Review

Biological Psychiatry

Mapping Cytoarchitectonics and Receptor Architectonics to Understand Brain Function and Connectivity

Daniel Zachlod, Nicola Palomero-Gallagher, Timo Dickscheid, and Katrin Amunts

ABSTRACT

This review focuses on cytoarchitectonics and receptor architectonics as biological correlates of function and connectivity. It introduces the 3-dimensional cytoarchitectonic probabilistic maps of cortical areas and nuclei of the Julich-Brain Atlas, available at EBRAINS, to study structure-function relationships. The maps are linked to the BigBrain as microanatomical reference model and template space. The siibra software tool suite enables programmatic access to the maps and to receptor architectonic data that are anchored to brain areas. Such cellular and molecular data are tools for studying magnetic resonance connectivity including modeling and simulation. At the end, we highlight perspectives of the Julich-Brain as well as methodological considerations. Thus, microstructural maps as part of a multimodal atlas help elucidate the biological correlates of large-scale networks and brain function with a high level of anatomical detail, which provides a basis to study brains of patients with psychiatric disorders.

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Understanding the anatomical basis for functional specialization and segregation requires one to approach the brain as a system that is organized on multiple spatial scales, from the micro to the macro level, and that is also acting on multiple temporal scales. Magnetic resonance imaging (MRI) helps investigate brain function and underlying networks in the living human brain but is less useful for revealing the underlying microstructure including the cellular and the fiber architecture (cytoarchitecture and myeloarchitecture, respectively). Cyto- and myeloarchitecture have been considered important biological correlates of brain function and dysfunction since the beginning of the 20th century (1,2), and their systematic analysis and mapping have led to a subdivision of the cerebral cortex into microstructurally different cortical areas. Brodmann based his work on the assumption that every cytoarchitectonically defined area contributes to a function in a specific way, although this could not be tested rigorously at that time for most of the areas (3). He published one of the most influential maps, which is still widely used to relate brain function and networks to the underlying brain areas. This and others' work formed the conceptual basis for the development of modern multimodal atlases, which allow one to link data from postmortem observations with in vivo imaging findings including long-range connectivity, functional networks, and activations (4).

The focus of this article is on two main organizational principles, cytoarchitecture and receptor architecture. The latter describes the distribution of receptors for different neurotransmitters as key elements of signal transduction. We describe our approach to mapping cytoarchitectonic areas in a sample of 10 postmortem brains and to computing probabilistic maps in 3-dimensional (3D) space. These Julich-Brain Atlas probabilistic maps are part of the EBRAINS multilevel atlas used to study structure-function relationships and can be accessed using the siibra software tool suite (5). The concept of the BigBrain as microanatomical model and template space that is applied, e.g., to studies of connectivity, is elucidated (6). We present tools that enable the application of cellular and molecular data from the atlas for MR studies of connectivity and modeling and discuss perspectives and pitfalls in this context.

CELLULAR ARCHITECTURE AND PROBABILISTIC MAPS

The brain contains approximately 86 billion neurons, the basic building blocks (7,8). While neurons in subcortical nuclei are distributed mainly in clusters, those in the neocortex or isocortex form a 6-layered architecture. The allocortex is phylogenetically older and consists of the paleocortex (e.g., olfactory bulb/tract, piriform cortex, superficial amygdala) and the archicortex (e.g., hippocampus). The number of layers varies between areas (e.g., 11 in the entorhinal cortex, 3 in the hippocampus). The 6 neocortical layers are arranged parallel to the cortex, show a specific input and output pattern, and differ in the distribution of cells and cell types. For example, while layers III and V contain pyramidal cells, layers II and IV appear rather granular; for an overview of cytoarchitecture, see (9). Modern functional MRI (fMRI), in particular at high field, allows one to resolve activity with increasing accuracy and to distinguish activations in supragranular from those in infragranular layers. This is the basis for studying, for example, mechanisms

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of feedforward and feedback pathways in the living human brain (10,11).

The cerebral cortex can be subdivided into areas based on cytoarchitectonic differences including layer thickness, cell density, and special cell types, e.g., Betz cells in the primary motor cortex or von Economo cells in the agranular insular and cingulate cortex (12). The existence and precise localization of cytoarchitectonic borders between areas has been proven using image analysis and statistical tests (13) and provides a solid basis for building a modern cytoarchitectonic atlas (14). Borders between areas coincide between different modalities, e.g., cytoarchitecture, receptor architecture, and fiber architecture, if the respective modality is sensitive to structural changes between two areas (Figure 1).

