1365

V

Neuroimaging
and Brain Research

Neuroimaging is an important technique for studying the neurobiological underpinnings of reading, reading disorders, and reading intervention. Children who have been identified as being at risk for reading difficulties or who display difficulties later in the development of reading abilities have participated in noninvasive neuroimaging studies before and after interventions or while taking part in remediation programs. Neuroimaging is a tool that enhances what scientists learn in behavioral studies about how reading develops or does not develop and helps researchers and educators understand the links between brain and behavior as they continue to study reading and reading disability. The goal of these neuroimaging studies is to determine 1) differences in brain function that accompany reading disability versus reading proficiency and 2) the effects of well-designed instruction on both reading and brain development. Section V of this volume presents the brain research on reading. Reading is a complex cognitive activity that requires the coordination and integration of many skills. What educators do is literally change how the brain functions! That clearly highlights not only the excitement but also the awesome responsibility that lies in teaching children to read. And, these changes can be found in images of the brain while individuals are performing reading tasks. The science that has developed this evidence is functional neuroimaging. In Chapter 16, Andrew C. Papanicolaou, Kenneth R. Pugh, Panagiotis G. Simos, and W. Einar Mencl, four neuropsychologists who conduct neuroimaging research in reading, explain two major types of functional neuroimaging: magnetoencephalography

(MEG) and functional magnetic resonance imaging (fMRI). They also give illustrations of how these technologies are used to study reading and discuss processes that children use in compensating for reading disabilities.

In Chapter 17, Sally E. Shaywitz and Bennett A. Shaywitz demonstrate the application of fMRI technology in studying the development of reading over time. They present data from the Connecticut Longitudinal Study, in which they have followed students from kindergarten into young adulthood. The fMRI data they present demonstrate differences in brain activation in good and poor readers. In this chapter, the authors discuss the definition, history, and neurological bases of reading disabilities.

1365

16

Functional Brain Imaging

An Introduction to Concepts and Applications

ANDREW C. PAPANICOLAOU, KENNETH R. PUGH,
PANAGIOTIS G. SIMOS, AND W. EINAR MENCL

The purpose of this chapter is to outline two representative brain imaging methods, magnetoencephalography (MEG), otherwise known as magnetic source imaging (MSI), and functional magnetic resonance imaging (fMRI), both of which are used in research on reading. We also explain how researchers establish the correspondence between images of brain *activation* patterns obtained with each of these methods and psychological *functions*. MEG and MRI provide distinct but complementary information on those brain systems that support the development and expression of complex cognitive skills such as reading. This type of information is of particular importance in understanding the neurobiology of normal cognitive development; specific impairments in children with developmental brain disorders; and the ways in which targeted interventions might alter functional brain organization in these children, resulting in enhanced cognitive performance.

BASIC CONCEPTS

Baseline Activation

Activation is what functional images of the brain show. It represents biochemical and physiological events that are categorized as the neurophysiological processes of *metabolism* and *neural signaling*.

Metabolism includes changes in the regional rate and volume of blood, relative quantities of oxygen in the blood, rates of consumption of oxygen or glucose, and many other changes. Signaling among neurons mainly involves electrical currents that are sent between and within cells.

Some of these biochemical and physiological events are associated with electromagnetic signals that radiate from their point of origin inside the brain to its surface, where they can be recorded by special instruments. Because functional imaging does not change or affect these electromagnetic signals, it is considered *noninvasive*.

The processes of metabolism and of signaling are continuous, but the rates vary from one brain region to the other. In fact, each region has its own characteristic level of *baseline activation*. Obtaining the baseline activation profile is the easiest form of functional imaging because such profiles reflect the total amount of activation of each brain region, which remains more or less constant over time. Consequently, if one could view and measure directly the rate of metabolism or the rate of signaling of neurons in each part of the brain and plot it over time, one would likely arrive at a figure similar to Figure 16.1. Moreover, if one were to obtain, at different points in time, functional images of this activation profile, the images would be very similar, as shown in Figure 16.1.

The main use of functional images of baseline activity is to reveal malfunctions, or pathological deviations, from the expected baseline rates of metabolism and signaling of particular areas of the brain, either abnormally low (*hypoactivation*) or abnormally high (*hyperactivation*). There are two kinds of such deviations or malfunctions. The first is *chronic*, or constant over time, and the other is *phasic*, appearing intermittently at particular times. An example of chronic malfunction is Parkinson's disease, in which a particular brain area, the internal globus pallidus, is constantly hyperactive and its constituent neurons are signaling (and metabolizing) at high rates.

An example of a phasic malfunction is an epileptic discharge resulting in transient deviations from the normal level of activation of the affected structures. Such deviations may be captured in images taken when the deviations occur. The brain regions that function abnormally can then be identified by comparing those images with others taken before or after the abnormal episode.

Function-Specific Activation Patterns

Neuropsychologists are most interested in the functional images of activation patterns that are related to specific psychological
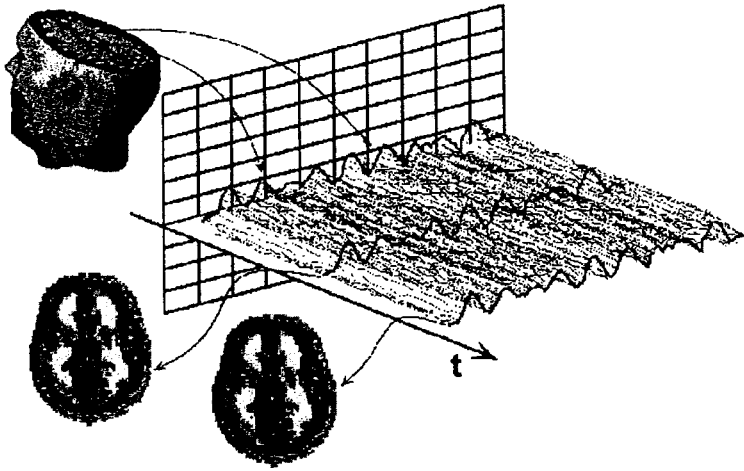
Figure 16.1. A schematic rendering of a hypothetical activation profile of a section of the brain. Each wavy line represents the degree of activation of each small region of the brain, as it changes slightly from moment to moment. This baseline profile of activation is represented here in stylized cross-section images that could have been obtained at two different points in time. Because the profile remains more or less constant over time, the functional images are almost identical. (From Pananicolaou, A.C. [1998]. *Fundamentals of functional brain imaging: A guide to the methods and their applications to psychology and behavioral neuroscience* [Fig. 2]. Lisse, The Netherlands: Swets & Zeitlinger; reprinted by permission.)

functions. This is because it seems that the correspondence between a given activation pattern and a given function reflects aspects of the neurophysiological mechanism necessary for each function.

A *function* is the process of production of a set of similar phenomena (whether subjective, e.g., perceptual experiences, or objective, e.g., movements) that serve a common purpose. A *brain mechanism* is a set of events that take place in particular brain areas in a particular order, resulting in the generation of the phenomena that define each function.

When the mechanism is operating, a particular pattern of activation occurs, but this pattern may be difficult to see because it is embedded in the global profile of the baseline activity. To separate out the activation pattern for this particular function, a laboratory situation must be set up to elicit that naturally occurring function on demand while the participant's brain activity is recorded. To do so, researchers may present stimuli of the same kind as those that naturally trigger the function and may instruct the participants to deal with the stimuli as they would under normal circumstances. The stimuli and the instructions constitute the experimental *task*. Typically, participants are asked to make an overt response (e.g., by

pressing a button, by speaking out loud) to indicate that they have processed each stimulus. If the stimuli and the task instructions do elicit the function, the task is said to be *ecologically valid* and capable of activating the brain mechanism of the function.

With appropriate tasks and analytic methods in place, scientists can, in principle, isolate brain areas that are associated with specific cognitive functions and their component processes. However, it is not quite that simple. Several issues must be considered when attempting to establish a meaningful link between cognitive systems and behavioral expression, on the one hand, and the underlying neurobiological mechanisms, on the other. First, there is good evidence that specific cognitive functions are represented in multiple areas of the brain that work together; this is referred to as *functional connectivity*. Therefore, it is important to try to describe the relative timing and coordination of these different areas for specific cognitive functions. These kinds of analyses can increase the psychological relevance of the neuroimaging studies. Moreover, in the context of pediatric neuroimaging research, it is important to develop protocols that permit the examination of change within an individual over time. Finally, a better understanding is needed of variation in competence in cognitive domains such as reading, attention, or math, in relation to variation in brain circuitry. Imaging studies take on greater relevance when relevant brain–behavior correlations can be established. Essentially, researchers seek to account for individual differences in behavioral performance and individual differences in the underlying circuits that support these behaviors. In the following sections, we explain the basics of current brain imaging techniques and then consider their application to reading development and reading disability (RD).

