS Atlas and its offer, or on the side of such external initiatives and their exploitation goals, will be discussed in *Part 2. Brain Atlasing Initiatives in the World, Atlases Taxonomy and Conclusions*.

The second reference template integrated into the EBRAINS Atlas framework is the BigBrain template.

BigBrain template. The BigBrain is an ultrahigh-resolution three-dimensional (3D) model of a human brain at nearly cellular resolution of 20 micrometers. The model is based on a full 3D reconstruction from digital scans of 7404 histological sections, which were stained for cell bodies. The dataset contains the reconstituted sections in the axial, coronal and sagittal dimensions at 20 micrometer resolution. It also includes full 3D volumes at different resolutions in the original histological space (matching the 2D sections), as well as in the MNI ICBM 152 and ADNI spaces (EBRAINS Interactive Atlas Viewer (siibra-explorer), n.d.-a).

It should be noted that the BigBrain was the first reference brain at microscopic resolution, and that it is free and publicly available (Amunts et al., 2013). Therefore, it follows the exploitation strategy of other brain templates such us the MNI ones, in a quest to become the standard micrometer resolution brain space[21].

Let's now explore the advantages and drawbacks presented by the BigBrain, in the words of its own builders (Amunts et al., 2013).

Advantages:

[19] Its recent publication (July 2020) may be the cause for its omission in corresponding EBRAINS KG datasets.

[20] Also, by *The Virtual Brain Cloud* Horizon 2020's project stemming from EBRAINS' *The Virtual Brain (TVB)*; and by the USA *Alzheimer's Disease Neuroimaging Initiative (ADNI)* (Dadi et al., 2020).

[21] Even though competitors to the resolution provided by the BigBrain have already appeared, (see (Edlow et al., 2019)), it still preserves the pioneer advantage, as proven by the re-registration of the atlas to two MNI templates by (Xiao et al., 2019). We will further explore both publications in *Part 2. Brain Atlasing Initiatives in the World, Atlases Taxonomy and Conclusions* of this market analysis.

- The BigBrain dataset "*represents a new reference brain, moving from a macro anatomical perspective to microstructural resolution. This model provides a basis for addressing stereotaxic and topological positions in the brain at micro-meter range (e.g., with respect to cortical layers and sublayers)*"
- The BigBrain "*allows the extraction of parameters of cortical organization by enabling measurements parallel to cell columns (e.g., cortical thickness, densities of cell bodies per column, surface measures) to provide a 'gold standard' for calibrating in vivo measurements of cortical thickness and other measures*"
- The BigBrain model "*allows the recognition of not only the borders between primary cortical areas (feasible, at least to some extent with advanced MRI technology), but also between higher associative areas*[22]" (often difficult, if not impossible, with previous identification techniques)
- "*Extraction of microscopic data for modelling and simulation*"
- "*Testing of hypotheses on optimal path lengths between interconnected cortical regions or on spatial organization of genetic patterning*"
- "*Fine-grain anatomical resolution is a necessary prerequisite to fully understand the neurobiological basis of cognition, language, emotions, and other processes, as well as to bridge the gap between large-scale neural networks and local circuitry within the cerebral cortex and sub-cortical nuclei*"
- "*Among other methodological problems, data processing becomes a major challenge for any project aiming at the reconstruction of a human brain at cellular resolution*". A challenge overcome with the release with of the BigBrain

Throwbacks:

- The variability existing across individuals (e.g., in cortical borders) and across developmental stages (e.g., pediatric vs aging brain; see (Evans et al., 2012)), requires additional BigBrain data sets. In this regard, *"labor-intensive work (...) is currently underway"*

As for the latter, it is remarkable that maps in the MNI space can be projected to the BigBrain template[23]. This enables information about intersubject variability, such as cytoarchitectonic or functional probability maps, to be transposed from

[22] These areas house cognitive processing and intervene between sensory inputs and motor outputs (*Higher Cortical Functions: Association and Executive Processing*, n.d.).
[23] Through a homeomorphic transformation between both spaces (Amunts et al., 2013).

MNI space to the BigBrain (Amunts et al., 2013). This possibility is key not only to facilitate the migration of data from the predominant standard, the MNI space, to the BigBrain: it is also fundamental for the brain user to understand that benefitting from the most precise brain template up to date is in his/her hands. Just one step further.

At this point, it could be useful to briefly analyze if brain features said to benefit from being mapped to the BigBrain in (Amunts et al., 2013) have indeed been incorporated to it – as long as we can acknowledge from the study of the EBRAINS Atlas. In particular, as indicated in (Amunts et al., 2013): "*We plan to establish links to other reference systems so as to combine high-resolution cytoarchitectonic data with, for example, gene-expression maps (32), neural projections (33) or future brain-activity maps (34)*", where ref. 32 is (Jones et al., 2009), ref. 33 is (Kasthuri & Lichtman, 2007) and ref. 34 is (Alivisatos et al., 2013).

In what refers to gene-expression maps, there are several datasets integrated into EBRAINS KG that respond to the query *gene-expression*, though a non-despicable number of them seem not to be projectable to the BigBrain space. However, the real deal in this domain is JuGEx, the EBRAINS Atlas' plugin that enables to analyze the transcriptomics data provided by the Allen Brain Atlas in the BigBrain space. JuGEx will be explored later in this market analysis.

Regarding neural projections, as described by (Kasthuri & Lichtman, 2007), it could be said that the construction of the HCP Short Fiber Bundles Map has someway filled this gap. Even though it is projected into the ICBM 152 2009c space, "*questions that relate to interconnectivity between different regions of the nervous system, (...) are more amenable to less fine-grained resolving techniques*" (Kasthuri & Lichtman, 2007) and, therefore – I presume, to less fine-grained templates. Eventual large-volume reconstructions, such as the HCP Short Fiber Bundles Map at the resolution of the BigBrain, may still exceed current computational capabilities (Kasthuri & Lichtman, 2007).

Finally, "*future brain-activity maps*", as referred to by (Amunts et al., 2013), were presented as a very broad idea in (Alivisatos et al., 2013) – even vague and always subject to several conditionals. For this reason, we won't analyze the mapping of these "*future brain-activity maps*" to the BigBrain any further.

To end this brief review of the BigBrain, it will also be useful to assess if the space has already been used to "*localize findings obtained in cellular neuroscience and mapping studies targeting transmitter receptor distributions (35), fiber bundles (36), and genetic data (32,37)*", where ref. 35 is (Zilles & Amunts, 2009), ref. 36 is (Axer et al., 2011) and ref. 37 is (Shen et al., 2012).

The use of the BigBrain for localization of genetic data has already been discussed some paragraphs ago. Regarding the use of the BigBrain for projection of high-resolution fiber bundle maps, it is remarkable that EBRIANS

KG contains the CHENONCEAU atlas (*EBRAINS KG Dataset - CHENONCEAU*, n.d.). This atlas contains a 3D map of long and short white matter fiber bundles at the mesoscopic scale[24] and, even though the atlas dataset is still embargoed and not registered to the BigBrain, this could be expected to happen soon. On the other hand, with respect to transmitter receptor distributions, EBRAINS KG does include transmitter receptors' density databases, but all of them are registered to the MNI space. Of course, and as already pointed out, all data projected in the MNI space can be homeomorphically transformed to the BigBrain. Still, it has not yet been done for the case of the transmitter receptor maps uploaded to the EBRAINS KG Database.

The first dataset natively mapped to the BigBrain is the template's **cortical layers segmentation**: a parcellation of all cortical and laminar surfaces in the BigBrain template. From the segmented intensity profiles, all six BigBrain's isocortex cytoarchitectonic layers were computed into surface meshes and voxel masks.

The second mapped dataset to the BigBrain is the template's own **isocortex**, which lacks any description. Even though this can be easily explained – this dataset is just a simple mask of the cortex, not really a map – it may be useful to provide a brief note about it, especially if we consider the Atlas as a potential tool for neuroscience education. The same happens with the subcategories *isocortex* and *non-isocortical structures* within the isocortex template.

To end the characterization of the templates accessible via the EBRAINS Atlas' siibra-toolsuite, let's briefly describe the two remaining ones: MNI Colin 27 and FSAverage. The **MNI Colin 27 template** is a stereotaxic average of 27 T1-weighted MRI scans of the same individual (Holmes et al., 1998), mapped to fit the MNI305 space. Although not capturing brain variability, it is well established in neuroscience due to its high definition (EBRAINS Interactive Atlas Viewer (siibra-explorer), n.d.-c). **FSAverage** is also one of the most commonly used surface-based templates (*The Princeton Handbook for Reproducible Neuroimaging*, n.d.), and meant a significant step forward in terms of registration accuracy of cortical functional and anatomical areas across individuals, compared to the Talairach coordinate system (Fischl et al., 1999). As already noted, the EBRAINS Atlas provides the Julich-Brain Cytoarchitectonic Atlas (Amunts et al., 2020) in these spaces.

Once all templates and maps that form the EBRAINS Atlas' Integrated Content category have been addressed, it is time to complete its description with the analysis of JuGEx (Bludau et al., 2018) and a brief description of VoluBA.

[24] Hundreds of micrometers, but less than a millimeter.

JuGEx enables to "*find a set of differentially expressed genes between two user defined volumes of interest based on JuBrain maps*" (EBRAINS Interactive Atlas Viewer (siibra-explorer), n.d.-b). In other words, JuGEx allows to discover quantitative changes in gene expression levels between volumes of interest through statistical analysis. For now, JuGEx only works with the JulichBrain Cytoarchitechtonic Atlas v1.18 or v2.9 in the MNI 152 ICBM 2009c space. Hence the importance of having projected the BigBrain to a standardized space, but also of promoting its use as a new standard. The plugin can be accessed from the *Plugins and Tools* menu of the EBRAINS Atlas' siibra-explorer, as a module included in the siibra-python client (*siibra-python*, n.d.) and in its original MATLAB implementation (*JuGEx | Forschungszentrum Jülich*, n.d.). It is noticeable that to download this MATLAB toolbox the user is redirected outside EBRAINS and needs to navigate two more webpages, with the subsequent loss of engagement for the EBRAINS website and for the overall download process.

Such a tool was made possible thanks to the **collaboration** between EBRAINS and the Allen Brain Institute, as the gene expression data is retrieved from Allen's Microarray gene data survey and then projected onto Julich-Brain maps. Such kind of collaboration with other brain atlasing initiatives seems fundamental to further develop the EBRAINS Atlas, as it combines the key strengths of each atlasing initiative (normally different to each other as we will see in *Part 2. Brain Atlasing Initiatives in the World, Atlases Taxonomy and Conclusions*). Such collaborations are also basic to foster the adoption of the BigBrain as a new standard.

As a brief note on future exploitation possibilities opened by JuGEx in its current state, it should be highlighted that this tool could enable to carry out the same differential analysis leaning on different gene expression maps, if developed and available. Such possibility would entail the need to collaborate with whichever brain initiative develops those maps, and so it would mean an opportunity to extend the use of the BigBrain and to better position it to become the micrometer resolution standard brain space.

On the other hand, **VoluBA** enables the spatial registration of a user volume of interest – small tissue blocks imaged at high resolution – to the BigBrain reference atlas. However, VoluBA is not integrated into the EBRAINS Atlas' siibra-toolsuite, with the subsequent loss of visibility entailed.

External Content (accessible only via EBRAINS KG)

Once all EBRAINS Atlas content accessible from the siibra-toolsuite has been explored, we can now dive into that only accessible from the EBRAINS KG, the project's database. At the highest level of aggregation, the EBRAINS KG repositories are classified into the following categories: *project*, *dataset*, *subject*, *sample*, *model*, *software*, *contributor*, with each category being subclassified into different filters.

Let's exemplify it. The *dataset* category is divided into the following filters: *species*, *data accessibility*, *modality* and *methods*, while datasets can also be queried based on *keywords*. Within the *species* filter, EBRAINS KG contains datasets not only from *Homo sapiens*, the one that interests us for this market analysis, but also from other primate and rodent species, such as *Macaca fascicularis* or *Mus musculus*, for example. The *data accessibility* filter distinguishes between *Free, Embargoed, Under review, Controlled access and Externally hosted* datasets, with the vast majority of datasets being labeled as *Free*. The *modality* filter seems to classify each dataset by its main characteristic(s); several modalities can be used to label a single dataset. The *methods* filter informs about the experimental and/or computational technique followed to obtain such dataset, while the *keywords* filter enables a restricted query based on predetermined keywords.

Even though some of the filters' options are self-descriptive, it would be recommendable to provide a definition of each option[25]. This would grant the user a better understanding of the available filters and, so, of the information available. Ideally, filters' options could also be grouped – at least for the *methods* filter – in a taxonomy, in order to ease the understanding of what information is actually available.

One filter that is not available, and that would serve as an indicator of how far is EBRAINS in its quest of becoming the go-to system, is the distinction between datasets created by the HBP-EBRAINS and those that were not. Throughout the exploration of the EBRAINS KG, users can get the feeling that most data come from the HBP. This is of course completely understandable, and progress in this sense has been made as proven by the integration of the HCP Short Fiber Bundles Map or the Allen brain transcriptomics atlas. However, further attraction and integration of third parties' databases seems necessary to achieve the one-stop-shop objective.

EBRAINS Atlas Digital Infrastructure

Within this category we will complement what has already been said about the EBRAINS KG and the EBRAINS Atlas' siibra-toolsuite.

The EBRAINS KG, as already discussed, is the database from which the EBRAINS Atlas' siibra-toolsuite retrieves all information shown, and where all other information is stored and - mostly publicly and freely - made available to users. Furthermore, the EBRAINS KG is, in essence, a metadata management system (*EBRAINS Knowledge Graph*, n.d.) to search and download brain data; to collaboratively create, edit and publish own metadata; to access it

[25] For each option, of each filter, of every category.

programmatically and even to visualize it. Such metadata store "*brings together information from different fields on brain research* [and] (...) *tracks the linkage between experimental data and neuroscientific data science supporting more extensive data reuse and complex computational research than would be possible otherwise*".

The process of uploading third parties' data to EBRAINS KG involves submission, review, acceptance, integration, publication and in-depth integration of data (*Share Data, Models and Software - EBRAINS*, n.d.). At the end of the process, the EBRAINS Data Curation team will have guided the interested user to make its data follow the openMINDS metadata format and be FAIR (Findable, Accessible, Interoperable and Reusable).

For completeness: the openMINDS (Metadata Initiative for Neuroscience Data Structures) initiative, powered by HBP and EBRAINS, "*develops and maintains a set of metadata models for research products in the field of neuroscience*" (*openMINDS - README*, n.d.). Such models "*support iterative elaborations of common standards* (...) *by probabilistic suggestion and review systems*". It is remarkable that openMINDS is compatible with its analogous in the US Brain Initiative thanks to the action of the International Neuroinformatics Coordinating Facility (INCF): "*INCF has served as a convener of the standards developers and the large-scale brain initiatives which has resulted in harmonization / interoperability of the ontologies and metadata standards adopted by HBP and BRAIN Initiative infrastructure projects*" (Amunts et al., 2014).

Regarding the siibra-toolsuite, where *siibra* stands for *software interfaces for interacting with brain atlases*, the first of its components to be ready was the siibra-explorer, "*a core part of the atlas tool suite*" (*EBRAINS - Nehuba*, n.d.) which is progressively incorporating more interactive components. The already introduced JuGEx and VoluBA prove that such extension is successfully taking place, (although VoluBA is not really integrated into the siibra-toolsuite, but rather meant to be accessed as a separate application, with the corresponding loss of visibility entailed). As we will see in *Part 2. Brain Atlasing Initiatives in the World, Atlases Taxonomy and Conclusions*, the siibra-explorer is possibly unique in its ability to combine a whole-brain template and microscopic resolution.

The second component of the siibra-toolsuite developed is the siibra-python, a client for working with the EBRAINS Atlas internal content programmatically, aimed "*to facilitate the reproducible incorporation of brain region features from different sources into reproducible neuroscience workflows*". It should be noted that this API is still in development and not yet stable, reason why it may still contain bugs (*siibra-python*, n.d.).

Both the siibra-toolsuite and VoluBA are protected under an Apache 2.0 (free, non-commercial) license.

Part 2

Brain Atlasing Initiatives in the World, Atlases Taxonomy and Conclusions

Part 2. Brain Atlasing Initiatives in the World, Atlases Taxonomy and Conclusions

In this second part, we will explore the main brain atlasing initiatives in the world: the content of such atlases, their related digital infrastructure and other miscellanea that could be of interest to this market analysis. For the sake of clarification, this part is not aimed at analyzing the immense landscape of brain maps and atlases available. Rather, it will target those that stem from initiatives with funding comparable to that of the HBP, which could be deemed analogous.

This reasoning was concretized through the exploration of the International Brain Initiative (IBI), its main stakeholders and their related atlases. IBI stems from the international recognition that studying the brain is "*an effort so large and complex that even with the unprecedented efforts and resources from public and private resources, no single initiative will be able to tackle the challenge to measure, map, image, model, simulate, understand, imitate, diagnose and heal the brain*", as expressed in the Initiative's Declaration of Intent (Declaration of Intent: It takes the World to understand the Brain, 2017). The world's brain initiatives part of IBI include the Brain/MINDS project (Japan), the Australian Brain Alliance, the Canadian Brain Research Strategy, the Brain Initiative (USA), the Korean Brain Initiative, the China Brain Project and, as related partners, the Kavli Foundation, the Chen Tianquiao & Chrissy Institute, the INCF (International Neuroinformatics Coordinating Facility), the International Brain Research Organization (IBRO), the Allen Institute, the Simons Foundation and the Korea Brain Research Institute. Of course, the Human Brain Project is part of IBI.

