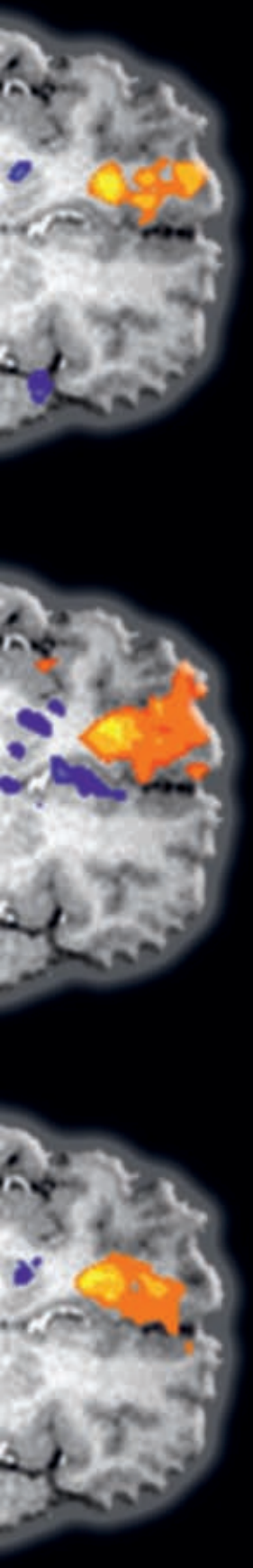
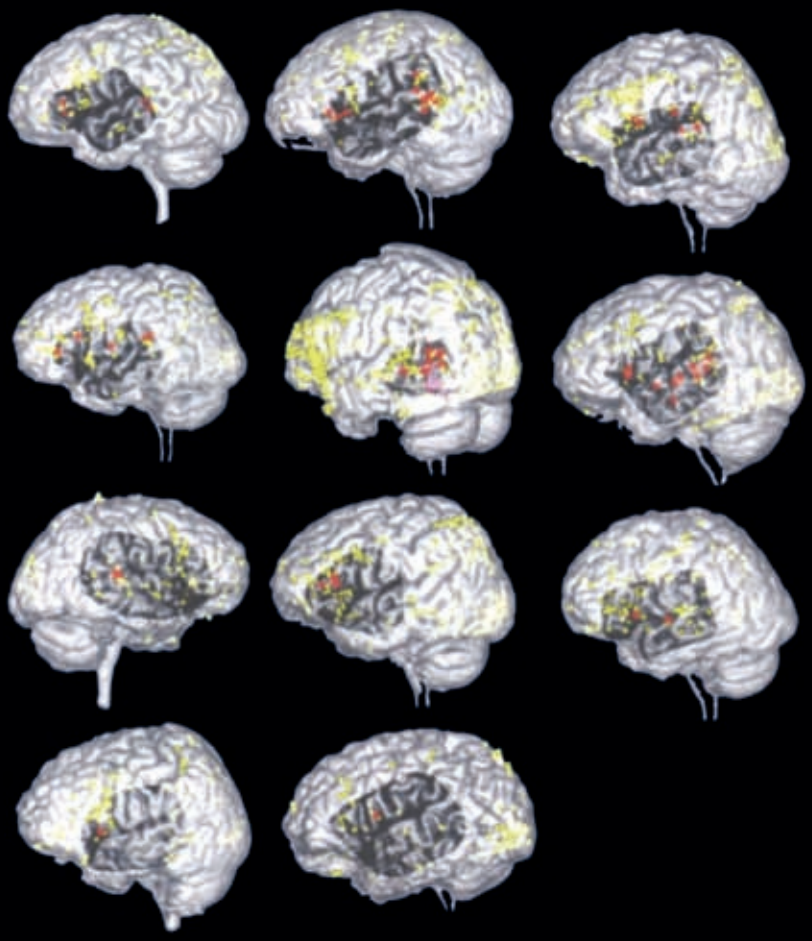


Functional MRI: Applications in Clinical Neurology and Psychiatry

Edited by **Mark D'Esposito**



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To Judy, Zoe and Zack

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Preface

Almost 15 years have passed since functional MRI (fMRI) was introduced as a new method for the non-invasive study of human brain function. The impact it had on the disciplines of neuroscience and psychology was immediate. Scientists investigating neural mechanisms underlying sensory, motor, and cognitive processes in humans with other methods – such as neuropsychological studies of patients with brain dysfunction or event-related potential recording – were presented with a new tool that had the potential to provide converging evidence to support their hypotheses. Importantly, the introduction of fMRI did not replace other neuroscientific methods for studying human brain function, instead, it provided a new and different way of examining brain-behavior relationships, and with superb temporal and spatial resolution. The success of fMRI has led to an exponential increase over the past five years in its use to study the brain function. A bibliographic search for the term 'fMRI' in MEDLINE in the year 2004 leads to almost 5000 citations. The results of this search also reveal that fMRI studies are being published in a wide range of journals across many disciplines. Advances in fMRI methods in both data acquisition and data analysis are occurring at a rapid pace, which will likely fuel even more widespread use of this tool in the future.

The clinical utility of fMRI has been slower to materialize when compared to the impact fMRI has had on basic neuroscience applications. There are probably many reasons for this observation. First, it will most likely take substantial experience and validation of fMRI methods before it replaces trusted and reliable diagnostic tools used by neurologists and psychiatrists, such as the Wada test or EEG. However, as reviewed in this book, many such fMRI methods are currently being developed and validated and are beginning to gain acceptance for clinical use. For example, there are several different fMRI language mapping protocols that provide information comparable to that provided by the Wada test. A second likely reason that clinical applications of fMRI have been slower to develop is that fMRI data collected from patients with neurological and psychiatric disorders are more difficult to interpret, compared with data collected from individuals with a healthy brain. Most often, fMRI data is treated as a 'brain map' in a qualitative fashion with attempts to interpret patterns of activity. To be clinically useful, methods for analyzing fMRI will also have to take a quantitative approach. Moreover, it will be imperative that any clinician who uses this method understands exactly what is being measured with fMRI. The first two chapters of this book provide an overview of how fMRI compares with other functional neuroimaging methods such as positron emission tomography (PET), and describe the basic underlying concepts and principles of fMRI, as well as approaches in its use for studying brain function.

Although we have less experience with 'clinical' fMRI data, there is significant momentum in the use of fMRI as a clinical tool, and numerous clinical fMRI studies are being published. In this book, we present a collection of chapters that highlight its application in neurological and psychiatric disorders. Prior to fMRI, PET was the predominant functional neuroimaging method for studying human brain function, thus, each chapter also reviews the relevant literature using this method. This book was not meant to be an exhaustive review

of all of the clinical uses of fMRI, instead, I have chosen selective examples of clinical conditions where I believe fMRI has made significant progress. I am confident that in the not too distant future, the number and range of clinical conditions that can be studied using fMRI will greatly expand.

After reading this book it should be clear that there are many different ways that fMRI could aid the clinician in the diagnosis or treatment of a neurological or psychiatric disorder. One way would be for it to develop as a reliable and valid diagnostic tool. For example, it may be capable of providing biomarkers that predict the development of neurodegenerative disorders such as Alzheimer's disease before the onset of symptoms, or guide a neurosurgeon's decisions prior to epilepsy or brain tumor surgery. Development of such biomarkers may help predict which patients may benefit from rehabilitation interventions or aid in the monitoring of therapeutic interventions. Another important contribution of fMRI would be for it to provide a better understanding of the pathophysiology underlying neurological and psychiatric disorders. As we review in this book, fMRI studies of clinical conditions have begun to provide insight into neurological disorders such as stroke, traumatic brain injury and neurodegenerative disease; psychiatric disorders such as schizophrenia, depression and anxiety; developmental disorders such as dyslexia; and other important clinical conditions such as pain and drug addiction. Thus, it is clear that fMRI has enormous potential for studying brain function and is poised to have a tremendous impact on many aspects of clinical neurology and psychiatry. For these reasons, I hope that trainees and clinicians that diagnose and care for patients with neurological and psychiatric disorders find the information provided in this book valuable.

Mark D'Esposito MD

Neurobiological correlates of imaging

1

Scott A Small

INTRODUCTION

Brain imaging, as a field within biomedical engineering, is in a perpetual state of development, and an exhaustive review of all imaging modalities cannot be provided. Rather, this chapter will focus on those modalities that have shown the greatest promise for clinical utility in neurological and psychiatric disorders – magnetic resonance imaging (MRI), single photon emission computed tomography (SPECT), and positron emission tomography (PET). More than understanding the engineering or physics that underlies each technology, it is the biological correlates of imaging that are of greater importance to us, as they dictate the clinical utility of each imaging approach.

Two biological questions should be asked of each imaging modality: What is the anatomical resolution of the image? What is the physiological source of the signal? Maintaining a clear understanding of the anatomy and physiology of brain imaging will aid in sorting through the application of each approach. The answer to the resolution question can be simply dichotomized into those techniques that possess microscopic (i.e. submillimeter[1]) resolution versus those that possess macroscopic (i.e. supramillimeter) resolution. This division will generally determine whether small brain regions – such as the nuclei of the basal ganglia or the cerebellum, or the subregions of the hippocampal formation – can be easily visualized. The answer to the second question regarding the physiological underpinnings of the signal turns out to be quite complicated, and accordingly will be discussed in greater detail.

Attempts have been made, in fact, to dichotomize the source of the signal into 'structural' versus 'functional'. This dichotomy is forced, however, and leads to oversimplifications – or, worse, results in misuses of each term. The meaning of the term 'functional' is particularly confusing, and clarification is in order. Functional imaging techniques have all evolved out of Kety and Schmidt's seminal studies in which they successfully adapted Fick's principle to measure blood flow in the living brain.[2] Although earlier experiments, such as those performed by Roy and Sherrington, supported a relationship between blood flow and brain metabolism, Kety and Schmidt were to be the first to quantify cerebral blood flow and to do so non-invasively. Fick's principle states that an organ must receive blood flow at a rate that is equal to the rate with which the organ metabolizes a constituent of blood, divided by the concentration of the constituent. The variation of Fick's principle that underlies most functional imaging techniques states that oxygen metabolism is proportional to cerebral blood flow (CBF) or to cerebral blood volume (CBV) and inversely proportional to deoxyhemoglobin content. Thus, from Fick's principle, it should be clear that 'brain metabolism' is the answer to the question 'What is the function in functional imaging?' (Figure 1.1).

Still, metabolism itself needs to be carefully defined in order to maintain a clear understanding of what it is we are actually imaging, and to prevent common misinterpretations –

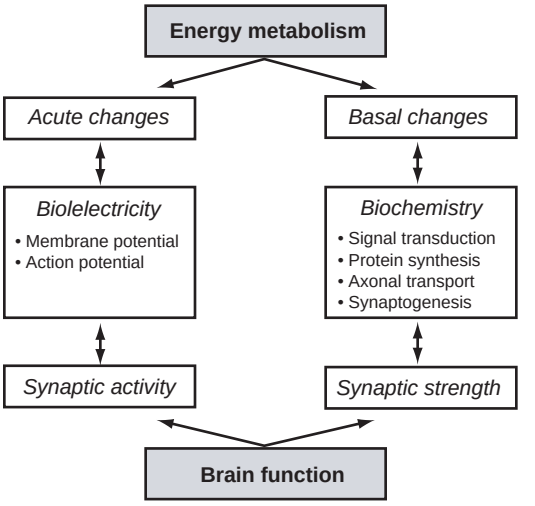

Figure 1.1 The neurophysiological correlates of 'functional' imaging. Establishing a clear relationship between brain metabolism and brain function prevents misuse of the term 'functional' imaging. Metabolism is a dynamic process divided into acute versus chronic changes. Imaging can capture both types of metabolic changes using an assortment of modalities as described in the text.

for example, that functional imaging is necessarily a measure of neuronal spike activity. Metabolism is best defined as the rate with which mitochondria produces adenosine triphosphate (ATP) to supply the cell's energy demands. Importantly, brain metabolism is a dynamic process, and a distinction has been made between acute changes in metabolism occurring over seconds and minutes, versus basal changes that occur over hours, days, or even longer[3] (Figure 1.1).

