

EDITORIAL

Spatial Normalization Origins: Objectives, Applications, and Alternatives

Spatial normalization, in the context of human neuroimaging, is the selective removal of inter-individual anatomical variance. The vast majority of the removed variance is attributable to differences in brain size and brain position within the imaging matrix. For this reason, even rather simple normalization algorithms [e.g., Fox et al., 1985] are surprisingly effective. Newer algorithms, such as those introduced in this issue by Friston et al. [1995] and Collins et al. [1995], remove the subtle but complex effects of shape variance, as well. Anatomical normalization allows images (or image-derived observations) from multiple subjects to be more accurately compared and combined. While alternatives can be posed (below), the 3-D neuroanatomical coordinate system introduced by Jean Talairach provides the most powerful and versatile general construct for spatial normalization. The three spatial normalization methods published in this issue [Collins et al., 1995; Friston et al., 1995; Lancaster et al., 1995] all fall within the broad domain originally defined by Talairach.

Talairach's insight was that brain anatomy can be addressed using Cartesian coordinates. This concept was explained, implemented, validated and applied in the *Atlas Stereotactique du Telencephale* [1967]. The *Atlas Stereotactique* is composed of five chapters. Chapter One introduces the concept of proportional normalization—scaling brains to a standard size—and describes the methods used to create the atlas. Chapter Two is the atlas proper, containing photographic plates of six human brains: two sectioned coronally, two sectioned axially and two sectioned sagittally. Prior to sectioning, each brain was rigidly registered, allowing their spatial relations to be preserved and 3-D coordinates to be applied. Chapters Three, Four, and Five can be viewed either as a series of validations of Talairach's spatial-normalization strategy, or, alternatively, as placing the first neural objects within a newly created 3-D model of the brain. The elegance of Talairach's concept is most powerfully revealed in Chapter Four, as Talairach reports spatial probability distributions for

both anatomical and functional landmarks. Anatomical landmarks were defined by angiography and pneumoencephalography. Functional landmarks were defined by intraoperative cortical electrical stimulation. Much of the current work in our field can be considered refinements and applications of the concepts and procedures provided by Talairach. While Talairach has published two additional atlases [Talairach and Tournoux, 1988, 1995], the 1967 *Atlas Stereotactique* remains a landmark work.

Application of Talairach's construct to functional neuroimages began rather slowly, but has steadily acquired acceptance. A fellow on sabbatical from Talairach's laboratory prompted Per Roland to use Talairach's mathematical terminology to report the results of a planar, ^{133}Xe brain-activation study [Roland et al., 1980]. In an effort to conform to the emerging standard, Fox and Raichle [1984] reported the first tomographic (PET) brain mapping observations within the Talairach space. After this normalization algorithm and its validations were published [Fox et al., 1985], Talairach's coordinates were adopted as the analytic and reporting standard for Raichle's laboratory, the first PET laboratory to do so. Transformation of entire images into the Talairach space—as opposed to computing the coordinates of activated locations—was first applied [Fox et al. 1986, Fig. 3] and then described [Fox et al., 1988] by Fox, Mintun, Raichle and colleagues. These averaged images were the first of what have come to be termed statistical parametric maps or, more properly, statistical parametric images. The great improvement in statistical power made possible by intersubject image averaging and facilitated by the distribution of software packages, such as SPM [Friston et al., 1991], for creating statistical parametric images have been instrumental in promoting the Talairach-space standard.

The Talairach space is most properly viewed as a modeling construct, rather than as an atlas (or collection of atlases), a reporting standard, or a class of analytic algorithms. The modeling construct is a Carte-

sian space, bounded to create an addressing scheme for the brain. Within this idealized "brain space," we place observations about structure and function. These observations can be group-mean effects (e.g., activated locations within a grand-mean image), individual effects (e.g., activated locations within the images of individual subjects), or even probabilities that a specific structure or function will reside at a specific coordinate. As all observations are referenced to the same spatial framework, they collectively constitute a 3-D model of the human brain that is continuously updated by the research community itself. Based upon this modeling construct, an electronic environment for retrieval and metaanalysis of function locations is already in place [Fox et al., 1994; <http://ric.uthscsa.edu/services/>]. A complementary electronic tool, describing structure-location probabilities within this space, is well underway [Mazziotta et al., 1995]. Thus, the concept of a cumulative brain model, implicit in the use of the Talairach space and clearly enunciated by Talairach nearly three decades ago, is becoming an electronic reality.