In what follows, most of the cited brain players will be explored, with a special focus to their related brain atlases, if any. Thereupon, a taxonomy of the main identified atlases will be built. Finally, a SWOT analysis combining Part 1 and Part 2 of this market analysis will follow, in order to fully understand the current position of the EBRAINS Atlas.

The Brain/MINDS project (Japan)

Even though the BRAIN/Minds project is focused on the marmoset brain as a way to further understand the Human Brain itself (Okano et al., 2016; Okano & Mitra, 2015), it has also gathered a Human Brain MRI Database (*Human Brain Images – Brain/MINDS*, n.d.). This set of images, both from healthy and diseased patients, aims to contribute to current research on human psychiatric disorders

(in this case, the databases include MRI scans from patients with schizophrenia and bipolar and major depressive disorders).

The rest of the project's resources are devoted to the marmoset, including a reference atlas, MRI data, a gene atlas and other electrocorticography and calcium imaging data. The data portal where all this information is made available – see (*Data Portal - Brain/MINDS*, n.d.) – is not comparable to the richness and possibilities of the EBRAINS KG. The 3D viewer devoted to the marmoset reference atlas is also much simpler and less interactive than the siibra-explorer, the EBRAINS Atlas' one.

The Australian Brain Alliance

The Australian Brain Alliance is focused on boosting Australia's brain science and neurotechnologies (such as neuroprosthetics), keeping the country at the forefront of both fields. Yet, the Australian Brain Alliance is not focused on brain mapping: "*Other international brain initiatives are tackling the fundamental and momentus challenge of mapping the trillions of connections in the brain. To complement this effort* (…)". Rather, it is aimed at "*understanding brain function, cracking the brain's code* (...), *new partnerships* (...) *and the translation of this new knowledge*" (*About | Australian Brain Alliance*, n.d.).

In particular, two of the four main challenges of the initiative (Richards et al., 2016): "*to optimize and restore healthy brain function throughout life* [and] *to develop neural interfaces to record and control brain activity to restore function*", might be eased by the information and services provided by the EBRAINS Atlas. Thus, the Australian Brain Alliance could be a potential external user of EBRAINS atlases.

It should be remarked that the Australian Brain Alliance has specific areas of interest (Australian Brain Alliance, n.d.-a), such us Huntington's disease, epilepsy, chronic pain and related mood disorders, motor neuron disease, Parkinson's disease, stroke, attention deficit hyperactivity disorder (ADHD) and schizophrenia. Other, more technological interests also include neuromorphic chips, brain stimulation for vision restoration – see Bionic Vision Australia (BVA) and its related spin-off, Bionic Vision Technologies (*Bionic Vision Technologies*, n.d.), brain inspired algorithms and tractography for safer brain surgery.

Particularly, the interest in tractography for safer brain surgery aims at developing more precise neuronavigation techniques. This goal is being achieved with MRtrix3 (Australian Brain Alliance, n.d.-c; Tournier et al., 2019), "*a processing platform for improved tractography modelling and display of crossing fibres*". MRtrix3, open-source and already in use in the surgical practice for children with epilepsy or brain tumors, is an evolution from the established deterministic, tensor-based tractography technique to a probabilistic one. Such

change "*improves white matter tract imaging and can also be applied to other imaging data* [diffusion MRI] *to improve outcomes for other types of surgery*".

Considering that MRtrix3 is free software distributed under the terms of the Mozilla Public License (freedom to redistribution and/or modification), it could be interesting to explore the possibility of using it for EBRAINS, either to improve further tractographies to be included in the EBRAINS Atlas or to incorporate it to the atlas itself as a plugin. In the latter case, if preceded by an agreement and properly advertised, the use of the EBRAINS Atlas by the Australian brain community could be boosted.

The Canadian Brain Research Strategy

Canada has long been one of the world leaders in brain research – let's remember, for example, that the name of the most used brain template, the MNI, is just the acronym for *Montreal Neurological Institute*. With such history, it can be said that Canada had already laid a good groundwork when the brain initiatives fever began in the 2010s. Thus, it only needed to build upon existing capabilities, for which it developed a new research roadmap called the Canadian Brain Research Strategy (CBRS). How and where does this strategy intersect with the EBRAINS Atlas?

As per the CBRS website, "*Canada's neuroscience strategy can distinguish itself from the others by focusing on understanding the brain's most fundamental processes*" (*History & Global Context – CBRS*, n.d.), a quest which for sure involves an extensive need for brain mapping and related infrastructure. Speaking of which, it should be noted that CBRS also plans to "*link together existing brain research initiatives and then maximize their potential through shared knowledge, infrastructure and data*" (*History & Global Context – CBRS*, n.d.), and even to "*foster and facilitate data sharing among the countries involved in the IBI* [with an] *International Neuroscience Open Data Platform*" (*Proposal – CBRS*, n.d.).

However, such international aspirations for a data platform seem to have been constrained to the national level, with the Canadian Open Neuroscience Platform (CONP) (*Canadian Open Neuroscience Platform*, n.d.) being already in place. Nowadays, the CONP counts with 57 datasets and some more pipelines coded, 75. It is remarkable that these datasets include the BigBrain, as McGuill University was part of the team who developed it (Amunts et al., 2013), as well as other varied, and mostly free-licensed sets. The user friendliness of CONP is not comparable to that of the EBRAINS KG, neither the filtering possibilities offered without the need to code a query. Furthermore, CONP does not offer any brain viewer. All in all, synergies with EBRAINS could be explored in order

to incorporate CONP's most interesting datasets. Some of them, focused on diseased patients, could complement EBRAINS KG healthy brains data.

In this sense, it could also be useful to explore synergies with Brain-CODE (*Brain-CODE | Ontario Brain Institute*, n.d.), originally conceived as a "*National biobank and database for patients with traumatic brain* injury" (*A National database for patients with traumatic brain injury - Brain Canada*, n.d.), now serving as Ontario's province database for patients affected by several neurological disorders.

The BRAIN Initiative (USA)

Together with the Human Brain Project, the US BRAIN Initiative, originally referred to as the *Brain Activity Map Project* (Alivisatos et al., 2012), is one of the longest (duration of 10 years) and largest (approximate funding of USD $4.5 billion) initiatives ever approved in the field of neuroscience (Australian Brain Alliance, n.d.-b). Established as a public-private partnership, the initiative is funded by various federal institutions, such as the US National Institutes of Health (NIH), as well as by several private foundations and research institutes, such as the Allen Institute for Brain Science or the Kavli Foundation (The BRAIN Initiative, n.d.-b). The BRAIN Initiative continues to receive public support, as evidenced by a $60 million budget increase for 2021 (*BRAIN Initiative $60M in additional funds for 2021*, n.d.).

The key goals of the BRAIN Initiative include, among others, the exploration of brain functionality, the study of links between brain function and behavior, and the facilitation of dynamic imaging (i.e., "*to produce a dynamic picture of the brain functioning in real time*") (The BRAIN Initiative, n.d.-a). The list is completed by the development of advanced neurotechnologies and of consumer applications. The first three objectives do involve brain mapping for sure but, what are the main mapping projects within the BRAIN Initiative? And which institutions are responsible for them?

The Allen Institute

Stemming from the Allen Institute for Brain Research (AIBR), one of the main private partners of the US BRAIN Initiative, the Allen Human Brain Atlas is one the most advanced maps of the human brain transcriptome (gene expression). This Atlas integrates different maps, such as:

- The Microarray Survey. Several datasets of "*genome-wide microarray-based*[26] *gene expression profiles in human brain (18 – 68 y.o.*[27]*) with accompanying anatomic and histologic data*" (Allen Institute for Brain Research, 2013b). It is remarkable that such database is complemented with:
    - Navigable MRI data for visualization of the sampled areas.
    - "*High-resolution histological dataset for visualization of brain tissue at the microscopic level*", from a minimum of 50 microns on, but normally starting in 250 microns (Allen Institute for Brain Research, 2013b).
    - "*Hierarchical anatomic naming system to provide anatomic context for histological and gene expression data, as well as expert neuroanatomic annotation of brain areas sampled*".
    - "*Gene expression data viewers* [that] *allow comparison of gene expression data by anatomic structure and gene probe*".
    - "*Differential expression queries for statistical comparison*", as the one enabled by JuGEx.
- The In-Situ Hybridization data. Aimed at providing "*gene expression data at cellular level resolution, in specific brain regions*", with the aid of "*colorimetric in situ hybridization (ISH) methods*" (Allen Institute for Brain Research, 2013a). Different projects used such technique, including:
    - The Cortex Study, a 1000 gene survey which goal was to "*characterize expression of genes from multiple gene classes in two cortical regions:* (...) [the] *visual cortex and* [the] *middle temporal cortex from multiple adult control cases (n = 2 – 6 per gene)*" (20+ y.o.). Genes surveyed included multiple coming from different functional and marker gene classes, "*including genes related to neuropsychiatric or neurological disease and genes of interest in comparative genomics*".
    - The Subcortex Study, which aimed to "*characterize expression of neurotransmitter system genes in subcortical brain regions*" (18 – 68 y.o.).
    - The Neurotransmitter Study, which purpose was to "*survey neurotransmitter system gene expression throughout human brain*

[26] "*Microarray technology is a developing technology used to study the expression of many genes at once. It involves placing thousands of gene sequences in known locations on a glass slide called a gene chip*" (*Microarray Technology*, n.d.).
[27] Years old.

(multiple cortical and subcortical regions - 176 genes in cortex; 88 genes in subcortex) in control cases" (18 – 68 y.o.).

- The Autism Study, focused on comparing "*cortical microstructure of control and autism cases*".
- The Schizophrenia Study, aimed at comparing "*controls and schizophrenics for differences in expression level or pattern in a brain region postulated to be affected in schizophrenia*".

It should also be highlighted that most MRI data used for both the Microarray Survey and some ISH analyses is freely available in the Allen's website (Allen Institute for Brain Research, n.d.-f) under a free non-commercial (unless granted) license (Allen Institute for Brain Research, n.d.-g). Such license is not generic, but rather customized for the interests of the AIBR. Could EBRAINS benefit also from having its own customized data and software license?

Last but not least, the AIBR has also developed a 3D viewer to explore the already explained maps. The Allen Human Brain Atlas viewer, called *Brain Explorer ® 2*, is only available as a desktop – offline – application. Furthermore, its installation requirements are negligible for today's commercial computers capabilities, thus revealing an outdated software (Allen Institute for Brain Research, n.d.-d), at least compared to the EBRAINS Atlas' siibra-explorer.

It should be highlighted, however, that such efforts seem to have been devoted to the Allen Mouse Brain Connectivity Atlas and the Allen Mouse Brain Atlas gene expression data, as both are now integrated into an avant-garde web-based 3D viewer, the *Allen Brain Explorer* (Allen Institute for Brain Research, n.d.-a).

From this milestone, it does not seem really complicated – to this inexperienced analyst – to develop an analogous version for the human atlas, an advancement which could position the Allen viewer in a comparable position to that of the siibra-explorer. This situation, summed up to the fact that the AIBR has already developed functional APIs (*Allen Brain Atlas API*, n.d.) – and even a software kit (Allen Institute for Brain Research, n.d.-c) – to enable users interact programmatically with its data, could make the EBRAINS Atlas' attractiveness fall behind. This is a risk that should be monitored. In any case, the AIBR does not seem to provide any database as accessible and powerful as the EBRAINS KG, which up to this point remains a competitive advantage of EBRAINS and the HBP. All mentioned, the AIBR digital infrastructure is available under the same free non-commercial (unless granted) license already mentioned.

To end with the Allen Institute section, two other developments deserve our attention:

- The Allen Adult Human anatomical reference atlases, 2D coronal atlases made up of sections cut at millimetric (0.4mm – 3.4mm) resolution (Allen Institute for Brain Research, n.d.-b).
- The BrainSpan Atlas of the Developing Human Brain, a "*full-color, high-resolution (from 250 microns on), web-based digital brain atlases accompanied by a systematic, hierarchically organized taxonomy of developing human brain structures*". This atlas contains gene expression and anatomic data, and the currently existing one ranges from 15 post conception weeks (PCW) to 34 years of age.

Such maps from the developing human brain cannot be found in the EBRAINS KG and are one of the lacks that both neurologists and neurosurgeons pointed out during our interviews (see *Part 3. Exploitation of the EBRAINS Multilevel Human Brain Atlas*).

The Kavli Foundation

Another important private partner of the US BRAIN Initiative is the Kavli Foundation, which supported the project since its very creation (*Unlocking the Mysteries of Human Brain | Kavli Foundation*, n.d.). This foundation "*is dedicated to advancing science for the benefit of humanity, promoting public understanding of scientific research, and supporting scientists and their work*". With this aim, the Kavli Foundation 1st) funds neuroscience research institutes[28] and 2nd) promoted the creation of Neuroscience Without Borders (NWB), a data standard for "*recordings and the metadata of cellular electrophysiology and optical imaging experiments*" (Teeters et al., 2015). It is remarkable that NWB is supported by several brain players such as the Allen Institute, the INCF, the Lawrence Berkeley National Laboratory, MathWorks or the Simons Foundation (*Neurodata Without Borders – The Kavli Foundation*, n.d.).

Another of the projects partly founded by the Kavli Foundation is BrainFacts.org, a website dedicated to brain outreach which offers articles, videos, and a basic 3D anatomic brain model, all for free (*BrainFacts*, n.d.). In particular, this BrainFacts 3D model is especially appealing as an educational tool due to its simple, aesthetically pleasing display; to the fact that it provides basic descriptions about the brain's main regions – and redirects the user to further information, if desired; and thanks to its annotation mode and screenshot plugins. All in, the BrainFacts 3D model should serve as a good reference point if the HBP Atlas is to be specialized as an educational tool at any point, especially regarding its interface charm and intuitive use.

[28] As well as other research centers in nanoscience, astrophysics and theoretical physics.

The Human Connectome Project

The Human Connectome Project is not funded by the BRAIN Initiative itself, but by the NIH Blueprint for Neuroscience Research. Even though it is not part of the BRAIN Initiative, the HCP can be regarded as part of the US efforts to further increase its neuroscience research and related capabilities. All in all, the HCP is an outstanding brain mapping initiative which should be explored before moving on.

The Human Connectome Project aims "*to map the neural pathways that underlie human brain function*" or, in other words, "*to acquire and share data about the structural and functional connectivity of the brain*". The Project began in 2010 and was structured around two complementary research consortia: the WU/Minn Project[29] and the Harvard/MGH-UCAL Project[30]. While the latter focused on the development of a "*new magnetic resonance imager optimized for measuring connectome data*", the efforts of the latter were invested in mapping "*human brain circuitry in 1200 healthy adults using cutting-edge methods of noninvasive neuroimaging*" (*Connectome Programs | Blueprint*, n.d.).

Deeper analysis of this WU/Minn atlas shows that all sampled brains were in health, with an age span of 22-35 years of age, reason why this connectome is called the Young Adult HCP (*Homepage - Connectome*, n.d.). The resolution achieved in the mapping process was in the millimeter scale (500um – 5mm). Even though all data is freely accessible, access is only granted on the basis of acceptance of some use terms (*WU-Minn HCP Consortium Open Access Data Use Terms - Connectome*, n.d.). In addition, especially sensitive datasets demand prior acceptance of further use terms, to avoid disclosure of subjects' identity (*WU-Minn HCP Consortium Restricted Data Use Terms - Connectome*, n.d.). All data is shared under a free non-commercial license.

Regarding the IT infrastructure of the HCP, all data produced by the Project can be found in the Connectome Coordination Facility: a database that houses all studies of the human connectome funded so far by the HCP. At the same time, such data can be treated with the Connectome Workbench: "*an open source, freely available visualization and discovery tool used to map neuroimaging data*", especially that of the HCP (*Homepage - Connectome*, n.d.). This offline, desktop software does not only include a GUI, but also a CLI for performing several algorithmic tasks. Such platform is complemented by separate MR and MEG data processing pipelines, which require the Workbench to run. The last

[29] Consortium of the Washington University in St. Louis, the University of Minnesota and Oxford University.
[30] Consortium of the Massachusetts General Hospital, Harvard University and the University of California Los Angeles (UCLA).

version of this Connectome Workbench was released in January 2020, what indicates that the software is still maintained[31]. All software mentioned was license under GNU Version 2, which enables its free redistribution, let it be for commercial purposes or not (*Workbench - Connectome*, n.d.).

Compared to the IT infrastructure of the EBRAINS Atlas, we still lack the API and related processing pipelines that will enable any user to really benefit from our data through its programmatic treatment. On the other hand, the EBRAINS Atlas' 3D viewer and the Connectome Workbench can hardly be compared: the latter seems to offer more options to treat connectomic data than the EBRAINS Atlas' siibra-explorer, but it was precisely designed for such data.