Acute changes typically reflect the metabolic costs of maintaining an electric potential across the membrane. Any transient shift in the postsynaptic potential will affect acute metabolism, and it is important to remember that postsynaptic potentials do not always lead to action potentials. Thus, acute changes in metabolism typically reflect bioelectric variability, with or without an action potential. Although bioelectrical states can extend for longer periods, basal metabolic changes more likely result from a wide range of biochemical processes, typified by their slower effects on brain metabolism. These biochemical processes include all of the molecular machinery required for normal neuronal function – such as signal transduction, second-messenger cascades, protein synthesis, axonal transport, synaptic release, and synaptogenesis.[4] Biochemical processes exact a high metabolic cost on the neuron, in fact requiring more energy than spike activity.[3]

The brain functions to encode internal and external information, to process this information, and to accordingly orchestrate motor output. The distinction between acute and chronic components of metabolism layers nicely onto the two dominant mechanisms with which the brain achieves these functions – by varying the strength or the rate of synaptic activity. The brain encodes information with unique spatiotemporal patterns of spike activity, and a measure of acute metabolism is the best approach for mapping these patterns. Many aspects of brain function, however, are mediated by changes in synaptic strength independent of electrical activity. This is particularly true for higher cognitive functions, for which the brain continues to process information long after the external stimulus has extinguished. Cellular underpinnings of memory, for example, involve a cascade of biochemical events that remain active throughout a protracted consolidation period – lasting weeks in rodents and months to years in primates.[5,6] Once initiated, these biochemical processes (which include signal transduction, protein synthesis, axonal transport, and synaptic growth) occur even in an electrically silent neuron. Importantly, most causes of higher-order brain dysfunction alter the basal metabolic state, accounting for why techniques sensitive to basal metabolism have proven most effective for clinical purposes.

With a greater appreciation of the factors that influence neuronal metabolism and their relation to neuronal physiology, it should be clear why simple divisions such as 'structural' and 'functional' imaging are unsatisfactory. For example, should PET studies that measure receptor density be considered structural or

Table 1.1 The clinical utility of each imaging modality is based on the physiological source of the signal and the anatomical resolution of the image

Measurement	*Signal source*	*Anatomical resolution*	*Clinical utility*
Volume (MRI)	Cell volume, extracellular fluid, cell density	Microscopic	Specificity, detection, clinical course
Oxidative metabolism, acute or chronic (MRI, SPECT, PET)	Cerebral blood volume, cerebral blood flow, deoxy-hemoglobin content	Macroscopic/microscopic	Specificity, detection, clinical course
Glucose metabolism (PET)	Glucose uptake	Macroscopic	Specificity
Spectroscopy (MRI)	NAA, myoinositol	Macroscopic	Clinical course
Radioligands (PET)	Amyloid plaques, receptors	Macroscopic	Specificity, clinical course

functional? What about spectroscopic studies that measure intracellular *N*-acetylaspartate important for normal neuronal physiology? Recent studies suggest that even volumetric measurements might reflect neuronal function more than simply cell loss.[7] The inherent ambiguity of these terms reduces their usefulness. In an effort to be more precise, imaging modalities will be categorized according to the actual source of the imaged signal (Table 1.1).

IMAGING MODALITIES

Each imaging modality will be discussed, with emphasis being placed on its neurobiological correlates. In some cases, these issues are straightforward and the discussion will be brief. In others, such as in modalities that image hemodynamic variables, a more detailed discussion is required. In general, an exhaustive citation list relevant to each imaging modality will not be provided. Rather, citations will be constrained to those that best illustrate or substantiate a point.

Imaging brain volume

The main development in volumetric MRI is not in image acquisition, where a fairly conventional pulse sequence is typically used, but rather in the postacquisition processing. A number of manual or semiautomated algorithms have been developed,[8–11] and in some cases measurements of particular brain regions such as the entorhinal cortex have been validated against postmortem tissue.[12]

Physiologic source of the signal

The full range of tissue factors that influence the area of gray or white matter remains unknown. Animal studies have shown that the initial assumption that atrophy of gray matter must necessarily reflect cell loss is untrue.[7] Other factors must play a role, such as perhaps cell volume, extracellular fluids, or even vascularity, which might be correlated with the physiological integrity of a brain region.

Anatomical resolution of the image

Volumetric MRI acquires images with microscopic resolution, providing superior visualization of brain anatomy. Nevertheless, many regions of the brain are not amenable to volumetric analysis. Identifying the precise circumference of a brain region is needed to calculate its area, which requires (a) that anatomical landmarks defining the border-zones between neighboring regions exist and (b) that these landmarks are visible with MRI. The subregions of the hippocampus proper – the subiculum and the CA subfields – illustrate important brain regions for which a precise area cannot be calculated. So, for example, even though the general locale of

the subiculum and the CA1 subfield can be identified on high-resolution images, the exact line that separates the two cannot be drawn without histological staining.[13] The area and volume of these hippocampal regions, therefore, can only be calculated in postmortem tissue.[7]

Imaging hemodynamic variables

From Fick's principles and from many empirical validations, we know that CBF, CBV, and deoxyhemoglobin content are hemodynamic variables that correlate with oxygen metabolism (see Siesjo[14] for a review and Hyder et al[15] for a more recent example). All of these variables can be measured with a range of imaging techniques. CBF can be measured with oxygen-15 (^{15}O)-labeled PET,[16,17] SPECT,[18] and two MRI approaches – arterial spin labeling (ASL)[19] and dynamic susceptibility imaging.[20] CBV is best measured with MRI; this is accomplished by altering the concentration of an intravascular contrast agent (either by increasing an exogenous agent by injection,[21,22] or by decreasing endogenous deoxyhemoglobin by having a subject breathe 100% oxygen[23]) and measuring the corresponding change in signal intensity.

MRI is also used to measure deoxyhemoglobin content. Relying on prior in vitro studies performed by Thulborn et al,[24] Ogawa was the first to show that the influence of deoxyhemoglobin on the MRI signal can be detected in the brains of living animals. By showing a reduction in signal contrast when rodents inhaled 100% oxygen, Ogawa et al[25] first established a relationship between MRI signal and deoxyhemoglobin. They then linked deoxyhemoglobin and metabolism by injecting drugs that altered the metabolic state of the brain and showing a corresponding change in the MRI signal.[26] Deoxyhemoglobin is a paramagnetic molecule, which from an imaging point of view means that it produces local inhomogeneities in T2*-weighted images; thus, the higher the deoxyhemoglobin content within a voxel, the lower the amplitude of the measured signal. Because of hemodynamic coupling (the mechanisms of which remain poorly understood), the blood supply of oxyhemoglobin outstrips its local consumption, so that the greater the rate of metabolism, the lower the deoxyhemoglobin content within a voxel. The simple principle to remember is that T2*-weighted signal intensity increases with increased oxidative metabolism.

Physiologic source of the signal

Brain metabolism is in a constant state of flux and there is no such thing as a 'resting' or 'steady' state. When imaging any hemodynamic variable, the question is whether one is capturing an acute change in hemodynamics, which typically reflects transient changes in bioelectricity, or a basal change, which reflects either long-term bioelectricity or any change in the neuron's biochemical state (Figure 1.1).

As discussed above, basal oxygen metabolism can be estimated with imaging techniques sensitive to CBF, CBV, and deoxyhemoglobin. Basal CBF can be measured with SPECT, PET, and ASL MRI. Basal CBV can be measured with PET, and with MRI by using either exogenous or endogenous contrast agents. As derived by a variant of Fick's principle, regional deoxyhemoglobin concentration is equal to oxygen metabolism divided by CBF, termed the oxygen extraction fraction. By using a combination of radiochemicals, PET can measure oxygen extraction fraction, and therefore deoxyhemoglobin concentrations. Although MRI is better known for mapping acute changes in deoxyhemoglobin content, an increasing number of studies are showing that basal deoxyhemoglobin content can also be captured with MRI.[27–29] Note that MRI can only estimate deoxyhemoglobin content, not deoxyhemoglobin concentration. Deoxyhemoglobin content is defined as deoxyhemoglobin concentration multiplied by CBV. The fact that a change in oxygen metabolism will change both CBV and deoxyhemoglobin concentration, and that the interrelation between these hemodynamic variables remains unclear, contributes to the difficulty in using deoxy-

hemoglobin content as a precise indicator of underlying metabolism.

Measuring acute changes in hemodynamics is most meaningful when time-locked with a stimulation event – which includes behavioral 'activation' tasks or electrical stimulation in the periphery or even within the brain itself. ^{15}O-labeled PET is the most common technique used to capture acute changes in CBF, although recent studies are beginning to use ASL MRI too for the same purposes. MRI is the most common technique used to capture acute changes in deoxyhemoglobin content – an approach termed BOLD (blood oxygen level-dependent) functional MRI (fMRI)[26] (see Chapter 2).

Using MRI to map acute changes in regional bioelectricity provides us with the truly remarkable ability to map where the brain represents external stimuli. The field of cognitive neuroscience, where questions are asked about normal brain function, has been radically transformed by this method. Although the excitement engendered by fMRI is justified, fMRI needs to be made more quantitative before it can be successfully applied to address clinical questions. Calibrating the hemodynamic response is considered one of the major challenges on the way to this goal.[15,30] The amplitude of the acute changes in signal is the common metric used to measure an acute hemodynamic response. It is now clearly established that the acute change in signal is dependent on the baseline condition,[31] which is essentially a reflection of the basal state. Thus, when comparing diseased and normal brains – where the basal states are known to be different[32] – identical changes in acute metabolism will elicit different amplitudes of the hemodynamic response. In this scenario, we would falsely conclude that we have detected an abnormality in acute brain metabolism.

It is also important to note that measures of hemodynamics are *indirect* measures of brain metabolism. Studies are beginning to show that the vascular mechanisms that govern the acute hemodynamic response are themselves affected by neurological disorders such as Alzheimer's disease,[33] and even by aging.[34] Thus, when a difference in hemodynamic response is observed between an Alzheimer's patient and a control subject, we cannot be certain whether this reflects an underlying difference in neuronal physiology or a difference in vascular responsivity. Gaining a better understanding into these disease-related changes in vascular factors is another challenge that faces BOLD fMRI before it can become a precise clinical tool.[35]

Anatomical resolution of the image

For technical reasons, PET and SPECT technologies – whether measuring acute or chronic hemodynamic changes – will always remain in the macroscopic range. For MRI measures of hemodynamics, the anatomical resolution depends on whether acute or chronic states are being imaged. Acute hemodynamic changes are by definition short-lived, and in order to capture these transient signal changes, images need to be acquired with high temporal resolution. As in the logic of any camera, temporal resolution trades off with spatial resolution, and most BOLD fMRI acquired with echo-planar imaging is in the macroscopic range. When mapping the chronic hemodynamic state, either by chronic CBV or by chronic deoxyhemoglobin content,[29,32,36] images can be acquired more slowly and can easily achieve microscopic resolution.

Imaging glucose metabolism

Within the annals of clinical neurology and psychiatry, [^{18}F]fluorodeoxyglucose (FDG) PET still remains the shining glory of functional imaging. This imaging approach has the longest history, and, together with SPECT,[18] is the approach that has shown the most clinical utility.[16,22,37]

Physiological source of the signal

The more energetically active a cell, the more glucose it needs to maintain its supply of ATP,

resulting in an increased regional uptake of FDG. The physiological source of the signal is simply glucose metabolism, and in many instances regional measures of glucose and oxygen metabolism are tightly correlated. This is not always the case, however, and it is important to appreciate the differences between the two measures of energy metabolism. When differences between glucose and oxygen metabolism are observed, they usually reflect different cell constituents within a brain region. Glia rely on glycolytic anaerobic as well as on aerobic metabolism, while neurons rely almost exclusively on aerobic metabolism. Thus, in vitro studies comparing the source of signal between maps of glucose and oxygen metabolism have shown that glia are the greatest consumers of glucose[38] while neurons are the greatest consumers of oxygen[39] within a brain region.

Anatomical resolution of the image

As in all PET technology, the spatial resolution is in the macroscopic range.

Imaging neurochemistry

Proton magnetic resonance spectroscopy (MRS) is an approach that images a select group of brain chemicals – including *N*-acetylaspartate (NAA), glutamine and glutamate, γ-aminobutyric acid (GABA), myoinositol, choline, creatine, lipids, and lactate.