In addition to the laminar pattern of the cortex, cell bodies and nerve fibers are arranged vertically to the cortical surface in minicolumns (15). The visibility of columns represents another distinguishing feature of cortical areas; e.g., the rain shower formation in extrastriate areas (16).

Differences between cytoarchitectonic areas are the most prominent indicators of cortical specialization and form the basis of cortical maps. Combined cytoarchitectonic and electrophysiological studies, pioneered by the Parma group for example, have demonstrated that response properties of neurons change at the border of cortical areas (17,18), i.e., they demonstrate the relationship of the brain's microanatomy and activity. However, to replicate such phenomena in the living human brain is not possible, and more indirect measures have to be applied. For example, cytoarchitectonic similarity is greater between connected areas, suggesting that microscale cortical cytoarchitecture is closely related to macroscale brain connectivity organization (19) and that disruption in connectivity in brain disorders such as schizophrenia is associated with alterations in microstructure (20). Maps of cortical areas are also predictive for local gradients of functional maps (21).

However, additional principles of brain segregation have been identified, both within an area and beyond the areas (22). Within an area, the border tuft and the fringe area within areas of the visual cortex were described in the 1960s (23) and later verified using polarized light and diffusion imaging (24). Callosal connections in the occipital cortex have been shown in the border regions of early visual areas as demonstrated by the Nauta method (25), and ocular dominance columns represent another change in connectivity within those areas.

The neocortex can also be classified according to the appearance of an internal granular layer IV into agranular (i.e., layer IV is not present in the adult brain such as the motor cortex, Brodmann area 4), dysgranular (i.e., it does exist but is not well visible as an independent cortical ribbon such as in Brodmann area 44), and granular cortex (containing a well-defined layer IV such as in the frontal pole). Thus, this view combines different areas into larger groups based on shared features of layer IV. Furthermore, receptor architecture can be used to identify families of cortical areas (see Molecular Architecture, Receptor Fingerprints, and Maps).

More low-frequency changes across several areas have been described, such as myelination trends (26) and gradations, i.e., directed, incremental changes at the transition zone between isocortex and allocortex and between proisocortex (2,27) and periallocortex (28), respectively. More recently, gradients have been described for receptors (29) and functional connectivity (30,31).

The term "gradients" has been used in different contexts and with different meanings. For example, the combined analysis of microstructure, receptor, and transcriptomic data has revealed hierarchical gradients when moving from one area to the next in 4 functional systems processing motor, somatosensory, auditory, and visual information (32). Such covarying gradients across areas show hierarchies of gene expression and function across the neocortex (33). Some authors have observed a divergence for transmodal areas processing working memory, social cognition, and cognitive control and hypothesized that the decoupling of microstructural and functional gradients might enable functional diversity and flexibility in transmodal areas (34).

In summary, evidence has been provided that cytoarchitecture is linked to molecular architecture and connectivity in a systematic way. Cytoarchictectonic areas provide a suitable reference to interpret findings on connectivity and function, while multiple effects are contributing to brain segregation.

To identify areas based on the folding pattern is not reliable because borders of most areas do not coincide with anatomical landmarks, except for a few, e.g., the primary sensory and motor cortex. Borders vary between brains regarding their relationship to sulci and gyri. For example, areas 44 and 45 of

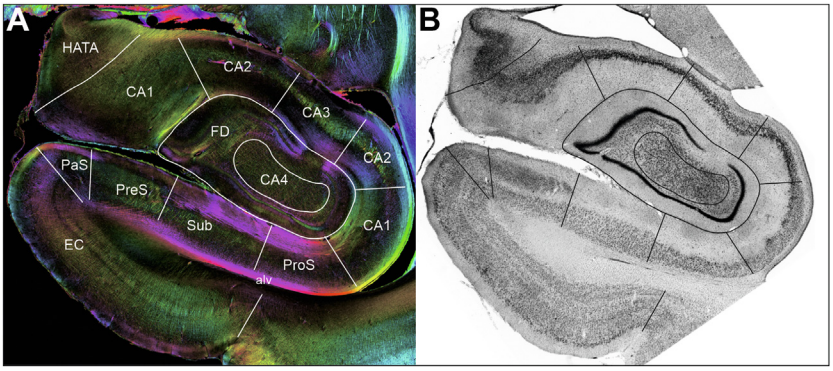

Figure 1. Correspondence of fiber- and cytoarchitecture. **(A)** Polarized light image of the hippocampus showing the fiber orientation at micrometer resolution. **(B)** Same section cell body stained. Hippocampal subdivisions correspond in both modalities (most prominent borders for areas PreS and EC). Areas are labeled and borders are indicated by white and black lines, respectively. alv, alveus; CA, cornu ammonis; EC, entorhinal cortex; FD, fascia dentata; HATA, hippocampal-amygdaloid transition area; PaS, parasubiculum; PreS, presubiculum; ProS, prosubiculum; Sub, subiculum.