Before closing this HCP section, it should be highlighted that the already mentioned Young Adult HCP is only the first connectome studied by the Project. Several more came later, including the Lifespan HCP, with group ages ranging from 20-44 PCW ("*Developing*"), 0 – 5 years old (y.o.) ("*Baby*"), 5 – 21 y.o. ("*Development*") and 36 – 100 y.o. ("*Aging*"). Also, several connectomes related to human disease were studied, such as that of Alzheimer, central field visual loss, anxiety and depression, epilepsy and brain aging and dementia, among others. An outstanding work from which the EBRAINS Atlas' content could benefit, as it already did developing the HCP Short Fiber Bundles map[32].

Brain Image Library, Brainlife & Neurodata.io

Even though tools such as the Brain Image Library, Brainlife and Neurodata.io are not directly Part of the US BRAIN Initiative, as happens with the HCP, they also do belong to the US efforts made in neuroscience, what justifies a brief analysis on them.

The Brain Image Library (BIL) is a "*public resource* [supported by the NIH] *enabling researchers to deposit, analyze, mine, share and interact with large brain image datasets*" for free. These datasets are integrated into a "*searchable web-accessible system*" (*About | Brain Image Library*, n.d.), redistributed –if not restricted– under a CC BY-SA 4.0 license (*Data Submission | Brain Image Library*, n.d.), and can be processed through HPC and AI pipelines provided by the Pittsburgh Supercomputing Center (*Computing and Visualization | Brain Image Library*, n.d.). BIL's customer base includes "*large confocal imaging centers that are generating petabytes of* (...) *datasets per year*" which are served "*an archive facility*" as well as the possibility to "*interact with and download library datasets*" (*About | Brain Image Library*, n.d.). BIL's partners also include the Center for Biologic Imaging (CBI) at the University of Pittsburgh, "*one of the largest optical imaging centers in the country*"; the Molecular Biosensor and Imaging Center at

[31] Or was until very recently.
[32] Which was inferred from the diffusion MRI dataset of the HCP.

Carnegie Mellon University; the Brain Initiative Cell Census Network (BICCN), part of the Allen Institute for Brain Science; and the Defining our Research Methodology (DORY) project, which "*facilitates the development of standards for 3D microscopy of intact brains*" (*Partners | Brain Image Library*, n.d.). BIL offers free trainings on how to use the platform (*Training | BIL*, n.d.).

Brainlife offers a "*community-based platform*" where users can freely publish their code and data as well as execute/analyze it through shareable, built-in cloud-computing resources (HPC) for neuroscience. Such data and code repositories are organized into projects, which allow to grant different levels of access to the involved users. Once a data analysis has been completed, the user is allowed to make it public via a brainlife.io publication, which allows externals to download and reuse the shared datasets and code (*Documentation Home | Brainlife*, n.d.). Unlike the Brain Image Library, data uploaded to Brainlife remains property of the original owner and retains all copyright and license attributes, with the data generated within the platform belonging to the project members (*Privacy Policy | Brainlife*, n.d.). Brainlife uploaded data can be visualized with FreeView, FSLview, or MRview; or rendered on the cloud through Docker and VNC (*Documentation Home | Brainlife*, n.d.). It can also be processed through MATLAB, Python or R workflows, which should be made available as public GitHub repositories (subsequently called a Brainlife "app"), as well as through CLI (*Apps | Brainlife*, n.d.). Brainlife sponsors include the NIH, the NSF or Microsoft Azure, among others (*Home | Brainlife*, n.d.). The platform offers free training as part of its extense documentation (*Tutorials | Brainlife*, n.d.).

Finally, with the mission of understanding and improving animal and machine intelligences, **Neurodata** houses four data repositories – *Open Connectome*, *Zebromes*, *MRI Cloud* and *Networks* – mainly focused on the human and the zebrafish brains, though atlases involving other species, such as the Adult Mouse Reference Atlas, from the Allen Institute, are also included. All data, even that drawn from third parties, such as the BigBrain, are hosted in Amazon Web Services on the Open NeuroData Registry (*Open NeuroData Registry*, n.d.). In particular, the connectomes hosted in the *MRI Cloud* repository are created with NeuroData's MRI Graphs pipeline and protected under the Open Data Commons Attribution License (ODC-By) v1.0 (*MRI Cloud | Neurodata*, n.d.), which grants free, commercial use. It is remarkable that Neurodata also offers a suite of applications to process and analyze the data, mainly coded in Python, R, MATLAB or C++ (*Code | Neurodata*, n.d.). Neurodata's main funders are the NSF and the NIH (*Funding | Neurodata*, n.d.). It does offer free training, but through sparse workshops (*Events | Neurodata*, n.d.).

To end with the US BRAIN Initiative section, it is worth mentioning that all software created by the Initiative as well as its data repositories can be found on https://neuinfo.org/ (Neuroscience Information Framework, n.d.).

The Korean Brain Initiative

The Korean Brain Initiative is the country's main project under its Korea Brain Innovation 2030 action. With its R&D focused in four core areas (Jeong et al., 2016), the first one is aimed at constructing "*maps of the brain at multiple scales based on the structural and functional network in the prefrontal cortex (PFC) and basal ganglia*, [in particular,] *nano-and meso-scaled mapping and single-cell transcriptome analysis will be adapted for multiple scales and integrated to create a more detailed and sophisticated brain connectome*" (Jeong et al., 2019). Expected for 2023 are two "*specialized brain maps*", one focused on the "*structural and mechanistic bases of higher brain functions, such as decision-making, attention, and memory* [and other on the] *progression of neurological disorders, especially those related to aging*" (Jeong et al., 2016). For the latter, studies will be based on "*functional mapping using fMRI and deep brain stimulation*" (Jeong et al., 2019).

The second Korean Brain Initiative's objective further relates to brain mapping, as it aims to develop neurotechnologies for this domain (Jeong et al., 2016), including brain-machine interfaces (Jeong et al., 2019). The third R&D core area, "*Strengthening artificial intelligence-related R&D*", is planned to be based on a strong circuitry study component and is thus also associated to brain atlasing. Finally, the fourth area, "*Developing personalized medicine for neurological disorders*" will require patients' brain maps and, therefore, the related IT to operate with such data.

At the level of IT Infrastructure, the Korean Brain Initiative framework considers the "*Strengthening* [of] *a sustainable infrastructure*" a key area to reinforce its neuroscience ecosystem: "*the initiative plans to increase core facilities and expand the Korea Brain Bank Network (KBBN), and to construct an accessible data station to share and store data*, [while] *building a pipeline to facilitate collaborative research and ex-change resources and research outcomes*". With such a statement, it seems difficult that the Korea Brain Initiative would be willing to share its data through a third party's platform on an exclusivity basis (e.g., EBRAINS KG). However, as "*Enhancing national and global networks*" is also considered key to boost the neuroscience environment, and as Korea already has experience working with the European Union – see the MESO-BRAIN Initiative, funded within the EC FET scheme – (Jeong et al., 2016), as well as with other Member States' research institutions (*International | KBRI*, n.d.) chances are that a strong collaboration with EBRAINS could be established.

Beyond data sharing, of course interesting, such collaboration could also aim at spreading the EBRAINS KG data management standard.

The China Brain Project

Information about the China Brain Initiative is quite restricted – at least for the non-Chinese speaking public – as evidenced by the fact that the IBI link to this initiative leads the user to the reference (Cyranoski, 2018), and not to any website as happens with the other international brain projects. However, some information can still be retrieved from various publications. That is the case with (Poo et al., 2016), where the China Brain Project is explained as part of the Neuron journal series on brain initiatives.

Established in 2016 and formulated as a 15-year plan (Poo et al., 2016), the longest foreseen international brain initiative (Australian Brain Alliance, n.d.-b), it is focused on understanding the neural basis of cognitive functions, with the subsequent goal of transferring such knowledge into 1st) brain-inspired computation, AI and brain-machine technologies, and 2nd) early diagnosis and intervention of brain disorders (Poo et al., 2016).

In particular, this interest in cognitive functions is translated into the research of neural circuit mechanisms of cognition, with special emphasis in the mesoscopic level and the "*architecture of neural circuits at single-cell resolution and on the spatio-temporal pattern of neuronal activity*". For such "*mesoscopic understanding of the brain,* (...) *mapping all local and long-range connections of each neuron ('single-neuron connectome') becomes essential for defining the neuronal type*. (...) *Once the cell type is defined, specific molecular probes expressed in neurons could be used to monitor and perturb their activity, in order to dissect neural circuit mechanisms underlying brain cognition and behaviors*" (Poo et al., 2016). Could the BigBrain be used at those molecular and cellular levels as the brain reference space? Such possibility should not be discarded, because even though (Poo et al., 2016) points mostly to Non-Human Primate (NHP)-based brain research, Chinese mappings such as The Brainnetome Project are focused on the human brain.

Furthermore, specific brain mapping projects undertaken by China[33] include The Brainnetome Project, the Grand Research Plan for Neural Circuits of Emotion and Memory in China and the Functional Connectome Project. The two latter are focused on understanding and characterizing basic structures and functions of neural circuitry and brain networks at different scales, ranging from the micro to the macroscale. All with the final goal of understanding the

[33] Initiated prior to the China Brain Project.

mechanisms of emotion and memory, among others, as well as brain diseases (Jiang, 2013).

The Brainnetome Project

The Brainnetome provides a whole brain, connectivity-based parcellation framework from in vivo, healthy subjects, providing information on both anatomical and functional connections – the "*connectivity architecture*" of the brain (Fan et al., 2016). All Brainnetome data, which resolution is in the millimeters scale (500um – 5mm) is openly available and shared under a free non-commercial (unless granted) license. As the Allen Institute did, this Brainnetome data sharing license is a customized – although poor in terms – license, what again rises the question about whether EBRAINS should have its own data sharing license.

On the IT level, the Brainnetome is equipped with simple, online 3D viewer and 2D connectogram. Both are also available as a MATLAB desktop toolbox, with few more options than the online version but still very limited compared to the Allen Brain Viewer and, of course, to the EBRAINS Atlas' 3D interactive viewer, the siibra-explorer. Yet, the Brainnetome also offers an automatic tractography-based parcellation pipeline, which can be operated both as a Command Line Interface (CLI) or as a GUI. Such pipeline is distributed under a free license (GNU Version 3).

Coming back to the China Brain Project and its IT side, data infrastructure and standardization are considered fundamental to leverage the Chinese "*advantage of large patient populations for brain disease studies*" (Poo et al., 2016). Given the lack of available information – at least, again, for the non-Chinese speaking public – a collaboration in this domain seems unlikely. Yet, Dr. Poo stated in (Grillner et al., 2016) that "*as opportunities arise for global collaboration, the Project's effort could be further directed toward inter-national standards and global sharing*. (...) *the China Brain Project can provide the driving force for more unified efforts that would have a strong international impact*".

Time will tell what role does the China Brain Project want to play in the international arena, but it is clear that 1st) it started later than its international counterparts, and 2nd) neuroscience is a "*relatively new research discipline in China,* (...) [with a] *small community* [that] *needs increased government support for building research capacity in nearly all areas*". All said, China's ability to grow rapidly when desired is worldwide renowned.

Atlases Taxonomy and Conclusions

The analysis of the previous brain research initiatives yielded a list of some of the most used and/or advanced brain atlases in the world: the Allen Human Brain Atlas, the Human Connectome Project, the Harvard – Oxford Atlas and the Brainnetome, summed up to the Julich Brain (which includes the BigBrain) and the DiFuMo maps included in the EBRAINS Atlas. For the sake of discovering further differences between them, we consider it useful to classify these six atlases into a taxonomy that would allow us to spot such contrasts. The resulting taxonomy is divided into three main categories, and groups 39 filters in total. A diagram of such hierarchy can be consulted in Figure 3. Of course, this is a reduced sample of all available brain atlases but, as happened with our analysis of the main brain research initiatives, we expect this taxonomy to give us valuable insights on the market context and exploitation possibilities of the EBRAINS Atlas.

A Taxonomy of Brain Atlases

(Exemplified for the BigBrain Isocortex parcellation map as of May 2022)

Content

1. Atlas within MHBA? (e.g., YES)
2. Atlas (e.g., Jülich-Brain)
3. Sub-atlas (e.g., BigBrain)
4. Stereotaxic coordinate space (e.g., BigBrain Space)
5. Stereotaxic coord. sub-space (e.g., Does not apply)
6. Volumetric parcellation (e.g., BigBrain Isocortex)
7. Atlas type (e.g., Deterministic (*stricto sensu*))
8. Atlas sample (e.g., Single-specimen)
9. # of subjects (if applicable) (e.g., Does not apply)
10. Sample type (e.g., Postmortem)
11. Sample condition (e.g., In health)
12. Sample scope (e.g., Whole brain)
13. Sample age-span (e.g., 65 y.o. female)
14. Atlas scale(s) (e.g., Spatial)
15. Content (e.g., Histology)
16. Sub-content (e.g., Does not apply)
17. Imaging technique (e.g., flatbed scanning, MRI)
18. Imaging modality (e.g., Does not apply)
19. Resolution (e.g., Micro (1um – 500um))
20. Dimension (e.g., 3D)
21. Data access (e.g., Open)
22. Data license (e.g., Free non-commercial (CC BY-NC-SA 4.0))

Digital Infrastructure

23. GUI (e.g., EBRAINS 3D interactive viewer *siibra-explorer*)
24. Physical support (e.g., Web-based navigator)
25. Physical sup. license (e.g., Free non-commercial (Apache 2.0))
26. Navigation (e.g., Spatial)
27. Software Kit (SK) available? (e.g., YES)
28. SK programming language (e.g., Multiple)
29. API available? (e.g., YES)
30. API programming language (e.g., Python)
31. CLI available? (e.g., NO)
32. CLI programming language (e.g., Does not apply)
33. SK / API / CLI license (e.g., Free non-commercial (Apache 2.0))
34. Atlas dataset file format (e.g., Minc, NIfTI)
35. AR/VR compatible (e.g., No info available) (Augmented/Virtual Reality)

Miscellanea

36. Sponsors (e.g., Public – Private nonprofit)
37. Projected final users (e.g., No info available)
38. Training available (e.g., YES)
39. Language (e.g., English)

Figure 3. A Taxonomy of Brain Atlases, exemplified for the BigBrain Isocortex parcellation map as of May 2022.

Content filters

These filters classify each atlas' information attending to several parameters identified throughout the development of this market analysis: whether the atlas is included in the EBRAINS Atlas, the characteristics of the measurements contained, their availability and, if so, under which license.

From the analysis of the content filters, several conclusions can be derived. First: the most important brain atlases developed so far do not – mostly – overlap with each other in terms of content, which is indeed in line with the Declaration of Intent of IBI (Declaration of Intent: It takes the World to understand the Brain, 2017). In this sense, the words of Prof. Sten Grillner, former HBP Subproject Deputy Leader, seem to be still valid: "*The different brain initiatives complement each other in many respects*", to which he added: "*What is critical is that these initiatives interact openly to facilitate progress in the understanding of brain function and to avoid competition*" (Grillner et al., 2016).

Related to this last quote, a second conclusion would be that avoidance of competition – and, thus, of overlapping – may be hindered when research is of strategic commercial and/or military interest. This may be, at a very early stage, the situation with China and its connectomics research for AI. This avoidance of competition does neither seem realistic if big industries, such as pharma, identify market potential for brain gene maps, for example. Such obvious competitiveness between brain research initiatives may not have developed yet due to either low TRL results or the broad, unexplored and thus still unknown uses of such basic research results.

Our third conclusion is related to the legal protection given to the atlases' content: nearly all of them make use of free non-commercial licenses. Some prefer those already established such as Creative Commons (BigBrain, Brain/MINDS 3D Human Image Dataset), but most of them make use of customized licenses, which enable them to retain further commercial power on the data (free non-commercial – unless granted – licenses). Such difference is key for the future exploitation possibilities of the data, mostly unknown considering these are basic research results. The EBRAINS Atlas does not follow any commercial nor customized license.

Our last conclusion regarding content is related to the resolution offered by the registered brain atlases. Most of their data is restricted to the millimeter scale (500um - 5mm) and only the Allen Human Brain Atlas and the BigBrain achieve higher resolutions (1um - 500um). This situation[34] may hinder the use of the BigBrain as a standard brain template, as few studies seem to be able to benefit

[34] Which is directly related to the MRI scans available for the measurements – the higher the magnetic field of the scan the greater the resulting resolution.

nowadays from the added value of its resolution. On the other hand, this could also be regarded as positive: the BigBrain is the first-mover of the field, and the subsequent advantage, combined with an unmatched quality, should ease its positioning as a new standard space. However, until this is achieved, efforts should still be devoted to foster its use by an ever-growing number of researchers. Meanwhile, other atlases will try to conquer the market and become the next micrometrical brain standard space – case of (Edlow et al., 2019; Lüsebrink et al., 2017) – and this is precisely why it is so important to rapidly leverage the first-mover advantage and great quality of the BigBrain.

