Integrating human brain maps

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Perception, action, cognition, and emotion can now be mapped in the brain by a growing family of techniques. Positron emission tomography, functional magnetic resonance imaging, event-related electrical potentials, event-related magnetic fields, and other non-invasive imaging techniques are rapidly evolving and providing an increasingly rich literature on the functional organization of the human brain. Although no two techniques map identical physiological processes or physical parameters, replications of functionally specific maps by different techniques indicate sufficient common ground for multimodality integration. The process of integration is multi-tiered. Recent advances in integration range from simple image fusion, to model-based synthetic analyses, to collective databases for neural-system modeling. Spatially, temporally, physiologically, and cognitively accurate computational models of the neural systems of human behavior are the ultimate objective of functional brain mapping. This objective will be reached only through integrating the diversity of modern brain-mapping methods.

Current Opinion in Neurobiology 1994, **4**:151–156

Introduction

Neural activations during complex human behaviors can be recorded by a growing family of 'brain mapping' modalities (techniques), including positron emission tomography, functional magnetic resonance imaging, event-related (electrical) potentials and event-related magnetic fields, and even by optical reflectance imaging. Collectively, these techniques are providing unprecedented insights into the functional organization of the human brain. Brain-mapping observations differ substantively among modalities: no two modalities detect the same physiological process nor suffer the same constraints on experimental paradigms. Despite this diversity, these observations appear to be replicable across modalities. These replications form the common ground upon which a framework for integration can be constructed. In the process of integration, the unique strengths of each modality must be preserved and complemented. Ideally, this process of integration will produce brain maps with millisecond temporal resolution, millimeter spatial resolution, and the sensitivity to map individual subjects as well as a population. In this review, we will discuss how this goal is being rapidly approached through recent advances in non-invasive brain-mapping methods and in strategies for integration of these diverse methods.

Advances in human functional brain mapping

Functional magnetic resonance imaging

Among brain-mapping modalities, functional magnetic resonance imaging (fMRI) — the use of MRI for imaging functional brain activity — has enjoyed the most technical advancement in the past year. When first introduced by Belliveau and colleagues [1], fMRI required intravenous administration of a contrast agent and use of a special gradient-coil system custom-made for ultra-high-speed ('echo-planar') imaging. In the past two years, these limitations have been progressively overcome. The increase in blood-oxygen content that is induced by neural activity [2] can now be detected using MRI, as a decrease in the local paramagnetic effects of deoxyhemoglobin, which is, in effect, an 'endogenous' contrast agent [3••,4••,5–8]. The speed of echo-planar imaging (typically one frame per second) is uniquely suited to mapping the time course of the hemodynamic response to neural activity [3••,4••,5–8] and to time-series statistical analyses [9,10]. Whereas conventional gradient coils cannot match the temporal resolution of echo-planar imaging, the oxygen-contrast method works well on clinical MRI units [11•–13•]. Thus, the large, installed base of clinical MRI units can now be used for functional brain mapping. In the face of such rapid developments, the growing numbers of

Abbreviations

CT—X-ray computed tomography; **EEG**—electroencephalogram; **ERF**—event-related magnetic field; **ERP**–event-related (electrical) potential; **fMRI**—functional MRI; **MR**—magnetic resonance; **MRI**—MR imaging; **PET**—positron emission tomography.

 ISSN 0959-4388

fMRI brain-mapping reports should present no surprise [3••,4••,5–10,11•–13•,14–16].

Positron emission tomography

Positron emission tomography (PET), although not currently evolving at the same rate as fMRI, remains a mainstream method for functional brain mapping [17–30]. Modern PET cameras sample the entire brain, an important advantage over current fMRI. An important 'new' direction is single-subject mapping and the study of individual variations in the functional map. Lower-order cortical areas (primary visual cortex, primary sensorimotor cortex, *et cetera*) are readily detected with PET and have been mapped in individuals for several years. Signal-to-noise limitations in higher-order areas were the original impetus for the development of intersubject averaging [31]. Intrasubject image averaging [32,33•] and the development of volumetric acquisition have improved signal-to-noise sufficiently for mapping of higher-order cortical areas in single subjects. Single-subject functional maps, in turn, can be co-registered with a subject's anatomical images, creating an integrated map of structure and function [26,33•].

Event-related potentials

Event-related potential (ERP) research has typically capitalized on its millisecond temporal resolution, and has focused on issues relating to timing and sequence. (For a review of recent ERP research, see [34•].) A dramatic series of technical and algorithmic developments, however, are rapidly improving its potential for spatial localization. Recording channels have increased from 4–12 simultaneous sites 10 years ago to as many as 128 today, a dividend of recent advances in computer technology. Advanced analytic algorithms capitalize on this high sampling density, to markedly improve source localization [35–39,40••,41]. Fusion of ERPs with anatomical images provides both neuroanatomical correlation and constraints for source-localization algorithms [40••,42,43•,44•,45,46]. Neural-systems ERP mapping, combining millisecond timing and subcentimeter spatial localization, are now being reported [47•,48–50].