Broca's area show considerable intersubject variability, while other areas such as the primary visual cortex vary to a lesser degree (14). The Julich-Brain probabilistic maps of cytoarchitectonic areas reflect these differences between brains by integrating and superimposing individual maps from 10 postmortem brains into a common reference space (14). They quantify the probability of an area at each position in stereotaxic space and display it in a color spectrum from low to high. Maximum probability maps have been calculated, which show brain areas in a nonoverlapping mode by assigning each position in the reference space to the area with the highest probability (35).

MOLECULAR ARCHITECTURE, RECEPTOR FINGERPRINTS, AND MAPS

Neurotransmitter receptors are key molecules of information transfer between neurons and can be studied using quantitative receptor autoradiography (36). They are expressed at varying intensities throughout the human brain [e.g., Zilles and Amunts (37), Palomero-Gallagher *et al.* (38)]. In general terms, receptors for the excitatory neurotransmitter glutamate and the inhibitory neurotransmitter GABA (gamma-aminobutyric acid) are present at considerably higher densities in the cerebral cortex than receptors for modulatory neurotransmitters, and most receptors are found at higher densities in the superficial than in the deep cortical layers (39). The laminar distribution patterns of neurotransmitter receptors correlate with synaptic densities, but differences in receptor densities should not be interpreted as directly reflecting cytoarchitectonic layers or cell packing densities (39). Simultaneous analysis of the distribution of cell bodies and of multiple receptor types along the cortical ribbon has shown that changes in receptor densities are indicative of borders between areas and that receptor architectonic borders occur at positions comparable to those of cytoarchitectonic borders both in the isocortex and allocortex [e.g., Caspers *et al.* (24), Palomero-Gallagher *et al.* (40)] and are sometimes more sensitive regarding borders than cytoarchitectonics (41). However, what makes this multimodal approach so powerful is actually the fact that not all receptors reveal all possible cytoarchitectonic borders, so that each neurotransmitter receptor can identify families of cytoarchitectonically distinct but neurochemically related areas (42). Indeed, similarities between areas in their receptor fingerprints, i.e., in their specific codistribution patterns of multiple receptors, constitute the molecular underpinning of communication between these areas and thus confers them with the ability to build a network that subserves a specific functional system (43). Furthermore, receptor fingerprints differ between functional systems and segregate cortical types and reveal hierarchical processing levels [e.g., isocortex vs. allocortex or unimodal vs. multimodal areas (39,44)].Thus, receptor fingerprints enable analysis of the brain's structural segregation and its functional connectivity principles.

Importantly for translational studies, the regional differences in receptor distribution patterns as revealed by means of receptor positron emission tomography (PET) are comparable to those obtained with in vitro receptor autoradiography, provided that the same ligand (or different ligands, but of comparable specificity and type) is used for both modalities [e.g., Hurlemann *et al.* (45), Kumar *et al.* (46), Paterson *et al.* (47)]. Recently, a 3-dimensional normative receptor atlas has been provided by Hansen *et al.* (33). The PET-derived receptor data showed brain structure and function coupling, correspondence to connectivity, and neural dynamics (magnetoencephalographic data) and neuroatrophy in brain disorders such as attention-deficit/hyperactivity disorder, autism, and temporal lobe epilepsy. Another study by Kaulen *et al.* (48) provided an atlas showing the in vivo distribution of glutamate and $GABA_A$ with potential benefit for psychiatric diseases. While receptor PET has the advantage of permitting the study of molecular dynamics at the receptor level and can reveal their relationship to behavior and disease in healthy subjects and patients [e.g., da Cunha-Bang and Knudsen (49)], in vitro receptor autoradiography has the advantage of providing a higher spatial resolution and of addressing many different receptor types in the same sample. Therefore, in vitro receptor autoradiography represents a powerful tool for the analysis of the pathogenesis of neuropsychiatric disorders in which receptor alterations are often associated with more than one transmitter system. To combine data from receptor studies (both in vivo and in vitro) with findings from cytoarchitecture, connectivity studies, and functional imaging, it is necessary to integrate them into a common reference space and to use an atlas in which different data modalities across the different scales are represented.

