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Neural modeling and functional brain imaging: an overview

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Abstract

This article gives an overview of the different functional brain imaging methods, the kinds of questions these methods try to address and some of the questions associated with functional neuroimaging data for which neural modeling must be employed to provide reasonable answers. © 2000 Published by Elsevier Science Ltd.

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1. Introduction

This special issue of Neural Networks represents the first effort at communicating a series of articles that employ neural modeling techniques in the context of data obtained using functional brain imaging methodologies. Functional neuroimaging affords a new departure for computational neuroscience, for until rather recently, the vast majority of neural modeling studies focused on understanding electrophysiological data acquired from microelectrode recordings in nonhuman animals. As we hope the subsequent articles demonstrate, functional brain imaging data are unique in a number of respects, including their richness and complexity, and understanding these types of data presents a formidable challenge that only computation modeling can help overcome.

This article provides a brief overview of the different functional brain imaging methods, the kinds of questions these methods attempt to address and some of the questions associated with functional neuroimaging data for which neural modeling must be employed to yield reasonable answers.

As we proceed, a few important points ought to be kept in mind. First, most functional neuroimaging studies are performed on awake, human individuals who often are engaged in some type of sensory, motor or cognitive task. The ability to perform these types of studies has essentially produced a conceptual revolution in the study of human cognition. For the first time, we can quantify most of the brain's activity as specific behaviors are carried out in both normal subjects and in neurological and psychiatric patients. Second, until recently, almost everything we knew about the neurobiological substrates of brain function came from investigations of single neural entities. That is, the standard approaches recorded data from a single brain region (or neuron), or investigated the effects of a single lesion. As we shall see, functional brain imaging data essentially are collected simultaneously from much of the brain. This is important, for it means that we are now in a position to think about how networks of interacting brain regions function so that specific cognitive tasks can be carried out. It is perhaps this feature of functional brain imaging data, more than any other, that compels the need for neural modeling.

2. A brief overview of functional brain imaging

The various types of functional neuroimaging methods[1] are based on two quite different kinds of modalities: (1) *hemodynamic–metabolic* — included here are positron emission tomography (PET), single photon emission tomography (SPECT), functional magnetic resonance imaging (fMRI), all primarily used in humans, and optical imaging and the autoradiographic deoxyglucose method, used

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[1] We list only the techniques that are commonly used. A number of older procedures, such as 2D surface imaging using, for example, the Xe inhalation method, are rarely employed today.

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mostly in nonhuman animals;[2] and (2) *electric–magnetic* — included in this domain are electroencephalography (EEG) and magnetoencephalography (MEG), both used mostly with human subjects. These two major types of imaging — hemodynamic and electric–magnetic — have fundamentally different characteristics, the most prominent of which are concerned with temporal resolution and the amount and kind of spatial information each provides.

2.1. Hemodynamic–metabolic methods

The hemodynamic–metabolic methods are based on the hypothesis advanced more than a century ago by Roy and Sherrington (1890) that changes in neural activity lead to changes in both cerebral blood flow and oxidative metabolism. Although the exact cellular mechanisms by which neural activity is coupled to blood flow and metabolism remain uncertain (for reviews, see Jueptner & Weiller, 1995; Magistretti & Pellerin, 1999; Villringer & Dirnagl, 1995), it currently is thought (e.g. Magistretti & Pellerin, 1999) that synaptic activity leads to increased glucose metabolism, primarily to restore ionic gradients. In turn, energy metabolism and cerebral blood flow are linked during normal physiology, even though decoupling may occur under certain pharmacological interventions, or under some pathophysiological conditions.

Whatever the mechanisms, the different hemodynamic–metabolic techniques image various aspects of the blood flow-energy metabolism spectrum, and use these measurements to infer something about local neural activity. PET commonly is used to measure either regional cerebral blood flow (rCBF) or regional cerebral glucose metabolism (rCMRglc), the latter also being the quantity imaged by the autoradiographic deoxyglucose method; fMRI is sensitive to the oxygenation state of blood, as is optical imaging.

2.1.1. Positron emission tomography

The autoradiographic method for measuring rCMRglc in nonhuman animals, developed by Sokoloff et al. (1977), determines the uptake of radioactive deoxyglucose. This method was modified for use with PET where [^{18}F]-fluorodeoxyglucose generally is employed as the radiotracer (Phelps et al., 1979; Reivich et al., 1979). With PET, it is also possible to measure rCBF (Herscovitch, Markham, & Raichle, 1983; Raichle, Martin, Hercovitch, Mintun, & Markham, 1983). Although some human cognitive studies that evaluate rCMRglc have been performed (e.g. Gur et al., 1983), most measure rCBF.

PET dominated the field of functional neuroanatomy from the early 1980s until the mid-1990s. The method works by detecting the coincident gamma rays produced by the annihilation of positron–electrons pairs. PET has greater spatial and temporal resolution, as well as greater sensitivity, than does SPECT (which detects single gamma rays produced by gamma emitting radioligands; SPECT has the virtue, however, that an on-site cyclotron is not needed because radioligands can be purchased commercially). Detecting the coincident gamma rays allows one to determine the line along which the radioactive decay occurred. Following the administration of a positron-emitting radionuclide, an image of the distribution of radioactivity in the organ of interest (e.g. brain) is generated by combining the coincidence detection of the annihilation gamma rays with the reconstruction algorithms of computed tomography. The spatial resolution of PET generally is between 5 and 10 mm.

One method commonly used for measuring rCBF with PET involves the bolus injection of $H_2{}^{15}O$. Because ^{15}O has a half-life of 123 s, multiple scans (e.g. 6–12), each representing a different cognitive condition, can be performed in the same scanning session. Thus, the subject can act as his own control, and because the time between injections for rCBF is about 10–15 min, the subject can remain fixed in the scanner, allowing comparisons between scans to be made on a voxel-by-voxel basis (e.g. Fox, Mintun, Reiman, & Raichle, 1988; Friston, Frith, Liddle, & Frackowiak, 1991; Friston et al., 1995). Another advantage of PET using $H_2{}^{15}O$ to measure rCBF concerns the time interval over which data are collected. These imaging techniques assume that rCBF or rCMRglc is in a relative "steady-state" during the scanning session, and what is observed is the time-integrated activation of a set of neural circuits over the period of the study. For rCBF, the time interval is about 20 s–1 min, depending upon the precise technique used, whereas for rCMRglc, it is about 30 min.

2.1.2. Functional MRI

In the past 5 years fMRI has developed into the most prominent method used for functional brain imaging.[3] The signal most commonly measured is the change in blood oxygenation and blood volume resulting from altered neural activity; this technique is called BOLD — blood oxygenation level-dependent contrast (Kwong et al., 1992; Ogawa et al., 1992). Deoxygenated hemoglobin acts as an endogenous paramagnetic contrast agent. Increased blood flow reduces the local concentration of deoxygenated hemoglobin

[2] The distinction we make between those techniques performed on humans and those used with nonhumans has become increasing blurred in the last few years; all the techniques used in humans also have started to be employed in primates and other mammalian preparations; likewise, imaging of intrinsic optical signals has been used on human subjects undergoing neurosurgical procedures.

[3] The use of PET to image human cognition retains somewhat of an advantage over fMRI in certain situations. Subject movement in the scanner can be a greater problem for fMRI than for PET. Thus, it can be more difficult to study some patient groups using fMRI than using PET. The same is the case for language production studies. Because the gradient coils used with fMRI can be quite noisy, auditory studies also are more difficult with fMRI than with PET. Moreover, some parts of the brain, particularly the ventral portions of the temporal and frontal lobes, are affected by large magnetic susceptibility artifacts, resulting in a loss of fMRI signal. Finding ways to work around these problems is an active area of research (Howseman & Bowtell, 1999).