Event-related magnetic fields

Event-related magnetic fields (ERFs) also are in the midst of rapid evolution. (For a review of recent ERF research, see [34•].) As with ERPs, the number of recording channels has increased dramatically from only one or two 10 years ago, to as many as 61 independent recording sites today [51]. Source analysis algorithms have improved dramatically, sharing much with ERP algorithms [51,52•,53–57]. As with ERPs, ERFs require modeling to compute spatial location of active sites. Fusion with an anatomical image (e.g. MRI) allows correlation to neural structure and constraints for source localization. A 'limitation' of ERFs — selective sensitivity to sulcal sources — and the lesser distortion of ERFs by the skull combine to give ERFs an advantage over ERPs for source localization (of sulcal sources) [53,55]. For this reason, high-resolution spatial mapping has generally been more successful and more widely reported with ERFs [58,59,60•,61–63,64•,65,66•].

Merging maps within subjects

Image fusion

The complementarity of imaging modalities makes within-subject integration of brain maps scientifically and clinically appealing. Simple fusion (co-registration) of tomographic modalities (e.g. PET and MRI) is relatively straightforward. The fusion of activation maps with three-dimensional renderings of brain anatomy is still more useful. Merging of group-mean PET images with atlas illustrations or with group-mean MRI images has been done for several years. More recently, Watson and colleagues [33•] co-registered PET functional-activation maps of a visual-motion-detection area with MRI-derived renderings of the cortical surface in twelve subjects. These integrated maps illustrate the variability of the cortical folding patterns and the degree to which they can predict functional location. Although graphically very appealing, the shortcoming of such fusions is their inability to quantify the variability they so elegantly illustrate. Without some means of anatomical quantification, within-subject mergers of functional and structural maps remain essentially pictorial.

Fusion of surface detection methods (e.g. ERP and ERF) with volumetrically true techniques (e.g. MRI, PET and CT: X-ray computed tomography) is far more challenging than mergers of two tomographic modalities. The problem becomes tractable only through modeling. Strategies for fusing ERP or ERF with MRI have taken two forms. One is the projection of surface distributions onto the underlying brain, typically 'sharpened' by a signal-processing techniques, such as ERP current source density analysis [36,38,39,41,67]. This approach can give coarse localization information concerning activity from superficial sources, but the accuracy and validity, especially for more complex distributions, is rather limited. The second approach is inverse modeling, that is, estimating the locations and strengths of the neural sources from the ERP or ERF waves. As the 'inverse problem' is under determined, a solution requires both a model and simplifying assumptions [37,40••,53,55,56,68]. For simple neural activations, such as some of the early stages of cortical sensory processing, a single-source model can be a reasonable assumption and can provide a good fit of the scalp recorded data. This is especially true for ERF recordings, due to their more selective sensitivity (i.e. being sensitive to sulcal sources only) [58,60•,61,62,64•,65]. Results from PET and fMRI studies suggest strongly, however, that higher stages of processing require multiple, spatially distributed activation sites. Inverse modeling of multiple dipoles is very susceptible to errors in initial assumptions [37,40••,53,55]. An underestimate, for example, of the number of contributing dipoles is likely to cause mislocalization of the remaining dipoles, sometimes to a considerable degree. Successful solutions to this complex problem

will probably incorporate two strategies: behavioral paradigms and difference-wave analyses that simplify the source distributions, and incorporating constraints from other methodologies.

Model-based data synthesis by means of cross-methodological constraints

An emerging, highly sophisticated strategy for integrating brain-mapping modalities is mutually constrained data reduction. One example of this approach is to use CT and/or MR images to obtain information on actual head (and brain) shape to improve the accuracy of the 'forward solution' used in estimating the ERP and ERF scalp distribution that a set of model sources would produce [36,44•,45]. An approach with even greater potential, however, is to also incorporate prior knowledge to constrain the inverse calculations [40••,46,55,56,68]. ERP and ERF activity is generated by cortical current dipoles oriented perpendicular to the cortical surface [40••,55]. Extracting the cortical surfaces from MRI, therefore, can constrain the localization modeling for ERPs and ERFs. The complementarity of ERFs, which only detect sulcal activity, and ERPs, which have greater sensitivity to gyral sources, makes a mutually constrained analysis considerably more powerful than either alone [37,40••,53,69]. Finally, focal activations in a PET or fMRI study can be assumed as probable source generators, thereby constraining the inverse problem. An implicit but pivotal assumption of mutually constrained activation experiments is comparability of behavioral paradigms and neural activation patterns.