MAGNETOENCEPHALOGRAPHY

The Nature of Activation Imaged

Signaling among neurons constitutes one of the basic forms of activation that can be imaged with the current brain imaging methods. It consists of electrochemical events that take place at the synapses and in the axons and dendrites of neurons. With the exception of

the phenomenon of neurotransmitter release and uptake, which does not directly involve electrical activity, neuron activation involves flow of electrically charged particles, or ions, which results in electrical current.

If one could directly view the variation of the electrical currents at every set of cells in the brain and plot these variations as a function of time, one would obtain the typical picture of activation shown in Figure 16.1. Let us then assume that a set of cells that are typically not synchronized begin to signal in unison. This can take place, for instance, with a delay (e.g., 200 milliseconds) after the presentation of an external stimulus (e.g., a printed word). The cells' combined electrical currents will create a large deviation from the baseline level of activity. In such cases, using MEG can help provide answers to questions such as where the source of this deviation is (i.e., which part of the brain hosts the activated neurons). Needless to say, the pattern of activation of the brain itself is hidden from view. Researchers have only indirect access; they are limited to recording electromagnetic energy that can travel outside the head, as shown in Figure 16.2. This energy is called *magnetic flux.*
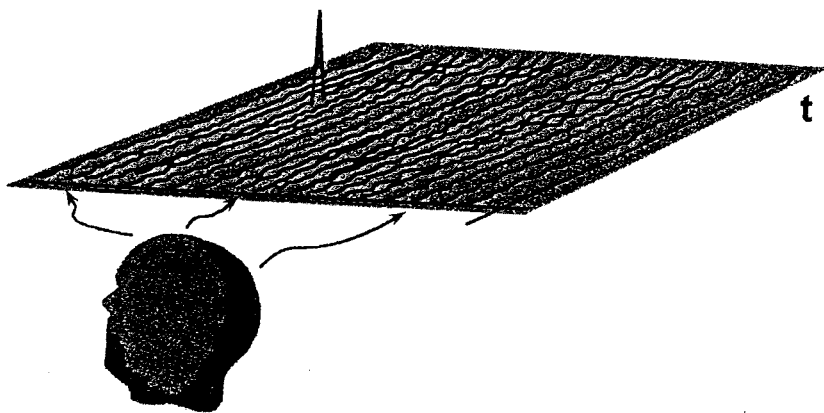

Figure 16.2. A schematic rendering of the electromagnetic signals recorded on the head surface that echo the electrical currents inside the brain. A transient deviation in electromagnetic signal intensity over a particular region of the head surface reflects the coordinated signaling activity of a large set of neurons somewhere in the brain. (From Pananicolaou, A.C. [1998]. *Fundamentals of functional brain imaging: A guide to the methods and their applications to psychology and behavioral neuroscience* [Fig.10]. Lisse, The Netherlands: Swets & Zeitlinger; reprinted by permission.)

Recording Magnetic Flux

Magnetic flux is recorded using superconducting loops of wire positioned over the head surface. With enough magnetic sensors placed over the entire head surface, the shape of the entire distribution of magnetic flux created by a brain activity source can be determined. Based on the surface flux distribution, the position and strength of the brain source (or activated brain region) that produced the flux can be estimated. The activated brain region is identified using three *fiducial points* that are defined on the participant's head surface. Usually these are clear anatomical landmarks, such as the ridge of the nose and the ear canals.

These reference points define a system of three coordinate axes (x, y, and z) that intersect somewhere near the center of the head. The position and orientation of the source of the magnetic flux is defined with reference to this coordinate system. Usually, markers are attached on these three points, and a structural MRI is taken, either before or after the MEG recording session. The positions of the markers are visible on the MRI scans, which helps the researcher determine the relative position of all brain structures with respect to the position of the source of activity. This process is known as *co-registration* of the MEG-derived active source on the structural MRI.

The Averaging Procedure

Since the early 1980s, advances in electronics and software used to reduce the contribution of extraneous sources of magnetic flux to the MEG data have made it possible to detect changes in magnetic flux associated with the presentation of a single stimulus, such as a printed word. Additional procedures are often used, however, to extract activation patterns specific to particular brain functions that are embedded in the global, baseline activation profile. In the case of MEG, such extraction is accomplished with an averaging procedure that is helpful when the amount of neural signaling for a particular function that differs from the baseline is very small. The output of this procedure is an event-related magnetic response or field (ERF), a time-varying record of magnetic flux at each of several recording locations (usually 148–300) around the head, as shown in Figure 16.3.
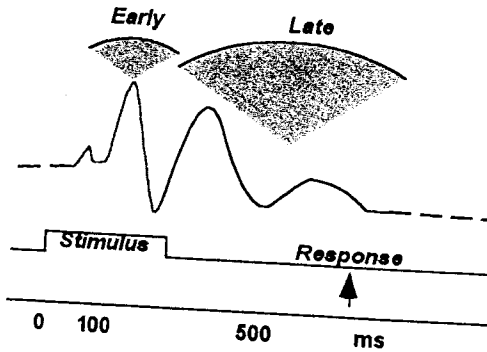
Figure 16.3. Averaged event-related magnetic field (ERF) in response to auditory or visual stimuli. Stimulus onset (set at 0 milliseconds [ms]) determines the onset of the ERF, which consists of an early (sensory) portion and a late portion. The participant's mean (behavioral) response time is indicated by the arrow.

The early portion of the ERF corresponds to activation of the sensory cortex specific to each type of stimulus (i.e., visual, auditory), enabling researchers to identify simple sensory functions. In contrast, late portions of the ERF reflect activation of the association cortex. By mapping late activity, the brain circuits that support higher cognitive functions can be studied in real time, *as* the stimulus is processed and *before* a response is made by the participant.

By analyzing the surface distribution of the averaged flux at several time points, scientists can identify the brain regions that produce the recorded magnetic activity. In this way, the source(s) that account for the recorded magnetic flux at each time point can be calculated and projected onto the structural images of the brain. Figure 16.4 shows some examples of functional images for different simple sensory functions.

The same general procedure is used to extract the activity specific to a more complex cognitive function. For example, to image the mechanism of verbal memory, the researcher may present spoken or printed word stimuli to participants with instructions to, say, identify words that occur more than once in a session. If the study is successful, the early portion of the ERF should be accounted for by sources in the primary auditory cortex, whereas the sources that account for the late portions of the ERF should outline the mechanism of the function that was produced in response to the task, in this case verbal episodic memory.
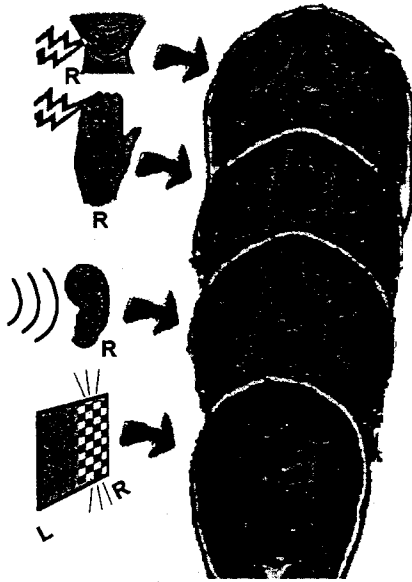
Figure 16.4. Typical magnetoencephalography (MEG) images displaying neurophysiological activity related to somatic, auditory, and visual sensation. Dark patches represent the location of the sources of magnetic flux observed briefly (< 0.1 seconds) after the presentation of a somatic stimulus (parietal cortex), an auditory stimulus (temporal cortex), or a visual stimulus (occipital cortex).

FUNCTIONAL MAGNETIC RESONANCE IMAGING

The Nature of Activation Imaged

As mentioned previously, there are two basic types of brain activation: neural signaling and metabolism. The rate of metabolism varies as much as the rate of signaling. Metabolic rate varies first from one type of tissue to another and second within a given tissue sample, depending on the amount of work the brain tissue performs. Because the main type of work neurons perform is signaling, changes in the rate of signaling are correlated with changes in the metabolic rates of neurons.

The sequence of physiological processes that are observed in functional magnetic resonance images can be summarized as follows: If a particular sample of tissue (set of neurons) engages in increased signaling, its metabolic rate increases, causing the brain to consume more oxygen; this increased oxygen consumption in

turn causes lower amounts of hemoglobin (oxygenated blood) in that area. This change in the concentration of hemoglobin becomes apparent about 2 seconds after the increase in the signaling rate. Next, the reduction of hemoglobin triggers a vascular reaction resulting in an oversupply of oxygenated blood to that tissue sample 5-8 seconds later.