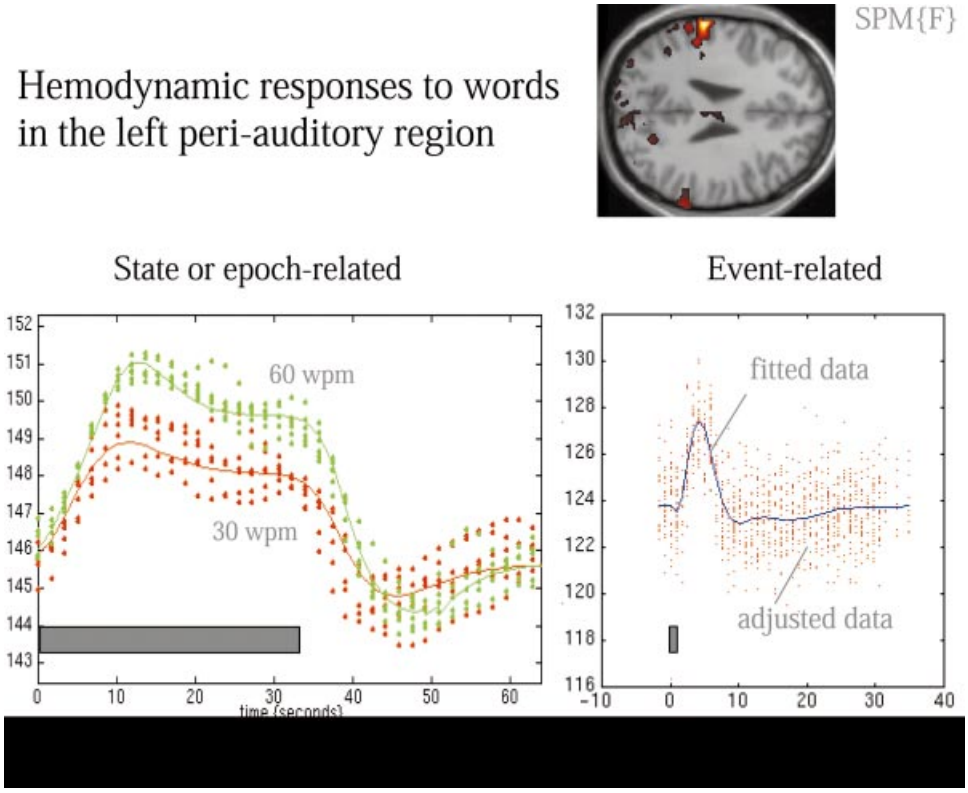


Fig. 1. Examples of block and event-related fMRI designs. (Left) Block design. Subject, during separate 34 s fMRI scans (one volume acquired every 1.7 s), listened to words presented at the rates of either 60 (green) or 30 wpm (red). The fitted peri-auditory responses (lines) and adjusted data (dots) are shown. The solid bar denotes when words were presented. Results show greater activity for the higher presentation rate. (Right) Event-related design. Same subject as in the block design listened to single words presented once every 34 s (small black bar at bottom shows when the word was presented). Shown are the adjusted fMRI data and the fitted response. Shown at the top is a map of the statistically significant event-related responses displayed on a T1-weighted structural MRI slice. A strong activation in the left peri-auditory area is visible. (Adapted from Friston, 1997c.)

causing an increase in the MR signal on a $T2^*$-weighted image (Ogawa et al., 1993; for reviews, see Howseman & Bowtell, 1999; Turner, 1995). These signals, which require no injections of contrast media, can be detected using conventional MRI scanners, although special hardware (i.e. fast gradient coils) are needed. fMRI has a spatio-temporal scale of about 1–3 mm and one or more seconds. The lower limits on the *effective resolution* of fMRI are physiological, being imposed by the spatio-temporal organization of evoked hemodynamic responses (2–5 mm and 5–8 s). To a first approximation one can think of the observed hemodynamic response as a smoothed version of the underlying neural activity.

Cognitive studies employing fMRI can be performed in two ways: (1) in block designs, which are analogous to the way PET studies are performed, either epochs of related stimuli are presented, or else a continuous task is performed during the scan; the ensuing signal is interpreted as a brain-state dependent measure; (2) in event-related designs, responses to a single type of stimulus can be measured by averaging the responses to multiple presentations, analogously to evoked potentials in electrophysiology (see below) (for reviews, see D'Esposito, Zarahn, & Aguirre, 1999; Josephs & Henson, 1999; Rosen, Buckner, & Dale, 1998).

An example of a typical block design study is presented in Fig. 1. Shown are fMRI data acquired from a single subject using echo planar imaging (EPI)[4] (Friston, 1997c). A single brain volume was obtained every 1.7 s. In one block, the subject listened to words presented at the rate of 60 words per minute (wpm) for 34 s, while in another 34 s duration block, the words were presented at the rate of 30 wpm. Blocks were separated by periods of rest. Fig. 1 (left) shows the adjusted data (dots) and the fitted responses to each condition (30 and 60 wpm) in left peri-auditory cortex, demonstrating that there is more neural activity for the higher stimulus presentation rate. An event-related design is shown in Fig. 1 (right), where the fMRI data were acquired from the same subject while listening to single words presented once every 34 s. Fig. 1 (top) shows a map of the statistically significant event-related responses displayed on a T1-weighted structural MRI slice; a strong activation is seen in the left peri-auditory region.

[4] One of the significant technical developments that made fMRI possible for cognitive studies was EPI (Mansfield, 1977), which allowed one to collect fMRI signals very quickly; with this technique, data from a single slice can be acquired in about 50 ms (Howseman & Bowtell, 1999).

2.2. Electric–magnetic methods

The second major type of functional brain imaging measures either the electric or magnetic fields associated with neural activity (for reviews, see Gevins, Smith, McEvoy, Leong, & Le, 1999; Picton, Lins, & Scherg, 1995; Rugg, 1999). The oldest functional neuroimaging methods applied to humans were those that recorded electrical activity from the scalp. Included in this category are EEG, which are continuous recordings lasting tens of seconds to minutes, and event-related potentials (ERPs), the electrical responses to specific cognitive stimuli; ERPs typically correspond to about a second's worth of neural activity. Researchers also have been able to record the magnetic fields generated by the electric current flows related to neural activity, giving rise to the use of magnetoencephalography (MEG) to study cognitive function (for detailed reviews of these methods, see Gevins et al., 1999; Hamalainen, Hari, Ilmoniemi, Knuutila, & Lounasmaa, 1993; Hari, 1996; Roberts et al., 1998; Taylor, Ioannides, & Mueller-Gaertner, 1999; Wikswo, Gevins, & Williamson, 1993). These techniques produce signals with a temporal resolution in the millisecond range, which is comparable to that at the neuronal level.

Many ERP studies have used a standard set of scalp electrodes (standard in the sense of number, 19 (called the 10–20 system), and location on the scalp). Sources of electrical activity spread by volume conduction in the brain, skull and other tissues to these scalp electrodes, resulting in an electric potential at a skull location that is summed from widely distributed electrical sources in the brain. In the last few years, there has been increased use of larger electrode arrays (e.g. 122 channels: Gevins, Le, Brickett, Reutter, & Desmond, 1991) and spatial signal enhancing algorithms, leading to much less spatial blurring.

The electrical activity associated with neuronal function results in the generation of very small magnetic fields that can be measured using detectors such as superconducting quantum interference devices (SQUIDs). Current MEG whole-head machines may employ 148 or more measuring coils.

Because a single ERP/MEG response has a small magnitude compared to the background EEG/MEG noise, signal averaging techniques are used to increase the signal-to-noise ratio. The net effect is that an ERP/MEG waveform represents the average over a number of trials (often between 20 and 50) (Picton et al., 1995). As mentioned above, this event-related approach has recently been applied to fMRI data.

A number of techniques exist that attempt to use the distribution of scalp-recorded electrical or magnetic activity to infer the location of the sources (often represented as simple electric or magnetic dipoles) that give rise to this activity. This effort is nontrivial because of what is called the inverse problem: there is no mathematically unique solution to the problem of determining the number and location of dipoles that could produce the measured surface distribution of activity (Nunez, 1990). Furthermore, except for the simplest paradigms, multiple sources need to be located because complex cognitive tasks are likely to be mediated by networks of interacting brain regions. In the last few years, research has focused on using anatomic and physiologic constraints, some obtained by PET or fMRI, to aid in dipole localization (e.g. Dale et al., 2000; Heinze et al., 1994; Toro, Wang, Zeffiro, Thatcher, & Hallett, 1994), although there are a variety of problems that make this difficult to do (for a discussion, see Rugg, 1999). Nonetheless, at present the electric–magnetic functional imaging methods yield, at best, high temporal resolution data at a few well-defined brain locations, whereas the hemodynamic–metabolic methods produce low temporal resolution data simultaneously everywhere in the brain, but with a spatial resolution of a few millimeters. One of the main challenges in functional brain imaging is to bridge the information provided by these two methodologies, and this is certainly one area where computational neuroscience may play a central role (Horwitz & Sporns, 1994; Taylor, Krause, Shah, Horwitz, & Mueller-Gaertner, 2000).

