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What is Where and Why it is Important

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The paper by Devlin and Poldrack entitled 'In praise of Tedious Anatomy' deals with an increasingly important topic. Namely, how do we effectively communicate, with appropriate accuracy and precision, the 'where' of our measurements? They make cogent arguments for the use of anatomical maps to reference the location of functionally active regions of brain as measured with fMRI. We agree with this premise and would like to amplify further (with some additional suggestions) the rationale for equating functional measures with observations about structure. But before we do that, it might be useful to first generalize this issue, as one that pertains to 1) comparing data collected across multiple subjects, modalities, experiments and laboratories and 2) integrating this data as a comprehensive whole.

Specifying the site of activation, in anatomic terms, is intended (in part) to provide the ability to compare and contrast different studies. The notion of an atlas is, among other things, to help with this localization. Unfortunately many anatomic terms are sometimes interpreted variably and the boundaries of anatomic regions are sometimes in dispute. Given the mostly descriptive history of anatomy, its application, in a traditional sense, to modern volumetric MRI surveys of the brain sometimes produces more problems than it solves. Atlases such as the (Talairach and Tournoux, 1988) are woefully inadequate as an anatomic reference but did encourage the use and further development of spatial normalization schemes to reduce size and shape variability of brains. Other atlases such as (Ono et al., 1990) and (Duvernoy, 1991, Schleicher et al., 2005) provide far more complete and detailed delineations but either do not provide any principles or algorithms for spatial normalization or Cartesian coordinate systems. And finally, the question of how a single brain based atlas can represent a population is rarely argued anymore.

Describe Where you are

What then can facilitate this need to compare and contrast brain image data? We believe this requires more complete descriptions. Just as when we give directions to our house we might say, "… the address is 123 Main street, it's the third house on the left after the intersection, it's a white house with a porch, two stories tall…", etc. If using certain Global Positioning Systems (GPS) we might specify the latitude and longitude, in coordinates. We provide several ways to locate and identify the house. The different descriptions, collectively, make it easy to find and often compare it to others that may be geographically close. In brain mapping, this is difficult because often the only reference we have is an accompanying macroscopic structural MRI. So we might say the site of activation is in Brodmann area 46 or Talairach and Tournoux coordinate (x,y,z) or in the *pars opercularis* of the inferior frontal gyrus. We might say the

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activation occurred in the sulcus near the anterior temporal branch of the posterior cerebral artery or was concentrated in layer 4 of the cortex. None individually is very precise but in combination provide increasing degrees of specificity. Collectively, these descriptions make it easier to identify and compare the region where the activation occurred.

Integrate the data

What makes this notion of utilizing multifactorial descriptors intriguing, is the emergence of ever more novel classification schemes to help identify regions, circuits and systems of the brain. No longer are we confined to anatomic divisions defined by cell type or packing density observed using classical histological techniques. Complementing the cytoarchitectural descriptions of (Brodmann, 1909), (von Economo and Koskinas, 1925), (Duvernoy, 1991), (Ono et al., 1990), and (Mai J, 1997) are atlases of chemoarchitecture (Zilles et al., 2002), neurotransmitters (Schleicher et al., 2005), gene expression patterns (Mansour A, 1995), angioarchitecture (Nowinski et al., 2005), and white matter connections (Mori et al., 2005), among other things.

Unfortunately, most of these newer classification schemes are still works in progress. They may not cover the entire brain. They may still be based on one or few brains. They may not be compatible with methods to place them in correspondence with experimental data or they may have limited resolution, etc.

However, when combined, they can overcome their individual limitations. Although not yet available, efforts to computationally integrate these atlases are in progress ((Nowinski et al., 1997); (Maldjian et al., 2003); (Carmack et al., 2004); (Nowinski, 2004). Ontologies that provide relationship definitions between classification schemes are being created (Martin et al., 2003) and applications of historically important maps to interrogate modern MRI are now possible (see Figure 1). For these studies, elaborate surface-based and volumetric warping approaches have been developed to enable the transfer of classical maps into digital coordinates, and between digital atlases and individual datasets. Once available, the integration of these atlases will provide a far more specific and descriptive notion of what is where. After all, the separation of these classification schemes was borne out of necessity to collect the data, not because any one is more important than any other. Classification schemes each have a role to play as all are important. However, they should be integrated.

Group Statistics

Can an atlas based on any one single individual be representative? The Devlin and Poldrack paper, makes a clear and convincing argument that this is inappropriate. Numerous other papers (Van Essen, 2005); (Toga et al., 2006)) have come to the same conclusion and many population based atlases have emerged in response to this need (Mazziotta et al., 2001). But the same logic can be carried to the next level by creating many different population based atlases, each specific to the group demographics, disease, age or other characteristics of the subjects being studied. These provide not only population statistics within the map but arguably better represent the morphological signature of that particular cohort. What must be included in all analyses are confidence statistics on where the activity takes place. Whether this entails a statistic on probability, percentile or other metric may depend on the experimental design and other factors.

Adoption of a single normal atlas, even a probabilistic version, for all subject studies provides for the nominal capability for easier comparisons but in doing so fails to adequately measure the nuances within each group.