Talairach's neuroanatomical modeling construct is not without its critics. The most common criticism—that an atlas cannot capture the anatomical variability among individuals—is superficial. The space itself readily accepts brains of differing morphology and provides the only generally applicable means of quantifying these differences. This application of the Talairach construct is well illustrated by the recent report of Andreason and colleagues [1994], in which neuroanatomical abnormalities in schizophrenia were identified by contrasting spatially normalized MRIs of schizophrenics with those of controls. A more substantive criticism is that volume (x-y-z) coordinates are an inherently inappropriate terminology for neuroanatomy. While this is an arguable point, the proposed alternative terminologies and referencing schemata have serious limitations of their own.

The traditional terminology of gross morphology is the most commonly proposed alternative to Talairach's space. Locations are described by relation to visible landmarks. Subcortically, landmarks are nuclei, tracts, ventricles and the like. Cortically, landmarks are the folding patterns of the brain: sulci and gyri. A fundamental problem in giving primacy to landmarks is that a continuous, well-defined space is precluded. Secondary and tertiary sulci and gyri have incomplete penetrance [Ono et al., 1990], creating sporadic "holes" in the addressing scheme. Watson et al.'s [1993] "solution" to this problem was to insist that all the observed activations (of V5/MT) would have fallen on the lateral occipital sulcus, if the sulcus had been consis-

tently present. (Which it was not). This ad hoc solution is actually an implicit appeal to a 3-D space in which each landmark, present or absent, has an absolute address. This "hole" problem has no counterpart in Talairach's space.

Another problem with using gross landmarks is imprecision. Even when "at" an identifiable landmark, for example, the precentral gyrus, the extent of tissue fitting this description can be large. A natural accommodation to this imprecision is to subdivide the landmark. Often this is done by reference to an implied 3-D space: for example, "the anterior (y), superior (z) aspect of the medial (x) portion of the precentral gyrus". Alternatively, purely local coordinate frames can be applied to the landmark. For example, Grafton et al. [1991] applied polar coordinates to the precentral gyrus. Grabowski et al. [1995] applied planar coordinates to the calcarine fissure. Even if such efforts are successful and internally consistent, the problem remains of knitting together the patchwork of local reference frames and of filling in the "holes" left by impenetrant landmarks.

Perhaps the most troubling concern about the "gross space" is cortical structure-function correspondence, or the lack thereof. Even in his original work on cytoarchitecture, Brodmann (translated by Garey [1994]) repeatedly cautions that many functional zones bear no consistent relationship to visible landmarks. For example, concerning primary visual cortex (area 17), Brodmann warns, "The borders of this area, especially laterally, are extraordinarily variable, which is particularly important for pathology. But even medially there are no regular and constant relationships to any 'limiting sulci'." [Garey, 1994, pp. 120]. This suggests that the concept of "limiting sulci," upon which the "gross space" rests, is inherently flawed. Subsequent studies of human cytoarchitecture continue to confirm the wisdom of Brodmann's warnings [Clark, 1993; Gebhard et al., 1993].

A final problem with the "gross space" is its impracticality. While the imprecision of this space hints at ease of implementation, the exact opposite is the case. All image analysis is predicated upon interpretation and segmentation of the image by a neuroanatomical expert. At best, this is labor-intensive and costly. Far more troublesome is the observation that even trained experts are highly unreliable at identifying major landmarks, such as the central sulcus [Sobel et al., 1993]. All in all, the minor imprecisions and inconveniences of Talairach's spatial construct pale in comparison with the practical and theoretical limitations waiting just beneath the surface of traditional terminology.