2.3. Functional brain imaging: what are the questions usually asked?

The major questions usually asked of the hemodynamic methods center on identification of the brain regions involved in mediating a specific brain function. The electric–magnetic methods have excellent temporal resolution, but since their ability to provide good spatial information is poor, the major questions they used to address concern the temporal dynamics of different sensory, motor and cognitive functions.

2.3.1. Data analysis paradigms for the hemodynamic methods

Two fundamental assumptions, each of which leads to a different data analysis strategy, govern how functional brain imaging data are used to make inferences about which brain regions are involved in particular cognitive and sensorimotor functions. The first, which leads to what has been called the subtraction paradigm (Horwitz, 1994) hypothesizes that different brain regions are engaged in different functions (i.e. computations). This notion, called functional specialization (Friston, 1997c; Zeki, 1990), is the predominant assumption used by most working neuroscientists today. In PET/fMRI studies, this assumption is implemented by comparing the functional signals between two (in its most simple formulation) scans, each representing a different experimental condition (Posner, Petersen, Fox, & Raichle, 1988). The loci of the large differences in signal between the two presumably delineate the brain regions differentially involved in the two conditions. An example of this approach was given by the block design fMRI study illustrated in Fig. 1 (Friston, 1997c). There the tasks of interest were

listening to words at two different presentation rates (60 and 30 wpm, respectively). The results demonstrated that left peri-auditory cortex had greater activity for the higher presentation rate than for the lower, and that both resulted in higher activity in this region when compared to rest.

Quite sophisticated experimental designs can be handled, especially using fMRI. Their analysis requires a number of steps involving image processing and statistical evaluation. One commonly used method, Statistical Parametric Mapping (Friston, 1997a) consists of modules for: (1) executing various image preprocessing steps (e.g. correcting for head movement); (2) mapping individual images into a common anatomical space (usually referred to as Talairach space, since it is based on the stereotactic atlas of Talairach and Tournoux (1988)), thus allowing intersubject averaging on a voxel-by-voxel basis; (3) using the general linear model to perform univariate statistical tests at each brain voxel; and finally (4) making statistical inferences about the observed responses using distributional approximations from the theory of Gaussian fields (Friston et al., 1995; Worsley, 1994).

The second assumption leads to what has been termed the covariance paradigm (Horwitz, 1994) and rests on the notion of functional integration (Friston, Frith, Liddle, & Frackowiak, 1993; Gerstein, 1970). The assertion here is that the task represented by an experimental condition is mediated by a network of interacting brain regions, and that different tasks correspond to different functional networks. Thus, by examining the covariance in brain activity between different brain areas, one can infer something about which areas are important nodes in the network under study, and how these nodes are functionally connected. Because functional neuroimaging methods generally obtain data simultaneously from multiple brain regions, they are ideal and essentially unique for use with the covariance paradigm. These two ways of looking at functional neuroimaging data complement one another; both are necessary to thoroughly understand the functional imaging data resulting from any experiment.

In PET/fMRI studies, the quantity that is determined using the covariance paradigm is called the functional connectivity (Friston, 1994), and it corresponds to the interregional covariance or correlation in functional activity within a specific cognitive task (Horwitz et al., 1992a) (note: because PET and fMRI generally are spatially smoothed, we can think of a single voxel as representing a region, since it represents the activity in a local area around it). Fig. 2 shows an example of the use of the covariance paradigm to evaluate the functional connectivity between rCBF in a single reference voxel and rCBF in all the other voxels in the brain. The data shown come from a PET/rCBF study (Horwitz, Rumsey, & Donohue, 1998) in which 17 normal subjects (in the task under consideration) pronounced pseudowords while being scanned. The reference voxel is located in the left angular gyrus. In agreement with the classic neurologic model for reading, which is based on studies of patients with acquired reading disorders (i.e. alexia), rCBF in the left angular gyrus shows strong functional connectivity with rCBF in visual association areas in occipital and temporal cortex, and with rCBF in language areas in superior temporal and inferior frontal cortex. In contrast, these strong functional connections are absent in subjects with developmental dyslexia, which led to the conclusion that dyslexia is characterized by a functional disconnection of the angular gyrus that mirrors the anatomical disconnection seen in alexia.

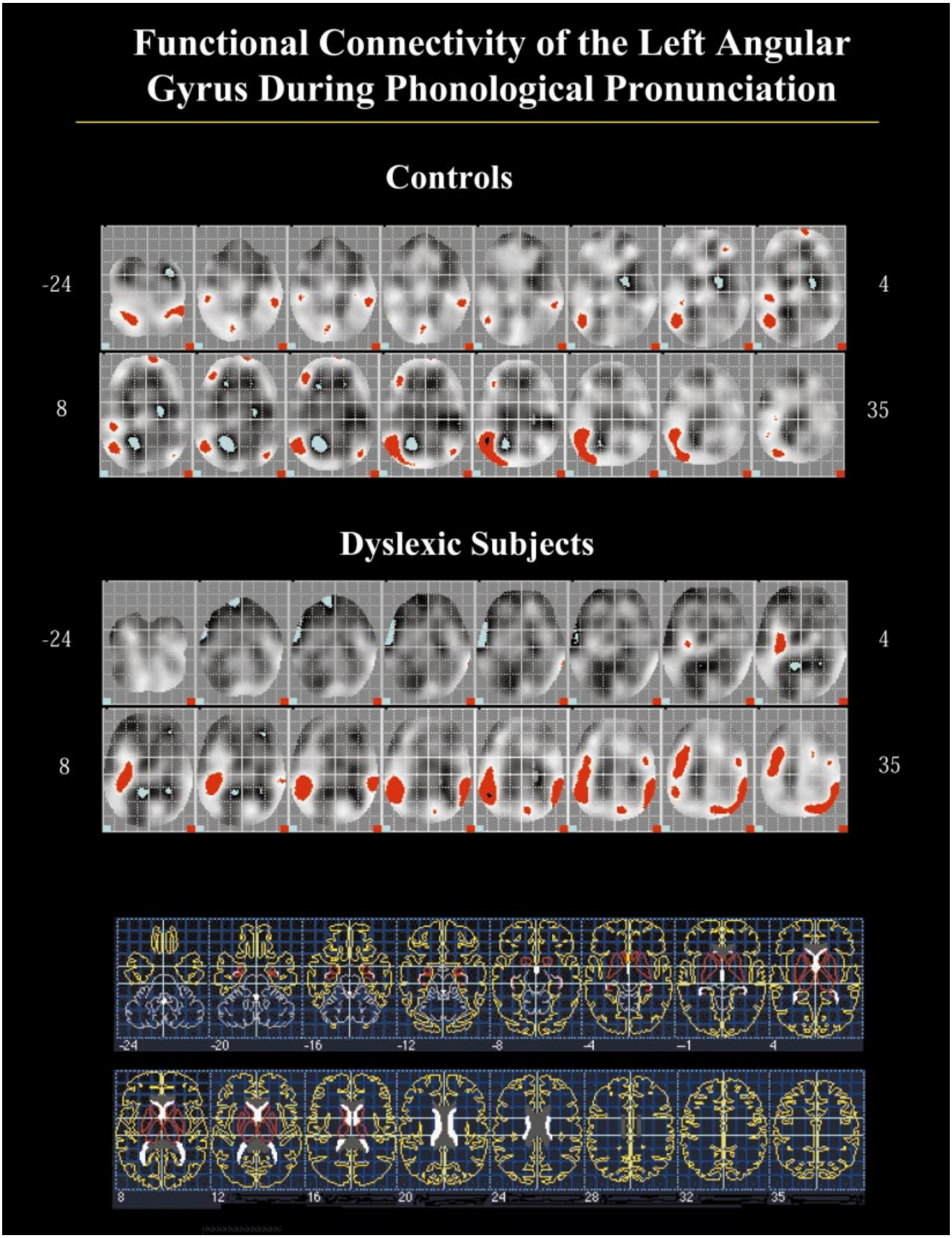
The example just given shows the functional connectivity between a single reference voxel and all other brain voxels. Of course, one is often interested in the correlational structures that characterize the functional connectivity amongst all brain voxels for multiple cognitive conditions. A number of ways for obtaining these have been developed, including principal components analysis (e.g. Friston et al., 1993; Lagreze et al., 1993), multidimensional scaling (e.g. Friston, 1994), and the method of partial least squares (McIntosh, Bookstein, Maxby, & Grady, 1996). A discussion of these methods for characterizing distributed functional systems in PET/fMRI data can be found in Friston (1997b).