Digital Infrastructure filters

These filters classify each atlas' digital infrastructure: GUI, if any, its characteristics and license; related Software Kit (SK), API and CLI, if any, their features and license; and the atlas' dataset file format and whether the digital infrastructure (in particular the GUI) is compatible with Augmented / Virtual Reality (AR/VR). Because this taxonomy was focused on individual atlases and not on research initiatives, information about databases was not registered to the taxonomy itself. Rather, it has already been presented in the respective analysis of each brain initiative.

Regarding GUIs, it is remarkable that most atlases offer a 3D viewer of their data, let it be web-based or as a desktop navigator, being a shift to the former format the current trend. From the explored viewers, it should be stressed that not all of them offer the same features – most of them are in fact specialized and restricted to their own data. To this regard, the EBRAINS Atlas' 3D viewer seems to be the most advanced web-based viewer nowadays, as it enables users to project their information to the BigBrain through the online platform VoluBA[35] (EBRAINS, n.d.-c). For the rest of the viewers, comparisons could be made in pairs but, more broadly, it should be noted that desktop viewers miss the immediacy and ubiquity of the online access, despite how powerful they may be (e.g., take the Connectome Workbench provided by the HCP).

Regarding API and CLI access, most atlases do provide it. Several of them also offer a complementary SK, let it be independently (such as for the Allen Atlas or the HCP), or within an existing software (such as the JuBrain Anatomy Toolbox v3.0, included in the SPM suite). In the case of the EBRAINS Atlas, the siibra-python API is not a stable version yet (*siibra-python*, n.d.) and some operations performed could yield wrong outputs. This lag is the greatest EBRAINS Atlas' disadvantage that could be found comparing atlases digital infrastructure.

At this point, a brief mention to the atlases' associated databases is mandatory. We have already explained them in each initiative's respective section and the

[35] HCP's Connectome Workbench also allows to open external files grouped under a .spec file.

conclusion is evident: among such initiatives, EBRAINS KG seems to be the most powerful brain research database available so far, at least from the user perspective: anyone with a – minimally acceptable – dataset can upload it to EBRAINS KG and benefit from its curation services. Nowadays free to use, it is unclear what business model will EBRAINS KG follow. One possibility, if the necessary resources are available, would be to further develop it as a Database as a Service (DaaS) (MongoDB Inc, n.d.). Furthermore, if summed to the HPC capabilities of EBRAINS, the whole could even become an Infrastructure as a Service (IaaS) (IBM Cloud Education, 2019).

If we now broaden our scope and look outside the main brain initiatives, competitors to the EBRAINS KG appear on the horizon. That is the case, for example, of the US *Neuroscience Information Framework* (NIF)[36], which uploaded resources double that of the EBRAINS KG[37]. In fact, the NIF is – by its own words – the "*largest searchable collection of neuroscience data, the largest catalog of biomedical resources, and the largest ontology for neuroscience on the web*" (Neuroscience Information Framework, n.d.). As could be expected, the NIF does also offer users the possibility to upload their data to the database, and it does so in a quite successful way, taken the number of resources available.

Being the NIF a clear competitor to the EBRAINS KG, it is remarkable that the offer of the former does not include so far, for example, HPC services (Neuroscience Information Framework, n.d.), which EBRAINS does. In other words, the NIF is, as a database, more advanced in terms of content than the EBRAINS KG, but as a whole and if properly exploited, EBRAINS integrates more services, and thus offers a much more complete solution than that of the NIF alone. The same could be said if we compare the EBRAINS KG to other neuroscience databases which, on the other hand, are mostly smaller than the EBRAINS KG.

All in all, competition between brain research initiatives may not yet encompass atlases' content, but it does exist when it comes to their respective digital resources. This is indeed the realm where research initiatives don't depend – almost[38] – on each other to progress. Also, taken that most research results are publicly available, a user could eventually access them through several viewers/APIs/Databases, thus being the quality of those viewers / APIs / Databases (and respective CLIs/SKs) the decisive reason to choose one or the other.

[36] Not part of the BRAIN Initiative, but of the NIH Blueprint for Neuroscience Research.
[37] As of July 2021.
[38] Most initiatives are part of the INCF network, which means they should aim to an Open, FAIR and Citable neuroscience (Abrams et al., 2021).

To end this digital infrastructure filters section, it should be highlighted that no scanned atlas provided information on whether its 3D viewer was or not – or planned to be – compatible with AR/VR. Such void could actually be profited from one of the atlasing initiatives if it decided to, 1st) invest and adapt its viewer to AR/VR, 2nd) promote it as a state-of-the-art tool in Medicine Schools all around the globe and 3rd) foster its adoption as an essential part of the toolbox of every new neuroscientist / neurologist / neurosurgeon. With time, those new generations of scientists and Medical Doctors would pervade research institutes and hospitals, making whatever corresponding atlas the common one to be used. A strategy to penetrate the market from its very base. On the other hand, such an investment in AR/VR could also be profited to turn atlases – whenever possible – into neuronavigation tools.

Miscellanea filters

These filters included the type of sponsor, the projected final user of the atlas, if it provides training on how to use its different features and in what language it is available (as expected, English in all cases).

Regarding sponsors, all of them range from public to private nonprofit to a combination of both. Projected final users were in no case concretized, apart from the "generic" academic community and the clinic. This did not seem strange as 1st) this is basic science, and its results could impact much more domains than originally expected, and 2nd) basic science projects do not normally start with a user forecast[39] of their – potential – results, but with a rationale on how they will continue to advance basic science. Finally, regarding training, only big initiatives such as the HBP, the HCP or the Allen Institute offer it. In particular, the Allen Institute organizes a Distinguished Seminar Series and frequent workshops to raise awareness about its activity (Allen Institute for Brain Research, n.d.-e). The HCP used to offer – prior to the pandemic – intensive training courses in some of the main world neuroscience hubs (Human Connectome Project, n.d.). Interviews will prove how important it is for the spread of the atlas to offer such training.

[39] Even though it would not be a bad idea.

SWOT Analysis of the EBRAINS Atlas

Legend | C – Content · DI – Digital Infrastructure · M – Miscellanea

Strengths

- (C) Built-in templates enable a wide precision range, from the micrometer to millimeter scale
- (C) State-of-the-art anatomical, functional and connectomical information integrated in a single atlas
- (C) Contains the BigBrain, the most precise three-dimensional model of a human brain (ultrahigh resolution of 20 micrometers; nearly cellular resolution)
- (C) Contains the largest atlas to date of reproducible short fiber bundles (less than 8cm) of the human brain
- (C) Integration of the most advanced human brain transcriptomics' atlas (Allen Human Brain Atlas) with the BigBrain to perform gene expression differential analysis
- (C) Proved capacity to add value to third parties' datasets (from HCP, with the Short Fiber Bundles Map; from the Allen Institute, with JuGEx)

- (DI) No other neuroscience database in the market offers as much complementary services as the EBRAINS KG (e.g., HPC)
- (DI) State-of-the-art web-based 3D interactive viewer GUI, the *siibra-explorer*, linked to a database as powerful as the EBRAINS KG
- (DI) Enables users to project their information to the BigBrain through the online platform VoluBA
- (DI) Data curation services available for non-HBP/EBRAINS users
- (DI) Ontologies and metadata standards interoperable with those of the US BRAIN Initiative

- (M) Training on how to use the EBRAINS Atlas available

Weaknesses

- (C) Lack of atlases covering the development of the human brain
- (C) EBRAINS KG resources are provided mainly by HBP
- (C) Free, non-commercial licensing of state-of-the-art content (BigBrain template, Short Fiber Bundles Map) hinders exclusivity-based exploitation strategies
- (C, DI) Generalized used of generic, free, non-commercial intellectual property licensing (Creative Commons, Apache)
- (DI) The EBRAINS Atlas' API is not a stable version yet
- (DI) VoluBA is not integrated into the siibra-toolsuite, with the subsequent loss of visibility
- (M) Low (nonexistent?) presence of private nonprofit funders

Opportunities

- (C) Take advantage of the BigBrains's first-mover advantage and position it as the standard micrometer-resolution brain template[40]
- (C, DI) Create a customized, more flexible intellectual property license for EBRAINS content, digital infrastructure and services
- (DI) Void in the educational market: no atlas has been adapted to AR/VR → Market penetration opportunity in the next users' generation
- (DI) Further develop EBRAINS services complementary to the KG in order reinforce its branding as a complete service, moving away from a just-database consideration
- (M) Improve training by showcasing real use cases, and inviting those real users to a discussion on how to benefit from the tool

[40] It is remarkable that such positioning has already started happening. An example can be found in (Xiao et al., 2019), which further improves registration of the BigBrain to already established templates, in this case to the MNI PD25 atlas and the ICBM152 2009b atlases (in both its symmetric and asymmetric versions).

Threats

- (C) As long as there is no widespread micrometer-resolution brain template, several developments will try to become so – case of (Edlow et al., 2019; Lüsebrink et al., 2017). Furthermore, some of (Edlow et al., 2019) content is pre-installed within Lead-DBS software and can be selected for visualization in its the 3D viewer, a use case which is exemplified in the publication itself. Could that be a possibility for the BigBrain, too? It is also noteworthy that, even though (Edlow et al., 2019) was published years after the release of the BigBrain – which can be found in (Amunts et al., 2013), it does not even cite its existence. At the very least, an example of a terrible literature review
- (C) The US Neuroscience Information Framework (NIF) uploaded resources double that of the EBRAINS KG (as of July 2021)
- (C, DI) Use of custom intellectual property licensing by other brain initiatives could grant them further exploitation power over their results, thus placing them in an advantageous position over the EBRAINS Atlas in certain markets
- (C, DI) Taken that most research results are publicly available, a user could eventually access them through several viewers/APIs/Databases, thus being the quality of such digital infrastructure the decisive reason to choose between platforms

Part 3

Exploitation of the EBRAINS Multilevel Human Brain Atlas

Part 3. Exploitation of the EBRAINS Multilevel Human Brain Atlas

In this third and last part we will explore the exploitation possibilities of the EBRAINS Atlas as perceived by six different interviewees: four neurologists, one neurosurgeon and one former surgeon working now as Medical Director in the neurotechnology industry. Their insights, which will prove extremely valuable, were classified into three broad categories, *Research, Clinic,* and *Education*, attending to the exploitation domain judged in each observation.

As one of our interviewees said: "*The brain is the ultimate challenge*". This is precisely why we made sure that each of the six experts met had a different focus: from dementia to spinal injury and neurorehabilitation, from epilepsy to memory disorders, among others. Yet, their conclusions intersected several times, unraveling hotspots to the exploitation of the EBRAINS Atlas at all three levels: Content, Digital Infrastructure and Miscellanea.

As a broad overview, our industry expert highlighted four main markets for the EBRAINS Atlas: research, education, diagnostics and therapy guidance and monitoring of the results of clinical treatment. Additionally, he also pointed to health aging as an emerging market in which the EBRAINS Atlas could find its market share.

In Research

Most of our interviewees were connected to brain research, let it be as full-time researchers or as clinicians involved in some research project. Depending on the level of involvement in basic neuroscience research, their knowledge and use of brain atlases proved to vary significantly. Together with their insights about the spread and use of atlases in their working environments, it could be concluded that senior, fundamental researchers are most versed in brain atlases, while junior, applied researchers are more inexperienced. If we start our analysis of the research market with the insights of those junior, applied researchers (i.e. clinicians), several remarks require our attention.

Our **first interviewee** is a young **clinical neurologist** (hereafter, I#1) specialized in dementia, whose interest in neuroimaging analysis stems from his PhD thesis. There, he was introduced to neuroimaging processing with software packages such as SPM and FSL. It can therefore be concluded that this clinician is educated in the basics of neuroimaging analysis, and that he was able to provide credible insights on the use of such kind of analysis in his department. This is particularly important as he conveyed that "*the nuclear medicine doctor*

or radiologist doing neuroimaging continues to rely largely on a purely visual analysis, (…) [partly due to the fact that] *you need knowledge about these tools. There are many neurologists and clinicians who do not even know that they* [atlases as the EBRAINS Atlas] *exist*". Furthermore, this interviewee also provided a possible reason for such ignorance, arguing that "*the main problem is* [that] *(...) these are tools designed for research,* [a domain] *in which almost everyone has a series of skills (...) that at a more general use level are not available. Especially in the medical-clinical field*".

It should be noted that this interviewee was not aware about the existence of the EBRAINS Atlas prior to our meeting invite. However, he did acknowledge the existence of the Allen Human Brain Atlas. And even though with such partial perspective, he was able to pinpoint one of the main drawbacks of the brain atlases landscape. As literally expressed: "*I miss something that integrates information. A single atlas containing information from multiple sources*". In other words, he was missing a boosted version of the tandem EBRAINS Atlas - EBRAINS KG.

For the current state of the EBRAINS Atlas, other relevant information conveyed included the fact that most of his clinical work requires millimeter resolution, and that today's growing trend is personalized medicine, developing treatments based on each patient neural networks' state. He also mentioned that, nowadays, a non-despicable number of patients undergo advanced MRI to obtain their tractography and functional resonance. He also presumed that these imaging studies could eventually be linked to simulations for deep brain stimulation, another of his practice domains.

The **second** young **clinical neurologist interviewed** (hereafter, I#2) specialized in epilepsy, further developed the argument of I#1 about the lack of education in the use of brain atlases, and emphasized their importance: "*We use the neuroanatomy we learned during the residency and throughout the medical career, and this has become obsolete with respect to what you show there* [the EBRAINS Atlas]". Thus, he clearly indicated the enormous potential of the EBRAINS Atlas, both in education and for applied research purposes.

For the latter, I#2 understands brain atlases such as the EBRAINS Atlas as really powerful tools, let it be to project brain imaging studies into a same reference space, let it be to carry out group studies: "[The connectome] *is relevant clinical information to* [do inference studies and] *understand what is happening to a group of patients. However, this would still have a research or semi-research character, in this case*". Following such "*semi-research character*", and as he repeatedly pointed out: "*from a clinical point of view we have not arrived there yet*". The reasons for this gap may be varied, but one found to be repeated throughout the interviews is that "*The atlas gives you information to carry out research studies but, many times,* [it cannot be applied] *to the individual*

patient". In other words, there seems to be an important gap on how to transition from the information given in the atlas to its application in patients.

In a more exploratory note, I#2 also wondered if the EBRAINS Atlas would enable a better distinction between brain areas and, therefore, of their interfaces. Always with the final goal of bringing such research advancements into the clinical practice.

Our **third interviewee** is a **senior clinical neurologist** (hereafter, I#3) specialized in spinal injury and neurorehabilitation at the *Hospital de Parapléjicos de Toledo*, one of the world's top centers for those two fields. He brought three interesting research avenues to the table: 1st) the need for an atlas that comprises spinal circuitry in a detailed way. 2nd) The need to understand where some symptoms emerge: "*We have a lot of questions about where some symptoms actually occur. We see that the patient is in pain, but* (...) *knowing why some have it and others don't is not so easy to explain with the classic model of the pain circuit*". 3rd) The anatomical distribution of some receptors, "*like the CB1 receptor*".

Our **fourth interviewee** is the **Neurosurgery Department Head** of one of Madrid's most important hospitals (hereafter, I#4).

As conveyed by I#4: "*We have several research lines* [in which the atlas could be of help]. *One of them consists of identifying deep brain stimulation targets using tractography;* [other] (...) *includes brain mapping, both functional and tractographic, to be useful in surgery. We are also interested in brain plasticity: how these maps change – and that may have an impact on the EBRAINS Atlas* [i.e. could lead to a possible collaboration with EBRAINS]".

In relation to the first research line indicated, the identification of deep brain stimulation targets, I#4 also expressed his desire of having simulations that enable to find those targets: "*One of our dreams* [together with the Director of the Magnetoencephalography Laboratory] *would be to do simulations*. (...) *When it comes to identifying targets for deep brain stimulation,* (...) *there is no model that allows us to simulate what would happen if I injured this nucleus, given the patient's connectomical data and its comparison with a normal model; or which node would you have to manipulate to make this system look as close to normal as possible. And maybe that would be a project that could fit in* [a possible collaboration with EBRAINS]". Again, more evidence on how valuable it is to strengthen the EBRAINS Atlas with the rest of EBRAINS services.

So far, it can be concluded that:

1st) I#4's statement regarding their interest in brain plasticity confirms one of the weaknesses identified in the previous section's SWOT analysis: that the EBRAINS Atlas lacks atlases covering the development of the human brain, which hinders further studies of brain plasticity.

2nd) Outstanding brain professionals in the clinic are willing to collaborate and explorer potential uses of the EBRAINS Atlas. Our interviews only covered six brain professionals from Spain, and with such a low sample we already found motivated experts willing to explore possible synergies. Boosting the HBP voucher programme could be suggested to enable those collaborations to materialize.

Our **fifth interviewee** is a clinical neurologist specialized in memory disorders and fully devoted to neuroimage research (hereafter, I#5). He is also the **Director of the Neuroimage Department** of one of Spain's most important centers for Alzheimer research.