An excellent example of the above constraint-driven approach was developed by Dale and Sereno [40••]. In their study, the cortical surface is first extracted from MR images and then tesselated (i.e. divided up) into small polygons. A dipole is associated with each of these small polygons, oriented normal to its surface. These potential dipoles are scanned in a probabilistic way to estimate their contributions to the recorded ERP and/or ERF activity. Their framework can be applied to either ERP or ERF data — or even better, to recordings of both from the same subject — and uses all the time points in the ERP/ERF waveforms for additional information and constraints. In addition, the probablistic calculations can be biased by *a priori* information from PET or fMRI activation studies. This approach — although difficult to implement and perhaps tending to overemphasize focal sources (relative to distributed ones) — holds great promise as a model strategy for integration of brain-mapping modalities.

Integrating maps among subjects

The long-term goal of human-brain mapping is the creation of physiologically and anatomically accurate spatial and temporal models of the neural systems underlying human behavior. To accommodate the multiplicity of neural systems, as well as population variables (such as gender, handedness, and native language), multiple models will be needed. Population models derived from brain images will necessarily be composites, formed from groups of subjects. Integration of images from different subjects is predicated on anatomical normalization. Anatomical normalization, in turn, is predicated upon the use of one or more standard 'anatomical spaces', within which data can be integrated.

Anatomical normalization

Formalization of brain anatomy into a mathematically well-defined space for intersubject integration of functional and structural maps is a problem with no easy solution. Normalization of the entire brain necessitates the use of a three-dimensional, anatomical space. To date, no algorithm for normalization of the entire brain has achieved a unique correspondence between spatial coordinates and traditionally defined anatomical structures. 'Morphing' algorithms, however, are steadily improving [70,71]. A very recent development, the 'convex hull' algorithm [70], promises to be a particularly powerful technique for spatial normalization.

Normalization based on specific structures is an alternative to normalization of the entire brain. Intersubject registration to a specific sulcus or nucleus provides a local refinement of whole-brain morphing. Extraction and normalization of the cortical surface is another frequently encountered example. Flattening the cortical surface into a rectilinear, two-dimensional array is one alternative [72]. 'Relaxing' the cortex into lisencepahaly [40••] may provide an ontogenetically and phylogenetically more primitive anatomical model, within which intersubject integration can be accomplished. Whichever algorithm ultimately emerges as the standard, integration of brain maps among subjects will necessarily rely on some sort of anatomical normalization. The development and validation of these tools remains pivotal for intersubject and interlaboratory comparisons and for the integration of brain maps and models.

Intergroup statistical parametric mapping (population analysis of image data)

An emerging application of anatomical normalization is group-mean mapping of abnormal affective and cognitive states. For example, Drevets and colleagues [73] created a functional map of 'depression', in the form of a pixel-by-pixel comparison of a composite image of depressed patients with a composite image of normal controls. Population analyses using composite images rely heavily upon precise anatomical normalization (see above). The similarities between Drevets' map of unipolar depression and Pardo's map of self-induced dysphoria [74], however, speak eloquently for the power of these techniques.

Databases, metanalysis, and system models

Registration of brain maps to a standard and, thereby, to one another is a basis for databases of brain-mapping research. Properly designed, databases are

tools for metanalysis and vehicles for comparing and integrating maps among laboratories, among imaging modalities, and among populations. Fox and colleagues [75] have developed BrainMap, a database for comparing functional maps derived from human brain-imaging studies. BrainMap facilitates accurate interpretation of existing activation research through detailed experimental and behavioral coding and rapid visualization of activation maps. Given the breadth of the field, neuroscience will require a large number of databases targeting specific research methods and bodies of knowledge.

Modeling the neural systems of cognition from brain-imaging studies will be the next great challenge. Giving rapid access to the cumulative knowledge of the field, databases should be a powerful resource. Spatial and temporal models are needed to express the neural activation patterns associated with specific behaviors. Friston *et al.* [76,77] have been very active in exploring the use of correlational analysis to establish functional connectivity from PET data. Path analysis is a less direct approach for obtaining similar information [78]. Event-related co-variances may also be a powerful tool for charting the flow of neural activation during information processing [79]. Despite these advances, the most appropriate conceptual framework remains to be established within which the computations performed by the neural systems (measured using brain-imaging studies) can be modeled mathematically [80].

Conclusions

Mapping the neural systems of human cognition is proceeding rapidly. New imaging modalities are providing previously unimaginable access to the neural substrates of human behavior. Maps of neural systems require integration within single subjects, between subjects, between populations, and between modalities. Integration is logistically and mathematically complex, but strategies for such integration are being developed and tested. The collective observations of the human brain-mapping community are becoming so numerous and complex that community databases are being created to organize these observations. Shared databases are proving powerful tools for synthesis and metanalysis. Neural systems models, however, need to be developed to capture the richness of the observations of this field.

Acknowledgements

This work was supported by a grant from the EJLB Foundation.

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