2.3.2. Analysis of EEG/MEG data

As stated before, the high temporal resolution of EEG/MEG data leads naturally to using these techniques to answer questions about the timing of cognitive processes. Moreover, the amplitude of a specific waveform may differ between experimental conditions or groups, suggesting that the condition or groups utilize different cognitive processes. Both timing differences and amplitude differences can refer either to the scalp recorded fields, or to dipole sources that have been localized to specific brain locations.

We shall use three language studies to illustrate these points. Hagoort, Brown, and Osterhout (1999) review the various ERP components that are related to how sentences are parsed by the human brain. One such component is the N400, a negative potential that peaks about 400 ms following the presentation of certain stimuli, whose amplitude is increased when the semantics of the word eliciting it is inappropriate for the context of the sentence (Kutas & Hillyard, 1980). For example, the last word of the sentence “I eat peas using a feather” would generate an N400, whereas the last word of the sentence “I eat peas using a fork” would not. Some have interpreted the N400 as representing the manipulation of the semantic fit between the word and the sentence in which it is found. The N400 generally is largest for the scalp electrodes over posterior brain locations.

Differences in latency of a waveform, not amplitude, can distinguish the processing of different types of word. As Hagoort et al. (1999) show, closed-class words (e.g. nouns, adjectives, verbs) elicit a slightly earlier N280 (a negative ERP peaking about 280 ms after word presentation) than do open-class words (e.g. prepositions, conjunctions, articles). The effect is largest over left anterior


Functional Connectivity of the Left Angular Gyrus During Phonological Pronunciation
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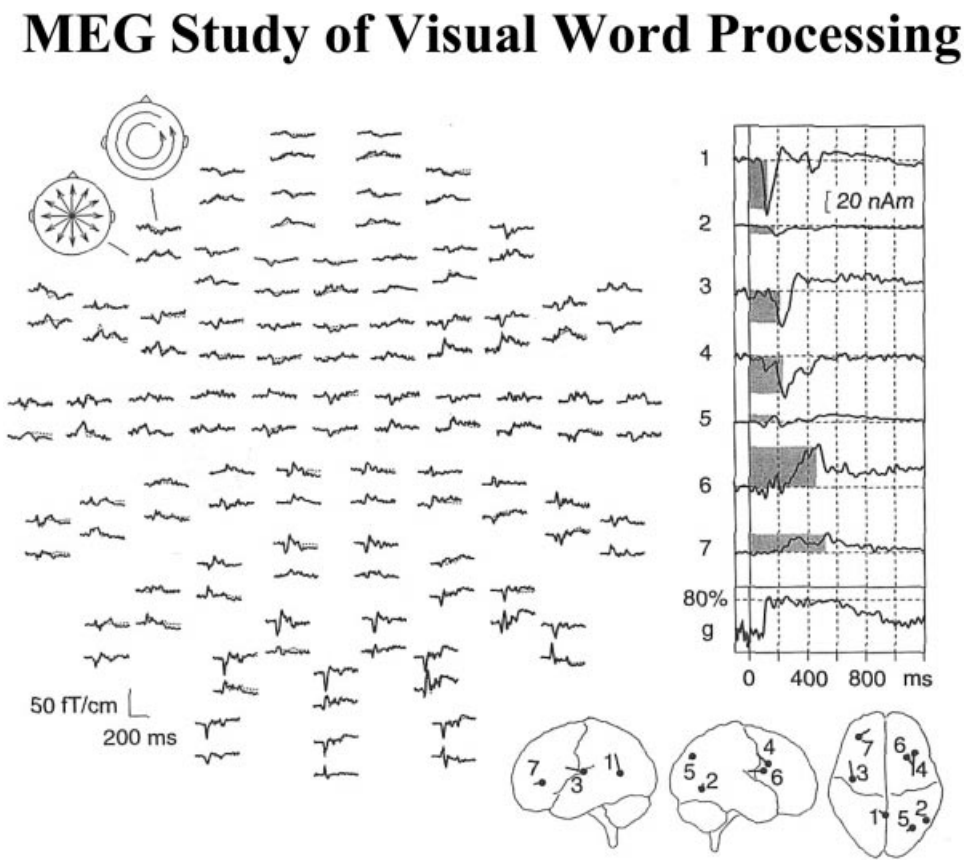

Fig. 3. Example of an MEG study. Shown are magnetic responses to visually presented words from 100 ms before stimulus onset to 800 ms after it (the responses from detectors in a helmet are shown from above, but flattened onto a plane) in a single control subject. The data were modeled by seven equivalent current dipoles, identified at distinct latencies and shown on the brain drawings (lower right); each dot represents the location of the dipole, each tail the direction of current flow. The amplitudes of these sources as a function of time are shown on the right. (From Salmelin et al., 1996, used with permission.)

electrode locations. The interpretation of what this latency difference means is still at issue, although the results do suggest it may be attributable to differences in how open and closed-class words are processed syntactically.

We now discuss an MEG study of visual word processing by Salmelin, Service, Kiesila, Uutela, and Salonen (1996) in which normal and dyslexic readers passively viewed single words while being scanned with a whole-head MEG system that employed 122 SQUID sensors. The magnetic signals were used to determine the brain locations, orientations and magnitudes of dipole current sources. A number of distinct dipoles were identified, some of which had different latencies of onset (see Fig. 3). One particularly noteworthy finding concerned a dipole in the left temporo-occipital area, where control subjects showed a strong activation about 180 ms following word presentation. The dyslexic subjects, on the other hand, either failed to demonstrate this activation, or else if they did, it was with a slowly increasing late response. Interestingly, this left temporo-occipital region is an area found by Horwitz et al. (1998) to have strong functional connections with the left angular gyrus in normal readers, but not in dyslexics (see Fig. 2).

Finally, we should mention that EEG/MEG data can also be evaluated by methods that examine something akin to the functional connectivity measures that were discussed for PET/fMRI. Assessing functional connectivity between different cortical regions by evaluating the cross-correlation between scalp electrodes has a long history (e.g. Adey, Walter, & Hendrix, 1961; Barlow & Brazier, 1954; Gevins et al., 1985; Livanov, 1977), and a variety of techniques

Fig. 2. Example of functional connectivity analysis for PET. Shown are the correlation coefficients (functional connectivity) between rCBF in a reference voxel in the left angular gyrus and rCBF in all other brain voxels in control (top) and dyslexic (middle) subjects during the pronunciation of visually presented pseudowords. At the bottom are modified drawings of the corresponding axial slices from the Talairach atlas (1988) (the left side of the brain is on the left side of each image; the top of each image is the front of the brain). The numbers at the sides of each row correspond to the distance (in mm) above or below the intercommisural plane. The reference voxel is denoted by the black dot on the 24 mm slice. The intensity level (gray scale) corresponds to the value of the correlation coefficient (the whiter the scale, the more positive the correlation), with significantly large positive correlations shown in red and large negative correlations in cyan. Results show strong positive correlations between rCBF in the left angular gyrus and rCBF in visual association regions and in language regions in temporal and frontal cortex in controls, but not dyslexic subjects. (Adapted from Horwitz et al., 1998.)

have been used. Different methods focus on correlating various features of the spatiotemporal waveforms associated with electric–magnetic activity. For example, one commonly used approach evaluates the coherence, which is simply the correlation between EEG signals at different scalp sites in the frequency domain (e.g. Pfurtscheller & Andrew, 1999). The amplitude of an EEG signal is thought to provide a measure of the amount of synchrony of a localized neural population within range of the scalp electrode. Coherence, on the other hand, reflects the dynamic functional interrelation between spatially separated electrode sites, and is assumed to correspond to synchronized activity between electrical activity in distinct brain regions. Because neural activity is quite dynamic, methods also have been developed to examine coherence (Andrew & Pfurtscheller, 1996) or temporal covariance (Gevins et al., 1985, 1999; Gevins & Bressler, 1988) for individual trials.

