

Response

On the fundamental role of anatomy in functional imaging: Reply to commentaries on “In praise of tedious anatomy”

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We would like to thank all of the authors for their engaging and enlightening commentaries on our target article. It is heartening that there was such a great deal of agreement among the commentators with many of the points made in our article. Here we will highlight several points of agreement, note several remaining points of contention, and discuss a number of issues raised in the commentaries. We hope that this set of papers can together serve both as a roadmap for future work and as an impetus for further improvement of practices in the field, such that all researchers will come to agree that “anatomy is not tedious: it is fundamental” (Passingham, 2007).

Guidelines for methodological description

A first point that seems to be universally accepted is the need for better description of registration methods in neuroimaging papers. It is time that the terms “Talairach space” and “Talairaching” be banished as generic descriptors of stereotactic spaces and spatial normalization, respectively, in favor of much more specific details regarding the exact methods, spaces, and templates used for spatial normalization. The need for these details is highlighted by the results of Van Essen and Dierker (2007), who showed that there are systematic spatial differences that result from normalization to different templates (e.g., MNI302 vs. Talairach), and more strikingly, from normalization to the same template using different methods (linear registration in FLIRT vs. nonlinear registration in SPM2).¹

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¹ The insufficiency of current (informal) reporting standards extends beyond spatial normalization methods to many other aspects of neuroimaging methods as well, such as statistical modeling and inference. There is an ongoing effort to standardize methods for reporting of all aspects of neuroimaging studies (fMRI Methods Working Group, 2006), and it is likely that a set of standards for the field will be implemented by major journals in the coming years. We strongly encourage this kind of standardization for reporting. It should be made clear that such standards are not meant to limit the kinds of methods that can be reported; indeed, we are very excited about the development of novel techniques for spatial modeling of brain structure (Toga and Thompson, 2007). However, regardless of what specific methods a paper uses, it is critical that they are described sufficiently well that others can evaluate and reproduce them.

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Explicit methodological description is critically important for databasing and neuroinformatics efforts, such as the BrainMap project (Laird et al., 2005a). Methodological details regarding spatial normalization are essential in order to ensure that activation foci are properly mapped into the common space. The results of Van Essen and Dierker (2007) suggest that even further accuracy and power in meta-analyses could be obtained by using information about the spatial characteristics of the specific software and template used in each study. Formal ontologies for neuroimaging methods and data, which aim to systematize the information needed to describe these methods, are currently under development.

Beyond Talairach space: an emerging standard?

Although there is no doubt that the Talairach and Tournoux (1988) atlas played an important role in the development of functional neuroimaging, the commentators agreed that it has outlived its usefulness and should be abandoned, both as a reference space and as a tool for localization of activation. In our article, we suggested that the MNI305 space be adopted as a new standard; in fact, given its use as a normalization target by major fMRI analysis packages including SPM and FSL, it appears to be the de facto standard in the field. We stand by our argument in favor of standardization on MNI305 because we believe that it is critical that there is a “lowest common denominator” standard for the field — and MNI305 appears to be the best candidate to date. At the same time we agree with many of the points made by Toga and Thompson (2007) regarding the potential dampening effect that adoption of a standard might have on the development of novel atlases. Given the rapid pace of technical development in neuroimaging, any “standard” should be viewed as temporary, lest the field become ossified. We also concur with the arguments of Toga and Thompson (2007) regarding the development of group-specific probabilistic atlases. To the degree that the atlas more closely reflects the population in a study, then the results obtained by applying that atlas will be more accurate, so this is certainly desirable.

An interesting point raised by Van Essen and Dierker (2007) regards the use of linear versus nonlinear registration methods. Nonlinear methods are better able to precisely match the shape of structures across brains and result in decreased variability in the

spatial location of structures across individuals. However, as Van Essen and Dierker note, this precision is a “double-edged sword”: when a dataset normalized using nonlinear methods is compared to an atlas created using linear registration (or a different nonlinear method), there is increased variance between the dataset and the atlas. Once again, these considerations argue for the need for greater specificity in methods reporting, so that any potential differences between resulting spaces can be dealt with properly.

The role of cytoarchitecture

One of the more controversial issues among the commentators regarded the proper role of cytoarchitecture in functional imaging. The common use of Brodmann’s area (BA) labels in functional imaging reflects the fact that cytoarchitectural coherence is taken to imply functional coherence. The commentators largely agreed that, if one is going to use BA labels to describe functional imaging results, they must be based on something other than an informal transfer of the original maps to an atlas (as in the T&T atlas). As noted in the target article, the difficulty lies in how to validly identify these regions; as Amunts et al. (2007) outline in detail, macroanatomy does not provide a reliable guide to cytoarchitecture. The probabilistic atlas approach of Amunts and colleagues appears to be the best current method for assignment of BA labels, though high field structural MRI holds promise in this regard as well (e.g., Augustinack et al., 2005).