Recording Functional Magnetic Resonance Images

Scientists cannot directly view the levels of hemoglobin in brain tissue. The presence of hemoglobin, however, is associated with the presence of hydrogen atoms that produce electromagnetic energy. Recording these signals from hydrogen atoms enables scientists to estimate the distribution of hemoglobin throughout the brain and represent it in images. Electromagnetic energy associated with hydrogen atoms can be recorded by placing the head inside a very strong magnetic field, which is produced by an electromagnetic coil. This device is the same as the one used to obtain structural images of the rest of the body for diagnostic purposes.

Using different combinations of magnetic coils placed around the head, researchers are able to arrange the shape of the magnetic field so that every region of space or element of space (voxel) inside the MR magnet has a slightly different and unique value. Using this information, researchers are able to identify specific brain areas having abnormally high or low baseline activation. Activation that is specific to particular functions, however, requires additional procedures to be extracted from the global, baseline activation.

## The Hemodynamic Response Function

Unlike the responses obtained by MEG, the blood oxygen level dependent (BOLD) response measured by fMRI reflects physiological changes that take place in the brain shortly after a particular cognitive function has already taken place. In response to a single stimulus event, this hemodynamic response function typically begins rising from baseline at approximately 2 seconds post-stimulus, rises to its peak at approximately 5 seconds, and slowly returns to baseline by approximately 16 seconds. Differences in the response magnitude between tasks or groups are assumed to reflect the relative increases

(or decreases) in the underlying neural activity. Statistical analysis is employed to identify those differences that are reliable and replicable.

The Integration and Subtraction Procedure

General pattern extraction for fMRI involves the procedures of *integration* and *subtraction*. Although the stimuli during fMRI may be presented at the same rate as for MEG, in fMRI recording of the electromagnetic signals must be made over a longer time span that includes enough time to obtain the requisite number of electromagnetic signals to construct an image before, during, and/or after the participant performs a task repeatedly, as shown in Figure 16.5.

Researchers, however, are not able to see any systematic difference in the segments of the *during* patterns because that pattern is contained in and fused with the ongoing global activation or baseline activity that corresponds to all functions concurrently performed by the brain. It is assumed that the *before* and *after* periods do not include the function of interest. Thus, the *before* and *after* images should be nearly the same and the activity of the brain during those
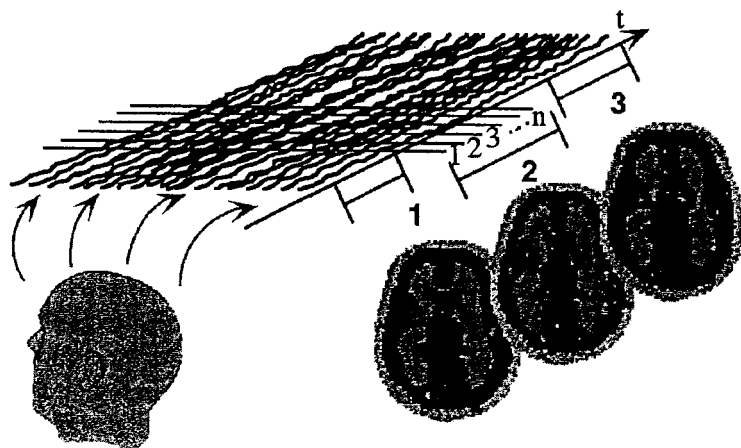
Figure 16.5. Electromagnetic signals recorded with functional magnetic resonance imaging (fMRI) over time intervals 1) before, 2) during, and 3) after the presentation of stimuli (the onset of which are indicated by horizontal lines). Signals recorded during each interval are integrated to construct a functional (or activation) image. (From Pananicolaou, A.C. [1998]. *Fundamentals of functional brain imaging: A guide to the methods and their applications to psychology and behavioral neuroscience* [Fig. 61]. Lisse, Netherlands: Swets & Zeitlinger; reprinted by permission.)

periods should also be present as background during the task perfor-
mance. Because it is further assumed that the background global
activation and the function-specific pattern are independent, they
should be able to be separated by simple subtraction. Subtracting
either the *before* or the *after* image from the *during* image, therefore,
gives the activation pattern for the performance of the function.

Usually, the *before* and *after* images are not exactly the same
because the baseline state of the participant rarely stays the same
over long periods of time. Consequently, the subtracted image of
the function-specific pattern may also be different. Therefore, these
baseline and functional images are obtained several times to assess
the reliability of the task-related difference relative to changes in
baseline state (integration of images). How a researcher obtains a
stable background activation image (also known as the problem of
obtaining the appropriate control image) is of great importance, espe-
cially when complex functions are concerned.

The General Linear Model

In the vast majority of cases, the statistical significance of differences
between experimental conditions (e.g., different types of stimuli,
tasks, and instructions to participants) or groups are assessed using
the general linear model, or GLM, a broad formalization that includes
more familiar analysis techniques such as analysis of variance
(ANOVA) and multiple regression (Frackowiak, Friston, Frith,
Dolan, & Mazziotta, 1997; Hays, 1998; Kirk, 1982). This approach
is linear in that data are modeled as a linear combination of a set of
predictor variables, plus variance caused by the systematic influence
of unknown variables (e.g., fatigue) or by random fluctuations of
brain activity over time (which are referred to as *noise* in the activa-
tion patterns). For a single participant, these variables typically indi-
cate which stimuli he or she received and which task the participant
was performing at each point in time throughout image acquisition.
Across participants, these predictor variables often include scores
on behavioral tests or reflect clinical group membership or demo-
graphic status.

The vast majority of early fMRI studies employed *block* designs,
characterized by the alternating presentation of one or more experi-
mental conditions (e.g., two types of print) with a control condition

(e.g., rest, fixation) across blocks. Each block of the experiment (whether it contains the experimental or the control condition) lasts for a relatively long period (typically 20–40 seconds). Within each block, multiple trials are presented, but these trials are from a single experimental condition only. In this type of design, the intensity of the electromagnetic signal measured from each brain area is averaged across the entire set of trials composing a single block. Then differences among experimental conditions, or between each experimental condition and the control condition, are assessed for each brain area separately, and a functional image reflecting these differences (or lack thereof) is constructed.

Recently, event-related designs have gained substantial popularity in the imaging field following advances in analysis methods. This technique allows the BOLD responses associated with a specific stimulus event to be examined on a trial-by-trial basis. In this case, signal intensity is integrated over a shorter period of time, usually 2–3 seconds, which is a substantial improvement over the 20- to 40-second integration time of block designs.

Across-Subjects Analysis

Computing probability values within a single participant allows generalization of results only to the population of repeated scans within that same participant. Under certain circumstances, such as in case studies, this kind of generalization may actually be useful. In the more typical situation, however, researchers wish to know whether an effect measured in the current sample can be generalized to the population from which the sample was originally drawn (e.g., the entire population of proficient readers). For practical and computational reasons, the direct test of a specific hypothesis commonly involves a two-step procedure: First the size of the effect of interest (the parameter estimate) is obtained separately for each participant, and then the reliability of these estimates is assessed across participants using GLM analyses (Holmes & Friston, 1998; Kirk, 1982; Woods, 1996).

Brain–Behavior Analysis

Primary analyses inevitably compare activation levels across tasks or groups. These are extended with brain–behavior analyses, in which

the goal is to predict behavioral performance from brain activity levels. Because both behavioral performance and brain activity levels are measured (dependent) variables, the researcher can indicate whether the two are associated but cannot make claims about the true direction of causality. For each voxel, the correlation between the behavioral score and the activation level is computed across the sample. Areas where activity significantly correlates with the behavioral score exhibit (at least) a continuous linear relationship, in the sense that greater activity in a particular brain area or areas is associated with better performance on the experimental task.

Functional Connectivity Analysis

The univariate techniques just described, although useful for detecting localized effects, fail to take into account a basic characteristic of the brain, namely, that any complex function is determined by the interaction of many parts of the brain. The goal of connectivity analyses is to understand the causal influence, or *effective connectivity*, that each brain region exerts on every other (Friston, 1994; McIntosh, Nyberg, Bookstein, & Tulving, 1997). Although this influence is not measured directly, the correlations between activity measures of pairs of brain regions can be readily quantified; these correlations are measures of *functional connectivity* and serve as the basis for functional connectivity analysis.