Physiological source of the signal

Spectroscopic measurements of NAA nicely illustrate the confusion between the terms 'structural' and 'functional' imaging. When initially studied, it was thought that NAA levels are a marker of cell number and that a decrease in NAA suggested cell loss. We now know that NAA reduction can be transient, and so NAA levels are thought to reflect the functional integrity of the neuron.

Anatomical resolution of the image

Spectroscopy acquires images in the macroscopic range.

Imaging radioligands

For both scientific and practical reasons, fMRI is largely replacing PET for mapping brain metabolism. Scientifically, fMRI provides superior spatial and temporal resolution, and can reliably map changes in individual subjects. Practically, MRI scanners are more readily available, and are safer for the subject as well as less expensive for the investigator. Nevertheless, radioligand mapping is the imaging domain in which PET still reigns supreme. A number of studies have used radioligand PET to assess the concentration of various receptors in the Alzheimer's disease brain.[40] The most recent and exciting development has been the introduction of radioligands that bind amyloid plaques and map the concentration of the plaques in different brain regions.[41,42]

Physiological source of the signal

Either density of receptors or density of amyloid plaques can be mapped with radioligand PET.

Anatomical resolution of the image

This is in the macroscopic range.

CONCLUSIONS

In vivo brain imaging has transformed the field of clinical neuroscience. The first generation of brain imaging techniques has perfected our ability to visualize macroscopic structural lesions – anatomical malformations, neoplasms, hemorrhagic and occlusive strokes, infections, sclerotic plaques, hydrocephalus, etc. For practitioners who focus on these disease processes, the thought of diagnosing and monitoring therapeutic interventions in the absence of brain imaging is virtually inconceivable.

For many disorders of the brain, however, dysfunction is caused by impaired neuronal physiology more than by altered gross anatomy – these include many developmental disorders, most psychiatric diseases, age-

related cognitive decline, and even the earliest stages of neurodegeneration. Because of this pathophysiological feature, many of these disorders cannot be visualized with 'structural' imaging, and are even invisible under the microscope. By perfecting the ability to visualize physiological dysfunction, the next generation of brain imaging – functional imaging – will not only revolutionize the clinical management but also contribute to our basic understanding of this class of disease.

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Interpretation of clinical functional neuroimaging studies

2

Geoffrey K Aguirre

INTRODUCTION

The first functional magnetic resonance imaging (fMRI) scans of a human being were obtained on a clinical MRI scanner.[1] This is not surprising as, at the time, virtually every MRI machine into which a human could fit was in clinical practice, reaping the benefits of the previous decade of rapid development of imaging technology. Belliveau's groundbreaking observation of visual cortex activation was performed using bolus injections of an MRI contrast agent, but subsequent studies quickly adopted Ogawa's technique[2] of measuring the endogenous effects of deoxygenated hemoglobin. In the years that have followed, blood oxygen level-dependent (BOLD) fMRI has become a pervasive method in the normative study of the human brain. In contrast to the rapidity with which BOLD fMRI has transformed cognitive neuroscience, clinical applications have come more slowly. As the chapters in this book attest, however, the time is now ripe to reap the benefits of clinical fMRI.

This chapter provides an overview of fMRI concepts and approaches, with a particular focus upon the clinical uses of fMRI. After a brief overview of the physics and physiology that provide the basis of the BOLD fMRI technique, the properties of the BOLD fMRI system that impact paradigm design are considered, particularly the sluggish nature of the hemodynamic response and the presence of slow drifts and fluctuations in the fMRI signal over time. This is followed by a discussion of how classic 'blocked' and 'event-related' approaches are simply extreme points within a continuous space of possible designs that exchange statistical power for task predictability. The chapter concludes with a consideration of the types of clinically relevant information that might be gleaned from a functional neuroimaging study, and provides an inferential framework for such approaches.

THE ORIGIN OF THE fMRI SIGNAL

The existence of fMRI depends upon two rather fortuitous properties of physics and physiology. The first is that hemoglobin, the primary oxygen-carrying molecule in the blood, has different magnetic properties when bound and unbound to oxygen. The second is that there is an exquisite coupling of local neuronal activity and blood flow within the brain. As a result, changes in neural activity result in perturbations of the local magnetic field via changes in blood flow. Although the mechanisms that mediate neurovascular coupling are still very much under investigation, the properties of this relationship are fairly well described. Increases in neural activity are accompanied by increased metabolic demands, leading to a transient decrease in local oxygen content.[3] A compensatory vascular response follows within 1–2 s. It appears that the aspect of neuronal activity that drives this delayed hemodynamic response is the local field potential: a measure of synchronous dendritic activity over a population of neurons.[4] The increases in local blood flow and volume produce an overabundance of oxygenated hemoglobin, decreasing the deoxyhemoglobin concentration.[5] This is sometimes

referred to as a paradoxical change, as increased metabolic activity leads to decreased deoxyhemoglobin.

Deoxyhemoglobin has stronger magnetic properties than oxyhemoglobin. Therefore, a decrease in the deoxyhemoglobin concentration results in a decreased perturbation of the local magnetic field (referred to as a susceptibility gradient). The local perturbation of the magnetic field can be measured using MRI techniques, specifically the T2* relaxation time.[6] fMRI data, then, are images of the brain over time that measure T2* and reflect, through a chain of associations, local neuronal activity. It is because imaging contrast is mediated by blood flow and oxygen concentration that this method of fMRI is called blood oxygen level-dependent (BOLD). There are several excellent reviews of these details for the interested reader (see e.g. Moonen and Bandettini[7]).

BOLD fMRI data in raw form are volumetric images of the brain, obtained every couple of seconds, over the course of minutes to a couple of hours. Just as the image on a television screen is composed of small dots called 'pixels', the three-dimensional images of the brain provided by fMRI are composed of small, three-dimensional dots called 'voxels' (as they have volume). Typical BOLD fMRI experiments obtain a complete image of the brain every 2–3 s, and are composed of voxels that are 3 mm × 3 mm × 3 mm in size (requiring approximately 40 000 voxels to cover the entire volume of the brain).

The spatial and temporal resolution of BOLD fMRI is limited by the neurovascular coupling that is the source of contrast. While MRI images can readily be obtained every 100 ms, and with spatial resolution on the order of tenths of a millimeter, this fine resolution has little practical advantage. Changes in neural activity give rise to a change in BOLD fMRI signal that evolves over seconds (described in detail below). As a result, BOLD fMRI images are seldom acquired more frequently than once a second. Additionally, a point of neural activity engenders a change in BOLD signal that spreads over several millimeters;[8] thus, BOLD images are typically composed of voxels (the smallest volume 'pixel' of which the image is composed) no smaller than 1 mm on a side.

An important property of the BOLD fMRI signal is that it has no simple, absolute interpretation. This is because the particular signal value obtained is not exactly a measure of deoxyhemoglobin concentration, but is instead a measure weighted by this concentration (i.e. it is T2*-weighted) and is also influenced by a number of other factors that can vary from voxel to voxel, scan to scan, and subject to subject. As a result, experiments conducted with BOLD fMRI generally test for differences in the magnitude of the signal between different conditions within a scan. One could not, for example, directly contrast the absolute level of the BOLD fMRI signal obtained within the temporal lobe of schizophrenic patients with that from controls with much hope of obtaining a useful statistical test. Notably, this is not necessarily true of all fMRI methods. For example, arterial spin-labeled (ASL) perfusion MRI[9] can provide a quantitative measure of cerebral blood flow that is in absolute units (e.g. cm^3 of blood/100 g of tissue/min). Because of this property, and others mentioned in greater detail below, perfusion fMRI may have particular application to clinical fMRI.

THE PROTOTYPICAL fMRI STUDY

There is now a bewildering array of paradigm designs and analysis approaches that are applied to BOLD fMRI. Later in this chapter, a heuristic is provided for considering different experimental designs. Let us start, however, by considering a 'prototypical' fMRI study to introduce several concepts.

Suppose that we wish to measure the magnitude of the neural response within the primary visual cortex to a standardized flash of light in a group of subjects. Perhaps we ultimately wish to compare the evoked response between patients with optic nerve damage and those without. It might be the case that evoked neural activity is consistently

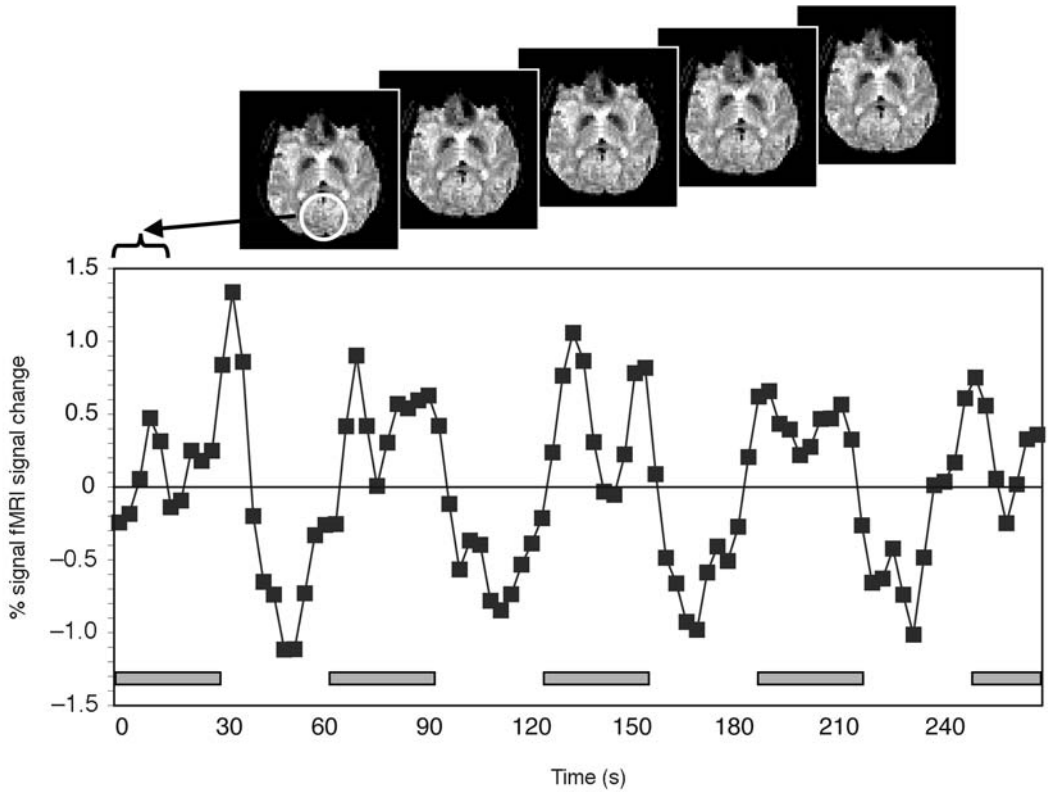

Figure 2.1 Example of a BOLD fMRI time series that might be obtained from the visual cortex during 30 s periods of visual stimulation alternating with 30 s of darkness. A single, axial slice through the raw, echo-planar images is shown for the first five time points.

less in those patients who have been afflicted with optic neuritis, so that measurement of such a response in future, unselected patients may have diagnostic value (replacing the visual evoked potential study that measures surface electrical potentials).

Consider the data that we might obtain from one, normal control subject in this study. The subject is placed in the scanner and, while whole-brain BOLD fMRI images are collected every 3 s, the subject is presented with alternating periods of 30 s of flashing lights followed by 30 s of darkness. After the data have been collected, we anatomically define the location of the primary visual cortex, and then examine the BOLD fMRI signal that was obtained from this region. Figure 2.1 shows one axial slice through the first five BOLD fMRI images across time, and the corresponding average signal that was obtained from within the primary visual cortex. As can be seen, there was a rise and fall of the BOLD fMRI signal over time, corresponding to the periods when the lights were on and off. We could perform a statistical analysis to confirm the impression that the BOLD fMRI signal responded to the presentation of lights. We could further measure the magnitude of the signal change between the light and dark conditions, and compare that with other subjects and between patient and control groups.

