INCF Program on Digital Brain Atlasing

Towards a multi-modal human brain atlas

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Seattle, Washington
INCF Program on Digital Brain Atlasing workshop:
Towards a multi-modal human brain atlas

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Executive Summary

The original objective of the INCF Program on Digital Brain Atlasing was to provide the vision and direction necessary to make the rapidly growing collection of multi-dimensional data of the rodent brain widely accessible and usable to the international research community. Now, the Program would like to extend its efforts to the human brain. To this aim, a workshop was held to determine the current state of human brain mapping and atlas generation, INCF convened a 2-day workshop with scientists representing different aspects in this field to discuss the challenges and potential of a multi-modal human brain atlas model. Specifically, scientists from the brain mapping subfields of: High field MR imaging, Microstructure, Macroscopical and high throughput MR data, Functional brain atlases, and Time domain presented an overview of the atlasing needs of their respective brain mapping fields and discussed the following questions:

• How do you envision a comprehensive multi-modal model of the human brain?
• Which data should be included in the multi-modal model of the human brain?
• Which data standards are necessary?
• How do we handle ontology?
• Which reference spaces should be supported?

The participants agreed that a single (even multi-modal) human brain model would not be an appropriate choice; instead, they believed that a truly multi-modal human brain model would live in a collection of a few interoperable brain templates bridged by established pipelines. The participants identified 4 key challenges that must be overcome to achieve the multi-modal model they envisioned. The challenges identified were (i) correspondence between reference spaces, templates, and atlases, (ii) heterogeneity of features, (iii) integration of information into labels and maps, and (iv) the decision between labeling regions or mapping features. To resolve these challenges and move towards the envisioned multi-modal model, the participants believed that (i) pipelines would have to be created to go between the various templates, (ii) a framework that integrates heterogeneous information at different levels of abstraction would have to be established, and (iii) distinction would have to be made between labels and descriptions.

In addition to scientists from the different brain mapping fields, scientists from the Neuroinformatics community were also invited and presented informatics-based approaches to brain mapping. The overall objective of the 2-day workshop was to identify the key challenges impeding this vision of a multi-modal human brain atlas and discussed what developments are needed to put it into reality.

Introduction

The last two decades have seen an unprecedented development of human brain mapping approaches at various spatial and temporal scales. Together, these developments have provided a large fundus of information about many different aspects of the human brain including the micro- and macro-structural segregation, the regional specialization of function, and connectivity, as well as temporal dynamics. They have also led to differentiations of the brain mapping field along several major lines such as, structure vs. function, postmortem vs. in vivo, and individual features of the brain vs. population-based aspects, as well as slow vs. fast dynamics. In order to understand human brain organization, its function, and pathology, it seems inevitable that these different aspects of brain mapping need to be integrated into a multi-modal human brain model. Before such a human brain model can be developed, the constraints must be elaborated in order to enable: (i) integration of different spatial and temporal scales as well as different data modalities into a common reference system and (ii) efficient data exchange and analysis.

Overview of the human brain mapping subfields

High field MR imaging

Speakers: N. Harel and F. De Martino

During this session, the speakers presented the current state and future perspectives of in vivo brain mapping using high field imaging. High field MR imaging has enabled sub-millimeter spatial resolution for functional and structural imaging, thereby providing new horizons for the in vivo mapping of the human brain. Examples of such mapping are the investigation of functional properties of cortical columns and the delineation of intra-cortical anatomical features. The speakers also addressed how information gathered from high field MR imaging may be aligned with information gathered from other brain mapping approaches, e.g., to investigate the relationship with classical micro-anatomical features as well as to integrate high-field data with functional and structural in-vivo information acquired at different scales.
**Macroscopical and high throughput MR data**

Speakers: J.B. Poline; G. Dehaene-Lambertz, D. Van Essen

Mainly driven through the feasibility of acquiring structural MRI data in large, population-based cohorts and the availability of automated image processing, macroscopical brain atlases have evolved into multi-dimensional descriptions of the anatomical features reflecting, for examples, inter-individual differences, development, and degeneration. While providing new insights into brain morphometry, population-based atlases have only rarely been integrated with information from high spatial and temporal resolutions. During this session, the discussion focused on the current state of the art and how they envision the contribution of macroscopical population atlases on brain morphology to a multi-modal atlas. In addition, they also discussed what they perceived as necessary developments for the integration of large-scale, (relatively) low resolution with smaller, high-resolution approaches.