Regarding the use of brain atlases in his everyday duties, I#5 conveyed: "*I use brain atlases increasingly. With the advent of more and more of these atlases* [such as the EBRAINS Atlas], (...) *you can no longer say that everything was judged by the clinical eye*". To which he pointed out: "*There's always the choice of which atlas you use, because there are certain atlases that have brain sections that are bigger than in other atlases*. (...) *You wonder what's correct and what isn't*. (...) *There's still no agreement in which is the atlas, and I don't think there will be*". With such a statement, one can rapidly confirm that the immense landscape of available atlases will only continue to grow in the future. Thus, and as already discussed, becoming the new standard template will not be easy for the BigBrain but, if achieved, it could benefit from the unfair competitive advantage of being one of the few – if not the only – reference spaces used in the micrometrical scale.

During this discussion, I#5 rapidly particularized his examples for the case of deep brain stimulation, one of his research techniques: "*Atlases are helpful*. (...) *Particular parts of the brain are more complex than others* (...) *so, for example,* [regarding] *deep brain stimulation electrodes for the psychiatric patient,* (...) *you want to use atlases to work out exactly where your electrode is*". In particular, I#5 mentioned that the atlas used for his deep brain stimulation studies is the Harvard-Oxford atlas, "*mainly for rapid cortical assignment*", as provided by the LeadDBS software (Horn & Kühn, 2015): "[With Lead DBS] *we can track* (...) *what cortical area which electrode contact is in*. (...) *Then, by eye, you have to go and make sure it's all correct*". Finally, he concluded: "*Everything we use for the deep brain stimulation* (...) *is included with the Lead* [DBS] *software*". When asked about the resolution needed, I#5 conveyed that one millimeter isotropic spatial resolution is enough, for the moment, for deep brain stimulation purposes, "*because you stimulate quite a large amount of tissue*".

Deep Brain Stimulation

Deep Brain Stimulation (hereafter, DBS) is a neurosurgical procedure that enables direct measurement of pathological brain activity and subsequently deliver of adjustable stimulation to focal brain regions, all with the aim of having a therapeutic effect in disorders correlated with dysfunctional circuitry (Krauss et al., 2021; Lozano et al., 2019). In other words, DBS enables circuit-based neuromodulation (Krauss et al., 2021). Furthermore, the duality of DBS as probe and modulator led to its current use in research for a broad scope of disorders, such as those related to memory, limbic, cognitive and – of course – motor functions (Lozano et al., 2019).

Until recently, DBS had only been approved – both at the US and EU level – for its clinical use in Parkinson's disease, dystonia and essential tremor (Lozano et al., 2019), as well as obsessive-compulsive disorder (Vázquez-Bourgon et al., 2019). Epilepsy joining the group lately, first in Europe (Epilepsy Foundation, n.d.-a) and then in the USA (Epilepsy Foundation, n.d.-b). But not only is DBS used in motor circuit disorders: it has become a standard of care for these conditions.

Even though DBS has not been approved yet for its clinical use in other diseases, several have witnessed considerable research advances regarding the implementation of this tool. Amongst them: chronic pain; psychiatric indications such a major depression, bipolar disorder, obsessive-compulsive disorder and anorexia nervosa; and Alzheimer's disease. For the latter, as an example, initial studies reported "*substantial stabilization of cognitive decline in some patients*" (Lozano et al., 2019).

In the technology side, DBS systems have evolved in the last decades from an external system, controlled with a handheld radiofrequency transmitter, to fully internalized devices – rechargeable batteries included. The latter are nowadays capable of simultaneous stimulation and recording and integrate closed-loop designs to account for one or more feedback signals, such body position and motion or signals that also allow for predictive symptom management, among other features. Electrodes have evolved accordingly, and now enable directional stimulation using radially segmented contacts (Krauss et al., 2021).

Finally, some of the major players present in the neurostimulation / neuromodulation market include St. Jude Medical (now part of Abbott), Medtronic, Boston Scientific, Beijing PINS Medical Co., SceneRay, PINS, Neuropace and Aleva Neurotherapeutics, among others (Fortune Business Insights, n.d.-a; Krauss et al., 2021).

Once the atlases resolution discussion has been opened, we brought the interview to the possibilities offered by the BigBrain, to which I#5 first pointed out: "*My PhD uses the BigBrain atlas for displaying where the electrodes are,* (...) *for visualization*. [In this regard,] *I think that the overlayers provided by the BigBrain are visually, aesthetically nice to demonstrate several aspects of neuroscience*. (...) [But] *you don't make any inference based on the BigBrain*". Considering that such a brain expert could further benefit from the micrometrical resolution provided by the EBRAINS Atlas, we specifically asked about such scenario. The next analysis, which is continuously referring to deep brain stimulation, followed:

"*The issue is whether in the future we have resolution that is sufficient to need such high-resolution atlas*. (...) *Not just because of the resolution of the scan, but it's also the fidelity of the co-registration of one scan onto another*. (...) *To be down to a micron resolution of where we need to stimulate is difficult, also because there's interindividual differences in anatomy so that my micron may be quite different from your micron*. *Would we ever get to the stage where we know exactly which micron of brain we want to stimuli? That's quite a long way away,* [although] *I'm sure we will be able to do that* (...) *with research*. [Also,] *the X-ray shadow* (...) *produced by electrical contacts* (...) [is] *relatively large, bigger than the resolution of some of these neuroanalysis. In the future, if these issues are improved,* (...) *so that we can see, for example, the electrodes that have these tiny hairs – the 'microwires' they're called – then yes* (...): *we'd want a micro resolution atlas in which to visualize where the microwire may be*".

To further complement his argument, I#5 also referred to the case of epilepsy research: "*The same goes for recording of epileptic activity. At the moment, the majority of the electrodes that are implanted are not in the epileptogenic area.* (...) *You have a big coverage and then you can look at all the contacts and infer where the activity is coming from, whereas if you were only measuring from a micron, you may not see anything at all*".

However, at the end of our resolution discussion, I#5 also pointed out that "*seven Tesla MRI scanning* (...) *is what is really gaining the resolution in terms of individual subject. MRI scanning where you can look deep into the level of individual cortical layers. So the resolution increase in the scanning is coming. Whether or not are we able to improve all the co-registration that may be also quite a big hurdle*". Some examples of such high field brain maps have already been mentioned in this analysis – see (Edlow et al., 2019; Lüsebrink et al., 2017). Particularly, (Edlow et al., 2019) remarkably claims to become the next micrometer resolution brain template and can be already found pre-installed in Lead-DBS for visualization in its 3D viewer.

In order to make the most out of the knowledge and experience of I#5, we broaden the scope of our questions and asked him about all future applications

he could foresee for an atlas such as the EBRAINS' one. Several insights are remarkable:

"*I think the biggest use for the atlas* [the EBRAINS Atlas] *will most likely be in the improvements of MRI scanning*". Also, "*improvements in general knowledge of neuroanatomy, cytoarchitecture,* [as] *it informs what the underlying tissue is*". I#5 provided a more detailed argument for this last application: "*This a sort of approach for when, for example, you want to divide into grey and white matter. You project brighter tissue probability maps, you know more less where things are and, on the basis of that, you refine things to then do the segmentation on the individual level. The better you tissue probability maps are, the better your prior for this type of analysis*".

Furthermore, as happened with I#3, I#5 expressed that "*I would need something else to motivate me to really use them* [the EBRAINS Atlas] *more*". In particular, in I#5's case that something would be: "*Thinking a bit further ahead with my research, if I would go into the EBRAINS Atlas and click on an area, and immediately that would be a fast demonstration of areas that are structurally connected*". Accordingly, we further asked I#5 about the fiber tract maps available within the EBRAINS Atlas, to which he replied: "*These are fiber tracts that people that know anatomy already know more less*". From this discussion, and considering something similar happened with I#3, it can be concluded that the content offered by the EBRAINS Atlas lacks specificity. But, in general, the immense variety of possible brain maps to be included will always make the EBRAINS Atlas lack specificity in some or another way. Then, the relevant question is: in what maps should the EBRAINS Atlas specialize? That is definitely a very good question, and its answer should depend on several factors, such as the size of the user / customer community targeted – the bigger, the better – and the resources available to further develop the tool.

At this point of the conversation, we decided to enter a discussion on the EBRAINS Atlas' related digital Infrastructure. At first, a very brief check of the available datasets in the EBRAINS KG let I#5 with the – not really incorrect – impression that most data contributors were funded by the Human Brain Project. That let him to wonder if this situation could introduce a bias in the data contained in the EBRAINS KG. An appreciation to be monitored. It is also remarkable that, as already indicated in Part 1 of this market analysis, I#5 spotted that the methods publication accompanying the DiFuMo atlas had not been peer-reviewed yet. At the moment of releasing the first version of this market analysis (June 2022), such publication is already peer-reviewed, but the fact that the DiFuMo atlas was uploaded to the EBRAINS KG before such reviewal had taken place caused a negative impression on I#5. Again, something to bear in mind.

Deepening into the infrastructure offered by the EBRAINS KG itself, I#5 highlighted that "*the interesting thing is that you have a lot of information, all in*

the same place". After some more exploration of the database, he continued: "*The great thing is that they will help you to make your data federated and interchangeable*". He finally concluded: "*The* [EBRAINS Knowledge Graph] *is great for data sharing*".

Once the EBRAINS KG had been explored, we came back to the viewer, and I#5 agreed that: "*It is helpful for anyone working in neuroimaging because you can put in the coordinate* (...) *and it'll take you to the place and tell you where you are. It's not the only software that does it,* (...) *within SPM, you can select which atlas you want and have your localization mapped*". However, and as he recognized that the EBRAINS Atlas "*has to become the go-to system,* [because] *everyone is using different softwares or systems that do similar things*", he also realized that several of the maps offered are already centralized somewhere else: "*SPM* (...) *is similar to what this major function* [the EBRAINS Atlas] *does; the white matter tract atlas is nice, but then there's one in FSL...*". At that point, he also recalled that, so far, the EBRAINS Atlas "*is all web-based so, for example, I would need to know how to use my current MATLAB analysis pipelines with this tool*". And he concluded: "*I have a pipeline in which I use these cytoarchitectonic maps, I've been using them for a while now, and I think is nice it is all centralized, but it's already centralized somewhere else* [the SPM toolbox]". [Important NOTE: as already explained in Part 1 of this market analysis, the EBRAINS Atlas is not web-based anymore, as it also offers programmatic access through the siibra-toolsuite. However, this interview was carried out before such toolsuite was released].

In fact, it is not only that part of the EBRAINS Atlas' content may be centralized somewhere else, but also that the creators of such content (case of the Julich Brain, for example) provide in their website (Forschungszentrum Jülich, n.d.-b) the link to both platforms, the EBRAINS Atlas and the SPM toolbox, thus missing the opportunity of directing the user only to the – furthermore less renowned – EBRAINS Atlas. On the other hand, it is understandable that, not having the EBRAINS Atlas a stable API yet, Jülich redirects to a toolbox that is indeed stable, so as to not loose user engagement with their developments.

Something similar happens with JuGEx, which desktop version can be downloaded from the Jülich website (Forschungszentrum Jülich, n.d.-a) and the EBRAINS KG, too. Thus, users' engagement is split – and will probably be tilted towards Jülich's website, the most renowned of the two.

SPM and FSL

SPM, the Statistical Parametric Mapping toolbox, is the name given to a series of software releases, all coded in MATLAB, for analysis of functional brain images. The software's main tools include image registration and statistical inference capabilities, a functional connectivity analysis service and optimized general features (reading/writing, user interfaces) (Ashburner, 2012). All of them have been continuously upgraded since the first release and until now, with SPM12 being the current version (last updated January 2020) (Statistical Parametric Mapping website, n.d.-d). It should be highlighted that SPM counts with an active user community, who have created a vast amount of SPM compatible extensions in the form of toolboxes, utilities, batch systems and brain templates (Statistical Parametric Mapping website, n.d.-c). Abundant training on the use of SPM is offered both by the developers of the software and by external organizations (Statistical Parametric Mapping website, n.d.-a), and the project even published a book which "*provides the background and methodology for the analysis of all types of brain imaging data*" (Statistical Parametric Mapping website, n.d.-b).

FSL, the FMRIB Software Library, "*is a comprehensive library of analysis tools for FMRI, MRI and DTI brain imaging data*" (FSL website, n.d.-b). Apart from the functional, structural and diffusion MRI tools included, FSL also offers extensions for statistical analysis, a 2D/3D brain volume viewer – rather old compared to current viewers – or the possibility to work with several atlases, among others. Such atlases include the MNI 152 space, a Human Connectome Project -derived space, the Jülich histological (cyto- and myelo-architectonic) atlas or the Harvard-Oxford cortical and subcortical structural atlases, among others (FSL website, n.d.-a).

With his conclusions, I#5 unveiled one of the key battles that the EBRAINS Atlas will need to fight in the following years: to overcome the inertia of already existing platforms, such as SPM and FSL, to become the go-to system. Of course, and as mentioned several times already, the accompanying services offered by EBRAINS will be key in that quest; to provide solutions for more specific uses of the EBRAINS Atlas' content – as SPM or FSL do – will also be decisive. At the same time, I#5 also highlighted other possible avenues to future develop the EBRAINS Atlas: "*I think the future* [of the EBRAINS Atlas] *is providing data on more levels. For example, they have started linking receptor density levels to the different anatomical locations, so you have a very thorough description of where you are in the brain.* (...) [The HBP / EBRAINS] *would want the rest of the community to follow suit and that's going to be the hard part I think:* (...) *persuading people that have been not in the Human Brain Project to put their data on* [the EBRAINS KG]. (...) *Going back to your original question: you would need good persuasion skills, and I think the way to do that would be*

explaining the issues behind federated data and how the Human Brain Project can help you".

Finally, our **sixth and last interviewee** is a **former surgeon and current Medical Director** (hereafter, I#6) of one of the top Positron Emission Tomography (PET) companies in the world. Such professional career gives I#6 a great background in the clinical context, but he also provided us with several insights about the research market worth mentioning.

To begin with, I#6 expressed his fascination about the EBRAINS Atlas: "*For its scientific application the atlas is the best that has ever been done*". He then continued discussing its current state: "*Now the n* [of subjects scanned] *is one*. (...) *This is great* (...) *for anatomical landmarks*". However, I#6 also pointed out that, to exploit all the potential of the EBRAINS Atlas and suit it to the greatest number of possible applications, age segmentation of the provided maps should be regarded as the next developmental step.

Furthermore, once I#6 had noted that "*The* [EBRAINS] *atlas is tremendously useful because the brain has never been seen in the level of detail with which this atlas presents it*", he also expressed that "*it could be improved with functional data*". Accordingly, we asked I#6 about the functional maps available within the EBRAINS Atlas, to which he replied with a key clarification. I#6 indicated that functional MRI and tractography maps are extremely valuable because they reflect the information avenues, the circuits involved in one or another brain function. However, he also explained that only PET is able to inform about the traffic itself, about the information circulating down those avenues. In his own words: "*PET adds a fundamental characteristic which is that, apart from generating images, it quantifies brain activity*". To exemplify so, he referred to dopamine circuits, one of the structures "*only visible with PET*". Once this difference had been clarified, thinking further ahead – considering the possible integration of PET information in the EBRAINS Atlas – I#6 conveyed: "*The possibility of doing things with MRI and PET at the same time - which does not even have to be at the same time, because fusion can be done very easily,* (...) *thus yielding personalized anatomical maps - opens totally unsuspected fields for research or to explore pathologies*".

At this point of the interview, we considered it relevant to start discussing about spatial resolutions. I#6 was clear: "*I am a doctor, not a scientist. Those in my profession are interested in the millimetric precision*". In particular, I#6 remarked that the last generation of the brain-dedicated PET being developed by his company has "*1.5 millimeter resolution and high sensitivity. We can speak of changes in the cortex at the level of its six layers*. (...) *The best brain-dedicated PET so far*".

And even though I#6 may not be so far interested in the micrometric precision offered by the EBRAINS Atlas, he helped us identifying potential markets for

this feature: "[For] *the maximum level of detail* [resolution], *I think research centers and the pharmaceutical industry may be the two easiest markets. Because all the others already work at the millimeter level: neurosurgery, radiotherapy, surgeries, treatments, behavioral therapies…*". And, regarding the micrometric resolution, he continued: "*Others may try to enter intracellularly*. (…) *The intracellular dimension can be very valuable. The only thing is that it has to be associated with the millimetric one, because we are talking about changes in neurons in areas of the brain that until now were not well identified*". In brief, he concluded that, "*In the research market, the atlas is already interesting. There are more or less 100 advanced neurological research centers in the world. A quarter in China, half of them in the US and the rest in other countries. There is already an established market*". We will talk about the pharmaceutical industry market in the next subsection of *Part 3* of this analysis, *In the Clinic*.

To end with the research market insights provided by I#6, two of them should be highlighted: "*Having the most detailed map that has ever existed is a big step that is going to get many people thinking*". In other words, it is not until advancements materialize that people start to consider the possibilities entailed by such innovations. Thus, I#6 was pointing out – and he did several times throughout the interview – to the advertisement and promotion of the EBRAINS Atlas as a direct way to further discover its possible applications and related markets.