This simple paradigm illustrates several basic points about BOLD fMRI data. First, the effect of flashing lights upon the neuroimaging signal can only be assessed by comparison with the periods of darkness. If the subject had been presented with a continuous period

of flashing lights, then no modulation of the signal would be obtained and there would be nothing to measure. Second, this paradigm makes use of a 'blocked' alternation between stimulus conditions – a block of 30 s of flashing light is alternated with a block of 30 s of darkness. This is in contrast to other approaches (so-called event-related designs) where stimuli are presented more rapidly and in a less predictable order. In this simple example, the two conditions compared were fairly elementary. Other types of fMRI designs might compare more complicated mental operations, such as the cognitive process of working memory and an appropriate control condition. Finally, from inspection of the graph of the BOLD fMRI signal, it can be seen that the changes in the signal seem to follow the changes in light stimulation after a delay of a few seconds.

SYSTEMS, HEMODYNAMIC SIGNALS AND TEMPORAL NOISE

In the preceding example, we measured the BOLD fMRI signal that followed the presentation of a light stimulus to a subject. One useful way of considering the study is in terms of systems theory. Simply defined, a system is something that takes input and provides output. There are many examples of systems, such as a stereo speaker that takes electrical input through a wire and provides acoustic output. What is the system under study in the example experiment provided above? A useful way to answer this question is to consider that two, separate, systems are at work in an fMRI study. The first system is that of cognition, in which the inputs are the instructions, stimuli, and tasks presented to the subject, and the output is the pattern of neural activity evoked within the brain. The second system is the domain of physiology and physics, and mediates the transformation of neural activity inputs into blood flow responses and imaging signal. For our example, the first, neural, system converted the light stimulation into neural activity in primary visual cortex. The properties of this system are determined by the connections between, and dynamic properties of, the retina, lateral geniculate nucleus, and visual cortex. The second system is that of BOLD fMRI, which transforms local neural activity into the T2*-weighted BOLD signal. In this example, and in most clinical applications, it is the response of the first system that is principally under study. An exception might be studies of stroke and compromised vascular states (see Chapter 8), in which the properties of the transformation of neural activity into a change in blood flow may be of interest.

If it were the case that the properties of both systems were unknown, then the relationship between cognition and BOLD fMRI signal would be underdefined: one would be unable to assign a given change in imaging signal to cognition or neurovascular coupling. Fortunately, the properties of the second system (the BOLD fMRI system) are lawful and well described, even if the exact mechanisms of the transformation are still not well understood. Indeed, one of the advantages of viewing BOLD fMRI in terms of systems theory is that we gain the ability to describe the transformation of neural activity to imaging signal without having to consider the mechanistic details that provide the transformation.

As it turns out, BOLD fMRI behaves very much like a linear system. Linear systems have properties that make them particularly amenable to study. For example, doubling the size of the input to a linear system doubles the size of the corresponding output. Properties such as this make it possible to accurately predict what the output of a linear system is to any particular input. The predictive abilities of a linear system can be completely characterized by a property called the impulse response function (IRF), which is the output of the system to an infinitely brief, infinitely intense input. In the context of BOLD fMRI, the hemodynamic response function (HRF) is taken as an estimate of the IRF of the BOLD fMRI system, and is the change in BOLD fMRI signal that results from a brief (<1 s) period of neural activity. Knowledge of the shape of the HRF allows one to predict the

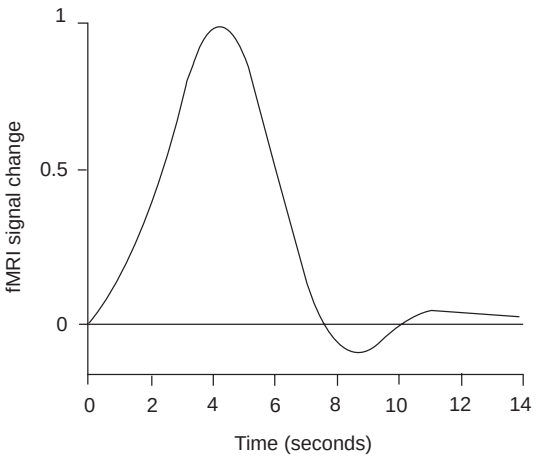

Figure 2.2 The BOLD hemodynamic response. This is the average BOLD signal change that follows a brief period of neuronal activity.

BOLD fMRI signal that will result from any pattern of neural activity.

The HRF can be measured empirically from human subjects by obtaining the BOLD fMRI signal that is evoked by experimentally induced, brief periods of neural activity in known cortical areas (e.g. neural activity in the primary motor cortex in response to a button press). Figure 2.2 presents the shape of the average HRF that might be found within the motor cortex across a population of healthy, young subjects. As can be seen, the shape of the HRF reflects the relatively slow changes in vascular physiology that follow changes in neural activity, and the response rises and falls smoothly over a period of about 16 s. While the shape of the HRF varies significantly across subjects, it is very consistent within a subject, even across days to months.[10] There is some evidence that the shape of the HRF varies from one region of the brain to another (perhaps from variations in neurovascular coupling), but this is a difficult notion to test as it is necessary to create evoked patterns of neural activity in disparate areas of the brain that can be guaranteed to be very similar.

Although neural activity can rise and fall rapidly (on the order of milliseconds), the shape of the HRF tells us that changes in blood flow respond much more slowly (on the order of seconds). One consequence of this is that rapid changes in neural activity are not well represented in the BOLD fMRI signal. The 'temporal blurring' induced by the HRF limits the patterns of neural activity that might be detected using BOLD fMRI. Specifically, the smooth shape of the HRF makes it difficult to discriminate closely spaced neural events. As a consequence, many fMRI paradigms are designed to evoke relatively prolonged changes in neural activity, as was the case in our paradigmatic example above. With clever experimental design, however, it is still possible to use BOLD fMRI to detect (1) brief periods of neural activity, (2) differences between neural events in a fixed order, spaced as closely as 4 s apart, (3) differences between neural events, randomly ordered, closely spaced (e.g. every second or less), and (4) neural onset asynchronies on the order of 100 ms. As is described in greater detail below, there is a cost in statistical power that accompanies these designs.

Another important property of BOLD fMRI data is that the signal over time is rather unstable. Regardless of whether the subject is engaged in the performance of a task or resting quietly, the BOLD fMRI data contain large drifts and surges over time. This noise in the data becomes more and more prominent at longer and longer timescales (and can be termed low-frequency noise). In addition to complicating statistical analysis of such data,[11] the presence of the low-frequency noise in BOLD fMRI data renders slow changes in neural activity difficult to detect. Notably, the effects of the slow hemodynamic response and the noise properties of BOLD fMRI are in opposition. The shape of the HRF would tend to favor paradigms that induce slow changes in neural activity, while the presence of low-frequency noise would argue for experimental designs that produce more rapid alterations in neural activity. As it happens, knowledge of the shape of the HRF and the distribution of the noise is sufficient to

provide a principled answer as how best to balance these two conflicting forces.

Perfusion fMRI was mentioned before as an alternative fMRI method that is able to provide quantitative measures of cerebral blood flow over time. Perfusion imaging is also notable for the absence of the long-timescale noise that plagues BOLD fMRI studies.[12] As a consequence, perfusion fMRI is well suited to the study of slow changes in neural activity, and might find application in the study of (for example) rehabilitation or emotional states.

CLINICAL CONSIDERATIONS OF THE HRF

As has been described, with knowledge of the shape of the HRF, one can make accurate predictions regarding the transformation of neural activity into BOLD fMRI signal. These predictions can be used for optimizing paradigm design, by asking which patterns of induced neural activity would produce the largest and most easily detected changes in BOLD fMRI signal. Knowledge of the HRF can also be used in a statistical fashion to identify cortical areas where predicted changes in neural activity have taken place. If the task paradigm is expected to produce a particular pattern of neural activity, then it is possible to identify cortical locations where the predicted pattern of BOLD fMRI signal was observed. It is this predictability of the BOLD fMRI system in its mapping of neural activity to BOLD signal that makes possible the use of the technique to test ideas about the brain and behavior.

Because of the central role played by the HRF in dictating optimal paradigm design and the analysis of BOLD fMRI data, it is important to ask if aging and disease pathology can alter the properties of the HRF. This is a critical issue if one wishes to compare BOLD fMRI responses between, for example, young and elderly subjects, or between a patient population and age-matched controls. Consider again our prototypical fMRI experiment. There, we measured the neural response within the primary visual cortex to a standardized flash of light. Suppose we had measured this response within a group of 10 college-age students and a group of 10 healthy, elderly subjects. If we found that there was a smaller BOLD fMRI signal change in response to the light in the elderly group as compared with the young group, we would conclude that less neural activity is evoked in the visual cortex in the elderly group. An alternative explanation, however, is also available. If it were the case that the coupling of neural activity and blood flow response is altered in the elderly as compared with young controls, then the same magnitude of neural activity in the two populations might produce different BOLD fMRI signals.[13] Clinical studies that make use of fMRI are rather susceptible to this confound, where differences in the population HRF might be mistaken for differences in the neural response (for a comprehensive review, see D'Esposito et al[14]). It is possible that drug treatments or pathological states might alter neurovascular coupling and produce these effects.

A general approach to addressing concerns regarding neurovascular coupling is to measure a hemodynamic response in each of the two populations to be compared using a paradigm that is not expected to differ between the groups. For example, one might wish to examine the effect of drug administration upon the working memory response of the prefrontal cortex in children with attention deficit hyperactivity disorder. To ensure that any difference between the treatment and control populations is the result of a difference in neural activity in the prefrontal cortex, and not the effect of the drug upon neurovascular coupling, a simple control task, such as paced finger movements, can be performed. If there is no difference between the populations in the neural activity evoked by this control task within the primary motor area, then it is less plausible that a global change in neurovascular coupling can explain the effects seen in the prefrontal cortex during the working memory challenge.

PARADIGM DESIGN

Control of mental operations

In our prototypical fMRI experiment, we compared the neural activity obtained during presentation of flashing lights and darkness. In other clinical applications, it is often the case that more complex mental states are to be examined. Instead of the effects of flashing light upon neural activity, one might wish to measure the effects of holding information in memory or making judgments about the appearance of objects. Many studies have as a requirement that some aspect of the stimulus or mental operation be varied so that the neurocomputational correlate of its processing can be studied. In the following, two broad classes of experimental manipulation of mental states are described.

Cognitive subtraction is the prototypical method of isolation of a cognitive process. Typically, one condition of an experiment is designed to engage a particular cognitive process, such as face perception, working memory, or semantic recall. This 'experimental' condition is contrasted with a 'control' condition designed to evoke all of the cognitive processes present in the experimental period except for the cognitive process of interest. Differences in neural activity between the two conditions are then attributed to the cognitive process of interest. In essence, a mental state is isolated in an 'all or none' fashion. In our example experiment, periods of flashing light were contrasted with periods of darkness to isolate the neural response to light perception. In a study that sought to assess the neural correlates of working memory, periods during which the subject held information across a brief delay might be contrasted with periods that did not require retention of information.

While it is a widely applied approach, cognitive subtraction is prone to some failures of inference. For example, we do not have direct control over the mental states of the subject, so the danger is always present that the subject might engage in a confounding mental operation in addition to the one of interest. Additionally, cognitive subtraction relies upon the assumption that a cognitive process can be added to a pre-existing set of cognitive processes without affecting them (an assumption termed pure insertion). This might fail if, for example, the act of pressing a button to signal a working memory judgment is different from pressing a button in response to a control task. Effects upon the imaging signal that result from this difference in motor output would be erroneously attributed to working memory per se.

Several other cognitive process manipulations have as their goal a reduction in the reliance upon the assumption of pure insertion. The cognitive conjunction design[15] was developed for this purpose. The method uses a set of paired cognitive subtractions, each of which need not completely isolate the cognitive process of interest. The imaging data are then analyzed to find areas that have a significant, consistent response across subtractions. The identification of the same region across multiple pairs of subtractions strengthens the conclusion that the area is activated by the cognitive process that is isolated in each of the subtraction pairs.