There are two general approaches to assessing functional connectivity: within subjects and across subjects. Within-subject connectivity analyses quantify region-to-region correlations over time, often within a given task (Biswal, Yetkin, Haughton, & Hyde, 1995; Hampson, Peterson, Skudlarski, Gatenby, & Gore, 2002; Lowe, Mock, & Sorenson, 1998). A high correlation between two regions means that their activity levels tend to fluctuate up and down together over time, implying that one may affect the other (either directly or indirectly). Although within-subject connectivity analyses can theoretically provide the most direct evidence of interregional cooperation within a single brain, it also brings distinct challenges to analysis. Because the hemodynamic response function is slightly different from region to region, two regions whose signal intensities are highly correlated may not in fact exhibit a strong correlation in their BOLD time courses. Across-subject measures of

functional connectivity deal with this problem by first extracting measures of activation from each participant, then computing region-to-region correlations across subjects (Horwitz et al., 1992; McIntosh et al., 1997; Pugh, Mencl, Shaywitz, et al., 2000). Strong correlations indicate that these regions tend to be activated in concert, which implies that they function together as part of an integrated functional network.

Multivariate Analysis

Analyses mentioned thus far have been either purely univariate (i.e., t-test, ANOVA) or bivariate (i.e., multiple regression, brain–behavior correlation, interregional correlation). True multivariate analyses simultaneously assess activations across a larger number of regions or the entire brain, in an attempt to understand the neural systems underlying behavior. A wide range of methods have been employed, including principal components analysis/independent components analysis (PCA/ICA) and multivariate analysis of variance (MANOVA); here, we briefly describe one particular method, partial least squares (PLS).

PLS is a regression-based method with multiple applications in neuroimaging (McIntosh, Bookstein, Haxby, & Grady, 1996; McIntosh et al., 1997; Mencl et al., 2000). Various forms of PLS are employed to assess different questions, although the underlying mathematics is similar. In short, a *data matrix* of activation values is constructed, consisting of one row for each participant and/or experimental condition and one column for each region or voxel measured. A design matrix is also created, coding predictors of interest, typically task contrasts or behavioral scores. The data are correlated with the design matrix to create a cross-correlation matrix of each region with each effect. This (typically large) set of correlations is subjected to singular value decomposition, which consolidates the covariance into a small set of components of ordered importance. Each component can be described by *brain loadings*, which identify how strongly each region participates in the component, and *design loadings*, which indicate how strongly each predictor participates in the component.

In task PLS, the goal is to identify a small set of brain-wide images that optimally discriminate the activation differences among

a set of tasks (McIntosh et al., 1996). Here, the design matrix is composed of orthogonal regressors that contrast task effects. Each extracted component identifies a set of (often distributed) regions that show a similar response pattern (brain loadings) to a particular linear combination, or contrast, among the tasks (design loadings). In brain–behavior PLS, the goal is to identify a set of brain-wide images that optimally correlate with exogenous predictor variables, typically behavioral scores or demographic variables (McIntosh et al., 1996; Mencl et al., 2000). The design matrix is composed of one or more behavioral variables, and extracted components identify sets of regions that correlate similarly to the behavioral predictors and/or contrasts among the behavioral predictors. Last, seed voxel PLS builds on the bivariate approach to determining functional connectivity (McIntosh et al., 1997). One or more source regions are selected, and the activation values for these regions are entered as predictors in the design matrix. Extracted components identify sets of other regions that correlate similarly to the seed regions and identify whether these correlations are similar or different across the tasks. Each of these variants exemplifies the shift in focus from analysis of individual voxels or regions to analysis of brain-wide patterns of activity.

APPLICATIONS OF FUNCTIONAL IMAGING

A Typical Neuropsychological Study

Most psychological functions are complex, involving a series of interconnected cognitive operations, although how many depends on the particular theory being investigated. For example, it can be claimed that for a person to understand the meaning of words heard, first acoustic analysis is necessary for determining the physical features of the word stimuli, then phonological analysis is needed for identifying the language-relevant features, and finally semantic analysis (also involving memory) is used for identifying the meaning of the set of phonological features that constitute each spoken word. Now, to find the activation pattern specific to each cognitive operation, an experimental design involving more than just one control task is necessary.

An activation pattern may be recorded using a brain imaging technique while participants listen to words and indicate by means of some discriminant response that they comprehend the words' meaning. That pattern is supposed to contain activity specific to the semantic (S), the phonological (P), and the acoustic (A) processes, as well as activity due to the rest of the ongoing or baseline processes (R) performed by the brain. Therefore, the pattern obtained during the task would be a composite of subpatterns S + A + P + R.

A second activation pattern may then be recorded while the participants listen to the same words but are now told to ignore what the words mean, to attend to some of the words' phonological features instead, and to respond each time they hear a word that contains a particular phoneme combination (e.g., /rt/ as in *cart*). This second pattern is supposed to contain all of the component operation-specific patterns the first one did, except for the pattern specific to the semantic analysis operation; consequently, the second pattern would be a composite of subpatterns P + A + R.

Then, a third activation pattern can be obtained while the participants hear the same words but are told to ignore everything else about them, attend exclusively to the words' acoustic features (e.g., relative loudness), and respond each time they hear a word played at a slightly lower volume than the rest of the stimuli. In this case, the pattern is supposed to consist of only the activity specific to acoustic processing plus any additional ongoing processes that may take place concurrently, namely subpatterns A + R.

Assuming that all three experimental tasks required the same level of alertness and effort and that they were completed to the same degree of accuracy, one may subtract the second from the first (i.e., [S + P + A + R] − [P + A + R]) to obtain the activation profile specific to the semantic analysis operation (S), and the third from the second (i.e., [P + A + R] − [A + R]) to obtain the activation profile specific to the phonological analysis operation (P). To obtain the sign of the acoustic function (A), we would need an additional task involving ongoing processes (R) but not the acoustic function. We would perform the subtraction once again (i.e., [A + R] − R) to obtain the activation profile specific to the acoustic analysis operation.

It is obvious that for this scheme to work, the different functions postulated must be independent of each other, involving clearly separate mechanisms. These assumptions are not always true, and in some cases alternative (e.g., factorial, parametric) designs are

desirable (Friston, Zarahn, Josephs, Henson, & Dale, 1999; Pugh et al., 1996).

Uses of Function-Specific Activation Patterns

Function-specific activation patterns can and have been used to explore possible differences in brain mechanisms of particular functions in groups of individuals that differ in some prominent physiological or psychological characteristic, for example, gender, age, or presence or absence of learning disability. Here again, the validity of the functional images and the relative difficulty in establishing validity depend on whether individuals can be assigned unequivocally to a particular category, the degree to which the mechanism of the particular function is known, and whether individuals in the compared groups can perform the same function with equal ease. We discuss in some detail two examples of this type of application of functional imaging—gender differences and differences between children with RD and typically developing children—to illustrate this application's utility and the requirements for establishing its validity.

Research findings suggest that there are reasons to hypothesize that the brain mechanisms of language involve left hemisphere structures in men and both left and right hemisphere structures in women. Such a hypothesis and others of the same type can be readily evaluated through functional imaging. The requirements for evaluating them correctly, that is, in a manner that would allow reasonable interpretation of the results, are as follows.

First, all members of each group need to possess the characteristic on the basis of which they are classified together. In this example of hemisphere use in men and women, this requirement is perfectly satisfied because gender is usually unequivocal.

The second requirement is that no other prominent characteristic distinguishes the members of the two groups. If that requirement is not met, for instance, if several men in the group have cognitive impairments and some of the women are creative writers by occupation, any difference that may be found in the brain activation patterns of the two groups could not be uniquely attributed to gender. In general, this second requirement can be met only approximately; it is always possible to find characteristics that differ between any two groups of individuals besides the characteristic that defines the

group. For example, the members of the two groups could differ in height, weight, eye color, or some other trait. Thus, although it is not possible to select group members who are identical in everything except the group-defining characteristic, it is possible to select them such that they do not differ appreciably in a characteristic relevant to linguistic competence.

The third requirement is that members of both groups must be able to perform the same language task with equal ease and efficiency. Obviously the odds for doing so are better if the general level of group members' linguistic competence is approximately equal. If it is not, then to perform the same task, group members will have to exert different degrees of effort or will be more or less alert during the task. Both of these factors may affect group members' brain activation profile and either obscure, exaggerate, or modify possible differences in the language-specific activation patterns.

Each individual in each group may undergo imaging during a task believed to represent effectively the function of language. Assuming that the fidelity of these patterns is deemed satisfactory, one can examine whether the hypothesis is correct that the signs of the language mechanism in men are different from those in women. A quick way of estimating this is to average all of the patterns of men and to average all of those of the women to see whether there is an overall difference. Assuming that there is, one next has to establish whether the difference seen in the average patterns is a real or a circumstantial one. Any time that patterns are averaged, some pattern will be obtained. To verify that the patterns are not arbitrary, one can either compare the activation patterns of several individual men and women with the average patterns of their group (given that it is impossible to test all men and women on the planet) or examine whether the averaged group patterns reappear in replications of the study with the same or with different groups of individuals.