CYTOARCHITECTONIC AND RECEPTOR ARCHITECTONIC MAPS AS PART OF A MULTILEVEL BRAIN ATLAS

Cytoarchitectonic probabilistic maps have been used to build the EBRAINS multilevel brain atlas (https://ebrains.eu/service/human-brain-atlas/, https://atlases.ebrains.eu/viewer/go/julichbrain), a 3D reference atlas that links different aspects of brain organization at microscopic and macroscopic scales. The core idea of this atlas is to integrate different whole-brain maps as well as regional data in a common framework and to superimpose them in the same template. Therefore, the atlas supports multiple templates at different spatial scales and contains explicit links between the spaces.

The microscopic scale of the atlas is represented by the BigBrain model and template space (http://bigbrain.brainatlas.eu), i.e., a 3D reconstruction of a full series of cell body–stained sections of a human postmortem brain at 20-μm spatial resolution, a terabyte-sized dataset (6). The gray values of the BigBrain represent cellular densities and allow one to distinguish details in cortical layers and even in large cells. Automated mapping workflows have been proposed for this microstructural template, resulting, for instance, in a complete map of the 6 layers of the isocortex [http://layers.brainatlas.eu (50)]. It uses a classification of 3D cortical intensity profiles and 1D convolutional neural networks. In addition, highly detailed maps of cortical and subcortical areas based on image segmentations across thousands of histological sections have been computed, whereby 2D convolutional neural networks were trained on a scarce set of cytoarchitectonically identified areas (51).

The macroscopic scale of the atlas is represented by the Montreal Neurological Institute (MNI) reference space (52), which is used in many neuroimaging and clinical applications. It incorporates different templates including the MNI Colin 27

single-subject average as well as the ICBM 152 2009c asymmetrical multisubject average (spatial resolution of 1 mm). Both templates are fully mapped by probabilistic cytoarchitectonic maps. Because these follow the same delineation principles as the maps available in BigBrain space, they constitute a direct anatomical link across the scales. The BigBrain served as a basis to provide the first whole-brain model of cortical layers (50) and to study the 3D topology of the hippocampus (53). Ultra-high resolution 3D reconstructions of cortical areas and subcortical nuclei have been developed (51,54) and openly provided to the community. In addition, several new tools, such as the BigBrain warp toolbox (55) and PET tracer simulation (56), have been developed during the past years, and links to other community tools have been established; for an overview, see https://bigbrainproject.org/.

For more than 30 of these cytoarchitectonic areas, neurotransmitter receptor densities have been obtained using quantitative in vitro autoradiography (42). The datasets are directly linked to the multilevel atlas in the form of regional data features, identified by the cytoarchitectonic localization of the underlying tissue samples that are openly accessible.

Most recently, the volumetric cytoarchitectonic maps have been projected to the fsaverage surface space [https://surfer.nmr.mgh.harvard.edu/ (57,58)].

ACCESSING AND ANALYZING ATLAS DATA THROUGH THE SIIBRA TOOL

The different maps can be directly accessed using the siibra software tool suite, a software interface for interacting with brain atlases that provides both interactive and programmatic interfaces. This recently developed tool suite comprises a fully interactive web interface (siibra-explorer) as well as a comprehensive python library (siibra-python). In addition, an HTTP application programming interface is provided for connecting external applications (siibra-api; hosted at https://siibra-api-stable.apps.hbp.eu/). The underlying reference templates, parcellations, and data are stored as curated datasets in the EBRAINS Knowledge Graph (https://search.kg.ebrains.eu). The siibra tool integrates these datasets into the multilevel atlas and links them with other resources, e.g., from studies of connectivity.

The interactive siibra-explorer https://atlases.ebrains.eu/viewer provides a 3-planar view of a reference volume combined with a rotatable overview of the 3D surface. Different templates and maps can be selected using the layer navigation panel (Figure 2), allowing one to change between MRI-scale views and the full resolution of the BigBrain as well as a 3D view for convoluted and inflated surfaces. Precomputed nonlinear transformations will be used to preserve the view across spaces in terms of its 3D position, orientation, and zoom level (Figure 3), thus presenting the corresponding anatomical region in the new space. By selecting a brain region, a side panel is presented that provides a description and link to detailed metadata in the Knowledge Graph, a list of regional data features linked from the Knowledge Graph and additional online resources, as well as an interactive browser for regional connectivity profiles from different imaging cohorts. Regions can be selected by clicking or by navigating an interactive, searchable region hierarchy tree. The viewer provides an extensible plugin architecture, which includes an