**The time domain**

Speakers: P. Valdes-Sosa, P. Tass, and W. Vanduffel

In spite of the fact that neuronal computations and interactions happen at the millisecond scale and complex patterns of synchronized oscillations may represent a key feature of computation in the brain, developments in electrophysiological approaches and atlas-based brain mapping have largely evolved on separate, yet parallel tracks. MEG and EEG based approaches allow the assessment and modeling of neuronal activity and coupling at extremely high temporal resolution and hence the characterization of phenomena not accessible with other neuroimaging methods (such as frequency-dependent effects). In turn, spatial resolution is often rather coarse and systematic mapping scarce. During this session, the discussion focused on how electrophysiological approaches and the ensuing temporal information they provide may be incorporated into a multi-modal human brain model to allow a fusion between dynamics and anatomical features.

**Microstructure**

Speakers: K. Zilles, K. Amunts, and M. Hawrylycz

Since the original descriptions of regionally heterogeneous microarchitectonic properties across the cerebral cortex more than a century ago, the local distribution of histological features such as the density and size of cell bodies has been a hallmark of brain atlases. In fact, histologically defined areas are almost unanimously considered a key aspect of functional and structural segregation. More recently, atlases on microscopic properties of cortical areas also include maps of neurotransmitter distribution, gene expression, and fiber tracts, as well as other modalities. Importantly, they are based on statistical tools of analysis, and provide 3D information. During this session, the discussion focused on recent developments in terms of micro- to macroscopical integration and how brain atlases could bridge between microscopic features and in-vivo morphometry and function.

**Functional brain atlases**

Speakers: J. Van Horn, B. Thirion, and S. Eickhoff

The last couple of years have seen a surge in functional atlasing approaches based on the integration of information from many different activation studies. In particular, the availability of thousands of task-based neuroimaging results as well as widely available resting-state measurements now provides not only the opportunity to map structure to function (task A activates region X), but also function to structure, hereby creating functional maps of the cortex. Similar to macroscopical brain atlases, functional and connectivity based atlases primarily reflect large-scale models with relatively low spatial and temporal resolution. Moreover, functional brain atlases often employ rather abstract concepts of functional regions whose relationship to anatomical properties is frequently unresolved. During this session, the discussion focused on how functional and anatomical atlases may be reconciled and integrated into a coherent view of the structural-functional segregation of the human brain.
Discussion

Proposed format of a multi-modal human brain model

The participants agreed that we are currently in a position to use multi-modal registration methods to refine our probabilistic atlases to a high degree. They also agreed that a single, definitive atlas that would meet all needs was highly implausible. They believed that a multi-modal human brain model should be based on multiple informative atlases, so work should be focused on building the best atlases we can and develop the tools to go between them. It was their opinion that the community should decide which atlas to map to (choosing that for each application that best fits their data). The ability to migrate across to other atlases would then allow to build on the best of what we have today. Work should thus focus on making existing atlases interoperable. Code should be provided to enable people to go from their image to an established atlas and determine where they are. In addition, pipelines should also be developed and shared to provide an explanation of how to go from a to b.

The participants also agreed that atlases should have a coordinate system with robust labels attached to the coordinates (some may have several labels), which should go reliably between the major atlases. Moreover, the participants believed that there will be no absolute parcellation. Parcellations will evolve over time through community consensus. To support multiple ontologies, it was the opinion of the participants that a common reference frame that maps between different parcellations will need to be created. During the course of the discussions on how to implement this type of human brain atlas model, the participant identified the following key challenges that must be overcome.