Parametric designs offer another alternative to subtraction approaches. In a parametric design, the experimenter presents a range of different levels of some parameter, and seeks to identify relationships (linear or otherwise) between the imaging signal and the values that the parameter assumes. If we were to modify our prototypical experiment to employ a parametric approach, we might present flashing lights that varied in their degree of contrast. It would then be possible to measure the relationship between neural activity and stimulus contrast (a contrast response function). Particular disease states might be identified by an alteration in the shape of this function, as opposed to an absolute reduction in the magnitude of the neural response to maximal stimulation.

There are other types of clinical fMRI study that might not require experimental control of the behavioral state of the subject. For example, studies of seizure localization using

fMRI (see Chapter 6) do not attempt to induce particular patterns of neural activity in the subject, but instead detect neural activity that is spontaneously produced. Similarly, studies of visual hallucinations would measure the neural correlate of a brain state that is not directly under the control of the experimenter (or the subject!).

Timing of events

As BOLD fMRI experiments by necessity include multiple task conditions (e.g. an 'experimental' and a 'control' period), several ways of ordering the presentation of these conditions exist. In our prototypical experiment, periods of flashing lights and darkness were grouped into relatively long, alternating 'blocks' of 30 s each. In contrast to this 'blocked' design, we might have employed an 'event-related' approach, in which brief flashes of light would be presented every 10 or 15 s, or perhaps randomly intermixed with brief periods of darkness of different durations. While 'blocked' and 'event-related' approaches are often perceived as rather concrete categories, the distinction between these, and other sorts of designs, is fairly arbitrary. They are better considered as extremes along a continuum of arrangements of stimulus order. Consider every period of time during an experiment as a particular experimental condition. This includes the 'intertrial interval' or 'baseline' periods between stimulus presentations. In this setting, blocked and event-related designs are viewed simply as different ways of arranging periods of 'rest' (or no stimulus) with respect to other sorts of conditions. (For a more complete exploration of these concepts, see Friston et al.[16])

The trade-offs between different experimental designs can be understood in terms of three factors: detection power, randomness, and estimation efficiency.[17] Detection power is the statistical power that the design provides to detect induced changes in neural activity. The benefit of greater detection power is largely self-evident – the greater the detection power, for example, the shorter the duration of scanning needed to obtain robust results. Randomness describes the predictability of the order of the experimental conditions. For certain classes of study (e.g. tests of memory), it is important that the subject be unable to anticipate the upcoming trial type. In general, increasing the randomness of the design will tend to decrease the detection power. Finally, estimation efficiency is the ability of the design to measure the precise shape of the hemodynamic response function. It is mentioned here for completeness, but for most clinical studies, estimation efficiency will be a relatively unimportant consideration.

A blocked fMRI design is one that maximizes detection power at the expense of randomness. In these designs, two or more conditions alternate in a fixed order over the course of a scan. For most hypotheses of interest, these blocks of time will not be utterly homogeneous but will consist of several trials of some kind presented together. Blocked designs have the obvious difficulty that the subject can anticipate trial types, which may be undesirable in some settings. On the other hand, blocked designs have superior statistical power compared with all other experimental designs. This is because the fundamental frequency of the boxcar can be positioned at an optimal location with respect to the filtering properties of the HRF and the low-frequency noise. For typical shapes of the HRF and distributions of temporal noise, this ideal balancing point occurs with epochs of about 20–30 s in duration.

Event-related designs model signal changes associated with individual trials, as opposed to blocks of trials. This makes it possible to ascribe changes in signal to particular events, allowing one to randomize stimuli, assess relationships between behavior and neural responses, and engage in retrospective assignment of trials. These designs have reduced power compared with blocked designs. Conceptually, the simplest type of event-related design to consider is one that uses only a single stimulus type, and uses sufficient

temporal spacing of trials to permit the complete rise and fall of the hemodynamic response to each trial; a briefly presented picture of a face once every 16 s for example. This is frequently termed a sparse event-related design. Importantly, while this prototypical experiment has only one stimulus, it has two experimental conditions (the stimulus and the intertrial interval). If one is willing to abandon the fixed ordering and spacing of these conditions, more complex designs become possible. For example, randomly ordered picture presentations and rest periods could be presented as rapidly as once a second. The ability to present rapid alternations between conditions initially seems counterintuitive, given the temporal smoothing effects of the HRF. While BOLD fMRI is insensitive to the particular high-frequency alternation between one trial and the next, it is still sensitive to the low-frequency 'envelope' of the design. In effect, with closely spaced, randomly ordered trials, one is detecting the low-frequency consequences of the random assortment of trial types. These rapid event-related designs are fairly sensitive to the accurate specification of the HRF for their success.

There is a large range of 'hybrid' designs that seek to balance detection power and randomness. For example, 'stochastic variation' designs[16] can admit some (incomplete) degree of unpredictability to the ordering of the stimuli while still maintaining relatively high detection power. The recent work of Liu[17] provides an exhaustive consideration of the trade-offs between detection power and randomness.

It should also be noted that there are many other, 'specialist' fMRI experimental designs that do not easily fit the categories discussed so far. Within-trial discrimination designs[18] are used, for example, to discriminate periods of neural activity within a behavioral trial. The benefit of this approach is that closely spaced neural events can be discerned, even if their order cannot be randomized (for example, the delay period that falls between seeing a stimulus to be remembered and making a response based upon that stimulus). Neural-onset asynchrony designs[19,20] are used to detect differences in the timing of neural activity evoked by different stimuli. Here, a sparse event-related design is used, along with exquisite coupling of the timing of stimulus presentation to image acquisition. A difference in the time of onset of the smooth, BOLD hemodynamic response evoked by two different stimuli within a cortical region is sought. Traveling-wave stimuli are used to define topographic maps of cortical responses, the most familiar being the retinotopic organization of early visual areas.[8] These designs use stimuli that vary continuously across some sensory space (e.g. retinal eccentricity), and identify, for any point within a cortical area, what was the optimal position of the stimulus within the sensory space for the evocation of neural activity. These designs are often combined with cortical flat-map techniques for the display of results.[21]

STATISTICAL THRESHOLDS IN CLINICAL fMRI

The preprocessing and statistical analysis of BOLD fMRI data is a sizable and complicated topic that cannot be given a comprehensive review here (for a good overview, see Ashburner et al[22]). One topic, however, that is worth discussing in the context of clinical fMRI is the balance of statistical control of false-positive and false-negative results.

BOLD fMRI data are typically analyzed in a 'massively univariate' approach. One begins with a statistical model that contains covariates (predictors) of the expected pattern of BOLD fMRI responses, and this model is then evaluated at each of the (upwards of 40 000) voxels that comprise the entire brain dataset. The product is a statistical map, in which every voxel in the brain contains a corresponding statistical value for the contrast of the covariates of interest. The final step of the analysis involves assigning a level of statistical significance to those values. If the dataset were composed of a single voxel, then this would be a straightforward enterprise: a *t*-value of greater than 1.96 would be significant

at a $p = 0.05$ level (presuming many degrees of freedom and a two-tailed test). Because there are many voxels, however, we must correct for the likelihood that noise alone might render one *t*-value significant if many are tested. Solutions to perform this correction in the face of spatial smoothness (which renders adjacent voxels non-independent) exist within gaussian random field theory.[22]

Performing the appropriate, mapwise correction to control the false-positive rate can frequently yield a rather stringent statistical value necessary to label any result significant. This, in turn, raises concerns about 'false-negative' results, in which true experimental effects might be missed because the experiment is underpowered. While this is of some general concern in the normative studies of cognition to which fMRI is frequently applied, it is of particular concern for clinical applications of fMRI. Within the clinical context, the desired balance between false positives and false negatives is altered. For example, if one is using an fMRI study to define areas of 'eloquent' language cortex to be spared during a tumor resection (discussed further below), the cost of a false-negative result is quite high: cortex that may be important for language processing is not identified and is improperly removed. Therefore, an assessment of statistical power, while infrequently performed in cognitive neuroscience studies, should play an essential role in well-constructed clinical applications.

It may further be the case that the level on which statistical control of the false-positive rate is sought may differ between normative and clinical applications. Cognitive neuroscience imaging studies typically control the mapwise or regionwise false-positive rate, meaning that if 20 statistical maps were produced under null-hypothesis conditions (i.e. in the absence of any actual experimental treatment), only one would on average be expected to contain even a single false-positive voxel. In clinical applications, it may be sufficient to control the false-positive rate of voxels within a statistical map, as opposed to across statistical maps. Such a measure is provided by the false-discovery rate (FDR) approach.[23] Instead of controlling the false-positive rate at a mapwise level, the FDR method controls the proportion of false-positive voxels present within a single map. For example, an FDR threshold of 5% implies that, of the voxels identified as significant within a statistical map, 5% are on average expected to be false positives. The FDR threshold is adaptive, in that it becomes more stringent in the face of reduced signal, and in the limit is equivalent to traditional mapwise thresholds in datasets that contain no experimentally induced signal change. This is neither better nor worse than traditional mapwise control of the statistical significance, but is instead a different stance with regard to inference. FDR methods will likely be of considerable use in clinical applications. For example, it may be desirable to express the confidence of results of functional mapping for surgical planning in terms of the specificity of the population of voxels identified.

MODES OF CLINICAL INFERENCE WITH fMRI

Introduction

With a general understanding of the properties of fMRI and the types of paradigm designs that might be used, there now follows a survey of the types of clinically relevant information that fMRI can obtain. Different 'modes of inference', or ways of applying fMRI methods to answer particular clinical questions will be discussed. Each mode of inference requires certain assumptions and provides for different logically supported conclusions. Particular attention will be paid to those sorts of conclusions that can be deduced logically from the results of an fMRI study and those that, while not logically required, may be found to hold empirically. These categories are not meant to be exclusive or exhaustive, but hopefully will provide a guide to thinking about the properties of different clinical functional neuroimaging studies. While reference will be made to fMRI in particular, these notions apply in

general to any correlative neuroimaging method (e.g. positron emission tomography (PET) and event-related potentials). Further, the discussion will be restricted to functional imaging approaches that have as their central measure a change in neural activity. This is to distinguish these applications from other types of 'functional' imaging, such as receptor binding assays, measurements of resting cerebral blood flow, and other measures of metabolic function that are not directly related to alterations in regional neural activity.

Localization of necessity

One of the first clinical applications of fMRI was to presurgical mapping (see Chapter 10). The desired inference in this setting is to identify cortical tissue that is necessary for a given mental operation so that it is not removed along with pathological tissue during a subsequent surgical procedure. This mode of inference might be called 'localization'. For example, one might wish to identify those cortical areas around a glioma that are necessary for language, in order to minimize the risk of producing aphasia following tumor resection.[24] In such studies, the subject is presented with a task designed to selectively evoke a particular cognitive state of interest. The key assumption here is that the behavioral paradigm can isolate the mental operation of interest. Various techniques might be used (e.g. cognitive subtraction or parametric manipulation, discussed earlier) to isolate the mental operation of interest from the other processes that invariably are present (e.g. button pushing, preparing responses, etc.).

A critical aspect of clinical fMRI for localization is that, in a strict sense, the desired conclusion cannot be logically supported by the study! We wish to identify cortical areas necessary for a mental operation, in the sense that surgical removal of the area would impair the patient's ability to perform the task. The converse inference is also important: that we can identify areas that are not necessary for the mental process. Does finding activation of a cortical region in a functional neuroimaging study imply that the region is necessary for the cognitive process? In short, the answer is no. The primary cause of this state of affairs is the observational, correlative nature of neuroimaging. Although we make inferences regarding cognitive processes, these processes are not themselves directly subject to experimental manipulations. Instead, the investigator controls the presentation of stimuli and instructions, with the hope that these circumstances will provoke the subject to enter a certain cognitive state and no other. Although cooperative, the subject may unwittingly engage in confounding cognitive processes in addition to that intended by the experimenter, or alternatively, may fail to differentially engage the process. For example, a subject might constantly engage in the process of declarative memory formation, even during periods of time when he is 'supposed' to be performing some other, control behavior. It is therefore not possible to know if observed changes in neural activity in a brain region are the result of the evocation of the cognitive process of interest or an unintended, confounding process. Negative results (even in the face of arbitrarily high statistical power) are also not conclusive, not only because of the failure of perfect control of evocation of cognitive processes, but also because of the possibility that the neuroimaging method employed is not sensitive to the critical change in metabolic activity (e.g. the pattern of neuronal firing as opposed to the bulk, integrated dendritic activity).