We give two examples to illustrate these approaches. Weiss and Rappelsberger (2000) evaluated EEG coherence during memory encoding of words. Words that would later be correctly recalled showed larger coherence between anterior and posterior sites than did words not correctly recalled. This also was the case for interhemispheric coherence. This pattern of coherence was found for all frequency bands, except one of the alpha bands (8–10 Hz). In a study that examined the dynamically changing patterns of event-related covariances during a task that required subjects to make a finger response of a given pressure, indicated by a visual cue, Gevins et al. (1989) found a pattern of covariances during a 375 ms interval centered 687 ms post-cue that preceded subsequently correct responses, and a different pattern that preceded subsequently incorrect responses. These results suggested the presence of a cortical preparatory network, involving left frontal, midline antero-central and parietal sites, that is needed for accurate performance.

2.4. Two other methods of relevance

There are two other techniques for investigating human cognition have become prominent recently, and are closely tied to the functional brain imaging methods we have been discussing. One is the imaging of intrinsic optical signals (used primarily in nonhuman primates (Frostig, Lieke, Ts'o, & Grinvald, 1990; Grinvald, Frostig, Lieke, & Hildesheim, 1988; Ts'o, Frostig, Lieke, & Grinvald, 1990), although some studies in humans undergoing neurosurgical intervention have been carried out (Haglund, Ojemann, & Hochman, 1992)). The second is trancranial magnetic stimulation (TMS) (Cohen et al., 1998; Cracco, Cracco, Maccabee, & Amassian, 1999; Jahanshahi & Rothwell, 2000; Pascual-Leone, Walsh, & Rothwell, 2000), which has been used in conjunction with functional brain imaging to help elucidate functional connectivity (Paus et al., 1997).

2.4.1. Optical imaging

Although optical imaging is performed primarily in nonhuman animals, including primates, it has a close connection to the other hemodynamic–metabolic methods discussed above. There are two optical imaging techniques that have been widely used: (1) those employing voltage sensitive dyes (Grinvald et al., 1988; London, Zecevic, & Cohen, 1987); and (2) those based on the imaging of intrinsic optical signals (Frostig et al., 1990; Grinvald, Frostig, Siegel, & Bartfield, 1991; Ts'o et al., 1990). It is the latter that is of relevance both because this was the method used for many important primate experiments, and because the imaging of intrinsic optical signals can be accomplished in human intraoperative studies (for a review, see Haglund, 1997). Generally, in this type of imaging, brain tissue exposed after part of the skull is removed is illuminated by light of a specific wavelength, and the reflected light is measured by a charge coupled device camera. Brain activity produces local optical changes in brain tissue that affect the intensity of the reflected light. Although a number of factors contribute, it is thought that, like fMRI BOLD, changes in the concentrations of oxygenated and deoxygenated hemoglobin due to local neural activity play a large role (Malonek & Grinvald, 1996). Therefore, optical imaging, with its high spatial and temporal resolution, is in a good position to relate neural signals to the hemodynamic–metabolic measurements of functional activity (Frostig et al., 1990). For example, optical imaging has revealed the organization of ocular dominance columns in the awake monkey over a wide expanse of primary visual cortex (Grinvald et al., 1991).

2.4.2. TMS

Although first developed in 1985 (Barker, Jalinous, & Freeston, 1985), TMS has become a relatively popular method for investigating the role different brain regions play in human cognition only in the last few years (reviews can be found in Cracco et al., 1999; Jahanshahi & Rothwell, 2000; Pascual-Leone, Bartres-Faz, & Keenan, 1999; Pascual-Leone et al., 2000). TMS uses an externally generated changing magnetic field, applied by a coil placed over a subject's head, to induce electric currents in the brain. The faster the rate of change of the magnetic field, the larger is the induced current. Two types of TMS are generally performed — single-pulse TMS[5] and rTMS (repetitive TMS, in which a series of pulses at rates up to 50 Hz are applied). Single-pulse TMS appears to be completely safe, but rTMS can be dangerous, possibly leading to seizures, and strict guidelines for its use are employed (Wassermann, 1998). The spatial extent and depth of the brain area activated by TMS depend on a number of factors, including the design of the stimulating coil, and are difficult to determine with any precision. Although a study (Brasil-Neto,

[5] In some studies a double-pulse approach is used, in which a first pulse acts to either augment or inhibit the effect of the second pulse.

McShane, Fuhr, Hallett, & Cohen, 1992) applying TMS to motor cortex reported that it was possible to distinguish scalp positions 0.5–1 cm apart, the spatial extent of TMS in human cognition experiments generally is much coarser (Walsh & Rushworth, 1999). Likewise, the way in which TMS affects neuronal function also is not well understood, especially the manner in which neuronal populations are affected by the induced currents. It has been suggested by a number of workers (e.g. Pascual-Leone et al., 2000) that the main effect of a TMS pulse is a quick synchronized firing of neurons lasting a few milliseconds, followed by a relatively longer-lasting (20–200 ms) GABAergic-mediated inhibition.

There are three primary ways in which TMS has been used to study human brain function (Pascual-Leone et al., 2000): (1) inducing 'virtual lesions' by disrupting focal neural activity during a task; (2) chronometry — applying TMS to different brain locations at different times during a task to help elucidate its time course; and (3) applying TMS to one brain location and determining its effects elsewhere as a way to assess functional connectivity. An example of the virtual lesion method can be found in Epstein (1998), who reviews his own and others' research on using rTMS to disrupt language function (mainly for the goal of replacing the Wada test: Wada, Clarke, & Hamm, 1975 — the intracarotid injection of amobarbital during preoperative evaluation for neurosurgery near language areas). He found that rTMS can lead to speech arrest when applied to the facial part of the motor cortex, although inducing a true aphasia is rare. Interestingly, several studies have reported that TMS can facilitate performance on some tasks, including picture naming (Mottaghy et al., 1999; Toepper, Mottaghy, Breugmann, Noth, & Huber, 1998). In a noteworthy example (Walsh, Ellison, Battelli, & Cowey, 1998), both disruption and facilitation were found when TMS was applied to V5/MT, a motion processing area in extrastriate visual cortex, during different conjunction tasks. Subjects' performance was disrupted when the task involved motion processing (the conjunction of color and motion), but was improved when motion processing was irrelevant (the conjunction of form and color in the presence of motion).

As an example of using TMS to study chronometry, Cracco et al. (1999) provide an engaging set of findings showing how one can trace the temporal flow of symbolic information processing. It takes about 350 ms for a subject to begin vocalizing in response to a visually presented stimulus. Cracco et al. concluded that there is a 60 ms transfer time between the retina and primary visual cortex (found by applying single pulse TMS to occipital cortex at 20 ms steps from 0 to 200 ms following stimulus presentation); relay of the symbolic representation out of visual cortex takes about 120 ms; a further 120–140 ms is required for its transfer to and facilitation in frontal cortex; and, finally, about 100 ms more is needed for initiation of voice onset.

Finally, we mention that TMS has been combined with functional brain imaging, especially PET, to examine brain functional connectivity (Fox et al., 1997; Ilmoniemi et al., 1997; Paus et al., 1997). A study by Paus et al. (1998) illustrates the method. Primary sensorimotor cortex was stimulated by rTMS while subjects underwent PET. Each scan consisted of the presentation of a different number of 10 Hz trains (5–30, in steps of 5). Both under the coil, and in regions distant from the stimulation site (e.g. SMA, medial parietal lobe), rCBF was negatively correlated with the number of pulse trains. These findings were interpreted as showing that TMS was modulating neural activity in an interconnected neural system. In a similar vein, Ilmoniemi et al. (1997) demonstrated that EEG signals in brain areas far from the site of TMS stimulation can be altered.

3. A brief overview of neural modeling as applied to functional brain imaging

In retrospect, it seems strange that until recently there were few attempts to apply neural modeling techniques to functional brain imaging data.[6] Certainly, the data acquired from PET and ERPs were sufficiently complicated and multi-faceted that neural modeling would seem an appropriate way to deal with the complexity and to provide conceptualizations for the data. We suspect that the reasons this did not occur included the following: (1) most neural modelers were focused on neuronal, electrophysiological recording studies; as a group, there were not familiar with the data and questions arising from functional brain imaging; (2) most functional brain imagers were unaware of the advances being made in computational neuroscience, and thus, were not in a position to employ these techniques; (3) as we have stressed earlier, we believe that until recently both communities tended to think in terms of studying one neural entity (region, cortical column, neuron, synapse) at a time; as a result, neuroimagers failed to see the need for methods that would deal with interacting brain regions, and neural modelers failed to see the potential of functional brain imaging for providing the kind of data that would require network-level analyses; and finally (4) the timing may have been bad, in that computational neuroscience and functional brain imaging were both becoming more mature enterprises at roughly the same time; often, an immature area of research draws upon the resources found in more mature areas for support.