In the Clinic

For the clinical purposes**, I#2 conveyed several messages about his current and future needs**. Starting with epilepsy, he pointed out that the margin of error to localize the epileptogenic zone in a patient's brain – the zone where the epileptic seizure starts - is in the centimeter range, as the epileptogenic zone's size is in that same scale. Thus, he confirmed the argument already given by I#5 that going down to the micrometer resolution would be detrimental to locate the epileptogenic zone. He also claimed that nowadays surgical resections are rather coarse because there is a lack of understanding of the connectome of the patient. He also emphasized that, if the connectome was better understood, more specific areas of the brain could be targeted, thus achieving a better control of the patient's future seizures without the need to carry out a large resection.

On the other hand, I#2 interest on how the EBRAINS Atlas would enable a better distinction between brain areas and, therefore, of their interfaces, was concretized to the presupplementary area: "*Where does the pre-supplementary area begin and the supplementary area end? What are their margins? I do not want to touch this patient's supplementary motor area because I can leave him with a deficit. Will the atlas give me such information?*"

Finally, I#2 indicated that the clinicians who could be most interested in the EBRAINS Atlas would be epilepsy and movement disorders professionals.

Visualase® Laser Ablation

Among the techniques used by I#2, he highlighted laser ablation with *Visualase®*, an MRI-Guided system offered by Medtronic. It uses a 1.6mm diameter (approx.) laser applicator to generate heat and damage a targeted brain area, all monitored by MRI.

Techniques used in the past include Stereoelectroencephalography (SEEG). Its use was discontinued as the heat generated was not as controllable as with *Visualase®*.

I#2 also emphasized that the use of such minimally invasive techniques is a current trend. Apart from laser ablation, other examples of this techniques include high intensity focused ultrasound (HIFU), radiofrequency ablation (RFA) or cryoablation (Kennedy, 2005).

At the clinical level, **I#3 also gave us some really valuable insights**. As per his own words, I#3's group "*areas of* [brain] *stimulation are rather gross*", being the "*standard MRI brain, rude functional MRI descriptions and Brodmann areas*" enough for their purposes. In other words, I#3's clinical activity has "*never gone into such fine detail that we needed an atlas*". However, as he also expressed, "*little by little we are going in this direction*". In order to help us find new user communities he also pointed out that, if we look at psychiatric problems, "*the stimulation areas are probably much smaller than in neurological problems, and the need for precision much greater*". He also considered as obvious the use of the EBRAINS Atlas in epilepsy and brain stimulation.

Taking advantage if his other professional facet, I#3 also conveyed that "*as a non-invasive brain stimulation expert and as an entrepreneur in the sector, I believe that atlases are extremely useful and important to define therapeutic targets,* (...) *both in invasive and non-invasive brain stimulation*". He also pointed out that useful atlases for these therapies should have the same characteristics, except from focality and depth, "*two completely different aspects*" between the invasive and non-invasive modalities.

It is precisely in this domain of brain stimulation that further upgrades of the EBRAINS Atlas could convince I#3 to use it. When asked about what it would take for I#3's group to train themselves and start using the EBRAINS Atlas, he replied: "*For example, if the atlas contained the actual connections between the areas that we stimulate and where the effect of that stimulation can reach*". Such example was further clarified: "*More than an atlas that tells me what anatomical pathways exist, I would need an atlas that enables me to say: 'these pathways are*

the ones that I have activated to have this benefit'. That is, more a comparative atlas of what happens to my patients compared to what is the physiological atlas itself". As the reader could expect, such desire led us to discuss about simulations, which I#3 also considered important: "[I'm interested] *in simulations* (...) *of what happens to brain connectivity when you have a spinal cord injury*". Thus, another proof to reinforce the need to complement the EBRAINS Atlas with the rest of EBRAINS services.

Finally, I#3 draw our attention to the development of brain stimulation applications based on focused ultrasounds, "*be it the invasive modality, which uses ultrasounds to make lesions in discrete areas of the nervous system, or the non-invasive, that enables access to deeper targets*". Furthermore, he remarked: "*surely, companies working in HIFU* [High Intensity Focused Ultrasound] *are very interested in improving their knowledge of the circuitry*", thus pointing out to a possible new user / customer community for the EBRAINS Atlas. He also mentioned the deep brain stimulation industry and the brain computer interface industry - which electrodes are just several dozens of micrometers wide (Kim et al., 2018), as two that could benefit from the resolution provided by the BigBrain.

High-Intensity Focused Ultrasound (HIFU)

HIFU (High Intensity Focused Ultrasound) is a non-invasive surgical technique which main application is the local ablation of a targeted tissue. It works by maximizing energy accumulation in the focal area – of a few millimeters, thus leading to its heating and, lastly, to its coagulation and denaturing within seconds (Jagannathan et al., 2009; Quadri et al., 2018). Other applications of HIFU also seize its other related physical phenomena, as is acoustic cavitation, to generate microbubbles that oscillate and lead to mechanical disruption of ischemic stroke clots (Quadri et al., 2018).

Even though its initial developments can be traced back to the first half of the XX century, its further development was hindered, until the 1990s, by the lack of a technology package that 1st) dispensed the need for craniectomy to avoid beam distortion and, 2nd) enable to plan and monitor the HIFU treatment with adequate imaging tools (intraoperative MRI) (Jagannathan et al., 2009; Kennedy, 2005; Quadri et al., 2018).

HIFU has several applications in neurosurgery, ranging from tumor thermocoagulation, functional neurosurgery (precise ablation in the thalamus, subthalamus or basal ganglia, centers to conditions such as Parkinson's disease and essential tremor), enhancing drug delivery across the blood-brain barrier, sonothrombolysis for both ischemic and hemorrhagic stroke, immune-modulation and antitumor immunity or, as future applications, treatment of trigeminal neuralgia, neuromodulation and epilepsy (Jagannathan et al., 2009; Kennedy, 2005; Quadri et al., 2018).

As Head of a Neurosurgery Department**, I#4 introduced several fields of application for the EBRAINS Atlas** – or for its possible future upgrades, as well as valuable information about their current and future needs.

To start by the former, I#4 indicated that they use different sources of radiological information as well as different atlases. The latter are specially used in functional surgery, where I#4 mentioned the Mai atlas (Mai et al., 2015), with the Tailarach-Tournoux one being residually used. On the other hand, I#4 also indicated that, for hemispheric surgery, "*We do not use atlases, but we do generate a bit of tailor-made segmentations*. (...) *Parceling of the different cortical structures* (...) *in each patient*". To this regard, he noticed that his department started to use *Brainlab* company software (Brainlab AG, n.d.) a short while ago for the parcellation of cortical and subcortical structures. As expressed by I#4, the software has its own atlas incorporated. This raised the wonder of whether VoluBA could be used – or upgraded – for that same purpose, which seems feasible. It is also noteworthy that the company also offers neuronavigation solutions, among other products.

Following this distinction between functional and hemispherical surgery, I#4 further develop the medical conditions treated with each modality: "*In functional surgery we treat movement disorders: Parkinson's disease, tremor and dystonia; then also psychiatric surgery: obsessive-compulsive disorder, depression - occasionally, we have a project on schizophrenia; and we've faced eating disorders, too. And then, in hemispheric surgery, brain tumors are what interests us the most: gliomas* (...). *In other words, intrinsic brain tumors*".

With such a broad catalogue, we were curious about the maximum resolution needed for one of these surgeries: "*The greatest precision needed is in functional neurosurgery, which is in the milli, submillimeter scale. And for this, rigid stereotactic systems are needed*". Trying to get deeper on this matter, we wondered if it would be feasible to benefit from micrometer resolutions in the everyday brain surgical practice, to what I#4 replied: "*The more accurate an atlas is, the better. But, on the one hand, how do you transfer the information from the atlas to the specific patient? And, on the other, atlases are based on a lot of anatomical information but little on functional information*".

From this point, two avenues of discussion emerged:

1st) The need for atlases to incorporate more functional information, which I#4 believes is – or will soon become – trend.

2nd) How to transfer the EBRAINS Atlas to the clinical practice and, finally, to patients. In this respect, I#4 expressed: "*To me, it seems that a step needed to apply this information to patients is to be able to adapt all this information to their anatomy*". If such issue would be solved, I#4 envisioned several application domains: "*It would be very interesting to apply this information, for example, to planning in radiotherapy of brain tumors, to know which areas can be irradiated*

more, which areas will respond with plastic changes…". And furthermore: "*There are many more applications. The use of preoperative functional tests, the search for the neuropsychological functions to be applied during surgery depending on the path to be followed… These atlases* [the EBRAINS Atlas] *would be very useful to us*". Again, all with a single condition: "*I see countless applications, what happens is that I would like to know better how to do it in an operative way, how do you take this to the operating room, how do you apply it to the specific patient*".

Finally, and as already indicated in the previous *In research* section, I#4 emphasized the possibility of establishing a collaboration with EBRAINS: " [The EBRAINS Atlas] *could be an important data source to improve or process our interventions, and conversely, we could provide neurophysiological or anatomical information on what we obtain.* (…) *I see a possible collaboration in the context of project development*".

Regarding the **insights provided by I#6**, our PET company Medical Director, about the clinical market, these could be differentiated into, 1st) the general use and possibilities offered by brain-dedicated PET and, 2nd) the exploitation possibilities of the EBRAINS Atlas in the pharmaceutical industry. Hereafter, we will follow such scheme to end with the *In the clinic* section.

With respect to such general use and possibilities offered by brain-dedicated PET, I#6 conveyed: "*Both for early diagnosis and therapy guidance, PET has no competitors*". Yet, he was pointing out to brain-dedicated PET, as full-body ones "*have a big problem:* (…) *resolution. With MRI we detect things the size of the head of a pin. With a full-body PET or CT* [Contrast Tomography], *the size of a cherry*". Thus, he was specifically referring to the brain-dedicated PET developed by his company, which resolution is as high as 1.5 millimeters. To this regard, and as already indicated in the *In research* section, I#6 emphasized: "*The atlas* [the EBRAINS Atlas] *is very useful for us because of its high level of detail. Yet, we don't need the microscopic scale. What is provided with MRI resolution, that head of the pin, already fits us well*".

Recalling the first clinical tests of their brain-dedicated PET, I#6 reviewed several applications where the functional information provided by PET will be very much needed: "*The brain-dedicated PET was launched as a project aimed at cognitive impairment and dementias,* (…) *but we soon discovered* [that it also works very well for] *aphasia, epilepsy, Huntington's disease, multiple sclerosis and amyotrophic lateral sclerosis… It can be of help throughout the entire field of neurology*". But furthermore: "*PET* [in general] *has never been used in stroke because it lacked resolution. Also, PET machines are completely overwhelmed by cancer. Now, with a brain-dedicated one, it is not only that stroke can be monitored, but that there will be availability to do so, as well as to use PET with other brain related disorders*".

At this point of the interview, it was clear that the functional information provided by brain-dedicated PET is of interest to several user communities, reason why upgrading the EBRAINS Atlas with such information seems key to further strengthen its nowadays generic, holistic character. If achieved, such enhancement could further increase awareness about the EBRAINS Atlas and its offer among several customer communities. Following such listing of possible applications, and related to this awareness increase of the EBRAINS Atlas, I#6 pointed out: "*Creating needs in the medical profession is common practice.* (...) *Philosophy changes take time because the need is not obvious*. *Many times it is necessary to sell what is the utility that things have*". Again, the need to advertise and promote the EBRAINS Atlas to further discover some its possible applications and related user / customer communities.

Back to the clinical applications of the EBRAINS Atlas, I#6 highlighted its usefulness to understand where are located each patient's complications when their scans are compared with the EBRAINS Atlas' reference map. However, and as already repeated, he missed the age segmentation of the atlas. Even though I#6 emphasized that "*Having a middle-aged adult is a great start*", and that "*Next age-segmented templates to come will be obtained much easier*", he also conceded that "*For its clinical application, we need to have it* [the EBRAINS Atlas] *segmented, with a sufficient n of patients*". He also indicated that, right now, the EBRAINS Atlas is a generic atlas, and wonder whether in the future it could become specialized for certain applications, (e.g., through disease-based segmentation).

Precisely, I#6 considered age segmentation to be a necessary condition to attract the interest of the pharmaceutical industry. But what features of the EBRAINS Atlas could be attractive to this industry? As conveyed by I#6: "*PET not only helps in early diagnosis: it can also enable you to see if a treatment works.* (...) *You can do a dynamic study* [and administer] *a drug while PET is being done* [and monitor the effect of that drug]. (...) *Companies that work in pharmacology in the brain, and in its diagnosis and treatment, need a reference atlas and centers that work with that atlas to measure the effectiveness of their treatments*". Again, the importance of seizing the first-mover advantage of the EBRAINS Atlas and becoming 1st) the go-to brain atlas platform, and 2nd) the standard micrometrical resolution template.

Regarding resolution and deepening into the pharmaceutical industry, I#6 insisted: "*I believe that in pharmacology, for pharmaceutical companies that are doing drug development, being able to go down to the highest level of detail possible is going to be directly useful. That opens up a huge market*". However, he also warned us about the pharmaceutical industry's caution and inertia: "*The atlas's exquisite level of detail can make it applicable to pharmaceutical companies. What happens is that they won't see it in minute one. And some will never do*".

To exemplify where could such level of detail be useful, in addition to the intracellular dimension already mentioned in the *In research* section, I#6 pointed to gene therapy: "*People are starting to talk about gene therapies, which have not yet been used in the brain because it is scary. It won't take long for us to start treating congenital brain diseases with gene therapies*". Precisely, as pointed out by I#6: "*When we talk about gene therapies, the intracellular dimension is essential*". Considering that such an advancement could materialize in the years to come, when decades ago would have been pure science fiction, I#6 concluded: "*What is the limit? When you have the tool, you can measure it. When you don't have it, you can speculate*". Now we have the tool, the EBRAINS Atlas, and the only thing missing is to further discover its possibilities, to bring potential user communities into the process and, with every new milestone, to make sure that the relevant stakeholders are informed about such advancement.

Gene Therapy for Brain Disorders

Gene therapy is based on delivering DNA or RNA sequences "*to add, replace, repair, or even remove*" another gene sequence, in order to cure a disease or, at least, slow down its progression (Conniot et al., 2021).

Successful use of gene therapy in neurological diseases could result from RNA interference (RNAi) techniques and genome editing technologies. The former would ideally result in the inactivity – the silencing – of disease genes. The use of RNAi is, however, restricted to such targets where gene knockdown is beneficial. At the same time, RNAi is often unable to fully silence gene expression, thus lacking the efficacy needed when complete repression of such genes is required for therapy. On the other hand, genome-editing technologies, such as famous CRISPR, offer a promising tool for the correction or removal of harmful mutations, or the generation of protective ones (Conniot et al., 2021).

So far, gene therapy has shown encouraging results for the treatment of conditions such as Alzheimer's disease, brain tumors and Parkinson's disease. Several vectors, both viral (e.g., lentivirus, herpes virus, adenoviruses) and non-viral (e.g., cationic -positively charged- lypid-based particles or polymers, inorganic nanostructures) are in current use, each providing different advantages and throwbacks. Depending on such, on the spatial spread of the disease to be treated and on the capacity of the vector to cross the Blood-Brain Barrier and enter the cell, vectors may be administered through more or less invasive techniques, ranging from intracranial injections to intravenous delivery (Deverman et al., 2018).

To conclude with our interview, I#6 expressed the willingness of his company to further collaborate in the development of the EBRAINS Atlas with the integration of several of their PET brain scans into the tool. When further asked about the available information, he replied that, from their own 200 subjects PET brain atlas, "*30 or so make up the control group, which is what fits in the current EBRAINS Atlas*". With the incorporation of such information, the EBRAINS Atlas "*would fill the gap of the functional dimension. And it would achieve so with state-of-the-art PET data, those with the level of resolution of the MRI*".

Finally, to end with this *In the Clinic* section, one of I#6's quotes seems perfect: "*Innovation needs something to pull it off. In the case of our preclinical PET, the best in the world, it was the clinical demand.* (...) *For the atlas it is the same. It is a wonderful tool, but if there are people who pull the atlas for specific uses, it can be optimized*".

In Education

Almost all interviewees mentioned, at some point during the conversation, the added value that the EBRAINS Atlas is meant to provide in education. In this brief section we will present some of the insights they provided.

To begin with, I#2 surprised us when he acknowledged that, in their day to day duties, "*We use the neuroanatomy that we have learned during our residency and medical studies. And this is now obsolete with respect to what you show there* [in the EBRAINS Atlas]". Therefore, he then concluded that "*From an academic point of view,* [the EBRAINS Atlas] *has a much higher value than what we are used to*". Being the EBRAINS atlas such a novelty, it did not seem strange that I#2 also affirmed that they, as clinicians, would use the EBRAINS Atlas "*like the one that uses an atlas in book format*", thus overlooking all other possibilities offered by the tool. So far, it seemed that the EBRAINS Atlas could enjoy a considerable market in medical education.

Besides, when interviewing a more senior researcher as I#5, he did convey that the EBRAINS Atlas is "*a very good teaching tool for the younger people new to neuroanatomy,* (...) [because everything] *is at the touch of your fingers*", but he also pointed out: "[In Deep Brain Stimulation], *I prefer my own visual assessment of where electrodes are to begin with, before even using an atlas, cause I'm used to look where things are in the brain*". Thus, the inertia of the received education: even though in favor of using the EBRAINS Atlas in the classroom, the need for visual assessment will always be there and, when passed on to the next generation, could that hinder their use of new atlases and, so, these products' exploitation possibilities? It can be presumed there will always be a tradeoff which will need to be tipped in favor of the atlases side.