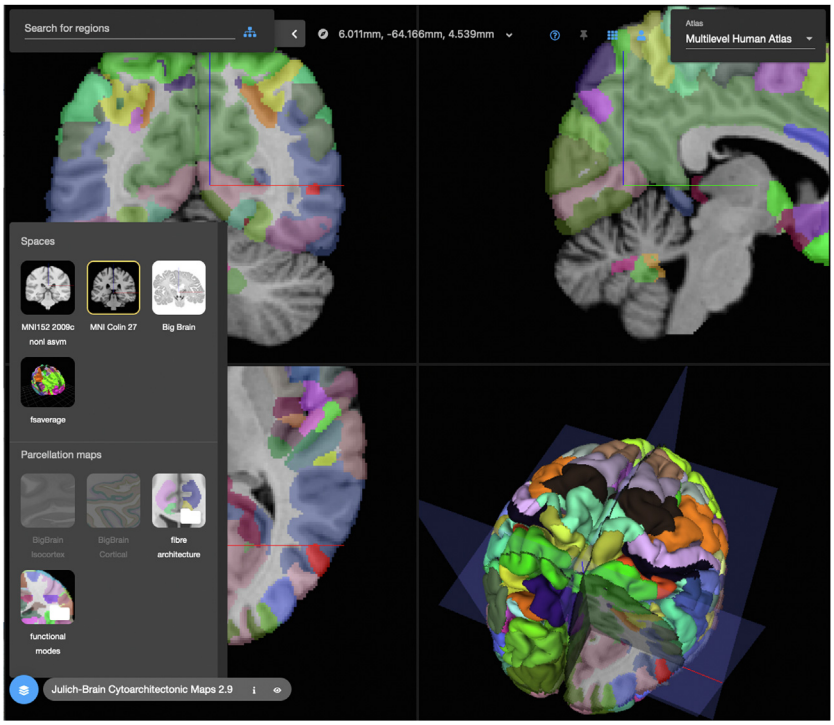

Figure 2. User interface of siibra-explorer, the interactive 3-dimensional viewer for accessing the multilevel brain atlas hosted at https://atlases.ebrains.eu/viewer. Julich-Brain cytoarchitectonic maps depicted in different colors in MNI Colin 27 space at 1-mm resolution, layer navigator panel opened, which showed the selectable reference spaces and parcellation schemes.

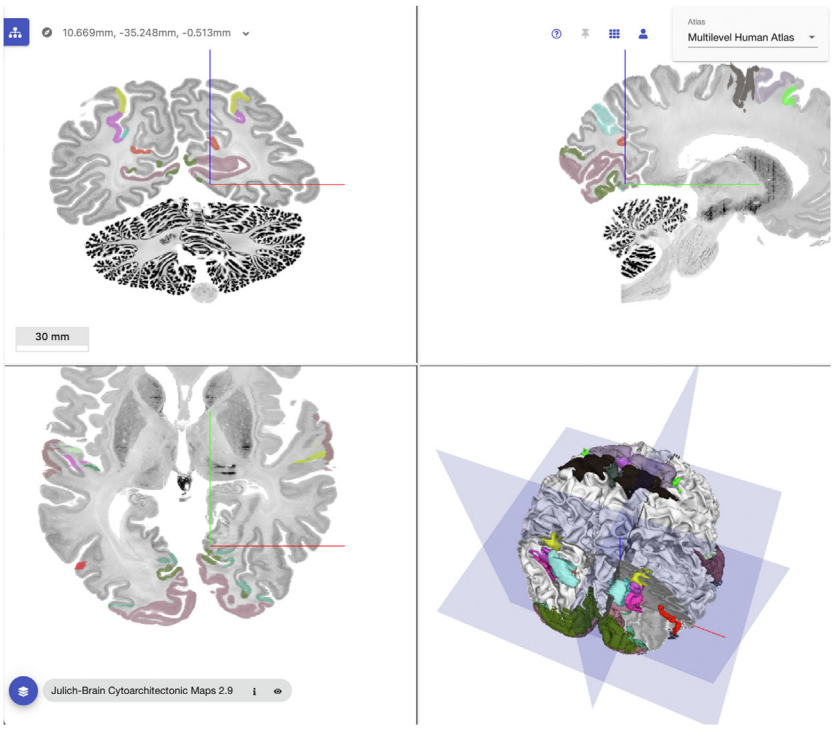

Figure 3. User interface of the siibra-explorer showing the approximately corresponding view as in Figure 2, which the viewer presents after switching to BigBrain space with 20-μm resolution. Cytoarchitectonically mapped areas in the BigBrain are labeled with different colors.

annotation mode for creating and sharing named locations, lines, and polylines, as well as some tools for interactive data analysis such as JuGEx (59).