An alternative terminology, much discussed but not yet readily applied in humans, is cortical "flattening". Cortical flattening is an anatomical modeling construct developed by Van Essen and colleagues [1986] in response to the many difficulties of using visible landmarks for describing the locations of functional areas. Following recordings and injections to identify individual functional areas, Van Essen physically stripped the cerebral cortex from the brains (of monkeys) and arranged it on a flat surface. In essence, his solution to the landmark problem was to ignore the landmarks and to create a new 2-D spatial construct: a cortical plane. One motivation for this development, which does not apply to human neuroimaging, is that it was needed to allow inspection of the entire gross cortex.

For human neuroimaging, the greatest potential advantage of an unfolded space is that the neighborhood relations of functional areas within the cortical plane are more explicit than in a 3-D space. For example, cortical locations on opposing shoulders of a sulcus will abut in a volume space but be far apart in the unfolded plane. Cortical unfolding is now being raised as a possible modeling construct for human neuroanatomy [Jouandet et al., 1990; Dale and Sereno, 1994]. The impediments to this undertaking are considerable. This anatomical construct is applicable only to cerebral cortex, leaving the great majority of the brain unaddressed. Unfolding algorithms are not yet well behaved. Flattened visualization formats are not at all intuitive. This visualization/intuition problem is further compounded by discontinuities and distortions introduced by the unfolding algorithms. In humans, surface flattening must be done by exhaustive, largely manual, post-processing of MR images. In short, this strategy is not yet (and may never be) a widely applicable anatomical construct.

Despite criticisms of Talairach's space, there is no alternative that is as well-defined, comprehensive and computationally friendly. The computational compatibility of Talairach's space is already being heavily exploited for the development of electronic tools for metanalysis and modeling [Fox et al., 1994; Arbib et al., 1995; Mazziotta et al., 1995]. As the new generation of spatial normalization algorithms, described in the present issue, becomes generally available, Talairach's construct will gain even more power. For the many among us who still find gross morphology the most intuitive conceptualization of brain anatomy, several laboratories are building "labeling daemons" that will instantly define the subset of Talairach's space bounding any nucleus, gyrus, tract or cytoarchitectonic area and vice versa. With these electronic guides, anyone

will be able navigate the Talairach space. Equally as important, these tools integrate traditional terminologies into Talairach's space, hopefully minimizing terminological conflicts while still reaping the many benefits of Talairach's profound concept.

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REFERENCES

- Andreasson NC, Arndt S, Swayze V II, Cizadlo T, Flaum M, O'Leary D, Ehrhardt JC, Yuh WTC (1994): Thalamic abnormalities in schizophrenia visualized through magnetic resonance image averaging. *Science* 266:294-298.
- Arbib MA, Bischoff A, Fagg AH, Grafton ST (1995): Synthetic PET: Analyzing large-scale properties of neural networks. *Hum Brain Mapp* 2:225-233.
- Clark S (1993): Callosal connections and functional subdivision of the human occipital cortex. In: Gulyas B, Ottoson D, Roland PE (eds): *Functional Organization of the Human Visual Cortex*. New York: Pergamon Press, pp. 137-149.
- Collins DL, Holmes CJ, Peters TM, Evans AC (1995): Automatic 3-D model-based neuroanatomical segmentation. *Hum Brain Mapp* 3:000-000.
- Dale AM, Sereno MI (1993): Improved localization of cortical activity by combining EEG and MEG with MRI cortical surface reconstruction: A linear approach. *Journal of Cognitive Neuroscience* 5:162-176.
- Fox PT, Mintun MA, Reiman EM, Raichle ME (1988): Enhanced detection of focal brain responses using intersubject averaging and change-distribution analysis of subtracted PET images. *J Cereb Blood Flow Metab* 8:642-653.
- Fox PT, Mintun MA, Raichle ME, Miezin FM, Allman JM, Van Essen DC (1986): Mapping human visual cortex with positron emission tomography. *Nature* 323:806-809.
- Fox PT, Raichle ME (1984): Stimulus rate dependence of regional cerebral blood flow in human striate cortex demonstrated by positron emission tomography. *J Neurophysiol* 51:1109-1120.
- Fox PT, Perlmutter JS, Raichle ME (1985): A stereotactic method of anatomical localization for positron emission tomography. *J Comput Asst Tomogr* 9:141-153.
- Fox PT, Mikiten S, Davis G, Lancaster JL (1994): BrainMap: A database of human functional brain mapping. In: Thatcher RW, Hallett M, Zeffiro T, Roy John E, Huerta M (eds): *Functional Neuroimaging: Technical Foundations*. San Diego: Academic Press, pp. 95-106.
- Friston KJ, Ashburner J, Frith CD, Poline J-B, Heather JD, Frackowiak RSJ (1995): Spatial Registration and Normalization of Images. *Hum Brain Mapp* 3:000-000.
- Friston KJ, Frith CD, Liddle PF, Frackowiak RSJ (1991): Comparing functional (PET) images: The assessment of significant change. *J Cereb Blood Flow Metab* 11:690-699.
- Garey LJ (1994): Brodmann's 'Localisation in the Cerebral Cortex'. London: Smith-Gordon, pp. 109-129.
- Gebhard R, Zilles K, Armstrong B (1993): Gross anatomy and gyrification of the occipital cortex in human and non-human primates. In: Gulyas B, Ottoson D, Roland PE (eds): *Functional*