Taking this discussion into consideration, it seems that it might be prudent to avoid dependency on a single modality, single group representation for every study as is argued in the Devlin and Poldrack paper. Any given imaging experiment will be better served by mapping to a population based atlas that closely resembles the cohort under study. We suggest that population atlases for groups such as Alzheimer's (Thompson et al., 2000); (Mega et al., 2005), schizophrenia (Narr et al., 2001); (Cannon et al., 2006)), pediatric populations (Wilke et al., 2003); (Gogtay et al., 2004); (Evans and Group, 2006)), autism (Joshi et al., 2004), even decades of life (Mazziotta et al., 2001) should be utilized, as appropriate, for the subject group.

Standardization is premature

Another of the points made in the Devlin and Poldrack paper is that a practical solution must be available in order to encourage usage. The MNI atlas was identified because it is in digital format, represents a population rather than an individual, and is distributed as part of common image analysis packages that provide algorithms to align data to it. Although it is available, adoption as THE solution could have the unwanted consequence of reducing enthusiasm for development of more specific atlases. It also may further encourage adoption of yet another sanctioned solution to those with limited experience and understanding of the (in) appropriateness of a particular atlas for interrogation of functional anatomy. Perhaps the paper title; 'In praise of Tedious Anatomy' could be broadened to say 'In Praise of Tedious Analysis'.

There are also ongoing developments in computational anatomy to create better canonical image templates to represent subpopulations, while retaining well-resolved anatomical features that are vital to assist automated algorithms for aligning data to them. These atlases may even have a time-varying component (Janke et al., 2001), allowing subjects of different ages to be brought into the atlas using an age-appropriate transformation. Rather than average images together voxel-by-voxel to produce a blurred template, as was done in many 'first generation' statistical atlases, many groups are developing practical methods to create well-resolved canonical atlas images that represent the statistical mean anatomy for a population, using deformation averaging (Collins et al., 1995); (Thompson et al., 2000); (Kochunov P, 2002); (Twining et al., 2005)), Lie group methods on deformation tensors (Woods, 2003); (Lepore et al., 2006)), or geodesics on groups of diffeomorphic flows (Joshi et al., 2004); (Miller et al., 2005); (Lorenzen et al., 2006)). These approaches are complex, but are advantageous as they are close (in a strictly defined mathematical sense) to the brains being normalized to them and are likely to improve spatial accuracy and reduce sources of bias when comparing datasets in a canonical coordinate system.

The utility of the atlas is only as good as the method used to map the data into it. Specifying the 'where' of functional activity requires a full and comprehensive description of how that was determined. What were the mapping algorithms that performed the registration or more likely the deformation to make the subject and the atlas spatially congruent? There are now many different approaches, with various limitations and assumptions, for mapping to an atlas. Some are based on volumetric registration, in which 3D transformations deform the full brain volume into correspondence with the atlas. These mappings were traditionally linear or piecewise linear (Talairach and Tournoux, 1988), but it is now more common to use polynomial, elastic or fluid transformations with thousands or millions of degrees of freedom to better adapt the individual data to the atlas (e.g., (Ashburner et al., 2000)). The principles guiding these registration approaches also continue to advance (e.g., (Chiang et al., 2006); (Leow et al., 2007)). Other approaches directly model the cortex, inducing a spherical or planar parametric reference grid onto the cortical surface, providing a mathematical framework to perform higher-order alignments of structure or function within the cortical sheet (Thompson et al., 2004); (Rasser et al., 2005)).

A likely innovation, over the coming years, is that surface-based and volumetric registration approaches may be routinely integrated when transferring data into an atlas coordinate space (Joshi et al., 2007). Despite their added complexity, surface-based approaches have some major advantages for integrating and localizing cortically-derived brain maps (e.g., (Fischl et al., 1998); (Zeineh et al., 2003); (Van Essen, 2005); (Goebel et al., 2006)) in that they respect the topology of the cortical sheet and allow improved alignment of functional, structural and architectonic maps across subjects and even across species. However, most brain mapping studies now use volumetric registration without explicit cortical modeling and without using cortical features as constraints, producing 3D statistical parametric maps that are difficult to cross-reference or reconcile with any representation of the cortex. Hybrid approaches using hierarchical deformations (e.g. (Thompson and Toga, 1996); (Joshi et al., 2007)) allow the full image volumes to be normalized along with the cortical surfaces and their internal sulcal landmarks, yielding spatially consistent statistical results in both the 3D volume and the cortical surface parameter space. These efforts may take some time to become routinely accepted, but the benefits of linking surface and volumetric data will make this integration highly probable. For these reasons, it is unlikely that any currently available standardized atlas will offer the generality and flexibility required to accommodate these future analytic developments.