The interactive functionality of the siibra-explorer as well as advanced features are available for integration in computational workflows through the software library siibra-python, which is directly installable from https://pypi.org/project/siibra/. The library offers data types and predefined objects for parcellations, maps, reference spaces, and multimodal data features and provides compatibility with common libraries such as numpy, pandas, matplotlib, nibabel, and nilearn. Detailed documentation is available at https://siibra-python.readthedocs.io, which also provides downloadable code examples with explanations.

APPLICATION SCENARIOS

The multilevel atlas is designed for integrating multimodal data from in vivo and postmortem studies and is linked with a growing amount of data (for accessible tools and data, see Table 1). In the following section, the scope of several applications will be illustrated.

Sharing and Analyzing High-Resolution Microscopic Data in the BigBrain Space

The BigBrain is suited for spatial anchoring of regional data from volumes of interest from histological experiments with high spatial resolution. VoluBA is a service for upload and interactive anchoring of such volumes into the BigBrain (https://voluba.apps.hbp.eu/#/) including imaging data from two-photon, light-sheet imaging or x-ray. As an example, a volume from 3D polarized light imaging (60) has been anchored to the BigBrain space, showing the distribution of nerve fiber orientations in the hippocampus. The embedding in the atlas allows one to compare modalities and appreciate the orientation, size, and proximity of the volumes of interest to other brain regions superimposed to the cytoarchitectonic BigBrain model (data at https://search.kg.ebrains.eu/instances/Dataset/b08a7dbc-7c75-4ce7-905b-690b2b1e8957).

Comparing Activation Data From fMRI Data With Cytoarchitectonic Maps

When fMRI studies have been transformed to the MNI reference space, areas of activation can easily be compared with brain regions of the atlas. For this scenario, the siibra-explorer allows one to overlay a local brain volume with the volumetric atlas by dragging the file onto the browser window. fMRI datasets can also be correlated with nuclear imaging (PET and single photon emission computed tomography maps) of various neurotransmitter systems by using the user interface of the JuSpace toolbox (61). Moreover, the atlas provides access to a high-resolution task-fMRI dataset (62).

Cytoarchitectonic Maps as Seed Regions for Analyses of Connectivity

The maps have been used for extracting region-averaged connectivity matrices from cohort studies. Several datasets of functional as well as structural connectivity in the form of streamline counts and lengths from diffusion imaging have been linked with the atlas (63–65), providing connectivity profiles as a regional feature type. In the siibra-explorer, they

Table 1. Overview of Available Tools and Data for Multivariate Analyses of Connectivity and Brain Function

Tools/Datasets	Description	Link or Reference
Tools		
Atlas viewer	Provides parcellation maps of cyto- and fiber architecture and connectivity in different reference spaces	https://atlases.ebrains.eu/viewer
JuGEx	Analysis of differential gene expression in cytoarchitectonic areas	https://ebrains.eu/service/jugex/ (59)
siibra software tool suite	Programmatic access to the maps of the atlas in python	https://siibra-api-stable.apps.hbp.eu/
EBRAINS Knowledge Graph	Flexible and scalable metadata management system with a search user interface, links the atlas to additional data stored in the Knowledge Graph	https://search.kg.ebrains.eu
VoluBA	Anchoring any volume of interest (e.g., high-resolution volume from optical imaging such as PLI in the BigBrain)	https://voluba.apps.hbp.eu/
JuSpace	Cross-modal correlation between fMRI and PET datasets	https://github.com/juryxy/JuSpace (60)
Datasets		
Julich-Brain cytoarchitectonic maps	Cytoarchitectonic probabilistic maps and MPMs of more than 145 areas, integrated in the atlas viewer	https://atlases.ebrains.eu/viewer (14)
Representation of cytoarchitectonic maps in FreeSurfer format	Integrated in the atlas viewer	https://atlases.ebrains.eu/viewer https://surfer.nmr.mgh.harvard.edu/
Structural connectivity	Maps of short- and long-range fiber bundles integrated in the atlas viewer	https://doi.org/10.25493/NVS8-XS5
Functional connectivity	Visualization and connectivity strength of functionally connected brain areas integrated in the atlas viewer	https://doi.org/10.25493/61QA-KP8
BigBrain model	Microscopic brain model	https://bigbrainproject.org/hiball.html (6)
BigBrain segmentation	Layer segmentation of the BigBrain for the isocortex	http://layers.brainatlas.eu (50)
High-resolution maps of the BigBrain	Deep learning approach to enhance the spatial resolution of brain areas in the BigBrain	(51)
IBC	Functional territories, Individual Brain Charting dataset	(61)