- Organization of the Human Visual Cortex. New York: Pergamon Press, pp. 101-110.
- Grabowski TJ, Damasio H, Frank RJ, Brown CK, Boles Ponto LL, Watkins GL, Hichwa RD (1995): Neuroanatomical analysis of functional brain images: validation with retinoptic mapping. *Hum Brain Mapp* 2:134-148.
- Grafton ST, Woods RP, Mazziotta JC, Phelps ME (1991): Somatotopic mapping of the primary motor cortex in man: activation studies with cerebral blood flow and PET. *J Neurophys* 66:735-743.
- Jouandet ML, Tramo MK, Herron DM, Hermann A, Loftus WC, Bazell J, Gazzaniga MS (1989): Brainprints: Computer-generated two-dimensional maps of the human cerebral cortex in vivo. *Journal of Cognitive Neuroscience* 1:88-117.
- Lancaster JL, Glass TG, Lankipalli BR, Howms H, Mayberg H, Fox PT (1995): A Modality-Independent approach to Spatial Normalization of Tomographic Images of the Human Brain. *Hum Brain Mapp* 3:000-000.
- Mazziotta JC, Toga AW, Evans A, Lancaster JL, Fox PT (1995): A probabilistic atlas of the human brain: Theory and rationale for its development. *NeuroImage* 2: 89-101.
- Ono M, Kubik S, Abernathy CD (1990): Atlas of the Cerebral Sulci. New York: Thieme Medical Publishers.
- Roland PE, Skinho JE, Lassen NA, Larsen N (1980): Different cortical areas in man in the organization of voluntary movements in extrapersonal space. *J Neurophysiol* 43:137-150.
- Sobel DF, Gallen CC, Schwartz BJ, et al (1993): Locating the central sulcus: comparison of MR anatomical and magnetoencephalographic functional methods. *AJNR* 14:915-925.
- Talairach J, Szikla G (1967): Atlas D'anatomie stereotaxique du telencephale. Etudes Anatomio-Radiologiques. Paris: Masson & Cie.
- Talairach J, Tournoux P (1988): Coplanar stereotaxic atlas of the human brain. New York: Thieme Medical.
- Talairach J, Tournoux P (1995): Referentially oriented cerebral MRI anatomy. New York: Thieme Medical.
- Van Essen DC, Newsome WT, Maunsell JHR, Bixby JL (1986): The projections from striate cortex V1 to areas V2 and V3 in the macaque monkey: Asymmetries, areal boundaries, and patchy connections. *J Comp Neurol* 244:451-480.
- Watson JDG, Meyers R, Frackowiak RSJ, Hajnal JV, Woods RP, Mazziotta JC, Shipp S, Zeki S (1993): Area V5 of the Human Brain: Evidence from a combined study using positron emission tomography and magnetic resonance imaging. *Cereb Cortex* 3:79-94.