In some cases, function-specific patterns that characterize particular diagnostic groups are visibly similar across members of the group and clearly different from those of nonmembers (see Figure 16.A at http://www.brookespublishing.com/mccardlemris). But even when reliable distinctions among brain activation profiles, consistent with expectations, can be obtained, these distinctions do not necessarily imply that brain activation profiles can be used to identify a particular disorder. To claim that a particular atypical activation profile is useful in identifying a particular condition, a researcher

must first demonstrate that individual participants can be correctly assigned to diagnostic categories solely on the basis of their functional images. Though as of 2004, no claims to that effect have been made directly, it is quite possible that with constant improvements in the fidelity of images, researchers may soon be able to do so.

Criteria for Establishing Function-Specific Activation Profiles

To describe the brain circuits that support any cognitive function, such as reading, in a comprehensive and accurate manner, every functional imaging method must be capable of providing the following:

1. Information regarding brain areas that show *increased levels* of neurophysiological activation during experimental tasks that exemplify the cognitive function under investigation

2. *Real-time* data regarding the temporal course of regional activation

3. Activation protocols that produce reproducible spatiotemporal activation profiles *both within and across individuals*

4. Independent confirmation, preferably from invasive functional brain mapping, that at least some components of the activation maps obtained with a particular task and data reduction protocol are *essential* for the performance of that task

5. Information on how brain activity measures relate to individual *performance* in these tasks

Although as of 2004 fMRI can address several of these criteria, only MEG has been able to address all five. Each method has limitations and advantages. The capacity to establish significant correlations between measures of brain activation and measures of behaviors only one of several pieces of evidence that establish the external validity of functional brain imaging data. Given that knowledge regarding the neurological basis of developmental conditions, such as reading or math disability, can have serious repercussions for educational policy, establishing that brain imaging procedures meet the above criteria is crucial. Several studies supporting the validity of MEG activation and analysis protocols have been successfully completed thus far (Breier et al., 2001; Breier, Simos, Zouridakis,

Wheless, et al., 1999; Castillo, Simos, Venkataraman, Breier, & Papa-
nicolaou, 2001; Maestú et al., 2002; Simos, Breier, et al., 2002; Simos,
Breier, et al., 1999; Simos, Breier, Wheless, et al., 2000; Simos, Breier,
Zouridakis, & Papanicolaou, 1998; Simos, Papanicolaou, et al., 1999;
Szymanski et al., 2001). Given that these studies have established
the overall scientific merit of imaging procedures (in this case, MEG
imaging protocols), researchers can now proceed to apply them to
the study of brain function related to education.

NEUROBIOLOGICAL STUDIES
OF READING AND READING DISABILITY

For neuroimaging data to be relevant to reading development, links
must be established between behavioral and cognitive processes and
those neural systems that support these processes. Thus, neuroimag-
ing research must be informed by cognitive behavioral research from
the outset. Behavioral studies have characterized critical cognitive
processes necessary to acquire fluent reading, and how these pro-
cesses are deficient in individuals with RD. The core difficulty in
RD manifests itself as a deficiency within the language system and,
in particular, a deficiency at the level of phonological analysis. To
learn to read, a child must first develop an appreciation that sound
changes in words change meaning (phonemic awareness) and must
understand that written words, too, possess an internal phonological
structure that is mapped onto the corresponding spoken words
(alphabetic principle). As many studies have shown, phonemic
awareness is largely missing in children and adults with RD (Brady &
Shankweiler, 1991; Fletcher et al., 1994; Rieben & Perfetti, 1991;
Shankweiler et al., 1995; Stanovich & Siegel, 1994). Phonological
processing impairments persist into adulthood (Bruck, 1992; Felton,
Naylor, & Wood, 1990; Shaywitz et al., 1999), and instruction in
phonemic awareness promotes the acquisition of reading skills (see
Chapter 8; see also Ball & Blachman, 1991; Foorman, Francis,
Fletcher, Schatschneider, & Mehta, 1998; Torgesen, Morgan, &
Davis, 1992; and Wise & Olson, 1995).

Neuroimaging has been employed successfully in the area of
reading development, RD, and intervention (see Chapter 17; see also
Pugh, Mencl, Jenner, et al., 2000., and Sarkari et al., 2002, for
reviews). Studies that meet all of the criteria for scientific merit just
outlined provide a highly consistent but rather basic view of the
brain circuit that supports reading (Simos, Breier, et al., 2002; Simos

et al., 2001; Simos, Fletcher, Foorman, et al., 2002). The following regions show increased levels of activation consistently, both within and across different individuals, and therefore are likely to constitute indispensable components of the brain circuit that supports reading: the primary visual cortex (which is necessary for the initial visual analysis of print), the association visual cortex in the ventral temporo-occipital areas, the posterior portion of the superior temporal gyrus extending posteriorly into the supramarginal gyrus (Wernicke's area), and the inferior frontal gyrus (Broca's area). With the exception of primary visual cortex, where activation is noted bilaterally for printed stimuli presented in the center of the visual field, activity in all other areas is stronger in the left hemisphere in the majority of readers who have never experienced difficulties in learning to read, regardless of age. Parts of the middle temporal gyrus, including the cortex within the superior temporal sulcus, are also observed to be involved, especially when real words (as opposed to meaningless yet pronounceable letter strings) are used as stimuli. When the same criteria of inter- and intraindividual consistency are applied, less common activation is observed in the angular gyrus.

Once researchers had established the elementary features of the activation profile associated with word recognition, several research groups designed studies to go further, addressing the neurobiological basis of reading and RD using hemodynamic imaging techniques (Pugh et al., 1996; Shaywitz et al., 1998; Simos, Breier, et al., 2002). Although the imaging protocols employed in these studies may not fulfill all of the aforementioned criteria, the study investigators sought to overcome this problem by relying on intricate experimental design and analysis techniques. The ultimate goal of these research efforts was to determine the specific role of distinct components of the brain circuit that supports reading in adults and, in some cases, children, who experience difficulty in learning to read.

Data from this set of studies indicate that at least two distinct brain circuits are involved in skilled printed word recognition. One circuit may be involved in a slow, presumably effortful process of word recognition that is responsible for the recognition of novel and uncommon words (e.g., *turpentine*). The other is a later-developing, faster circuit that processes familiar printed words (e.g., *morning*). The two circuits involve different regions in the posterior part of the left hemisphere (which in the majority of right-handed people mediates language functions in general). A key component of the slow-acting circuit is Wernicke's area, a region that is also responsible for processing spoken words. The fast-acting recognition circuit,

on the other hand, consists mainly of brain areas specialized for complex visual processing in the base of the brain. In MEG studies, activity in these areas during reading tasks is observed earlier than activity in Wernicke's area (Breier, Simos, Zouridakis, & Papanicolaou, 1998, 1999; Simos et al., 2001). The two circuits operate in conjunction with another area whose primary function is the planning of speech (articulation), namely Broca's area, in the anterior part of the brain (Pugh, Mencl, Jenner, et al., 2000). A variety of technologies have contributed to these findings, including MEG; fMRI; and a third brain imaging technique, positron emission tomography, which can only be used with adult participants (Fiebach, Friederici, Muller, & Von Cramon, 2002; Helenius, Salmelin, Service, & Connolly, 1998; Pugh et al., 2000; Pugh et al., 1997; Rumsey et al., 1997; Shaywitz et al., 1998).

On the basis of the neurobiological data, Pugh, Mencl, Jenner, et al. (2000) have proposed a theory of word recognition in which word selection in the brain is determined by the faster circuit for common words and by the slower circuit for new or uncommon words. The two systems correspond (but only loosely) to the two routes of classical dual route theory (Coltheart, Curtis, Atkins, & Haller, 1993). Although imaging evidence supports the existence of dual routes, as of 2004 no compelling data suggest that the fast route involves direct activation of meaning, as proposed in some versions of dual route theory. Phonological representation of words may still be involved either in mediating the activation between orthography and meaning or as an obligatory consequence after the activation of meaning directly by orthography (Simos, Breier, et al., 2002).

With regard to the slower circuit, the neurobiological theory is consistent with the other major (dual route) theory in proposing that this slow process produces phonological representations generated by subword analysis. Previous evidence from imaging is consistent with this idea because there is a strong correlation between activation of the slower circuit and activation of Broca's area. Direct evidence supporting the critical role of the slower circuit in sub–word-level phonological analysis comes from an electrocortical stimulation study (Simos, Breier, Wheless, et al., 2000): Electrical interference with a small portion of Wernicke's area consistently impaired the patients' ability to decode pseudowords. Whereas this ability relies primarily on the slow route, the ability to read real words with exceptional spellings, which could be accomplished by the fast route, remained unaffected. There is also indirect evidence that Broca's

area and at least one other component of the slower circuit (the supramarginal gyrus) support subword phonological analysis. Activity in both regions is 1) stronger for pseudoword reading than for real words; 2) stronger for uncommon words than for common words; and 3) stronger for tasks, such as rhyme judgment, that require phonological analysis (Pugh et al., 1996).