fMRI, functional magnetic resonance imaging; IBC, Individual Brain Charting; MPM, maximum probability map; PET, positron emission tomography; PLI, polarized light imaging.

can be used to explore connections of a brain region interactively; after selecting a source region and connectivity dataset, a list of connected target regions is presented, and connection strengths are used to colorize the parcellation map (Figure 4).

Studying Genetics: The JuGEx Tool

The siibra tool suite implements a direct interface to the Allen Brain Atlas application programming interface (Allen Institute for Brain Science; https://brain-map.org/api/index.html). Microarray measurements are linked to the atlas via the 3D coordinates of the tissue blocks, which are supplied in MNI reference space (Figure 4C). This interface enabled implementation of the JuGEx workflow, originally implemented in MATLAB (The MathWorks, Inc.) (59) as an extension of the siibra-python package (https://github.com/FZJ-INM1-BDA/siibra-jugex/), and makes it accessible as an interactive plugin in siibra-explorer. By selecting 2 regions of interest in the atlas, the workflow performs a differential analysis of the expression levels of candidate genes. This tool allowed disclosure of subregion specificity in the left medial frontal pole area Fp2 in patients with major depressive disorder (66).

From Large Cohort Data to Individual Profiles of Brain Aging

Brain aging is an individual phenomenon. Cytoarchitectonic maps can be used for deep phenotyping in the older adult population to link multilevel brain, cognitive, and lifestyle data to better understand the normal aging brain as well as the different brain-behavior relationships in brain disorders to the benefit of clinical psychiatry. In a pilot study, a subcohort of 5 males scoring low on a dementia screening test was analyzed as part of a large population-based cohort study, 1000BRAINS (63,67). As expected, individual cognitive profiles were highly heterogeneous regarding cognitive performance, lifestyle factors, and gray matter atrophy. However, cytoarchitectonically defined areas PFt, PG, 3b, and 45 of the subcohort deviated more than 2 standard deviations from the mean of the large cohort and were characterized regarding structural connectivity, receptor density, and *APOE* expression through the JuGEx tool. Such an integrative approach using micro- and macrostructural information was instrumental to explaining the individual phenomena and may lead to individual clinical diagnosis and tailored treatment strategies (67).

CRITICAL DISCUSSION AND CONSTRAINTS

Probabilistic cytoarchitectonic maps are reference data of a multilevel atlas used to enable the integration of different data of human brain organization that cannot be studied within one brain or one experiment as a prerequisite to studying structure-function relationships across the different spatial scales. There are several challenges. Human brains are anatomically variable with regard to the folding pattern, extent and localization of cortical areas, and relationship of the