3.1. Neuromodeling and PET/fMRI

There are three primary ways in which neuromodeling has been used in conjunction with PET and fMRI data (for overviews, see Horwitz & Sporns, 1994; Horwitz, Tagamets, & McIntosh, 1999). The first concerns efforts

[6] Actually, the electric–magnetic side of functional brain imaging employed neural modeling, as we shall see, early in its development. It is only recently that computational neuroscience has been used with PET/fMRI.

at determining how local changes in neural activity are transformed into changes in blood flow and metabolism. The second way has been through the employment of modeling to determine the systems-level networks mediating specific cognitive tasks (Friston, 1994; Horwitz, 1990; McIntosh & Gonzalez-Lima, 1991, 1994). Finally, in the last few years, several groups have begun to construct large-scale neurobiologically realistic models with which to simulate PET and fMRI studies, allowing one to relate systems-level results to those obtained at the neuronal and neural ensemble level (Arbib, Bischoff, Fagg, & Grafton, 1995; Tagamets & Horwitz, 1998; Taylor et al., 2000; Taylor & Taylor, 1999); see also Monchi et al. (2000) and Tagamets and Horwitz (2000).

The first way alluded to in the previous paragraph can be discussed very quickly. We misspoke in saying that neural modeling has been used to help elucidate the coupling between changes in neural activity and their hemodynamic–metabolic consequences, because essentially not much research of this kind has been performed. Since Roy and Sherrington's hypothesis (Roy & Sherrington, 1890) that changes in neural activity would lead to changes in blood flow and oxidative metabolism, there has been extensive experimental investigation on this topic. A large number of neurochemicals have been found that affect blood flow and/or metabolism (e.g. adenosine, nitric oxide, lactate, and most importantly, several neurotransmitters, including glutamate, acetylcholine and noradrenaline). A major difficulty appears to be that metabolism and blood flow, although normally coupled under physiological conditions, are apparently regulated by separate and possibly multiple mechanisms (see, for example, Villringer & Dirnagl, 1995 for a more detailed discussion). We are thus in the position where a large number of factors, many interacting with one another, mediate the couplings between neural activity and blood flow, neural activity and metabolism, and blood flow and metabolism. This is the type of situation where computational modeling may be quite helpful in determining which factors are major, which are minor, and the conditions under which the normal couplings are maintained (Horwitz & Sporns, 1994). Understanding the nature of these neural activity-metabolism/blood flow couplings is crucial because it is the foundation on which our interpretation of what a change in PET/fMRI activity means in terms of neural activity rests. For example, it is thought that the hemodynamic–metabolic measurements associated with PET and fMRI reflect synaptic activity to a larger extent than neuronal activity (Jueptner & Weiller, 1995; Mata et al., 1980), and because of this, increased excitatory and inhibitory synaptic activity probably result in increased PET or fMRI activity (Ackermann, Finch, Babb, & Engel, 1984; Horwitz & Sporns, 1994; Jueptner & Weiller, 1995). The conditions, and brain regions, where this is indeed the case, however, have yet to be fully established, and may in fact be quite difficult to determine experimentally. Robust conclusions from computational modeling can thus play a central role in helping to design appropriate experiments for addressing these issues.

3.1.1. Systems-level modeling of PET/fMRI data

As mentioned above in our discussion of the covariance paradigm, an analysis of brain functioning in terms of networks, rather than single regions, is necessary in order to fully grasp the complexities associated with cognition (Damasio, 1989; Horwitz, Soncrant, & Haxby, 1992b; Mesulam, 1990; Taylor, 1999). Indeed, Fuster (2000) has argued, along with others, that the concept of module, originating from studies of sensory physiology, has been overextended when applied to the neural substrates of higher level cognition, and perhaps the better paradigmatic notion is that of network. Thus, it is not surprising that the most extensive use of neural modeling with PET/fMRI data has been at the systems-level, where the main goal has been to determine what are the critical brain regions *and the strengths of their interactions* involved in mediating specific cognitive tasks. However, a major problem with using just the interregional covariances to infer network behavior is that large covariances in interregional activity can come about by both direct and indirect effects. That is, two regions may have a large correlation in activity if they are anatomically linked, and that link is functional in a specific task. However, they also could have a large correlation if they are not directly connected, but rather receive inputs from a third region, or are indirectly connected via other regions. Or, one could have combinations of all these going on simultaneously. The key distinction here is between functional and effective connectivity (Friston, 1994). The functional connectivity between two brain regions simply tells us how correlated are their activities. Their effective connectivity, on the other hand, is the explicit influence that one region's activity has on the activity of the second along the direct anatomical pathway linking the two.[7]

The evaluation of effective connectivity requires the use of systems-level computational modeling (Buechel & Friston, 1997; Horwitz, 1994; McIntosh & Gonzalez-Lima, 1994; Taylor, 1999). For a specified set of brain regions, explicit data about their anatomical connections (often based on the results from neuroanatomical studies in nonhuman primates) are combined with their task-specific interregional rCBF[8] covariances. Some type of computational optimization analysis is then used to determine the functional strengths (i.e. the effective connectivities) of each

[7] There seems to be confusion in the use of the terms functional and effective connectivity. Some researchers would like to say that two regions that are directly, or indirectly, connected anatomically, can be effectively connected during specific tasks. Perhaps a third term should be introduced to distinguish direct effective connectivity (implying a single anatomical fiber pathway between the two regions) from indirect effective connectivity (implying a functional chain of such anatomical linkages).

[8] Henceforth, for simplicity, we will refer to the functional measure of activity obtained by either PET or fMRI as rCBF, even though fMRI-measured BOLD activity differs in some important ways from rCBF.

anatomical link between regions that provide the closest match between the experimentally determined interregional covariances and those based on the computed functional strengths. The most popular approach for performing this analysis uses a technique called structural equation modeling (Hayduk, 1987; Joreskog & Sorbom, 1979). The final set of computed effective connections defines the functional network corresponding to each task under study. Of course, this is a model in the true sense in that only a few brain regions are included. One is explicitly attempting to distinguish those regions whose interactions are central to the tasks under investigation from those whose involvement is peripheral. As with all modeling efforts, one is essentially guessing what is important. However, statistical estimates of goodness-of-fit can be obtained that allow one to infer how reasonable the model is, and whether two or more functional networks differ.

An example of this type of neural modeling is given by the study of McIntosh et al. (1994), which used rCBF/PET data from two tasks employed to distinguish the neural substrates for object and spatial visual processing (Haxby et al., 1991; Ungerleider & Mishkin, 1982). Both tasks were match-to-sample; for object vision, the stimuli were faces, and for the spatial processing task, the stimuli consisted of a dot relative to a double line. Data from nonhuman primate studies (Ungerleider, Gaffan, & Pelak, 1989; Ungerleider & Mishkin, 1982) had suggested that visual processing for the object features (e.g. color, shape) takes place along a ventral cortical pathway, from occipital cortex through temporal cortex, and thence into the frontal lobe; the pathway for spatial vision follows a dorsal route from occipital to parietal to frontal cortex. McIntosh et al. (1994) found that for the object vision task the strongest positive effective connections were indeed in the ventral pathway, whereas for the spatial processing task, the largest positive effective connections were in the dorsal pathway. Moreover, they found that functionally, both visual processing pathways were not totally independent; strong effective connections between the two were present in both tasks.

Recently, Buechel, Coull, and Friston (1999) demonstrated that the effective connections linking the two visual cortical pathways can change in individual subjects during a single fMRI scanning session. They performed a study in which subjects were instructed to learn the spatial locations of a set of visual objects. During each scanning session, subjects were given eight trials for each of 10 object-location combinations. Using structural equation modeling, they found that the effective connection between posterior parietal cortex (in the dorsal pathway) and posterior inferior temporal cortex (in the ventral pathway) increased in value during the scanning session. Furthermore, the time course of these changes in effective connectivity was highly correlated with individual learning performance, suggesting that the associative learning was being mediated by the interregional interactions.