There was less agreement, however, on whether cytoarchitecture is a particularly useful tool for understanding functional organization. On the one hand, Amunts et al. (2007) argue strongly that cytoarchitecture “reflects the functional properties of the brain.” However, there are also well-known examples of important functional distinctions that occur within cytoarchitecturally defined regions (e.g., cytochrome oxidase blobs and interblobs within BA 17 — Livingstone and Hubel, 1984). Orban and Vanduffel (2007) capitalize on similar findings to downplay the usefulness of cytoarchitecture on its own as a guide to function. There was also debate over the utility of cytoarchitecture for the establishment of homologies across species. Whereas Passingham (2007) argues that cytoarchitecture is a useful means of establishing homologies regarding connective anatomy, Orban and Vanduffel (2007) argue that monkey fMRI is necessary as a link between human fMRI and monkey cytoarchitecture.

Consequently, we believe that including Brodmann areas when reporting activation is often unnecessary and unwarranted. In the absence of either direct evidence of microstructure or probabilistic maps of cytoarchitecture, there is no convincing reason for reporting BAs. The argument that by including BAs one can more easily compare one’s findings to previous studies is fallacious; if neither piece of information is correct, then the comparison is meaningless. Instead, we strongly advocate multifactorial descriptions of activations because they provide more information than any single source alone. Standard space coordinates should certainly be reported but at a minimum there should also be an anatomical description of the activation with reference to cortical and subcortical landmarks based on anatomical images collected as part of the study. When additional anatomical (e.g., microstructure, connectivity) or functional (e.g., localizers) data are collected, this too should be described. Together, this combination of information provides a far more accurate and precise description of one’s data.

Group versus individual studies

Functional neuroimaging is almost universally built around studies of groups rather than case studies of individuals. Group studies support inference from a sample to an entire population by treating subjects as a random effect, which allows characterization of the features of functional organization that are common to a population, as well as characterization of individual differences within the group. Furthermore, group analyses provide needed safeguards against false positives arising from a single individual. Because of the importance of group studies, it is essential that there be a common reference frame for the reporting of results, which we have argued should be the MNI305 space.

The results of group analyses also play an essential role in ongoing databasing effects (e.g., Laird et al., 2005a; Nielsen et al., 2004; Van Horn et al., 2001). These databases can provide a reference for researchers interested in characterizing the function of a particular brain region (e.g., Baas et al., 2004; Gilbert et al., 2006) or characterizing the functional anatomy of a particular task (e.g., Laird et al., 2005b; Owen et al., 2005) or cognitive domain (e.g., Wager et al., 2004; Wager and Smith, 2003). They can also provide the needed data to assess the information provided by reverse inferences, in which one uses activation in a particular region to infer the engagement of a particular cognitive process (see Poldrack, 2006). Finally, the ability to analyze large datasets across multiple studies has the potential to provide novel insights that would not be possible from single datasets. The accurate entry of datasets into such databases requires whole-brain data that are normalized into a common space, as well as a full description of the methods used for normalization.

Despite the importance of group analyses, there is also increasing interest in detailed functional–anatomical studies which often rely upon analysis of a small number of individual cases rather than a large group, as discussed by several of the commentators (Fadiga, 2007; Orban and Vanduffel, 2007; Tzourio-Mazoyer et al., 2007). Indeed, in some areas of neuroimaging (particularly imaging of low-level vision), the intense study of a particular brain region in a smaller number of individuals is the norm. In these studies, regions of activity are often defined not in terms of a coordinate space, but in terms of functional localizers (e.g., visual area V1 as defined by retinotopic identification, or face-sensitive regions in the fusiform gyrus). As the use of high-resolution fMRI increases, such studies are likely to become even more common.

Summary

We have highlighted the importance of methodological clarity and consistency in the context of anatomical localization, and the commentaries on our target article were largely in agreement with our arguments. Whereas the focus of our target article was on the methodological aspects of anatomical localization, several of the commentaries also highlighted the fact that anatomy is not just about location: The reason that anatomical localization is critical is that anatomy is directly related to multiple aspects of brain function (e.g., Leonard et al., 2006). As a result, accurate, informative reporting of anatomy is a fundamental, but underappreciated, element in functional neuroimaging. We hope that our target article and the associated commentaries will bring renewed attention to this important issue.

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