Challenges to a multi-modal human brain model

Interoperability between reference spaces, templates, and other atlases. The spatial superposition and comparison of different “brain atlases” will be crucial for accurate integration of different sources of knowledge and thus the multi-modal mapping of the human brain. As a result, establishing precise and representationally valid mappings between different standard spaces and templates is of the utmost importance to develop a multi-modal human brain atlas (Amunts, 2010), especially in light of the ever-increasing number of sub-group specific templates (e.g., for different age groups, ethnicities, and pathologies (Fonov, 2011)).

In this text, we refer to a template as an example of a brain scan(s) which is often a composite averaged across different subjects. We can think of an atlas as a way to label these images, deciding where the structures or features described by the atlas lie using the template coordinate system. In short, an atlas can be defined as a mapping between a template and a probability distribution associated with the set of labels. The mapping can simply be from one point in the coordinate system (x,y,z) to one specific label, but the definition above would account for probabilistic atlases (see some examples below). A “space”, in this context, is simply the coordinate system associated with a specific template.

While the methods for brain image registration are constantly improving (Klein, 2009; Klein, 2010), mapping between templates or individual subjects and a particular template is severely impaired by what has been termed the correspondence problem—biologically, it has its origin in the inter-individual variability in size, shape, and morphology of human brains. For example, not all macroscopic brain landmarks are present in the same way in each subject, especially for the highly convoluted cerebral cortex. The distribution of any biological parameter will, in addition, depends on:

I. the spatial scale investigated (the occipital lobe is always at the back of the brain, but the location of individual cortical areas is variable (Caspers, 2013))

II. on the brain region in question (normal variability depends upon the brain region)

III. the method employed for spatial normalization, e.g. the degrees of freedom for achieving spatial correspondence and the amount of subsequent smoothing registration

There are many cases where a one-to-one mapping of morphological features is not possible, e.g. when a particular gyrus or sulcus is duplicated or branched in one brain, but not in another. Consequently, aligning gross morphology, until recently a standard approach for matching between subjects and templates, may not represent the optimal way to map between spaces (Brett, 2002; Tucholka, 2012; Robinson, 2013; Smith, 2013).

Furthermore, the relationship between brain morphology and the representations of cortical areas or other functional specializations is also variable (Eickhoff, 2009). Hence, enforcing registration based purely on shape characteristics will lead to suboptimal
alignment of functional neuroanatomy and a loss of biological validity. The degree to which idiosyncrasies and variability should be handled in the spatial mapping between individuals, templates, and the ensuing atlases remains a challenge (Devlin and Poldrack, 2007) for which multi-modal registration algorithms is certainly part of the solution (Sabuncu, 2010).

It should also be noted that even when a one-to-one mapping is likely to exist, the community has not yet always agreed on some common procedure to identify regions or landmarks. A striking example of the current situation has been presented in Bohland (2009). This work demonstrates that even commonly referred brain regions (e.g. superior temporal gyrus) may have little correspondence depending on the atlas chosen. Efforts to specify a standard procedure to label regions and/or landmarks in the normal population are therefore critical to our ability to refer to the same brain areas across subjects (Klein, 2012). The variability induced by the spatial registration procedures adds to current mismatch of labels between studies.

**Consideration of heterogeneity of features.** The organization of the human brain includes three major axes: structure, function, and (functional or anatomical) connectivity (Eickhoff and Grefkes, 2011). Within each of these subdomains, many features can be differentiated which represent distinct, though not always independent, information. For example, the density of cell bodies is inversely correlated with the space occupied by synapses. Moreover, some features also have a hierarchical relationship to each other, such as the “Where” and “What” streams in the visual system or somatotopic and retinotopic representations. Incorporating many features into an atlas output space is a desired outcome which not a problem per se. Integrating these features accurately into a progressively more comprehensive multi-modal brain atlas entails substantial challenges posed by the heterogeneous nature of these features along several different representational frameworks. A critical aspect of these features is that they should be reproducible and carry information about their environment.