Full Provenance

Methods sections of published papers are full of program descriptions but not necessarily the specific algorithms used, their parameters, or the preprocessing steps undertaken before the programs are executed. We need a way to capture the full history of processing, in all its detail, to truly make data comparable. There are now several efforts to include this information in databases (Toga, 2002). There are even programs that retain descriptors of the algorithms chosen as part of the results (Rex et al., 2003). These must be included as part of any atlasing approach. If this information is retained as a processing pipeline that is efficient to calculate, statistics from previously published studies can be recomputed after transferring data to new coordinate systems, facilitating cross-study comparisons and meta-analysis. Storage of information on data provenance is vital to ensure that the findings of old studies can be leveraged in the future. Future analytic developments in data normalization and atlasing can then be brought to bear on previously published data, even if the findings were originally reported in coordinate systems that are obsolete or incompatible with current or future ones. With data provenance, statistical maps previously reported in one coordinate system can be transferred to another, without requiring us to be dependent on any current atlas, now or in the future.

Knowledge of the anatomy may be tedious to learn but it is clearly needed and no less important than all the elements of the experiment and analysis, the imaging protocol, the mathematics, the reference(s) and the visualization.

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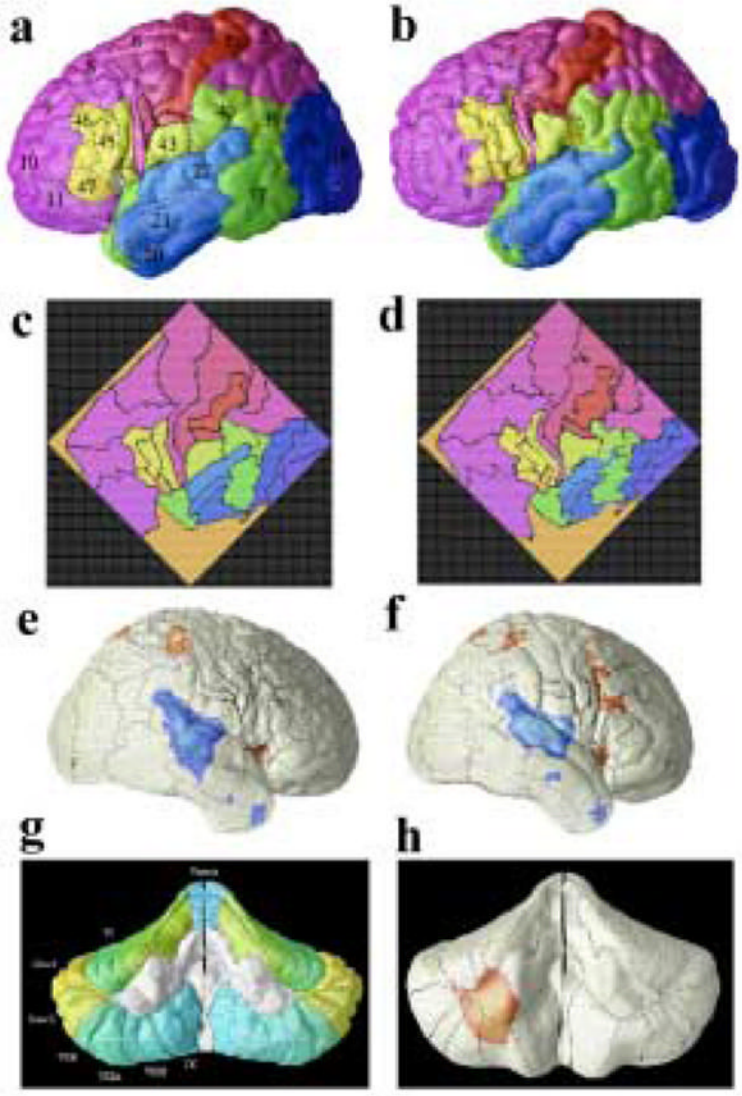

Figure 1. Elastic Normalization of the Brodmann and Schmahmann Atlases to Multisubject fMRI Data

As noted in Devlin and Poldrack, 2007, functional activations are often reported as occurring in certain Brodmann areas without any principled method to transfer atlas labels onto incoming data. Here the classical Brodmann cytoarchitectonic map (Brodmann, 1909) was transferred to a commonly used MRI-based imaging template (Holmes CJ, 1998) (a) and fluidly transformed onto new subjects' BOLD data in a functional imaging study (b). Sulcal landmarks were accurately matching in this warping process by using them as constraints to guide the registration of Brodmann areas in the cortical surface parameter space (c), (d). When multisubject fMRI data were analyzed using only a simple linear normalization to the MRI template (e), activation clusters were smeared out on the cortex. When fluid registration aligned fMRI to the group average cortical surface model, boundaries of activations closely matched Brodmann area 22 (*blue colors*), and frontal activations were also detected after reducing cross-subject anatomical misregistration. Such analyses are currently being adapted to transfer the anatomical partitions in the Schmahmann cerebellar atlas onto multi-subject maps of cerebellar surface activation, improving localization and interpretation of activation foci (h). This deformation of a canonical atlas is expandable, in principle, to include surface-based alignment

of empirical compilations of data on cytoarchecture (Zilles et al., 2002, Schleicher et al., 2005). [Data adapted from (Rasser et al., 2005); see also (Makris et al., 2003) for related work].