3.1.2. Large-scale neural modeling and PET/fMRI data

The interregional effective connectivity determined by systems-level modeling, as discussed in the previous section, provides information about how hemodynamic activity in one brain region is related to that in another brain region. Likewise, the subtraction paradigm tells us what brain areas have significantly different hemodynamic activities between two or more experimental conditions. A number of problems makes it difficult to use these results to gain information about the underlying neural activity during different components of the cognitive tasks being studied (Horwitz & Sporns, 1994; Horwitz et al., 1999; Taylor et al., 2000). We have already mentioned the lack of understanding of the mechanism(s) by which local changes in neural activity lead to local changes in blood flow and metabolism. There are other problems as well: (1) spatial resolution — even with fMRI, the spatial resolution of human brain imaging devices is large compared with the size of neurons or cortical columns; this means that multiple and diverse neuronal populations are lumped together in any resolvable PET or fMRI region of interest (even a single voxel); (2) temporal resolution — the temporal resolution for electrophysiological activity is on the order of milliseconds, whereas the temporal dimension for PET and fMRI is on the order of seconds to tens of seconds; (3) synaptic vs. neuronal activity — activity measured in nonhuman animal studies by single unit electrical recordings generally reflect the spiking behavior of neurons, whereas, the hemodynamic measurements associated with PET and fMRI, as mentioned above, most likely correspond to synaptic activity more than to the spiking activity of neurons (Jueptner & Weiller, 1995; Mata et al., 1980), although these two electrophysiological features are related; this also means, as indicated before, that both excitatory and inhibitory synaptic activity may result in similar PET or fMRI signals (Ackermann et al., 1984; Horwitz & Sporns, 1994; Jueptner & Weiller, 1995); and (4) connectivity — because the hemodynamic-measured activity most likely reflects synaptic activity in a brain region, this activity is a mixture of local synaptic activity plus afferent activity coming from all the regions that project to the region being examined; this makes the interpretation of why a region is active in one task compared to a second difficult to relate to other ways that are used to understand the role that a specific brain region plays in a cognitive function (e.g. lesion analysis and electrical recordings in nonhuman primates).

Recently, several groups have attempted to develop ways to bridge this divide between PET/fMRI signals on one hand, and neuronal activity on the other. Taylor et al. (2000) presented a general mathematical formulation for the dynamic behavior of coupled neural networks. Making a number of simplifying assumptions about the underlying neural activity and its relation to blood flow, they showed how synchronized neural activity between coupled populations can lead to the type of covariance structures that form the basis for analyzing systems-level networks using

structural equation modeling. Specifically, the detailed manner in which connection strengths can be related to underlying neural synaptic weights and to learning processes was developed. The need to extend the usual structural equations was indicated by considering the inhibitory and excitatory neural populations separately. The resulting structural equation models represented the neural activity as hidden variables, allowing the manner in which neural activity contributed to the blood flow measurements to be determined from experiment. Finally it was shown how the temporal features of neural activity could be included so as to lead to predictions for EEG/MEG measuring techniques.

A second approach, developed by Arbib et al. (1995) and Tagamets and Horwitz (Horwitz & Tagamets, 1999; Tagamets & Horwitz, 1998), aims at constructing neurobiologically realistic large-scale neural models with which simulated PET and fMRI studies are performed. These multileveled models contain a number of interacting brain regions, each of which is constructed out of multiple neuronal units (cf. Tononi, Sporns, & Edelman, 1992), and can therefore serve as platforms with which one tries to relate neural activity directly to PET/fMRI activity. For example, the Tagamets–Horwitz simulation model (Tagamets & Horwitz, 1998) consists of several brain regions corresponding to components of the ventral cortical visual processing stream discussed in the previous section (V1/V2, V4, IT and prefrontal cortex). Each of these regions in turn is comprised on multiple basic elements, each of which can be thought as representing a cortical column. Every basic element is made up of an excitatory–inhibitory interacting pair of neuronal units. Regions of the model differ in how these canonical elements are connected to one another. Primate neuroanatomical data, when available, were used to determine the strengths of the connections within each area, and between areas (both feedforward and feedback). It was demonstrated (Tagamets & Horwitz, 1998) that this model was able to perform a delayed match-to-sample task for simple shapes, while concurrently exhibiting electrical activities in each brain region similar to those seen in monkeys performing similar tasks (Funahashi, Chafee, & Goldman-Rakic, 1993; Fuster, 1990; Haenny, Maunsell, & Schiller, 1988). A simulated PET/fMRI scan consists of multiple trials, each of which comprises the presentation of a shape, a delay period, a second shape to which the model had to decide if it was the same as the first shape and an intertrial interval. Simulated PET/fMRI data were obtained by assuming that the absolute value of the synaptic activity, spatially integrated over each region and temporally integrated over an appropriate time course (about a minute for rCBF/PET simulations, about 50–100 ms for fMRI simulations)[9] corresponded to the functional brain imaging signal. When simulated rCBF (in a PET design) for the delayed match-to-same task was compared to rCBF for a control task consisting of the "passive viewing" of degraded shapes, percentages changes in each region were similar to those in found in a comparable human PET study (Haxby, Ungerleider, Horwitz, Rapoport, & Grady, 1995).

PET/fMRI predictions also have been made using the ACTION network cartoon model of the frontal lobes. This model has been used to simulate two tests that are sensitive to frontal lobe dysfunction (the Wisconsin card sorting task and the delayed matching task); the effects of degradations corresponding to Parkinson's disease or schizophrenia were determined (Monchi et al., 2000). At the same time, the effects of either Parkinson's disease or Huntington's chorea on action sequence generation by the model were simulated and compared to brain imaging data on globus pallidus activity levels (Taylor & Taylor, 1999, 2000a,b).

3.2. Neuromodeling and EEG/MEG

The earliest neural modeling efforts involving functional brain imaging data centered on EEG data, which seems obvious given that EEG was, in essence, the first of the neuroimaging modalities.[10] A central problem was to determine the neurophysiological substrate for the EEG/ERP signals. The basic mechanisms are now fairly well understood. The ionic currents that flow across the neuronal membrane give rise to potential differences between different locations in the extracellular space (i.e. sinks and sources). These sinks and sources (dipoles) can become macroscopic in extent if many similar elements of an anatomically ordered ensemble of neurons are activated simultaneously. Neuronal modeling of such ensembles led to the conclusion that in the cortex it is the activity of the postsynaptic potentials associated with pyramidal neurons, rather than action potentials, that mainly contribute to the extracellular potential fields (e.g. Nunez, 1990; Wood & Allison, 1981). It has been estimated that about 30 000 neurons must be activated simultaneously in order for a extracranial field to be detected (Williamson & Kaufman, 1990).

For both EEG and MEG much computational work (e.g. Hamalainen et al., 1993; Mosher, Leahy, & Lewis, 1999; Nunez, 1981) has been performed that allows one approximately to solve what is called the forward problem — given a distribution of electric or magnetic dipoles (or other electric–magnetic distributions, such as quadrupoles or distributed current densities), what are the electric or magnetic fields that can be recorded at the surface of the skull? Major issues concern whether one uses a spherical or

[9] Simulating an fMRI study requires several other steps, such as imposing a hemodynamic delay and temporally sampling the activity (see Horwitz & Tagamets, 1999 for details).

[10] Although EEG were discovered by Hans Berger over 70 years ago, and ERPs have been performed for over 40 years, it has only been in the last 20 or so years that these kinds of data have been converted into neuroimages (e.g. Coppola, Buchsbaum, & Rigal, 1982; Duffy, Burchfiel, & Lombroso, 1979; Gevins et al., 1985). The use of computational neuroscience to understand EEG/ERP signals predates the neuroimaging epoch.

nonspherical model of the head, how to handle the different tissue conductivities for EEG, and indeed, how realistic a model of the head is needed in general.

A more biologically realistic form of modeling has focused on efforts at computing electrocortical activity, as would be recorded by local field potentials, in terms of neuronal interactions within the cortex. These, in turn, can then be related to surface recorded evoked potentials (reviews of this area of research can be found in Freeman, 1975, 1987; Vaughan & Arezzo, 1988). One approach has been to determine the second spatial derivative of the field potential recorded at the cortical surface, a method called current source density (CSD) analysis, and to try to understand evoked CSD profiles in terms of interactions among neurons in the lamina of the cortex (Mitzdorf, 1988; Tenke, Schroeder, Arezzo, & Vaughan, 1993). For example, Tenke et al. (1993) used simulation to demonstrate that contributions from both thalamocortical axons and lamina 4C stellate cell activity in monkey striate cortex are needed to account for measured CSD profiles for visual evoked potentials.