It should also be noted that the spatial scale of many relevant features might depend on the amount of deformation that is enforced during spatial normalization, i.e. the parameterization and regulation of the registration method and/or filtering applied prior to data analysis. That is, there can be a complex interaction between the spatial scale of features that can be represented in a map, spatial registration, and the choice of the template and of the atlas. As a simple example, it has repeatedly been shown that functional maps may be markedly different depending on whether analysis is carried out on volume- or surface-based templates following volume- and surface-based registration, respectively (Tucholka, 2012; Van Essen, 2012).

Although mapping the human brain and creating a multi-modal atlas is intrinsically a spatial endeavor, the fact that features may be expressed at very different time scales should not be ignored. On the upper end of these temporal scales, changes over the lifespan, both in development and aging, entail a massive effect to characterize brain structure, function, and connectivity at different ages. Consequently, any map of regional organization must be considered a reflection of a particular developmental stage. This issue is further complicated by the fact that lifetime trajectories may differ over subjects, rendering brain maps substantially more variable during periods of intensive development (e.g., during infancy and childhood as well as aging) or in the presence of pathological processes. Although such differences in trajectories and in regional inter-individual variability are well known in the respective research fields, attempts to capture them into a spatial/spatiotemporal framework are few.

At the other temporal extreme, oscillatory brain activity and synchronization of neuronal networks represent the finest temporal scale of interest to researchers employing today’s human neuroimaging methods; given their dynamic and often context-dependent nature and their much coarser spatial resolution, such information is obviously difficult to present in an atlas. As a result, little effort has yet been made to integrate information on the topographic distribution of features on fast temporal scales into human brain atlases. Nevertheless, dynamic features like electrical transient and oscillations do have spatial properties as evident when looking at generator analyses or power maps.

Another important though often neglected scale is that of inter-subject averaging within the analysis of a neuroimaging experiment and also in the creation of that template itself (e.g., the MNI 305, MNI 152, etc. (Evans, 2012)). Many spatial features of brain organization show marked inter-individual differences and become lost when averaging across subjects. The orientation columns in the visual cortex provide the best example of such a feature. While these may be clearly identified in individual subjects, their arrangement and number is highly variable across subjects, resulting in a loss of feature information when pooling over different individuals (Yacoub, 2008).

At the other end of the averaging spectrum are those features that, because of insufficient signal or contrast to noise, are currently identified only at the group level such as task-based co-activation patterns that emerge from the aggregation of hundreds of neuroimaging experiments collectively involving thousands of subjects (Eickhoff, 2010) or structural covariance maps that are calculated by the correlation of anatomical features across subjects (Evans, 2013). Mapping the human brain and creating a probabilistic multi-modal atlas will provide information that allows inference on features and their variability across a population,
as illustrated by multimodal data obtained from the Human Connectome Project (Smith, 2013). The relationship between features that may bridge across scales, those that are only describable at the individual level, and those that are defined by across subject relationships are important frontiers for investigation.

Integration of information from different subjects and experiments. As stated above, an atlas can be defined as a mapping from one or more (individual or group) templates or maps which define the spatial framework to a probabilistic labeling. Post-mortem atlases are typically based on a single brain and single modality (e.g., Brodmann's cytoarchitectonic map). When using in-vivo measures of function and or structure, insufficient signal and contrast to noise have been the limiting factor to the identification of individual features. While these limitations may be resolved with the introduction of more advanced imaging techniques, population-average allow the detection of reproducible features across subjects. For example, the JuBrain atlas was constructed by registering ten brains on a template in order to represent inter-individual correspondence (Eickhoff, 2010; Zilles and Amunts, 2010).