Moreover, there is also evidence that beginning and early readers show activity in Wernicke's and Broca's areas but do not show substantial activity in the faster circuit, unlike more skilled readers (Booth et al., 2001; Shaywitz et al., 2002). When present, activity in visual processing areas in the base of the brain, which shows strong left hemisphere lateralization in adults, appears to be bilaterally symmetric in children, a finding consistent with the notion of a progressive specialization of the faster circuit in the left hemisphere with reading experience (Simos et al., 2001). Moreover, several studies have reported greater activation to real words than to pseudowords within the faster system, particularly at middle and inferior temporal sites (Fiebach et al., 2002; Tagamets, Novick, Chalmers, & Friedman, 2000). In addition, as discussed later in this chapter, the faster system's activation increases with age and reading skill (Shaywitz et al., 2002). A detailed discussion of the data supporting a processing distinction between the faster and slower circuits can be found in Pugh, Mencl, Jenner, et al. (2000).

Altered Circuits in Reading Disability

Readers with no impairment (NI) and readers with RD have clear functional differences with regard to the dorsal, ventral, and anterior sites discussed thus far. In readers with RD, a number of functional imaging studies have observed left hemisphere posterior dysfunction at both dorsal and ventral sites during phonological processing tasks (Brunswick, McCrory, Price, Frith, & Frith, 1999; Paulesu et al., 2001; Pugh, Mencl, Shaywitz, et al., 2000; Rumsey et al., 1997; Salmelin, Service, Kiesila, Uutela, & Salonen, 1996; Shaywitz et al., 1998; Shaywitz et al., 2002). This disruption is reflected by a relative underactivation of these circuits specifically in processing words and pseudowords, which requires decoding; this finding suggests a disruption of these regions in readers with RD. Indeed, a study using diffusion-weighted imaging analysis has documented anomalies in the nerve fiber pathways that connect Wernicke's area with the rest

of the brain, suggesting a possible mechanism for the often-seen functional anomalies, reflected, for example, in low reading scores (Klingberg et al., 2000).

The suspected functional deficit in posterior left hemisphere circuits can be observed with a high degree of consistency on a case-by-case basis, as suggested by the review of MEG data from a large group of children with severe reading difficulties imaged using protocols that meet the five criteria for scientific merit discussed previously (Sarkari et al., 2002). Underactivation in two key components of the slow circuit, Wernicke's area and the angular gyrus, is detectable as early as the end of kindergarten in children who have not reached important milestones in learning to read (Simos et al., 2003). In addition, the typical progression of activity from visual processing areas in the left hemisphere to mirror areas in the right hemisphere is reversed in children with more severe impairments. Complex statistical analyses show that intercorrelations between different component areas of the two circuits are low in readers with RD during word and pseudoword reading tasks but are strong in nonimpaired readers, suggesting a breakdown in the integrity of processing posterior left hemisphere regions (Pugh, Mencl, Shaywitz, et al., 2000; see also Horwitz, Rumsey, & Donohue, 1998, for similar findings).

Of particular importance, the suggested functional anomaly in posterior left hemisphere circuits was found only at the word reading level, for both real and pseudowords, in both adults and children. In contrast, on simple single-letter orthographic or phonological judgment tasks, no group differences were seen—either by activation analyses (Shaywitz et al., 1998) or by functional connectivity analyses (Pugh, Mencl, Shaywitz, et al., 2000). This strongly implies that left hemisphere posterior circuits, although poorly developed, are not fundamentally disrupted in readers with RD. Thus, altering the functional status of these circuits may be possible, providing that appropriate retraining procedures are implemented.

Compensatory Processing in Reading Disability

Many studies using various neuroimaging methods—MEG, fMRI, and PET—have examined phonological processing, word and nonword reading, and other tasks. These studies converge to indicate

that there is a left hemisphere anomaly and a compensatory shift to anterior brain sites (Broca's area) in individuals with RD (Brunswick et al., 1999; Richards et al., 1999; Rumsey et al., 1997; Salmelin et al., 1996; Shaywitz et al., 1998; Shaywitz et al., 2002; Simos et al., 2003).

Evidence of a second apparent compensatory shift—in this case, to posterior right hemisphere regions—comes from Sarkari and colleagues (2002), who found an increase in reading-specific activation in the right hemisphere homologue of Wernicke's area that could be considered compensatory. When coupled with hypoactivation of Wernicke's area (in the left hemisphere), presence of increased activation in the corresponding right hemisphere region can accurately classify kindergarten students as being at risk for developing reading problems with greater than 75% accuracy (Simos et al., 2003).

Hemodynamic measures permitting more detailed examination of this trend indicate that hemispheric asymmetries in activity in Wernicke's area and neighboring areas (the middle temporal gyrus and the angular gyrus) vary significantly among RD and NI groups (Shaywitz et al., 1998): There was greater right than left hemisphere activation in individuals with RD but greater left than right hemisphere activation in the NI group (see also Barnes, Lamm, Epstein, & Pratt, 1994; Pugh, Mencl, Jenner, et al., 2000; and Rumsey et al., 1999). In summary, readers in the NI group show strong, functioning left hemisphere posterior circuits in word and pseudoword reading, but individuals with RD do not. Instead, individuals with RD show evidence of two apparently compensatory responses to their left hemisphere posterior dysfunction: increased bihemispheric Broca's activation and an increased functional role for right hemisphere posterior sites.

Developmental Changes
in the Three Left Hemisphere Systems

As noted previously, researchers have examined developmental changes in the left hemisphere response to print stimuli in cohorts of individuals without reading impairments and individuals with dyslexia ranging in age from 7 through 17 (Shaywitz et al., 2002). The primary finding in these cross-sectional analyses was that as typically developing readers mature, there is a shift in the degree

of activation from right hemisphere and frontal lobe sites toward posterior left hemisphere regions (primarily complex visual processing regions). Indeed, when multiple regression analyses examined both age and reading skill (measured by performance on standard reading tests), the critical predictor was reading skill level. The higher the reading skill, the stronger the response in left hemisphere complex visual processing regions (other areas showed age and skill-related reductions). Thus, a beginning reader on a successful trajectory employs a widely distributed cortical system for print processing, including Wernicke's area, Broca's area, and complex visual processing regions in the right hemisphere. As reading skill increases, these regions play a diminished role while left hemisphere visual processing regions begin to carry rapid printed word recognition. This notion is supported by longitudinal MEG data demonstrating a progressive specialization of cortex in Wernicke's area and left hemisphere complex visual processing regions in the initial stages of reading acquisition (see Figure 16.6).

Intervention Studies

As described previously, a large number of studies suggest left hemisphere posterior anomalies in RD along with compensatory shifts to right hemisphere posterior regions and Broca's area. Moreover, there is some evidence from fMRI studies that higher levels of reading skill are strongly associated with the development of reading-specific
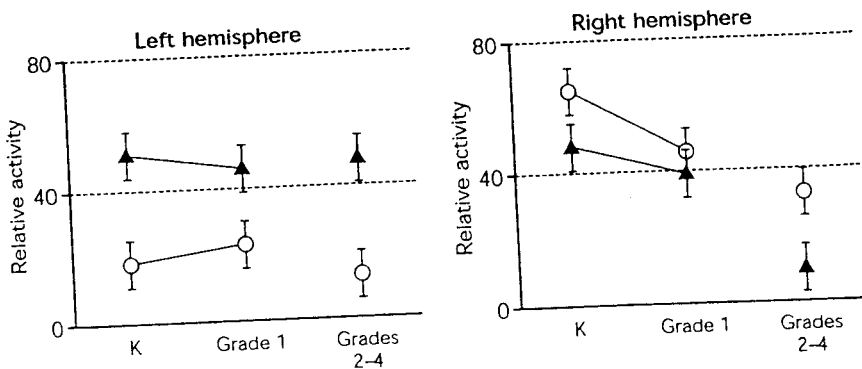
Figure 16.6. Longitudinal (kindergarten to first grade, n = 28; source: Simos et al., 2003) and cross-sectional data (second to fourth grade, n = 12; source: Papanicolaou et al., 2003; Simos, Breier, Fletcher, et al., 2000) regarding changes in the degree of activity in temporoparietal cortex during the early stages of reading acquisition and beyond. The vertical axis displays number of activity sources in Wernicke's area, normalized with respect to total brain activity to enable comparisons across groups.

responses in left hemisphere visual association areas that may be involved in processing word forms. Given this difference in developmental trajectories, researchers can begin to ask whether a given intervention, at a given age or for children with RD with a certain profile, will have the consequence of normalizing the trajectories in these children toward a consolidated left hemisphere posterior reading system.