At this point, we believe it is worth remembering part of I#1's interview, which confirmed the perspective obtained so far: "*the nuclear medicine doctor or radiologist doing neuroimaging continues to rely largely on a purely visual analysis,* [partly due to the fact that] *you need knowledge about these tools. There are many neurologists and clinicians who do not even know that they* [atlases as the EBRAINS Atlas] *exist.* (...) *The main problem is* [that] (...) *these are tools designed for research, [a domain] in which almost everyone has a series of skills* (...) *that at a more general use level are not available. Especially in the medical-clinical field*". Thus, the need to provide excellent training in the use of the EBRAINS Atlas before we can even think on trying to promote its use in medicine schools. Otherwise, when used in the classroom, both the lecturer and the students will only see it as that aesthetically nice "*atlas in book format*" that I#2 mentioned. It is much more than that, and everyone who discovers it should have enough information to acknowledge so since the first contact with the tool.

But once such milestones have been achieved, what could be next? Following our Atlases Taxonomy, neither have major atlasing initiatives made its atlases compatible with Augmented Reality (AR), nor did any of our interviewees mention such possibility. However, AR could mean a major advantage for the EBRAINS Atlas viewer in the field of education, and a key part of a market penetration strategy in the sector. Thus, AR seems to be a disregarded market gap in which the EBRAINS Atlas could become a first-mover.

Augmented Reality in Medical Education

Augmented Reality (AR) is, together with Virtual Reality (VR), one of today's trends in medical education (Kamphuis et al., 2014; Pantelidis et al., 2018; Parsons & Maccallum, 2021; Tang et al., 2019).

While VR focuses on building a fully computed-generated environment, the aim of AR is to overlay artificial images onto the real-world landscape. AR is nowadays widely used both in the clinic, "*providing extra information for the clinician during interventional procedures (CT/MRI guidance, visualization of paths)*", and in education. In the latter, anatomy - 3D visualization of anatomical structures, and physiology - understanding mechanisms in both spatial and time dimensions, are the two main application domains (Pantelidis et al., 2018).

But what does AR bring to medical education? Even though systematic literature reviews such as (Tang et al., 2019) conclude that "*the current quality and breadth of AR research in medical training is insufficient to recommend the adoption into educational curricula*", others disagree. That is the case of (Parsons & Maccallum, 2021) which, basing its analysis in five possible different gains*, concluded that "*studies that did not address any of the key affordances* [gains] *identified from the literature as being particularly relevant for the medical education context showed relatively poor learning outcomes*". All in, and while

bearing in mind that "*implementing such a novelty in the curriculum for medical professionals requires thoughtful development*" (Kamphuis et al., 2014), it seems the use of AR in medical education will only continue to grow. As a result, we propose it should be considered for the future development and exploitation of the EBRAINS Atlas.

*Reducing negative impact (risk, cost), visualizing the otherwise invisible, developing practical skills in a spatial context, device portability across locations and situated learning in context.

Exploitation Strategies

The exploitation strategies that could be followed by the EBRAINS Atlas are varied, and comprise multiple elements which could evolve or materialize in several ways depending on the resources available and the evolution of the targeted markets themselves. In this section, we will provide several possible future scenarios according to the resources available, and accounting for the expected evolution of the atlases market when possible.

To begin with, following the last *In Education* section, it can be concluded that the necessary groundwork to any possible exploitation strategy is training and education. For this domain we will formulate three possible scenarios, designed as cumulative, and which will therefore be explained in crescent order of available resources:

Scenario #1 – Training. In this scenario, the most basic one conceivable, EBRAINS would reinforce its online training offer for the EBRAINS Atlas, with a variety of demonstrations and periodic workshops that showcase all possibilities offered by the EBRAINS Atlas - as indicated by I#5, emphasis on "*explaining the issues behind federated data and how the Human Brain Project can help you*", for example, will be one of the keys. Ideally, sessions devoted to specific user communities would also be organized, while available information (e.g., the YouTube channel) on possible use cases is parallelly enriched. The Human Connectome Project or the Allen Human Brain Atlas are also already working on this scenario.

Scenario #2 –Training meets Education. In this scenario, which could be pursued almost along with Scenario #1 if enough resources are provided, EBRAINS would promote the use of the EBRAINS Atlas in medicine schools. At the same time, users' development of new EBRAINS Atlas use cases (let it be in research, in the clinic or in education) would be promoted through a periodic congress and/or competition. This would lead the EBRAINS Atlas to gain inertia from the very roots of the neuro- community, hopefully displacing other platforms such as SPM or FSL or, at least, placing itself as a direct competitor to both in the eyes of the neuro-community.

Scenario #3 – Education. In this scenario, only to be pursued after the previous ones, in order to benefit from the already built awareness, EBRAINS would adapt the EBRAINS Atlas to AR for its use in the world's most advanced medicine schools.

These are the three basic scenarios envisaged for what the interviews unveiled as a fundamental pillar to the advancement of the EBRAINS Atlas: training and education.

On a separate note, but also designed as cumulative and sorted in crescent order of available resources, we foresee the following scenarios for EBRAINS Atlas' content and related digital Infrastructure:

Scenario #1 – The already paced roadmap. In addition to continue uploading content elaborated by HBP – EBRAINS partners, and as indicated in the EBRAINS Atlases Service website (EBRAINS, n.d.-a), the EBRAINS Atlas' digital infrastructure will, under this scenario, be upgraded by:

- The release of an atlasing toolbox for neuroimaging, allowing probabilistic assignment of whole-brain signals to anatomical regions; the release of EBRAINS/Nilearn[41] interface for connectivity analysis; ilastik[42] made accessible as an EBRAINS web service, allowing to perform interactive image segmentation on EBRAINS image data (2022, Q1);
- The release of a new workflow allowing to project individual MRI scans to the human brain atlas for analysis; the alpha release of DataLad[43] accessibility layer for EBRAINS atlas datasets (2022, Q2);
- The beta release of EBRAINS/Nipy[44] software interface for connectivity analysis; the beta release of Neuron Morphology registration pipeline

[41] As per Nilearn website (Nilearn, n.d.): "*Nilearn enables approachable and versatile analyses of brain volumes.* (...) *It supports general linear model (GLM) based analysis and leverages* (...) *multivariate statistics with applications such as predictive modelling, classification, decoding, or connectivity analysis*".

[42] Quoting from its corresponding publication (Berg et al., 2019): "*ilastik* [is] *an easy-to-use interactive tool that brings machine-learning-based (bio)image analysis to end users without substantial computational expertise. It contains pre-defined workflows for image segmentation, object classification, counting and tracking*".

[43] Quoting from its corresponding publication (Halchenko et al., 2021): "*DataLad is a Python-based tool for the joint management of code, data, and their relationship, built on top of a versatile system for data logistics (git-annex) and the most popular distributed version control system (Git). It adapts principles of open-source software development and distribution to address the technical challenges of data management, data sharing, and digital provenance collection across the life cycle of digital objects*".

[44] Nypi, which integrates the already described Nilearn, is "*a community of practice devoted to the use of the Python programming language in the analysis of neuroimaging data*" (nypi, n.d.).

integrated to EBRAINS; updating of VoluBA with basic nonlinear registration capabilities (2022, Q3);

- The interactive segmentation of user supplied files in web-ilastik, with the possibility to submit results to EBRAINS curation services (2022, Q4);
- The release of a stable and fully documented EBRAINS/Nilearn interface for connectivity analysis; the integration of the neurogenpy library with EBRAINS, which allows analysis of gene expression data and learning of gene regulatory networks; the stable release of Neuron Morphology registration pipeline, allowing submission of outputs to EBRAINS data curation; the stable release of DataLad accessibility layer for EBRAINS datasets (2023, Q1);

Obviously, this is already an ambitious roadmap, but let us design two more scenarios, based on our interviews and, of course, with not as much detail as the one previously cited:

Scenario #2 – Reinforcing the holistic character of the EBRAINS Atlas. In this scenario, the EBRAINS Atlas content is reinforced with functional, PET data, as well as with the age segmentation of (part) of the already existing content. Note: even though the previous scenario includes supporting Freesurfer space – which, as already described in *Part 1*, is already age-segmented – it would be advisable, if resources are provided, to also carry out the segmentation of the BigBrain, following the developments started with the Julich Brain (Amunts et al., 2020).

Scenario #3 – Specializing the EBRAINS Atlas. In this scenario, the EBRAINS Atlas content would be segmented by user needs, following the interests of each of the previously selected – remember: the bigger, the better – user communities. On the side of digital infrastructure, such content would also be complemented with dedicated plugins / toolkits specifically designed for such communities (e.g., deep brain stimulation interface for both researchers and clinicians; neuronavigation software for neurosurgeons). This segmentation would require numerous inputs from the selected user communities, which could be gathered – as mentioned by I#4 – through the development of common projects, all framed and channeled through a reinforced voucher programme.

Neuronavigation

Neuronavigation is a surgical technique that enables "*real-time localization of a pointer in space in relation to the corresponding CT or MRI images*" (Grunert et al., 1998). Neuronavigation stems from the need to accurately locate intracranial lesions prior to their surgical removal. Even though some conditions may be removed with the only control of the surgeon's visual assessment ("*well-delineated lesions such as metastases, intraventricular tumors, and convexity meningiomas*"), it may not be possible to do so when the tissue to be removed cannot be differentiated from that of the normal brain, or when it infiltrates the skull base. In such cases, the needed visual control over the whole brain is provided by ultrasound, magnetic resonance or CT imaging (Grunert et al., 1998).

Resolution and accuracy are, of course, central to neuronavigation. The latter depends on three different factors (Grunert et al., 1998): mechanical accuracy of the device used, of the coordinate transformation ("*whether the cursor representing the tip of the pointer is correctly positioned in the image*") and of surgical application ("*measure of the target error during surgery*"; which accounts for intraoperative brain shifting). On the side of resolution, (Yoo et al., 2004) concluded – already in 2004 – that fMRI with isotropic spatial resolution of $2mm^3$ could be necessary *"for the unambiguous identification of cortical activation with respect to tumors and important anatomical landmarks*". Such millimeter resolution seems to still be the one available in MRI neuronavigation for the surgical practice (Sarkiss et al., 2016), though it is also remarkable that ultrasound-based navigation experiments carried out in mice seem to show promising micrometric error and, thus, resolution (Nouhoum et al., n.d.). Regarding Augmented Reality Neuronavigation (ARN) systems, their accuracy seems to be comparable to that of 2D neuronavigation systems, although there is still no standardized way to assess it (Fick et al., 2021).

Finally, some of the major players present in the neuronavigation market include Northern Digital Inc., ClaroNav, Medtronic, Stryker, BrainLAB AG, Synaptive Medical and Parsis Co. (Fortune Business Insights, n.d.-b). From the Australian brain ecosystem, Omniscient Neurotechnology Pty. is also noteworthy.

A schematic summary of the described exploitation strategies is presented in Figure 4.

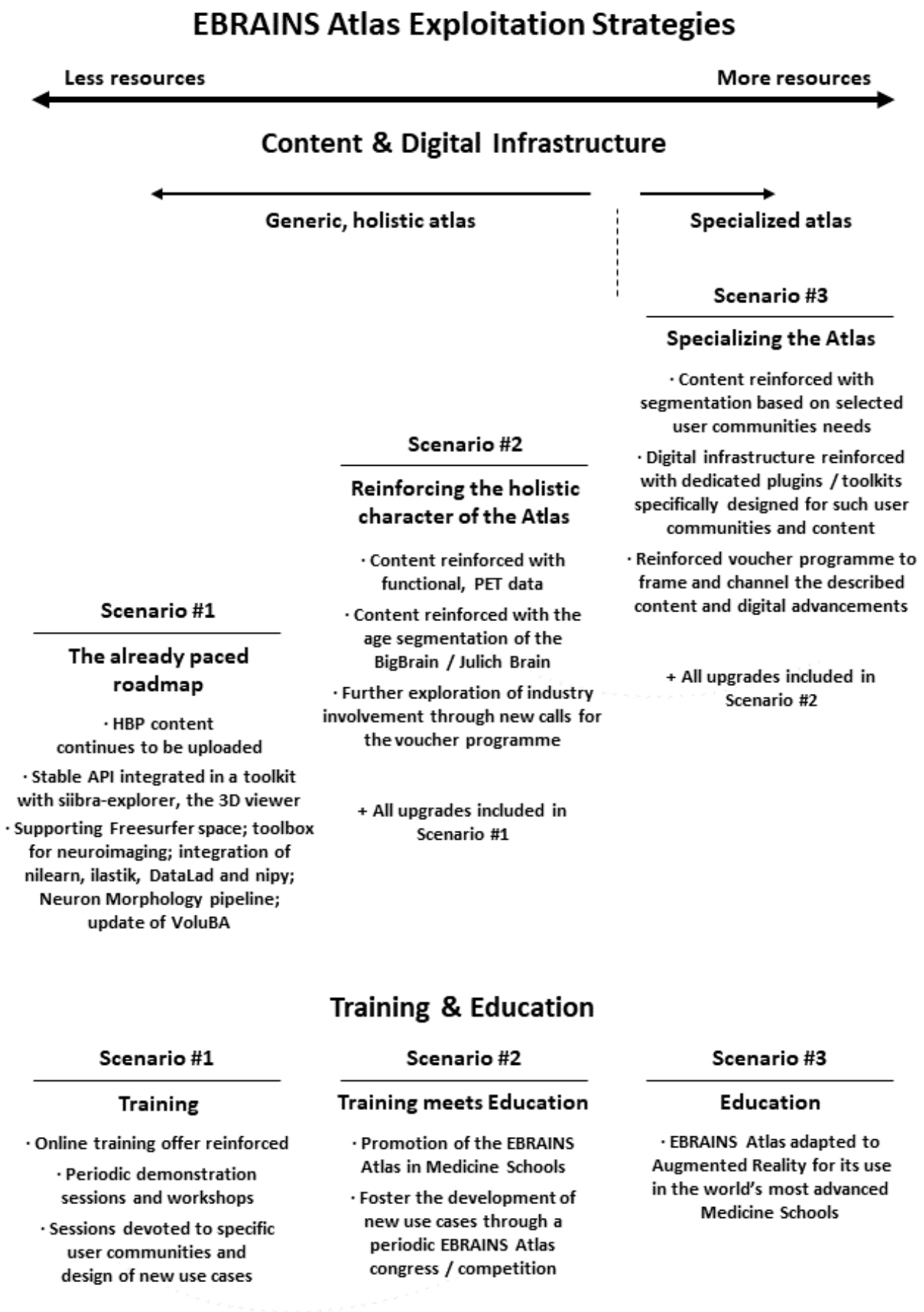

Figure 4. EBRAINS Atlas Exploitation Strategies scheme.

Private Players in Neurotech

Having explored the exploitation possibilities of the HBP Atlas at the research, clinical and educational level, and proposed exploitation strategies for them to become a reality, we believe that next essential step is to provide a list of some of the most important private players in neurotech; potential customers and/or partners to consider in the journey.

Some Big Neurotech Players

Philips

With its *Neuro suite* for image-guided therapy, Philips combines "*research and clinical studies to support more informed decision making for neurovascular intervention*". Among the tools integrated in this platform, called *Azurion*, several focus on achieving better 3D image visualization and guidance of neurovascular structures. In particular, the *Smart CT Roadmap* tool provides "*anatomical references to support precise navigation of guidewire, catheter, and device to the clot*" (Koninklijke Philips N.V., 2020), a realm where using the HBP Atlas could surely make a difference.

EGI & Magstim

Until 2020, Electrical Geodesics' (EGI) product portfolio belonged to Philips. This includes non-invasive multimodal technologies for the monitoring of brain activity, as well as transcranial electrical stimulation required for brain research. Since mid-2020, however, EGI belongs to the transcranial magnetic stimulation (TMS) provider Magstim (Newmarker, 2020). The former's main appeal is its high-density EEG, which allows to produce higher resolution data than conventional EEG. For Magstim, such technology "*closes the loop for the development of a comprehensive system for non-invasive neuromodulation*" (Krinke, 2020), Magstim's business core. Following the conclusions of our interviewee #3, further matches of the HBP Atlas with Magstim's clinical TMS navigation system, *StimGuide*®+, could be considered.

Medtronic

Medtronic's *StealthStation*™ *Surgical Navigation System* offers different "*cranial planning solutions* [that allow] *to view and manipulate patient images and plan* [surgical] *procedures*". Options range from merging scans and building models for tumor, shunt, or biopsy procedures, to viewing frame coordinates for stereotactic frame-based and DBS lead placement procedures. In particular, the combined used of the *StealthViz* and *StealthDTI*™ applications allows to import CTA, fMRI, PET, and MEG scans, among others; to "*segment critical anatomical structures with manual and semi-automatic tools*"; and to visualize both 2-D images and fast 3-D volume renderings (*Neurosurgery Planning | Medtronic*, 2020). Other Medtronic's complementary solutions include the *O-arm*™

Surgical Imaging System, for intraoperative imaging, landmark visualization and probe placement (*O-arm - Neurological Imaging | Medtronic*, 2020). Overlapping of these tools with the HBP Atlas is more than evident; potential collaborations could be explored.