3.3. Models of dynamics and functional integration

It should be clear by now that there is a close relationship between models of neuronal dynamics and the models used to analyze brain imaging data. In the following subsections we will consider modeling initiatives at three different levels or scales; microscopic, mesoscopic and macroscopic. All have very useful but complementary roles, which highlight the variety of approaches that can be taken to characterize the induction and orchestration of brain activity.

3.3.1. Microscopic approaches

These approaches rest upon detailed, biologically plausible, neuronal models that adhere, as closely as possible, to known neuronal physiology (e.g. Erb & Aertsen, 1992). The idea behind these approaches is to embody detailed cellular and electrochemical dynamics in models of neurons and neuronal populations so as to explore emergent behaviors that can be seen empirically. They normally employ differential equations and as many of the system's state variables as possible. The advantage of this approach is that the mechanistic underpinning of any emergent behavior can be evaluated in terms of simulated neurophysiological processes, where these processes may not be directly observable in vivo. The disadvantage of these models is that their validity cannot always be established using empirical observations. A nice example of this sort of approach that relates to neuroimaging is provided by the work of Chawla, Lumer, and Friston (1999a); see also Aertsen, Erb, and Palm (1994). These authors used detailed simulations of interacting neuronal populations, with Hodgkin Huxley-like dynamics, to explore the relationship between synchronization and mean synaptic activity. The aim was to establish some principles that could relate fast reciprocal exchanges among cortical areas to synchronization in the local field potentials (and EEG), and finally to the integrated measures of synaptic activity provided by neuroimaging. The key observation that derived from this modeling was that synchronization is necessarily associated with increases in mean synaptic activity (see Riehle, Grun, Diesmann, & Aertsen, 1997 for an empirical study of this issue). The mechanism is simple and compelling: in order for synchrony to be maintained, the effective membrane time constants of postsynaptic responses to inputs from other populations has to be small (i.e. express relatively high synchronous gain). Small time constants are associated with leaky membranes, induced by balanced increases in excitatory and inhibitory synaptic inputs. Put in another way, increases in mean synaptic activity increase membrane conductances, reduce effective time constants and preclude anything other than synchronous interactions. This sort of mechanism can be used to posit a relationship between rCBF (mean synaptic activity) and EEG (an index of synchronization). Increases in synchronous interactions with distant populations represent one way in which the effective connectivity among populations can be increased. If this is the case, then the mean synaptic activity may modulate the effective connection strength of afferents or sensitivity to inputs. This hypothesis was tested empirically, using fMRI and attention to visual motion, to show that increased responsiveness of V5 was indeed predicted by baseline activity (Chawla, Rees, & Friston, 1999b).

3.3.2. Mesoscopic approaches

Often one would like to use empirical data to constrain neuronal models. The problem is that very often we cannot directly observe all the 'hidden' state variables one would like to include in the model. However, there is a fundamental equivalence in dynamical systems theory that allows one to circumvent this problem. This equivalence provides the basis for: (i) the application of nonlinear system identification techniques to EEG and MEG data; and (ii) engenders the concept of 'neuronal transients'. The fundamental equivalence (Fliess, Lamnabhi, & Lamnabhi-Lagarrigue, 1983) referred to above relies on the fact that any nonlinear dynamical system, framed in terms of its inputs, its (possibly hidden) state variables and its outputs, can be represented in two equivalent ways. The first is in terms of the differential equations that govern the dynamics of the state variables and the second is in terms of the nonlinear convolution of the inputs that reproduce the outputs. The latter is usually formulated as a Volterra-series expansion of the inputs and is a function of the inputs at the present time and the recent past (Bendat, 1990). The critical thing to note here is that the first representation requires the state variables themselves (e.g. the depolarization of membranes in all cell compartments, the configuration of every channel, the phosphorylation status of every enzyme, the expression of every gene product and so on). However, the second

representation only needs the recent history of inputs, which are generally observable (i.e. the activity in distal populations delivering afferent input). By adopting the second representation we immediately arrive at two very important facts (Friston, 2000). Firstly the integration of connected neuronal systems can be formulated as a Volterra-series model of effective connectivity and secondly the only thing we need to know about neuronal dynamics is the recent history of activity in each constituent population or area (see also Stevens, 1994). This recent history is referred to as a 'neuronal transient' (Friston, 1995). By focusing on the population's input–output relationships one eschews the un-observable microscopic hidden variables and moves to a mesoscopic level of modeling. The disadvantage of mesoscopic modeling is that a 'black-boxness' is ascribed to the interacting components of the model. On the other hand, the advantages of being able to use empirical data in the models, or indeed use the models as the basis of an analysis, are profound.

The first thing about dynamical models of functional integration at the mesoscopic level is that they must have a Volterra-series formulation. In fact the model assumed in structural equation modeling is a limiting case (first order and instantaneous) of the Volterra model. Nonlinear models such as those employed in psychophysiological interactions (Friston et al., 1997) are again special cases that include second order terms but, like structural equation modeling, ignore the recent history. The explicit use of Volterra-series to model effective connectivity, in particular its nonlinear and dynamical aspects, is now being established in both MEG (e.g. Friston, 2000) and fMRI (e.g. Friston & Büchel, 2000).

The second thing that transpires at this level of modeling is the central role of neuronal transients — a characterization of neuronal dynamics that necessarily encompasses an extended temporal domain. The concept of neuronal transients is of course not new (cf. Abeles et al., 1995; von der Malsburg, 1985), but in the present context, leads to some important questions about the way one measures functional integration with EEG or MEG: neuronal transients in two coupled regions may mutually induce themselves but have very different temporal forms. This difference means that their frequency structure may differ, leading to a coupling in the expression of different frequencies in the two brain regions. This cross-frequency coupling is a hallmark of nonlinear coupling. In linear coupling only the same frequencies are correlated where, conventionally, these within-frequency couplings have been assessed using coherence analyses. Recently there has been a move away from coherence analyses towards models that try to capture nonlinear coupling. This has engendered a renaissance in the use EEG and MEG to address functional integration in the brain (e.g. Bressler, Coppola, & Nakamura, 1993; Friston, 2000; Muller-Gerking et al., 1996; Schiff, So, Chang, Burke, & Sauer, 1996).

3.3.3. Macroscopic approaches

We have focused above on the distinction between microscopic and mesoscopic levels of description. The macroscopic level is reserved for approaches, exemplified by synergistics (Haken, 1983, 1996), that try to characterize the spatiotemporal evolution of brain dynamics in terms of a small number of macroscopic order parameters (see Kelso, 1995 for an engaging exposition). For example, macroscopic variables can be extracted from large-scale observations, such as MEG, using the order parameter concept: order parameters are created and determined by the co-operation of microscopic quantities and yet, at the same time, govern the behavior of the whole system. Interested readers are referred to Jirsa, Friedrich, and Haken (1995) for a nice example. At this level of modeling the objective is to characterize and classify the emergent dynamics by looking for spatial modes of activity with temporal dynamics that can be explained by low-dimensional dynamical systems. This allows the inherent dynamical architecture of the system to be defined and is very appealing in that it aims to identify the essential structure of the system that can explain its behavior. The disadvantage is that the connection with more mechanistically grounded microscopic levels of description is generally difficult to establish.

4. Final remarks

Our overview of the field has hopefully demonstrated a number of key points. First, functional brain imaging is an area of neuroscience research that is rich with complex data, complex in both the temporal and spatial domain. These data allow one to investigate the neural basis for human sensory, motor, emotional and cognitive function. The second point is that this very richness precludes easy understanding and engenders the need for an equally rich computational approach to data analysis, and equally important, data interpretation. The third point is that computational modeling of functional brain imaging data can occur at multiple levels (microscopic, mesoscopic and macroscopic), which leads to the fourth point: namely, bridging models will be necessary to tie together all these approaches into coherent and consistent accounts of brain function. Our final point is that computational modeling and functional brain imaging data are at the beginning of a deep and strong relationship. We hope the papers presented in this issue act to motivate further ties between these two fields.

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