In a recent MEG study of eight children with severe RD who underwent a brief but intensive remediation program, the most pronounced change observed on a case-by-case basis was a several-fold increase in the apparent engagement of Wernicke's area (in the left hemisphere), accompanied by a moderate reduction in the activation of the corresponding right hemisphere area (Simos, Fletcher, Bergman, et al., 2002; see Figure 16.B at http://www.brookespublishing .com/mccardlemris). This increase in left hemisphere posterior activation after intervention was reported by Temple and colleagues (2003) in a subsequent fMRI study. These types of findings provide a good starting point for large-scale investigations of remediation and neurobiological change in varied populations of struggling readers.

CONCLUSION

Neuroimaging studies cut across multiple domains, including various age groups; levels of proficiency; and research on the brain, reading development, cognition, and instruction. These studies show that the brain is involved at all ages and levels of proficiency but do not indicate that the brain has a deterministic influence that can be separated from experience. Indeed, instruction and practice seems essential for developing and strengthening the neural networks that must be in place for the brain to support complex activities such as reading. Some of these appear to be specific to reading and are not activated by other language experiences or by exposure to written language. This type of knowledge must be integrated into the broader knowledge of research on reading. At the most dramatic level, neuroimaging research shows that teaching affects the brain in positive, long-term ways that are essential for the development of reading.

REFERENCES

Ball, E.W., & Blachman, B.A. (1991). Does phoneme awareness training in kindergarten make a difference in early word recognition and developmental spelling? *Reading Research Quarterly, 26,* 49–66.

Barnes, A., Lamm, O., Epstein, R., & Pratt, H. (1994). Brain potentials from dyslexic children recorded during short-term memory tasks. *Journal of Neuroscience, 74*, 227–237.

Biswal, B., Yetkin, F.Z., Haughton, V.M., & Hyde, J.S. (1995). Functional connectivity in the motor cortex of resting human brain using echo-planar MRI. *Magnetic Resonance in Medicine, 34*, 537–541.

Booth, J.R., Burman, D.D., Van Santen, F.W., Harasaki, Y., Gitelman, D.R., Parrish, T.B., et al. (2001). The development of specialized brain systems in reading and oral-language. *Neuropsychology, 7*, 119–141.

Brady, S., & Shankweiler, D. (Eds.). (1991). *Phonological processes in literacy: A tribute to Isabelle Y. Liberman.* Mahwah, NJ: Lawrence Erlbaum Associates.

Breier, J.I., Simos, P.G., Wheless, J.W., Constantinou, J.E.C., Baumgartner, J.E., Venkataraman, V., et al. (2001). Language dominance in children as determined by magnetic source imaging and the intracarotid amobarbital procedure: A comparison. *Journal of Child Neurology, 16*, 124–130.

Breier, J.I., Simos, P.G., Zouridakis, G., & Papanicolaou, A.C. (1998). Relative timing of neuronal activity in distinct temporal lobe areas during a recognition memory task for words. *Journal of Clinical and Experimental Neuropsychology, 20*, 782–790.

Breier, J.I., Simos, P.G., Zouridakis, G., & Papanicolaou, A.C. (1999). Temporal course of regional brain activation associated with phonological decoding. *Journal of Clinical and Experimental Neuropsychology, 21*, 465–476.

Breier, J.I., Simos, P.G., Zouridakis, G., Wheless, J.W., Willmore, L.J., Constantinou, J.E., et al. (1999). Language dominance determined by magnetic source imaging: A comparison with the Wada procedure. *Neurology, 53*, 938–945.

Bruck, M. (1992). Persistence of dyslexics' phonological deficits. *Developmental Psychology, 28*, 874–886.

Brunswick, N., McCrory, E., Price, C., Frith, C.D., & Frith, U. (1999). Explicit and implicit processing of words and pseudowords by adult developmental dyslexics: A search for Wernicke's Wortschatz? *Brain, 122*, 1901–1917.

Castillo, E.M., Simos, P.G., Venkataraman, V., Breier, J.I., & Papanicolaou, A.C. (2001). Mapping of expressive language cortex using magnetic source imaging. *Neurocase, 7*, 419–422.

Coltheart, M., Curtis, B., Atkins, P., & Haller, M. (1993). Models of reading aloud: Dual-route and parallel-distributed-processing approaches. *Psychological Review, 100*, 589–608.

Felton, R.H., Naylor, C.E., & Wood, F.B. (1990). Neuropsychological profile of adult dyslexics. *Brain and Language, 39*, 485–497.

Fiebach, C., Friederici, A., Muller, K., & Von Cramon, Y. (2002). FMRI evidence for dual routes to the mental lexicon in visual word recognition. *Journal of Cognitive Neuroscience, 14*, 11–23.

Fletcher, J.M., Shaywitz, S.E., Shankweiler, D.P., Katz, L., Liberman, I.Y., Stuebing, K.K., et al. (1994). Cognitive profiles of reading disability: Comparisons of discrepancy and low achievement definitions. *Journal of Educational Psychology, 86*, 6–23.

Foorman, B.R., Francis, D., Fletcher, J.K., Schatschneider, C., & Mehta, P. (1998). The role of instruction in learning to reading: Preventing reading failure in at-risk children. *Journal of Educational Psychology, 90*, 37–55.

Frackowiak, R., Friston, K., Frith, C., Dolan, R., & Mazziotta. (1997). *Human brain function*. San Diego: Academic Press.

Friston, K. (1994). Functional and effective connectivity: A synthesis. *Human Brain Mapping, 2,* 56–78.

Friston, K.J., Zarahn, E., Josephs, O., Henson, R.N.A., & Dale, A.M. (1999). Stochastic designs in event-related fMRI. *NeuroImage, 10,* 607–619.

Hampson, M., Peterson, B.S., Skudlarski, P., Gatenby, J.C., & Gore, J.C. (2002). Detection of functional connectivity using temporal correlations in MR images. *Human Brain Mapping, 15,* 247–262.

Hays, W.L. (1988). *Statistics*. Orlando, FL: Holt, Rinehart & Winston.

Helenius, P., Salmelin, R., Service, E., & Connolly, J. (1998). Distinct time courses of word and context comprehension in the left temporal cortex. *Brain, 121,* 1133–1142.

Holmes, A.P., & Friston, K.J. (1998). Generalizability, random effects, and population inference. *NeuroImage, 7,* S34.

Horwitz, B., Grady, C.L., Haxby, J.V., Shapiro, M.B., Rapoport, S.I., Ungerleider, L.G., et al. (1992). Functional associations among human posterior extrastriate brain regions during object and spatial vision. *Journal of Cognitive Neuroscience, 4,* 311–322.

Horwitz, B., Rumsey, J.M., & Donohue, B.C. (1998). Functional connectivity of the angular gyrus in normal reading and dyslexia. *Proceedings of the National Academy Sciences of the United States of America, 95,* 8939–8944.

Kirk, R.E. (1982). *Experimental design: Procedures for the social sciences*. Belmont, CA: Wadsworth.

Klingberg, T., Hedehus, M., Temple, E., Salz, T., Gabrieli, J.D., Moseley, M.E., et al. (2000). Microstructure of temporo-parietal white matter as a basis for reading ability: Evidence from diffusion tensor magnetic resonance imaging. *Neuron, 25,* 493–500.

Lowe, M.J., Mock, B.J., & Sorenson, J.A. (1998). Functional connectivity in single and multislice echoplanar imaging using resting-state fluctuations. *NeuroImage, 7,* 119–132.

Maestú, F., Ortiz, T., Fernandez, A., Amo, C., Martin, P., Fernández, S., et al. (2002). Spanish language mapping using MEG: A validation study. *NeuroImage, 17,* 1579–1586.

McIntosh, A.R., Bookstein, F.L., Haxby, J.V., & Grady, C.L. (1996). Spatial pattern analysis of functional brain images using partial least squares. *NeuroImage, 3,* 143–157.

McIntosh, A.R., Nyberg, L., Bookstein, F.L., & Tulving, E. (1997). Differential functional connectivity of prefrontal and medial temporal cortices during episodic memory retrieval. *Human Brain Mapping, 5,* 323–327.