Despite these caveats, it is still possible that clinical fMRI studies of the localization of mental operations can be successful. The reason is that, while it is not logically required that a localization study be able to define necessary regions, it may be the case that empirically the necessity of a cortical region for a mental operation correlates very highly with the results of an imaging scan. For example, there has been interest in using BOLD fMRI to replace the Wada or intracarotid amobarbital test (see Chapter 6). Performed to guide surgical resection of epileptic foci, each internal carotid artery is in

turn catheterized and instilled with anesthetic to determine which hemisphere is dominant for language. The hope is that BOLD fMRI can be used to determine which hemisphere responds to language tasks and replace this invasive procedure. While it is not logically required that the Wada test and the BOLD fMRI results be in accord, practically this has been found to be the case. Indeed, the careful work of Binder and his colleagues has been focused upon finding just the right behavioral paradigm that provides this high degree of correlation. In effect, the ability of a clinical fMRI study to localize necessary cortical regions for a given mental operation must be demonstrated empirically by reference to invasive methods (e.g. surgical resection, Wada testing, or transcranial magnetic stimulation), and cannot be assumed based upon the findings of imaging studies alone.

Detection of dynamic pathology

Essentially the complement of the previous application, fMRI may be used to identify cortex with pathological neural activity. The properties of this mode of inference derive from the use of fMRI to detect spontaneous patterns of neural activity that are unlike neural activity evoked by normal mental operations. The prototypical use is the detection of the cortical origin of seizure activity (see Chapter 6). Unlike many of the other applications of fMRI discussed here, the localization of pathological neural activity does not rely upon a behavioral or stimulus paradigm to create a particular pattern of neural activity, but instead is designed to detect endogenous, pathological neural patterns. Of course, the study might create circumstances favorable to the induction of seizure activity (e.g. sleep deprivation or photic stimulation). In the case of seizure mapping, the goal might be simply to diagnose the presence of seizures, or to identify cortex that, if removed, would reduce or eliminate the seizure activity. There are other neurological disorders that are marked by the presence of pathological patterns of dynamic neural activity. For example, migraine is marked by spreading neural depression that might be detected using fMRI.[25]

In some cases, the clinician may know the timing of the neural events to be detected through symptom occurrence or from other forms of monitoring (e.g. simultaneously acquired scalp electroencephalography (EEG)). In this case, identification of the location of the pathological activity is relatively straightforward, as the shape of the HRF can be used to predict the pattern of BOLD fMRI signal that would result from a region that had neural activity time-locked with the symptoms or neurophysiological recording. Under other circumstances, the clinician may wish to identify brain areas that demonstrate pathological patterns of neural activity, even when it cannot be specified when those events took place. To do so, it is necessary to specify signal parameters that can distinguish between normal and abnormal neural patterns. For example, one might find that a propensity for seizure activity in the mesial temporal lobes is marked by an oscillation in the fMRI signal of a particular frequency from this location. Actual applications would require far more sophisticated methods of signal processing.[26] Distinguishing such pathological signals from background noise and imaging artifacts presents the primary challenge for this type of application of fMRI.

Diagnostic and therapeutic classification

There is a broad range of clinical applications of fMRI that might fall under the title diagnostic and therapeutic classification. The goal here is to use the measured neural response to some behavioral or stimulus paradigm to place patients within a diagnostic category or to predict their response to therapy. fMRI might be used in this way to classify patients with psychiatric disorders or to predict which patients are likely to recover from brain injury and benefit from rehabilitation. In fact, the simple example study presented at the outset of this chapter, in which the response of the visual cortex to a

flash of light might classify patients as having optic nerve disease, is an example of this mode of inference.

Unlike applications that attempt to discern the necessity of a cortical area for a functional process, fMRI studies performed for diagnostic and therapeutic classification need only to establish correlation for their inference. Suppose that a particular magnitude of neural response within the frontal cortex during an attention paradigm strongly predicts if a child will benefit from drug therapy for attention deficit disorder. In a clinical sense, it is irrelevant if that frontal region is actually necessary for performance of the task, or if the pharmacological therapy actually acts at that cortical site – what is important is that the fMRI study is very good at predicting response to therapy, regardless of the underlying mechanism.

The critical requirement for a useful classification study is that the neuroimaging data provide information that could not be obtained by a more readily available physiological or behavioral measure. One might, for example, attempt to develop an fMRI test for Alzheimer's disease (see Chapter 3). Across an elderly population, activation in the hippocampus during performance of an episodic memory task might be found to correlate rather well with subsequent pathology obtained at autopsy. Such a test would only be useful, however, if the correlation were better than that provided by the behavioral performance on the test! This is a crucial point, as neural activity as measured by fMRI can be found to very accurately reflect simple behavioral performance measures.[27]

Under what circumstances might there be a divergence of performance and neural activity, such that the fMRI study might be of superior predictive value than behavioral measures? A ready analogy is provide by the application of the electromyogram/nerve conduction study (EMG/NCS) to prediction of recovery from peripheral nerve injury. Immediately following a compressive lesion to the peroneal nerve in the leg, for example, a patient might no longer be able to flex his foot at the ankle. On examination, the patient is unable to generate any measurable force in the affected muscles, but the clinician knows that some patients with this examination go on to improve whereas others will remain permanently weak. An EMG/NCS of the affected muscles and affected nerve can provide this prognostic information by determining if the nerve still has the ability to conduct electrical impulses, in which case the nerve is in continuity and there is a good chance for recovery over the next few months. The discrepancy between the predictive value of the clinical examination and that of the electrophysiological test is the result of a 'floor effect' in the measurement of weakness. No matter whether or not the nerve was in continuity, the effect of the trauma was to produce complete weakness now.

fMRI has great promise to become the EMG/NCS of cortical rehabilitation. It might be used to demonstrate that a cognitive pathway (e.g. for language) is 'in continuity' despite the presence of a severe deficit immediately following a lesion. Not just the degree of predicted recovery, but the assignment to different rehabilitative programs, could be informed by these methods.

Surrogate measure of behavioral state

Some diseases produce symptoms that are subjective, and can only be imperfectly measured by observation or patient report. The experience of pain is an example of this kind (see Chapter 9). In other cases, patients experience symptoms that they under-report, such as those with drug addiction who minimize their degree of drug craving. Some patients may have important internal cognitive states that are not evident to the clinician, such as patients who are 'locked in' from pontine lesions or those who are in a minimally conscious state following more extensive cortical damage.[28] Finally, there are patients who feign neurological deficit either due to psychopathology or in hope of secondary gain. In each of these cases, fMRI might be used to measure an internal mental

state of a subject that is not easily obtained through simple behavioral observation.

This application of fMRI reverses the usual direction of inference that is employed in neuroimaging studies. One begins by assuming that a particular cortical region is activated by a particular mental operation. The fMRI data are then examined to determine if increased neural activity was present within the specified region during the task – and, if so, the conclusion is drawn that the subject experienced the particular mental state of interest. To support this mode of inference, it is necessary to first demonstrate that neural activity in the monitored location is actually indicative of the mental state to be measured. What can provide this kind of evidence? Logically, only an exhaustive neuroimaging examination of every possible cognitive process, under every possible circumstance, could provide the necessary evidence. This is obviously impossible in practice, so a series of neuroimaging experiments that demonstrate activation of a particular region during a given cognitive process and no other usually suffices to support the assumption (a logical inference termed enumerative induction). For example, over a series of experiments, one might demonstrate that the degree of activation within an area of the insula is proportional to the degree of craving for rewarding stimuli in control subjects (e.g. food or nicotine[29]). In a population of patients undergoing behavioral therapy for drug addiction, measurement of the degree of activation within the insula in response to pictures of drug paraphernalia might be taken as a surrogate measurement of the effectiveness of reducing drug craving.

The general challenges of using surrogate markers in clinical trials and other therapeutic settings have been well addressed.[30] In the particular context of clinical fMRI, it should be noted that the value of the surrogate measure application is dependent upon the soundness of the assumption that activation in a region is a unique identifier of a given mental state. For early cortical areas, a unique mapping of neural activity to a particular sensory impression may be well justified, but as more abstract behavioral states are assessed by observation of association cortical areas, the assumption becomes more tenuous.

CONCLUSIONS

These categories should provide a useful guide for considering different clinical applications of fMRI techniques. As mentioned, this is not an exhaustive list, and one can conceive of clinical applications that do not fit well within these categories. For example, this chapter has not addressed the use of fMRI in patients to study redundant cortical systems for mental operations. This application is primarily used to better understand normative systems for cognition,[31] but may see clinical application as well.

Finally, it should be noted that these techniques of clinical fMRI have been described here in terms of the measurement of regional, bulk neural activity. More subtle measures are also possible. For example, one can assess the degree of effective connectivity between different cortical regions – the extent that one cortical region influences neural activity in another region.[32] Such a metric could be used with any of these described clinical applications. One might find, for example, that the signature of attention deficit disorder is decreased effective connectivity between prefrontal and parietal regions during attention-demanding tasks, independent of the average level of neural activity in each region.

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Alzheimer's disease

3

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INTRODUCTION

The application of neuroimaging technology to study Alzheimer's disease (AD) has been steadily increasing over the last two decades. To date, the majority of neuroimaging contributions to understanding the pathophysiology and clinical course of AD have utilized structural magnetic resonance imaging (MRI) and positron emission tomography (PET). Influenced by pathological data, which reveal that the earliest disease manifestations are in medial temporal lobe (MTL) structures such as the hippocampus and entorhinal cortex,[1] structural MRI studies have largely focused on volumetric measures of the MTL. Starting in the early 1990s, MTL volumes were shown to distinguish age-matched normal controls and AD patients, including those with very mild forms of the disease where the diagnosis of dementia was not yet conclusive.[2,3] Further studies using quantitative volumetric measures have now demonstrated that MTL volumes predict progression to AD from mild states of memory impairment[4–7] and correlate with impaired memory performance in AD patients,[8,9] thus supporting the contention that MTL volumetric measures are both clinically and biologically relevant. The application of structural MRI has continued to advance as other measures have complemented the volumetric studies. For example, the use of diffusion-weighted (DWI) MRI, sensitive to the random motion of water in the brain, revealed an increase in the apparent diffusion coefficient (ADC) in the hippocampus of AD patients that predicts progression to AD from mild impairment.[10,11]

Despite considerable data on anatomical changes accompanying AD, less is known of concomitant physiological alterations. Over the last two decades, and until very recently, studies that have explored physiological changes in AD have used functional tomographic techniques, specifically PET and single photon emission computed tomography (SPECT), for molecular imaging. These techniques generate three-dimensional brain maps of radionuclide distribution reflecting biochemical and physiological processes. The first studies, in the early 1980s, revealed regional changes in both oxygen and glucose metabolism in AD patients[12,13] that have been confirmed to be reductions primarily localized to the temporal, parietal, and posterior cingulate cortex.[14,15] In agreement with the volumetric MRI studies of the MTL, functional tomographic techniques have been shown to have both high sensitivity and high specificity for differentiating AD patients from healthy older individuals and those with mild cognitive impairment,[16,17] as well as predicting progression of the disease.[18–20]

In contrast to the two decades of AD research using structural MRI, PET and SPECT, it was only as recently as 1999 that functional MRI (fMRI) appeared in the scientific literature as a research tool to study AD.[21] fMRI, first developed in the early 1990s,[22] has been used predominantly by neuroscientists to examine the neural basis of cognitive and behavioral processes, and only recently has it been applied to study patients with neurological disease. Its widespread availability, noninvasiveness, high spatiotemporal resolution, and reasonable cost, especially when

compared with PET scanning, have all contributed to its increasing popularity. As with PET and structural MRI research, fMRI studies of AD have focused on two overlapping objectives: understanding the basic biological mechanisms and pathophysiology of AD, and the development of an effective diagnostic tool – a clinical biomarker. The development of fMRI as a biomarker is anticipated to influence clinical management of AD in three significant ways: differentiating healthy aging and AD, enhancing diagnostic specificity when evaluating a patient with dementia, and monitoring the biological progression of AD for the purposes of drug development and drug testing. In this chapter, we will review studies that have initiated this process and paved the way to achieve our clinical goals in AD management as well as expanding our understanding of the disease process.