Siemens Healthineers (Siemens)

Siemens offers different technologies related to improved diagnostic imaging through MRI. Among them, tools for MR Fingerprinting (MRF), which allows for simultaneous efficient quantitative measurements of multiple tissue properties with one acquisition (Ma et al., 2013), are one of its key foci. In particular, Siemens offers both an *MRF Development Kit*, for clinical and research applications (*MR Fingerprinting | Siemens*, n.d.), and a visualization tool, the *MR RoQT*, which includes image-based co-registration and is only meant for research purposes (*MR RoQT | Siemens*, n.d.). Other technologies offered by Siemens include the *Simultaneous Multi-Slice*, which "*helps cut neuro DWI scan times by as much as 68%* [and brings] *advanced DTI and BOLD into clinical routine*"; or the RESOLVE diffusion-weighted imaging (DWI) technique, "*that reduces blurring and susceptibility artifacts* [and offers] *high resolution DTI of the brain and spine*" (*MR Neuro Imaging | Siemens*, n.d.). It is also remarkable that the Siemens webpage offers a simple tool to calculate the user's revenue increase derived from their products, a useful and uncommon feature. To sum up, similarities between some Siemens tools and commercialization targets and those of the HBP Atlas are evident, and monitoring would be advisable.

General Electric Healthcare

General Electric (GE) also offers several MR applications related to neuroimaging (*Neuro Imaging - MRI | GE Healthcare*, n.d.). *Cube*, for example, reconstructs 2D slice-by-slice acquisitions into a single isotropic 3D, sub-millimeter resolution volume scan (*Cube | GE Healthcare*, n.d.). A process similar to that undergone in the creation of the BigBrain. GE's *BrainWave*, on the other hand, allows to obtain, "*process and display BOLD fMRI studies acquired with synchronized stimuli*", rendering 3D functional activation maps. The *BrainWave Fusion* tool, in particular, allows to "*fuse high-resolution anatomical images with fMRI activation maps and diffusion tensor tractography maps,* (...) *useful for evaluating the spatial relationship between activation patterns, fiber tracts, and underlying anatomy and pathology*" (*BrainWave | GE Healthcare*, n.d.). Once again, similarities with the EBRAINS Atlas' offer unfold.

Boston Scientific & Brainlab

Boston Scientific provides the Vercise™ suite of DBS systems (*Vercise DBS suite | Boston Scientific*, n.d.), all of which include a neural navigator for the exact positioning of the stimulation leads (electrodes). Its last version, *Vercise™ Neural Navigator 4*, offers "*intuitive directional steering controls, visualization of*

stimulation field modeling and insightful clinical effect annotations" (*Vercise Genus DBS System | Boston Scientific*, n.d.).

Boston Scientific's Vercise suite is possible thanks to its "exclusive" partnership with Brainlab, whose *Brainlab Elements* are the software modules integrated in the Vercise Neural Navigator (*Image Guided Programming | Boston Scientific*, n.d.). In particular, the Vercise navigator uses the *Elements Image Fusion*, *Elements Anatomical Mapping* and *Elements Lead Localization*, which respectively allow to "*automatically fuse a patient's MRIs and post-op CTs*", co-registering the patient imaging; to "*visualize patient specific anatomy*"; and to automatically detect and see in 3D the location and orientation of a DBS lead based on post-op CT artifact (*Brainlab Elements | Boston Scientific*, n.d.).

Other Brainlab software relevant to this market analysis include the *Elements SmartBrush*, for "*intelligent computer-assisted tumor outlining* [and] *multi-planar volume definition*"; *Elements Segmentation Cranial*, a "*fully automated, knowledge-based anatomical segmentation* (...) *based on a patented Synthetic Tissue Model*"; *Elements Trajectory Planning*, to "*plan multiple trajectories for neurosurgical approaches with* (...) [an] *adjustable 3D trajectory shapes for case-specific visualization* [and] *Axial, Coronal, Sagittal, Probe's Eye and Inline views for trajectory verification*"; *Elements Distortion Correction Cranial*, to "*compensate for distortions in MR datasets with multi-modal deformable co-registration* [and] *increase fibertracking precision*"; *Elements Fibertracking*, to "*process and visualize patient-specific DTI data to enable more refined surgical approaches* [while] *live tracking in 2D, 3D and Brain Projection views*"; or the *Elements Viewer* and the *Elements Viewer Smart Anatomy Cranial* which respectively allow "*fast and easy access to medical image data* [patient datasets] [and to] *interactively review plans in realistic 3D specifically for brain tumor and vascular indications*, (...) [while identifying] *superficial brain veins and vessels surrounding the tumor that may be critical during tumor resection or craniotomy*" (*Brainlab Elements | Brainlab*, n.d.). These software modules are complemented with Brainlab's stereotaxy and neuronavigation hardware technologies.

Thermo Fisher Scientific

Thermo Fisher Scientific provides the *Amira* software, a "*2D–5D solution for visualizing, analyzing and understanding life science and biomedical research data from many image modalities, including Optical and Electron Microscopy, CT* [or] *MRI* [among others]". It is aimed at research areas "*ranging from structural and cellular biology to tissue imaging, neuroscience, preclinical imaging and bioengineering*", and can be integrated with Python and MATLAB (*Amira Software | Thermo Fisher Scientific*, n.d.). Regarding its neuroimaging applications, Amira integrates "*frequently used image analysis techniques, such as filament tracing and editing, DTI analysis, brain perfusion analysis, and object tracking*" (*Amira Software for Neuroimaging | Thermo Fisher Scientific*, n.d.). It

offers a remarkable repository of use cases for tracing of brain neurons and vessels, mapping and perfusion and implant analysis (*Amira Use Case Gallery | Thermo Fisher Scientific*, n.d.).

Some Neurotech Startups & SMEs

Among the smaller neurotech players which activity is related to the HBP Atlas and its derived solutions, or that could even benefit from it, some relevant startups and SMEs identified include:

b2Quant **(Portugal)**, which offers design and development of "*reliable image analysis tools tailored to the purpose of each research project*"; with experience in multiple sclerosis, dementia and cerebral small vessel disease and example use cases available regarding FLAIR hyperintensities quantification and local and global brain atrophy (*b2Quant | Solutions*, n.d.).

Braindex **(France)**, focused on "*reducing the rate of neurological complications after surgery in patients over 60 years of age*", for which it has developed a "*brain functions monitoring device for clinicians during surgery*" (*About | Braindex*, n.d.). In detail, this device is a "*single sensor* [which combines] *a patented 3D spectro-imaging to target measurements of tissue oxygen saturation on the cerebral cortex, with a processed EEG focused on oversedation episodes*" (*Solution | Braindex*, n.d.).

Elminda's BNA™ (Brain Network Analytics) technology **(Israel)** integrates big-data repositories and deep-learning algorithms for the "*diagnosis, monitoring and treatment of brain-related disorders by measuring how effectively different parts of the brain are connecting and communicating*" (*Home | Elminda*, n.d.). In detail, Elminda's BNA "*creates high-resolution, three-dimensional representations of the functional neural pathways that are activated in response to* [repeatable] *tasks*", to then compare each patient's "*test results to their previous healthy-state baseline – or to a Reference Brain Network Model (RBNM) generated from an extensive population database*" (*MD Solution | Elminda*, n.d.). A feature really similar to that offered by the EBRAINS Atlas. Also based on its BNA technology, Elminda offers "*EEG/ERP based assessment technologies for pharmaceutical and academic clinical trials*" (*Pharma Solution | Elminda*, n.d.) as well as the Opti-Me solution, an "*EEG-based screening software solution that predicts responsiveness to both anti-depressants (SSNI and SNRI) and Transcranial Magnetic Stimulation (TMS) treatment, enabling tailored and optimized treatment based on brain-related biomarkers*" (*Predict Solution | Elminda*, n.d.).

RebrAIn **(France)**, a DBS technology developer focused on achieving optimal targeting through an AI algorithm and a collaborative health data registry, combined in the *OptimDBS* software (*Rebrain*, n.d.).

***Icometrix* (Belgium)**, which provides a nurtured portfolio of "*cloud-based AI solutions to quantify disease-specific brain structures on MR and CT*" (*Services | Icometrix*, n.d.), including the assessment of lesion dissemination in space and time (*Icobrain-ms | Icometrix*, n.d.); discover of abnormality patterns at the whole brain, ventricular or cortical level (*Icobrain-dm | Icometrix*, n.d.); or quantitative assessment of tissue perfusion (*Icobrain-cva | Icometrix*, n.d.), among others.

***Neurocare* (Germany)**, focused on "*neurotherapy for mental health, pain and rehabilitation using neuromodulation technologies integrated with psycho-therapy*" (*Company Profile | Neurocare*, n.d.). Among Neurocare's solutions are TES and TMS stimulators and, more remarkably, an MRI-based neuronavigation system for TMS (partnership with Rogue Research Inc.), the *Brainsight 2*, which enables visualization of the "*client's brain based on MRI data sets in order to move the coil to the desired brain structure and correctly position it*" (*Brainsight TMS | Neurocare*, n.d.).

***QMENTA* (Spain)**, which offers an AI-powered cloud-based solution for neuro research, clinical trials and clinical care studies. More specifically, QMENTA's solution "*simplifies compliant medical imaging data collection, with automatic anonymization, quality checks and modality tagging,* [supported by its*] 50 proprietary and standard biomarker tools and* [a database of] *more than 10 million brain images*" (*Home | QMENTA*, n.d.). Furthermore, QMENTA also offers a software platform which "*automatically ingests multi-modal data (including MRI, PET, CT, OCT and EEG)*" that can be later "*visualized, measured, classified and annotated*" (Platform | QMENTA, n.d.), to the extent that it can "*accelerate and improve the consistency and quality of brain disease interpretation*" (*Home | QMENTA*, n.d.). Data can also be integrated with a custom Python API, and researchers can even "*use the Software Development Kit to easily develop, test and run their own algorithms in a scalable cloud*" (Platform | QMENTA, n.d.). With over 1700 users, some of QMENTA's clients include Imaging Biometrics, Amylyx Pharmaceuticals or Hospital Sant Joan de Déu and IDIBAPS (*Home | QMENTA*, n.d.), two members of the Spanish EBRAINS node.

***QUBIOtech* (Spain)**, which focus partly overlaps with that of QMENTA: to provide AI-assisted analysis of biomarkers and in neuroimages (*Home | Qubiotech*, n.d.). With this aim, QUBIOtech provides Neurocloud, a "*cloud platform for the automatic processing of neuroimaging assisted by AI*" with applications in neurology, nuclear medicine and epileptology. In detail, Neurocloud has dedicated modules for "*automatic quantification of hypo and hypermetabolism and amyloid PET, automatic ictal and interictal SPECT subtraction and co-registration with MRI for very precise localization of the epileptogenic focus, volumetric analysis for the quantification of atrophy and lesions in MR imaging* [and] *quantitative analysis of DaT-SPECT* [(Dopamine

Transporter – Single Photon Emission Computed Tomography)] *image for the diagnosis and monitoring of Parkinson's disease*" (*Solutions | Qubiotech* , n.d.). As well as QMENTA, QUBIOtech's platform offers automatic generation of custom reports (*Home | Qubiotech*, n.d.).

***Medimsight* (Spain)**, also partly related to QMENTA and QUBIOtech as it offers "*a secure, unlimited, fast and affordable (free for research) cloud PACS* [with an] *open API to integrate with other vendors at all levels, including IA analysis, storage and analytics*" (*Home | Medimsight*, n.d.). Some of those vendors can be found in what Medimsight claims as "*the first AI cloud marketplace*" (*Apps | Medimsight*, n.d.), which contains 21 tools, several being open, third-party ones such as those offered by FreeSurfer or FSL. Medimsight's DICOM viewer, said to offer "*a very high performance and an intuitive interactive user interface*" (*Home | Medimsight*, n.d.), seems to clearly fall behind in relation EBRAINS Atlas' siibra-viewer.

***Advantis Medical Imaging* (Netherlands)**, which main product is a cloud-based, web platform designed to optimize brain MRI analysis, the *Brainance MD*. The platform's modules, all supported by a user-friendly 3D viewer, allow to perform diffusion analysis and fiber tracking; dynamic susceptibility contrast perfusion analysis, to inform about brain blood vessel structure and characteristics as a response to the injection of a specific contrast agent; fMRI analysis and a combination thereof in multi-modal studies (*Home | Advantis Medical Imaging*, n.d.).

***Oncovision* (Spain)**, an SME with almost 20 years of experience in the development and commercialization of medical imaging equipment. Among the solutions offered, Oncovision counts *CareMiBrain*, a brain-dedicated PET for the early diagnosis of neurodegenerative pathologies through the evaluation of the metabolic activity of a radiotracer. CareMiBrain, funded with more than €4 million by Horizon 2020 (*CareMiBrain | H2020*, n.d.), is now in its second clinical study phase, which will evaluate and compare its results to the neuroimages yielded by standard, whole body PET-CT scans (*Caremibrain | Oncovision*, n.d.). Proof of Oncovision's high quality equipment is the fact that its project *LivingBrain* was one of the only four selected in HBP's open call for industry engagement (*Open call for industry engagement | HBP*, n.d.). With LivingBrain, Oncovision aims at developing and testing a "*brain-dedicated prototyped PET system for the localization and quantification of molecular events in the living brain*", an instrument that "*would significantly exceed performance of the* (...) *CareMiBrain product*" (*LivingBrain | Oncovision*, n.d.).

***Positrigo* (Switzerland)**, a Zürich startup and potential competitor of Oncovision, which will soon offer a brain-dedicated PET system, the *NeuroLF* (regulatory approval is expected for the beginning of 2023 in Europe and the middle of 2023 in the US). Among the expected of the NeuroLF, Positrigo

counts dementia, neuro-oncology, epilepsy, movement disorders and research (*Product | Positrigo*, n.d.).

Imaging Biometrics **(US)**, which offers a suite of applications for analyzing MR images with a special focus on those resulting from neuro-oncology studies. In particular, "*clinically proven*" Imaging Biometrics software performs "*perfusion and diffusion brain mapping automatically on commonly available MRI studies*, [thus helping to] *identify areas of abnormal vascularity, improving accuracy for tumor grading and for differentiating recurrence from treatment response compared to conventional MRI*". It is also remarkable that the Imaging Biometrics *Delta Suite* "*allows the user to perform a range of common radiology tasks such as co-registering datasets, creating subtraction maps, and exporting class maps based on user-determined image thresholds*" (*Neuro-Oncology Solutions | Imaging Biometrics*, n.d.), operations similar to that executable within the HBP Atlas.

TheraPanacea **(France)**, which offers an AI-based software, the *ART-Plan*, for the delineation of "*target anatomical regions on 3D-images of cancer patients for whom radiotherapy treatment has been planned*". The software also offers an annotation module to "*create and edit the contours for the regions of interest*", and a *SmartFuse* module for the registration, display and comparison of 3D-images (*Products | TheraPanacea*, n.d.).

INBRAIN Neuroelectronics **(Spain)**, developers of a graphene-based wireless-powered brain interface, equipped with AI to achieve an adaptive closed loop for therapy personalization (*Home | INBRAIN*, n.d.). Recently, INBRAIN Neuroelectronics announced the creation of a new subsidiary, *Innervia Bioelectronics*, which will count with MERCK's collaboration for the development of "*smart neuro-modulation for targeted treatment of chronic diseases*" (*Innervia | INBRAIN*, n.d.).

NEUROSoft Bioelectronics **(Switzerland)**, which engineer subdural electrodes in the form of elastic, thin metal films of sub-micron thickness, devices claimed to be "*1000x softer and 2x thinner than current clinical electrodes*", as well as MRI compatible and easily foldable in the sulci (*Technology | NEUROSoft*, n.d.).

Neuroelectrics **(Spain)**, a neuromodulation company which offers a suite of brain stimulation and cloud-based monitoring services. These include a tES-EEG headset and its associated head model creation service, aimed at achieving model-driven montage optimization of the headset (*Home | Neuroelectrics*, n.d.). Neuroelectrics products' applications range from home therapy to neuroresearch, with the company sponsoring several clinical programs related to epilepsy, elderly falls or Alzheimer, among other conditions (*Research | Neuroelectrics*, n.d.).

***Byteflies* (Belgium)**, a health wearables developer with a specific solution for seizure monitoring (EEG, ECG, EMG, and actigraphy) (*Our Solutions | Byteflies*, n.d.).

***Cortirio* (UK)**, which functional near infrared spectroscopy (fNIRS) tool "*increases the spatial resolution of fNIRS to give useful medical imaging in a portable and wearable device*" (*Cortirio*, n.d.).

***Doitplenoptic* (Spain)**, developer of an optical microscope appliance which enables to record, process and visualize a 3D scene of a 2D sample, achieving resolutions of few micrometers (*Doitplenoptic*, n.d.).

***MAG4Health* (France)**, an incumbent startup (no product commercialized so far) that will offer a MEG with 64 sensors and 192 channels by the end of 2022. MAG4Health MEG's main feature claimed is its room temperature working regime, which allows to avoid cryogenics maintenance (*Product | MAG4Health*, n.d.).

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