Atlases' labels represent particular spatially constrained property of a specific cortical or subcortical location, e.g., a cytoarchitectonic pattern, a functional response, a connection pattern, or the location on a given gyrus. The labeling of any given location may be either probabilistic (in which each location is assigned a probability for each of the different labels in the respective map) or deterministic (in which the mapping attributes to each location one and only one labels, i.e. one label has probability one). Probabilistic labels are particularly common in population-based mapping where they denote, e.g. the percentage of subjects featuring a particular characteristic at any given location. In turn, deterministic atlases may be derived from parcellations in a single brain (i.e., by labeling anatomical features) or from probabilistic atlases (i.e., by taking the maximum probability maps, MPM, (Eickhoff, 2006)). Furthermore, an atlas may not have its input domain covering the all brain, some regions may not have any label attributed. Numerical representation of labels or brain signals and their probability/intensity are often called maps.

One important endeavor in the context of atlas generation is to integrate this wealth of individual information into a functional atlas. Databases like BrainMap, the Human Connectome Project (HCP), and Neurosynth represent important first steps into this direction as they, together with a robust taxonomy of experimental designs, allow meta-scale integration on imaging data and quantitative functional decoding (Laird, 2011; Laird, 2009).

Integrating the intrinsically heterogeneous and noisy information provided by the current neuroimaging literature with maps derived from other modalities, such as anatomical features or connectivity, remains an important challenge for the generation of a multimodal atlas. This can be facilitated by improvements in data acquisition and analysis, such as those achieved by the HCP for multiple imaging modalities (Van Essen, 2013; Smith, 2013).

Labeling regions or mapping features. Several questions regarding the ultimate goal of human brain atlassing arise from the inherent spatial complexity of the human brain. The brain may be parcellated (by deterministic labels or maximum probability maps) or (probabilistically) labeled by a large number of regionally specific properties: Is then the goal to identify and delineate distinct regions in the brain that are maximally different from each other and maximally homogeneous within them? Or rather is the goal to conceptualize an atlas as a multivariate and probabilistic description for each voxel of one or several template space? Note that the second goal is more ambitious and one should be able to achieve the first from the second. Another aspect of the atlas correspondence problem is the fact that atlases may attribute different labels (representing objects with different semantics) to a position in the template; thus, atlases representing brain organization may not align with one another or may reflect different organizational characteristics.

While providing a detailed multivariate description of each brain location (voxel or surface vertex) in an atlas has the seeming advantage in that more flexible assumptions are made with respect to the underlying functional organization, such atlases have substantial drawbacks when it comes to labeling a particular location the problem of defining where “I am” is merely postponed to later steps of analysis. Conversely, approaches aimed at parcellating the brain into distinct regions provide a counter advantage, as they allow for an easy communication of where in the brain a particular property is located, albeit at the expense of not reflecting the heterogeneous nature of regional differentiation and providing a “static” representation dependent on the set of features and the specific algorithm used for labeling.

Last, note that there is a fundamental difference between a brain characteristic that has a true probabilistic nature (e.g., the amount or percentage of dopaminergic receptors in a given regions) and the pseudo probabilistic nature because frequencies are computed (e.g., the hand motor cortex is located anterior to the central sulcus, but averaging hand movement fMRI dataset will show some probability that it is posterior to the sulcus because of the registration problem).
Recommendations

At the conclusion of the workshop, the participants devised a set of recommendations that INCF should adopt to help move towards a multi-modal human brain model. It was the opinion of the participants that Recommendations 1—3 compose a proposed “road map” forward towards a multi-modal human brain model. Recommendations 4 and 5 represent specific actions that INCF can take to facilitate the development of a multi-modal human brain model.

Recommendation 1

Establish reliable and precise mappings between different templates and atlas spaces. Given the highly diverse needs of different fields within neuroimaging with respect to standards and templates, a single reference brain for all applications and their ensuing maps seems highly implausible. In order to integrate information on the most diverse aspects of brain structure, function and connectivity into a truly multi-modal brain atlas, this atlas may thus live in the various template spaces bridged by established pipelines that make them interoperable.