DIFFERENTIATING HEALTHY AGING AND AD

At long last, we are on the cusp of offering effective treatment for AD. Even the most effective treatment, however, is anticipated to halt and not reverse neuronal dysfunction. Therefore, treatment will be most effective when administered to patients in the earliest stages of disease. We know that AD begins in the hippocampal formation before spreading to other areas of the brain[23] and the pathological hallmarks of AD – plaques and neurofibrillary tangles – have been identified during postmortem evaluation in individuals without dementia.[24] Corresponding to this anatomical pattern of progression, AD presents as mild forgetfulness years before the onset of dementia.[25–27] Unfortunately, as a wide range of animal studies have established, normal aging itself also targets the hippocampal formation.[28] Thus, by blindly assigning the diagnosis of early AD to any older individual with hippocampal-dependent memory decline, our sensitivity for detection will reach 100%, but our specificity will be unacceptably low. Imaging will enhance our ability to detect AD as early as possible only when it can distinguish AD from normal aging.

As discussed above, structural MRI studies of MTL volumes have already been somewhat effective in this goal. However, it is hypothesized that physiological changes will precede the development of gross atrophic changes, especially given the extent of tissue loss necessary for consistent MRI detection. Thus, it is anticipated that the identification of functional biomarkers using fMRI will aid in the identification of preclinical AD and lead to earlier treatment.

Over the last few years, research efforts have attempted to identify early evidence of physiological dysfunction by using fMRI to compare regional brain activity in four different populations: healthy older individuals, older individuals with risk factors for AD, those with mild cognitive impairment (MCI), and mild AD patients. Healthy older adults who are considered to reflect 'normal' aging, are normal–high cognitively performing individuals (compared with age-matched norms), with no neurological or psychiatric disease and minimal accompanying medical disorders. Individuals at higher risk for AD are frequently defined as healthy older adults who possess at least one apolipoprotein E (*APOE*) ε4 allele on chromosome 19 and/or a significant family history. Genetic studies have identified an association between the presence of the ε4 allele and late-onset AD, which begins after age 60.[29,30] MCI is considered a transitional stage between healthy aging and very mild AD.[31] MCI often refers to older individuals with complaints of a decline in their cognitive abilities, objective evidence of cognitive performance deficits out of proportion to that expected for age, and failure to meet commonly accepted criteria for dementia. However, this definition is not fully specified or agreed upon and varies greatly between studies. When memory loss is the predominant feature, MCI is defined as amnestic MCI (aMCI) and has been revealed to be a prodromal state of AD.[32,33] Indeed AD pathology has already accumulated in many of these individuals and thus it often reflects

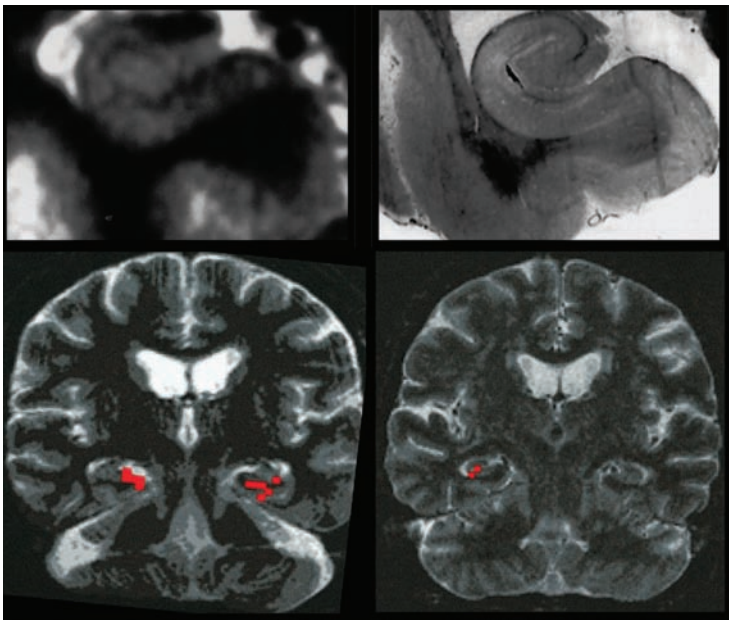


Figure 3.1 The BOLD response in the hippocampal formation induced by a cognitive 'stress test' dissociates Alzheimer's disease from age-matched controls. Top: Comparison of a high-resolution MRI image (left panel) with a postmortem histological slice (right panel) demonstrates that MRI can, in principle, visualize individual hippocampal subregions. Bottom: When viewing unfamiliar faces, the BOLD response in the hippocampal formation is diminished in an Alzheimer's disease patient (right panel) compared with an age-matched control (left panel). Whether this difference in BOLD signal reflects a disease-related change in vascular or neuronal physiology remains unknown. Adapted from Small et al.[21]

early-stage preclinical AD.[34] Mild, probable AD is defined by commonly applied criteria for dementia and the exclusion of an identifiable cause other than AD. fMRI studies of these populations have focused largely on comparisons of blood oxygen level-dependent (BOLD) activation patterns during a cognitive task, although there have been alternative approaches that study deactivations and chronic metabolism.

Alterations in regional activations

Most fMRI studies directed at achieving clinical goals are based on the experimental designs pioneered by cognitive neuroscientists that use behavioral tasks to probe neural function with the BOLD signal as a dependent measure.[22] The BOLD signal is an indirect measure of neural activity that is dependent on the blood flow-mediated relationship between neural activity and the concentration of deoxyhemoglobin within the surrounding microvasculature. When a neural event occurs anywhere in the brain, there is a local blood flow increase[35] that results in a decrease in the concentration of paramagnetic deoxygenated hemoglobin in the microvasculature surrounding the activated region.[36] This local increase in the ratio of non-paramagnetic oxygenated hemoglobin to paramagnetic deoxygenated hemoglobin[37,38] results in the detection of an increase in the BOLD signal.[39] This increase in regional BOLD signal is thus usually interpreted as an increase in neural activity.

The most common approach for studying AD has been to compare the degree of regional activation (BOLD signal magnitude and anatomical extent) while subjects representing various populations perform a task considered to tap into a cognitive process compromised by the disease. Based on this logic, the majority of studies have focused on memory tasks and fMRI BOLD signal changes localized to MTL structures.[21,40–44] Four of these studies compared the magnitude of MTL activation during tasks that involved visual memory encoding in healthy older adults and patients with mild AD.[21,40,42,43] The results of these studies were consistent with each other and identified a decrease in MTL activation in mild AD patients compared with healthy older controls (Figure 3.1), mirroring the findings of MTL atrophy using volumetric MRI techniques.[2,3] These studies established

that alterations in the magnitude of the BOLD signal in MTL structures during a memory task might constitute another indicator of early AD. However, they did not determine whether detectable functional changes precede gross structural changes as hypothesized, and still leave uncertainty as to the nature of the relationship between atrophy and changes in BOLD signal.

To truly assess the practical usefulness of fMRI as a diagnostic tool for AD, it is necessary to study individuals with the subtlest indication of dysfunction to determine whether it is possible to identify those who may have preclinical AD that is undetectable by other techniques. Small et al[21] studied several older adults with isolated memory impairment and identified a subset who had a similar pattern of decreased activity in hippocampal regions as AD patients. Comparable to this finding, a study of healthy older adults, MCI patients and early AD patients revealed a decrease in MTL activation during memory encoding in both the MCI and AD patients relative to the older controls.[40] However, these studies did not incorporate a longitudinal assessment, and so it is not possible to determine that the presence of decreased MTL activation predicts subsequent clinical course. A longitudinal fMRI study of 32 MCI patients revealed that a larger extent of activation of an MTL structure, the parahippocampal gyrus, was associated with greater clinical impairment (based on Clinical Dementia Rating score) at baseline and subsequent decline after a 2.5-year follow-up.[5] This increase may be the result of a compensatory response to accumulating AD pathology. As Dickerson et al[5] point out, there are numerous differences between studies that could account for such disparities with the Machulda and Small findings:[21,41] different population selection, data analysis methods, and subject performance.

Compensatory increases in brain activity have also been proposed to explain observations of increased regional activity in studies of normal aging[45] and studies of individuals without cognitive impairment who are at increased genetic risk for AD.[46–49] Carriers of the *APOE* ε4 allele, compared with non-carriers, have increased BOLD signal in multiple brain regions on memory tasks (hippocampus, parietal, and prefrontal cortex[46,48]) and a letter fluency task (parietal cortex[49]). These results suggest that older adults at increased genetic risk for AD may compensate for preclinical pathology by exerting additional cognitive effort to achieve comparable levels of performance that is then detected as increases in regional brain activity. Additionally, *APOE* ε4 allele carriers were found to generate the same activity pattern as non-carriers on an attention task, suggesting that the compensation is not merely a reflection of increased difficulty, but might have some specificity for the cognitive demands of the task.[47] However, these results are not entirely straightforward to interpret, as there are many differences in the precise regions of activity increases in these studies, as well as findings of identifiable regions of decreases (inferior temporal cortex[49] and hippocampus[48]).

In summary, comparability between these studies is difficult owing to numerous methodological differences and a high degree of individual variability that exists in both older controls and subtly impaired populations. Although an unequivocal conclusion is not yet possible, there is an accumulation of evidence that the earliest detectable changes may be regional compensatory activity increases, followed by decreases in activity as regions become increasingly damaged by AD pathology. The need for longitudinal fMRI studies with large numbers of subjects is necessary to confirm these inconsistent findings.

Alternative fMRI approaches

Not all fMRI studies focus on comparing areas of activation during a cognitive task. Two alternative fMRI approaches have been utilized to investigate brain differences between AD and normal aging: mapping deactivation patterns across the whole brain and mapping basal oxygen metabolism within

the hippocampal formation. The former relies on the presence of regional deactivations identified during cognitive tasks in young subjects. These regions of deactivation are consistently located in the posterior cingulate cortex, ventral anterior cingulate cortex, and inferior parietal cortex, and reflect greater activity during a rest period than during a task period (the rest period is often a baseline in fMRI cognitive experiments). These regions that are most active during rest have been proposed to constitute a 'default-mode network' involved in monitoring internal states that is suspended during goal-directed behavior.[50] Two studies have investigated alterations in the default-mode network in early AD. Greicius et al[51] used independent component analysis to reveal decreased resting-state activity in the posterior cingulate cortex and hippocampus, which they interpreted as a reflection of disrupted connectivity between these two regions. Lustig et al[52] revealed a failure of deactivation in AD, such that the posterior cingulate cortex decreased in activity in young adults soon after the onset of a semantic classification task, but remained active in AD patients. It is still unclear, however, how these changes in deactivation in the posterior cingulate relate to reductions in resting metabolism in the same region, a hallmark of AD patients studied with PET/SPECT.[15]

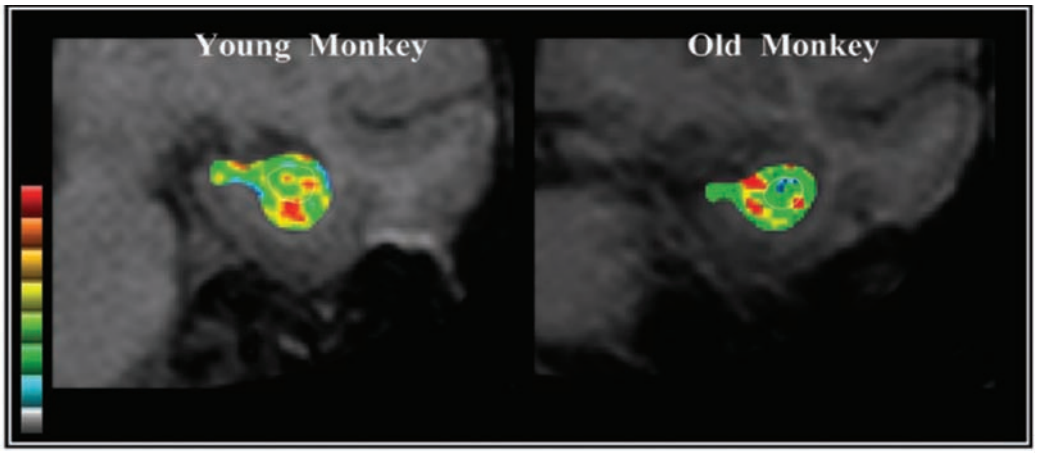
Using fMRI to investigate patterns of basal metabolism within a singular structure – the hippocampal formation – is a second approach that dissociates AD from normal aging. The hippocampus is a complex structure organized into separate but interconnected subregions: the entorhinal cortex, the dentate gyrus, the CA subfields, and the subiculum.[53,54] Each hippocampus subregion houses a distinct population of neurons unique in their molecular expression profiles. It is this molecular uniqueness that accounts for why each hippocampal subregion is differentially targeted by mechanisms of dysfunction.[28] Thus, although both early AD and normal aging cause hippocampal dysfunction, they are predicted to target different subregions of the hippocampal circuit. In order to test this prediction, an imaging technique requires submillimeter spatial resolution in order to visualize the diminutive hippocampal subregions.[55] Motivated by this need, a number of studies have relied on correlates of basal oxygen metabolism – either cerebral blood volume or deoxyhemoglobin content – to investigate the hippocampal circuit in AD and in aging.[56,57] As evidenced by extensive PET and SPECT studies, almost any cause of brain dysfunction manifests as defects in basal metabolism (for reasons discussed in Chapter 1), and relying on the basal state allows a significant enhancement in spatial resolution.