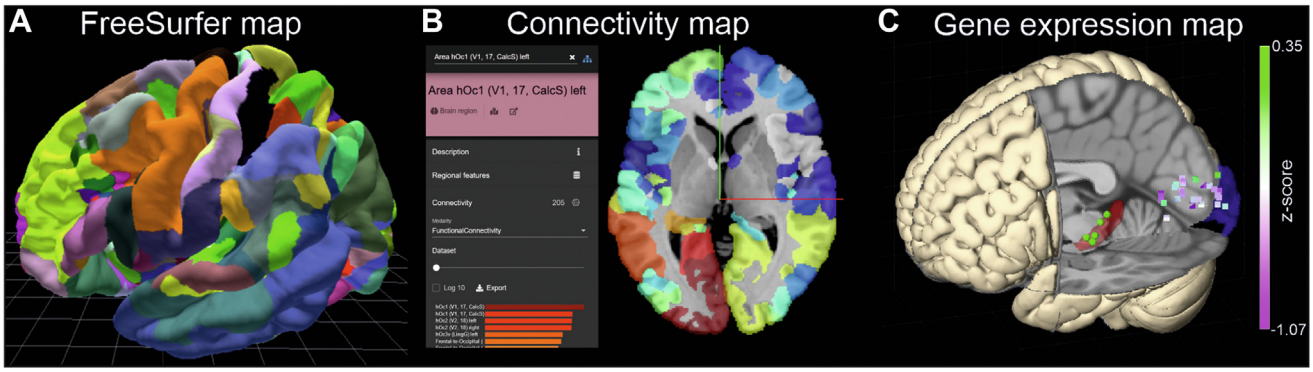

Figure 4. **(A)** FreeSurfer view of cytoarchitectonic maps. **(B)** Pull-down menu with connectivity map of area V1, left. Connected areas are colored, showing the connectivity strength from strong (red) to weak (blue). **(C)** Gene expression map showing differential expression of gene *GABRA3* between primary visual and auditory areas in relative units (*z* scores; see also Studying Genetics: The JuGEx Tool).

borders of these areas to the folding pattern. Similar is the case for brain activity and function. Cytoarchitectonic probabilistic maps capture anatomical variability but also include variability that is caused by methodological factors. It has been shown that variability is smaller in surface-based maps as compared with volume-based maps (68), which may increase precision in studying the cortex (69). Surface-based maximum probability maps have been computed in FreeSurfer reference space (https://ebrains.eu/news/new-maps-features-ebrains-multilevel-human-brain-atlas/) to address the need to study cytoarchitectonic correlates of functional activations in more detail. At the same time, the computation of surface-based maps cannot depict information on cortical depth and structures located deep in the brain, and topological errors cannot be excluded when extracting surfaces. Another limitation includes the limited sample size of 10 brains of the probabilistic maps as well as a natural bias toward older subjects, although the impact of these factors is deemed to be limited in studies of mapping. Image registration of postmortem brain data to a common reference space introduces inevitable inaccuracies. For example, when assessing structure-function relationships, more fine-grained structures, such as individual cortical layers, but also some small areas (a few millimeters large), are not captured properly at in vivo imaging resolutions, which might lead to weak associations between in vivo and postmortem data, undesired smoothing, and partial volume effects. Finally, several regions reveal a very fine-grained parcellation and a complex and variable folding pattern, e.g., the intraparietal sulcus (70–72) and the insula (73). Hypothesis-driven imaging experiments are necessary to identify the functional correlates and specific networks in which these areas are involved.

SUMMARY AND OUTLOOK

A multimodal reference framework has been provided for investigating brain organization across multiple scales based on the Julich-Brain Atlas. The atlas is interactive and provides detailed maps of cytoarchitectonic brain areas in widely used templates that are linked to receptor density data, structural diffusion tensor imaging–based connectivity data, and gene expression data from the Allen Brain Institute. It is publicly available to facilitate studies on structure-function relationships. Information about brain areas can be accessed via the Knowledge Graph of EBRAINS. The atlas is an ongoing project; new maps will be integrated in the atlas to stepwise substitute the gap maps, and the integration of bigdata volumes will play an increasing role in the future. Deep learning algorithms have become more and more powerful at detection and 3D reconstruction of brain areas at high resolution, benefiting the study of small and geometrically complex brain areas. It is planned that future tools will support exploration and access to data in the form of 3D graph-like structures, in particular streamlines, vasculature skeletons, neuron morphologies, and polyline annotations. Developing a modern brain atlas requires collaborations with experts in supercomputing and is necessary to scale up and improve the steps of image processing, e.g., in cell recognition. These and other future trends in neuroanatomy can be implemented in the Julich-Brain to keep it up to date as a tool for exploring brain organization and providing the knowledge base necessary to decode the pathomechanisms of brain diseases.

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ARTICLE INFORMATION

From the Institute of Neurosciences and Medicine, Research Centre Jülich, Jülich, Germany (DZ, NP-G, TD, KA); C. & O. Vogt Institute for Brain Research, Medical Faculty, University Hospital Düsseldorf, Heinrich-Heine-Universität Düsseldorf, Düsseldorf, Germany (NP-G, KA); Department of Psychiatry, Psychotherapy, and Psychosomatics, Medical Faculty, RWTH Aachen, and Jülich Aachen Research Alliance-Translational Brain Medicine, Aachen, Germany (NP-G); Helmholtz AI, Research Centre Jülich, Jülich, Germany (TD); and the Department of Computer Science, Heinrich-Heine-Universität Düsseldorf, Düsseldorf, Germany (TD).

Address correspondence to Daniel Zachlod, Ph.D., at d.zachlod@fz-juelich.de.

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