Recommendation 2

Provide a framework that may integrate heterogeneous information at different levels of abstraction. As noted, some features such as orientation sensitivity, oscillatory behavior, or structural covariance may only be fully understood at time-, space-, or averaging-scales which may not be directly reflected in a spatial atlas. Others such as task-fMRI results reflect information that in isolation is only of limited use. Finding approaches that either abstract their spatial properties or provide large-scale agglomeration across individual findings will thus be an important step towards the integration of these aspects into a multi-modal atlas.

Recommendation 3

Distinguish between labels and descriptions. A multi-modal brain atlas will need a coordinate system with a (limited) set of robust labels attached to these coordinates that go between the different templates. Although there will most likely be no absolute parcellation, these labels will facilitate communication between features and investigators. By the integration of a large amount of features reflecting regional properties in structure, function, and connectivity, the atlas then provides a detailed multivariate description for each voxel of the interoperable template spaces.

Recommendation 4

Lobbying

INCF should lobby funding agencies to finance consortia as well as to funding to support bi-lateral collaboration since atlas development is generally less likely to receive funding than (clinical) application. The key challenges and proposed roadmap forward established during this workshop should be incorporated into a white paper to serve as “proof of concept” and/or the basis of a grant for establishing bilateral collaboration.

Recommendation 5

Establish an inventory of reference templates

This recommendation is in response of the need to have a resource where scientist can find templates reflecting different ages, sex, species, etc…

Proposed next steps

White Paper. The participants believed that INCF’s efforts should focus on the publication of white paper that describes the key challenges and proposed roadmap forward developed during the workshop (See recommendations 1—3). They believed that the white paper should:

- Establish the framework for a multimodal human brain atlas.
- Define what template, atlas, labels, etc should be included in the atlas.
- Reflect the international nature of brain atlasing to pull in funding agencies from different countries.
- The technical aspects should be wrapped in their neuroscience context.
- A key point of the paper should be to establish a common language and what is needed to establish consensus.
References

Towards a multi-modal human brain atlas

Agenda

13 June 2013
19.00  Dinner
Crowne Plaza Hotel, Regatta Bar and Grille, 1113 Sixth Avenue

14 June 2013
09:00 - 09:15  Introduction to the Workshop
Katrin Amunts
09.15 - 10.00  Overview of INCF
Sean Hill

Session 1  High field MR imaging
10.00 - 10.25  Imaging the brain at ultra-high field MRI: from basic science to clinical applications
Noam Harel
10.25 - 10.50  Imaging the human auditory pathway at high fields: high resolution functional and anatomical characteristics
Federico De Martino
10.50 - 11.15  Coffee Break

Session 2  Macropscopical and high throughput MR data
11.15 - 11.40  Some requirements for the construction of atlases of the human brain from MRI databases
JB Poline
11.40 - 12.05  The origins of the human mind in the infant brain
Ghislaine Dehaene-Lambertz
12.05 - 12.30  An evolving set of multimodal atlases from the Human Connectome Project
David Van Essen
12.30 - 13.30  Lunch

Session 3  Time Domain
13.30 - 13.55  Integrating electrophysiological and neuroimaging data: the Cuban Human Brain Mapping Project
Pedro Valdes-Sosa
13.55 - 14.20  Unlearning pathological neuronal synchrony by coordinated reset neuromodulation
Peter Tass
14.20 - 14.45  Comparative functional mapping in humans and non-human primates with novel analytical tools
Wim Vanduffel

Session 4  Microstructure
14.45 - 15.10  Multimodal atlases of human and rat brains: Receptor and fiber architecture
Karl Zilles
15.10 - 15.35  Towards a three-dimensional cytoarchitectonic atlas
Katrin Amunts
15.35 - 16.00  Gene expression profiling and multi-modal human atlases
Michael Hawrylycz
16.00 - 16.30  Coffee Break
16.30 - 17.30  Discussion
19.00 - 20.00  Dinner
Wild Ginger, Asian Restaurant and Satay Bar, 1401 3rd Ave.