Mencl, W.E., Pugh, K.R., Shaywitz, S.E., Shaywitz, B.A., Fulbright, R.K., Constable, R.T., et al. (2000). Network analysis of brain activations in working memory: Behavior and age relationships. *Microscopy Research and Technique, 51,* 64–74.

Papanicolaou, A.C., Simos, P.G., Breier, J.I., Fletcher, J.M., Foorman, B.R., Francis, D.J., et al. (2003). Brain mechanisms for reading in children with and without dyslexia: A review of studies of normal development and plasticity. *Developmental Neuropsychology, 24,* 593–612.

Paulesu, E., Démonet, J.F., Fazio, F., McCrory, E., Chanoine, V., Brunswick, N., et al. (2001). Dyslexia: Cultural diversity and biological unity. *Science*, *291*, 2165–2167.

Pugh, K.R., Mencl, W.E., Jenner, A.J., Katz, L., Lee, J.R., Shaywitz, S.E., et al. (2000). Functional neuroimaging studies of reading and reading disability (developmental dyslexia). *Mental Retardation and Developmental Disabilities Review*, *6*, 207–213.

Pugh, K., Mencl, E.W., Shaywitz, B.A., Shaywitz, S.E., Fulbright, R.K., Skudlarski, P., et al. (2000). The angular gyrus in developmental dyslexia: Task-specific differences in functional connectivity in posterior cortex. *Psychological Science*, *11*, 51–56.

Pugh, K.R., Shaywitz, B.A., Shaywitz, S.E., Constable, T.R., Skudlarski, P., Fulbright, R.K., et al. (1996). Cerebral organization of component processes in reading. *Brain*, *119*, 1221–1238.

Pugh, K.R., Shaywitz, B.A., Shaywitz, S.E., Shankweiler, D.P., Katz, L., Fletcher, J.M., et al. (1997). Predicting reading performance from neuroimaging profiles: The cerebral basis of phonological effects in printed word identification. *Journal of Experimental Psychology: Human Perception and Performance*, *23*, 299–318.

Richards, T.L., Dager, S.R., Corina, D., Serafini, S., Heide, A.C., Steury, K., et al. (1999). Dyslexic children have abnormal brain lactate response to reading-related tasks. *American Journal of Neuroradiology*, *20*, 1393–1398.

Rieben, L., & Perfetti, C.A. (1991). *Learning to read: Basic research and its implications*. Mahwah, NJ: Lawrence Erlbaum Associates.

Rumsey, J.M., Horwitz, B., Donohue, B.C., Nace, K.L., Maisog, J.M., & Andreason, P.A. (1999). Functional lesion in developmental dyslexia: Left angular gyral blood flow predicts severity. *Brain and Language*, *70*, 187–204.

Rumsey, J.M., Nace, K., Donohue, B., Wise, D., Maisog, J.M., & Andreason, P. (1997). A positron emission tomographic study of impaired word recognition and phonological processing in dyslexic men. *Archives of Neurology*, *54*, 562–573.

Salmelin, R., Service, E., Kiesila, P., Uutela, K., & Salonen, O. (1996). Impaired visual word processing in dyslexia revealed with magnetoencephalography. *Annals of Neurology*, *40*, 157–162.

Sarkari, S., Simos, P.G., Fletcher, J.M., Castillo, E.M., Breier, J.I., & Papanicolaou, A.C. (2002). The emergence and treatment of developmental reading disability: Contributions of functional brain imaging. *Seminars in Pediatric Neurology*, *9*, 227–236.

Shankweiler, D., Crain, S., Katz, L., Fowler, A.E., Liberman, A.M., Brady, S.A., et al. (1995). Cognitive profiles of reading-disabled children: Comparison of language skills in phonology, morphology, and syntax. *Psychological Science*, *6*, 149–156.

Shaywitz, S.E., Fletcher, J.M., Holahan, J.M., Shneider, A.E., Marchione, K.E., Stuebing, K.K., et al. (1999). Persistence of dyslexia: The Connecticut Longitudinal Study at adolescence. *Pediatrics*, *104*, 1351–1359.

Shaywitz, S.E., Shaywitz, B.A., Pugh, K.R., Fulbright, R.K., Constable, R.T., Mencl, W.E., et al. (1998). Functional disruption in the organization of the brain for reading in dyslexia. *Proceedings of the National Academy of Sciences of the United States of America, 95,* 2636–2641.

Shaywitz, B.A., Shaywitz, S.E., Pugh, K.R., Mencl, W.E., Fulbright, R.K., Skudlarski, P., et al. (2002). Disruption of posterior brain systems for reading in children with developmental dyslexia. *Biological Psychiatry, 52,* 101–110.

Simos, P.G., Breier, J.I., Fletcher, J.M., Bergman, E., & Papanicolaou, A.C. (2000). Cerebral mechanisms involved in word reading in dyslexic children: A magnetic source imaging approach. *Cerebral Cortex, 10,* 809–816.

Simos, P.G., Breier, J.I., Fletcher, J.M., Foorman, B.R., Castillo, E.M., Fletcher, J.M., et al. (2002). Brain mechanisms for reading words and pseudowords: An integrated approach. *Cerebral Cortex, 12,* 297–305.

Simos, P.G., Breier, J.I., Fletcher, J.M., Foorman, B.R., Mouzaki, A., & Papanicolaou, A.C. (2001). Age-related changes in regional brain activation during phonological decoding and printed word recognition. *Developmental Neuropsychology, 19,* 191–210.

Simos, P.G., Breier, J.I., Maggio, W.W., Gormley, W., Zouridakis, G., Wilmore, L.J., et al. (1999). Atypical temporal lobe language representation revealed by MSI and intraoperative stimulation mapping. *Neuroreport, 10,* 139–142.

Simos, P.G., Breier, J.I., Wheless, J.W., Maggio, W.W., Fletcher, J.M., Castillo, E.M., et al. (2000). Brain mechanisms for reading: The role of the superior temporal gyrus in word and pseudoword naming. *Neuroreport, 11,* 2443–2447.

Simos, P.G., Breier, J.I., Zouridakis, G., & Papanicolaou, A.C. (1998). Identification of language-related brain activity using magnetoencephaolography. *Journal of Clinical and Experimental Neuropsychology, 2,* 706–722.

Simos, P.G., Fletcher, J.M., Bergman, E., Breier, J.I., Foorman, B.R., Castillo, E.M., et al. (2002). Dyslexia-specific brain activation profile become normal following successful remedial training. *Neurology, 58,* 1203–1213.

Simos, P.G., Fletcher, J.M., Foorman, B.R., Francis, D.J., Castillo, E.M., Davis, R.N., et al. (2002). Brain activation profiles during the early stages of reading acquisition. *Journal of Child Neurology, 17,* 159–163.

Simos, P.G., Papanicolaou, A.C., Breier, J.I., Wheless, J.W., Constantinou, J.E., Gormley, W.B., et al. (1999). Localization of language-specific cortex by using magnetic source imaging and electrical stimulation mapping. *Journal of Neurosurgery, 91,* 787–796.

Simos, P.G., Fletcher, J.M., Sarkari, S., Billingsley, R.L., Francis, D.J., Castillo, E.M., et al. (2003). *Early development of neurophysiological processes involved in normal reading and reading disability.* Manuscript submitted for publication.

Stanovich, K.E., & Siegel, L.S. (1994). Phenotypic performance profile of children with reading disabilities: A regression-based test of the phonological-core variable-difference model. *Journal of Educational Psychology, 86,* 24–53.

Szymanski, M.D., Perry, D.W., Gage, N.M., Rowley, H.A., Walker, J., Berger, M.S., et al. (2001). Magnetic source imaging of late evoked field responses to vowels: Toward an assessment of hemispheric dominance for language. *Journal of Neurosurgery, 94,* 445–453.

Tagamets, M.A., Novick, J.M., Chalmers, M.L., & Friedman, R.B. (2000). A parametric approach to orthographic processing in the brain: An fMRI study. *Journal of Cognitive Neuroscience, 12,* 281–297.

Temple, E., Deutsch, G.K., Poldrack, R.A., Miller, S.L., Tallal, P., Merzenich, M.M., et al. (2003). Neural deficits in children with dyslexia ameliorated by behavioral remediation: Evidence from functional MRI. *Proceedings of the National Academy of Sciences of the United States of America, 100,* 2860–2865.

Torgesen, J.K., Morgan, S.T., & Davis, C. (1992). Effects of two types of phonological awareness training on word learning in kindergarten children. *Journal of Educational Psychology, 84,* 364–370.

Wise, B.W., & Olson, R.K. (1995). Computer-based phonological awareness and reading instruction. *Annals of Dyslexia, 45,* 99–122.

Woods, R.P. (1996). Modeling for intergroup comparisons of imaging data. *NeuroImage, 4,* S84–S94.