Indeed, using these variants of fMRI, studies have shown that AD and normal aging target different hippocampal subregions:[56,57] The entorhinal cortex is the hippocampal subregion most vulnerable to AD, while the dentate gyrus is relatively spared; in contrast, the dentate gyrus is most vulnerable to normal aging, while the entorhinal cortex is relatively spared (Figure 3.2). This anatomical double dissociation, and the ability to visualize it in living subjects, forms the basis of a large-scale epidemiological study, in which cerebral blood volume maps of the hippocampal formation will be generated in hundreds of healthy elders, who will then be followed prospectively. This study will test the prediction that healthy elders with entorhinal-predominant dysfunction are harboring the earliest stages of AD.

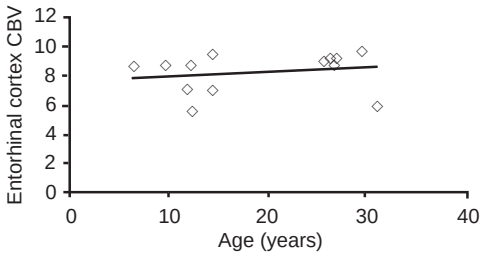
SPECIFICITY OF THE AD DIAGNOSIS

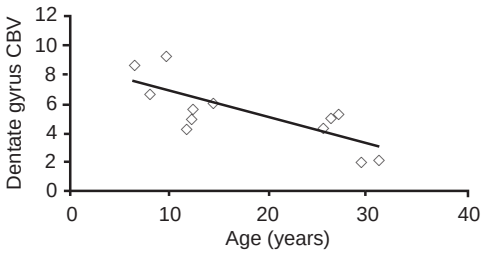
As a number of epidemiological studies have documented, the diagnostic sensitivity of AD, when presented with a demented patient, is quite high.[58] In fact, if we were to blindly assign the diagnosis of AD to every patient whose clinical evaluation suggests dementia, our sensitivity could well reach 100%. Our failure is reflected in poor diagnostic specificity – the ability to correctly diagnose the cause of dementia when presented with a

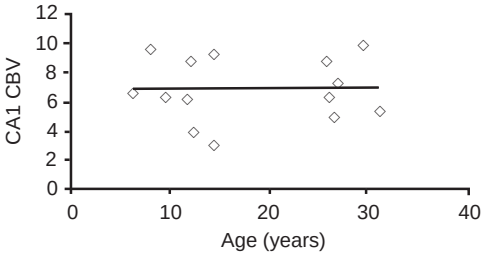
(a)

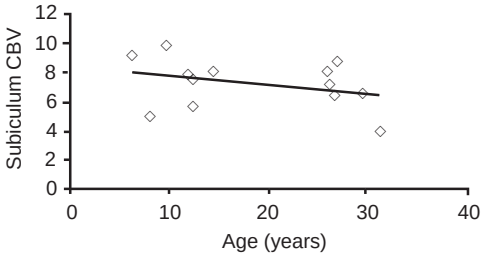

Young Monkey
Old Monkey

(b)

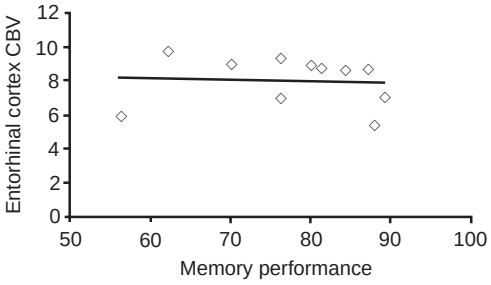

Entorhinal cortex CBV
Age (years)

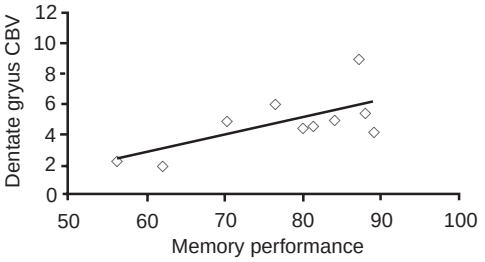

Dentate gyrus CBV
Age (years)

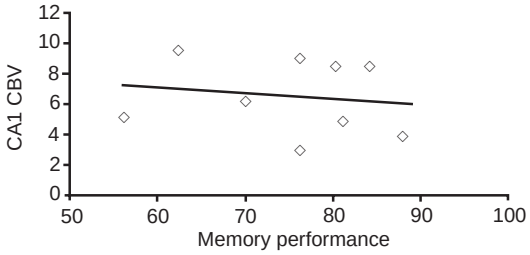

CA1 CBV
Age (years)

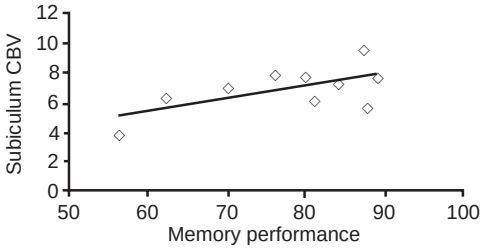

Subiculum CBV
Age (years)

(c)


Entorhinal cortex CBV
Memory performance


Dentate gryus CBV
Memory performance


CA1 CBV
Memory performance


Subiculum CBV
Memory performance

patient who has a non-AD etiology. The diseases that are incorrectly diagnosed as AD are typically within the general category of neurodegeneration, a list that includes dementia with Lewy bodies (DLB), frontotemporal lobe dementia (FTD), corticobasal ganglionic degeneration, progressive supranuclear palsy, Parkinson's disease with dementia, and prionopathies.[59] Imaging will improve our specificity, and our overall diagnostic accuracy, when it can positively diagnose both AD and non-AD causes of dementia.

One way to achieve the goal of increasing diagnostic specificity is to image the histological markers upon which neuropathologists rely to distinguish the neurodegenerative processes. In this regard, the field of in vivo imaging has entered an exciting new era, as evidenced by a couple of human PET studies[60,61] and more recent mouse MRI studies,[62–66] showing that amyloid plaques, one of the hallmarks of late-stage AD, can be detected in living subjects.

Relying on regional patterns of dysfunction is a second imaging approach that can distinguish between the neurodegenerative causes of dementia. This approach relies on a time-honored tenet in clinical neuroscience, which assumes that diseases will differentially target separate populations of neurons, and therefore separate regions of the brain. This view is partly supported by anatomical observations, showing that in a differential manner AD targets the medial temporal lobes, FTD targets the prefrontal cortex, DLB targets the basal ganglia and the occipital lobes, and corticobasal ganglionic degeneration targets the basal ganglia and the posterior parietal lobes or the premotor cortex. By the time a neurodegenerative process causes dementia, it has spread to large areas of the brain, and for this reason spatial resolution is not really a consideration. Furthermore, most sources of signal are likely to capture regional patterns of dysfunction.

A single fMRI study has attempted to exploit these regional patterns of dysfunction to distinguish between early FTD and AD at a stage at which they are indistinguishable by gross cerebral atrophy.[67] The investigators utilized a working memory task, the verbal *n*-back task, and parametrically varied the information load that the patients experienced. The study revealed that, compared with AD patients, FTD patients showed significantly decreased frontal and parietal cortex activation and a reduced linear increase in activation with load in frontal regions. This study reveals the promise of using fMRI to distinguish between neurodegenerative diseases when structural MRI is not contributory.

MAPPING THE CLINICAL COURSE

Although we have entered the era of pharmacological intervention for AD, this era has just begun and we do not yet have truly effective therapeutics that alter the underlying disease process. Thanks to the insights gained into the molecular biology of AD, there are now many pharmacological agents under development. Accelerating the development of effective anti-AD drugs is the third way in which imaging will impact AD. The ability to longitudinally test drug efficacy in an affected individual is always a more powerful approach than cross-sectional comparisons. Longitudinal drug testing is particularly important when testing the effect of a drug on a slowly progressing disease – as is the case in AD. In general, most imaging approaches will likely prove useful in drug

Figure 3.2 Alzheimer's disease and normal aging cause brain dysfunction by affecting basal metabolic rates. Compared with BOLD, MRI correlates of basal oxygen metabolism are more quantitative and can be generated with higher spatial resolution. (a) Cerebral blood volume (CBV) is one of three correlates of basal oxygen metabolism that can be measured with MRI. CBV maps of the hippocampal formation are shown for a young and an old rhesus monkey. (b) CBV was estimated from individual hippocampal subregions in 14 rhesus monkeys covering the age span. Among all hippocampal subregions, the dentate gyrus was the hippocampal subregion most vulnerable to the aging process. (c) Age-related changes in memory best correlate with age-related changes in dentate gyrus CBV. Adapted from Small et al.[56]

development. Of course, specific modalities might be better suited to a particular mechanism of action – for example PET imaging of amyloid plaques might be the modality of choice for testing an immunotherapy directed at reducing plaque load, and hemodynamic imaging might be the best modality for detecting changes in synaptic strength.

Several fMRI studies have explored the impact of cholinesterase inhibitor treatment, the main therapeutic intervention for AD, on the pattern of brain activity in patients with AD[68] and amnestic MCI.[69,70] Rombouts et al[68] studied the effects of a single dose of rivastigmine on AD patients and revealed increases in activation in the bilateral fusiform gyrus during face encoding and in the prefrontal cortex during a working memory task. Two studies have investigated the impact of cholinesterase inhibitor treatment on MCI patients using different agents: galantamine[70] and donepezil.[69] Goekoop et al[70] revealed an increase in BOLD signal in multiple brain regions for both an episodic memory task and a working memory task after 5 days of galantamine treatment, rather than with a single dose. The study by Saykin et al[69] showed that frontal activity increased from levels recorded at the beginning of the study after 5 weeks of donepezil treatment compared with unmedicated, age-matched controls. This increase correlated with improved task performance. Although these studies are encouraging for the use of fMRI in pharmacological evaluation, there are several limitations that should be accounted for in future studies. For example, none of the studies utilized a placebo control or a method to evaluate the influence of increasing cholinergic levels on the vascular system in order to determine whether the BOLD changes truly reflected neural activity rather than vasodilatation.

CONCLUSIONS

The dovetailing of advances in pathophysiology and in imaging technology is moving us closer to achieving our clinical goals of AD detection, diagnosis, and drug development. In fact, we have gained enough theoretical insight and technical sophistication that our current array of imaging tools are adequate to capture key elements of AD pathology. What is still lacking, in most cases, is empirical validation. As has been the case for structural MRI and functional tomography, fMRI studies will have to more conclusively establish the sensitivity and specificity for differentiating AD patients from healthy older individuals and the ability of fMRI to predict disease progression. Within the next few years, the neurobiological assumptions and the practical utility of fMRI will be rigorously tested – either by prospective epidemiological studies in humans or, more mechanistically, in animal models of disease.

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Drug addiction

4

Elliot A Stein

INTRODUCTION

Humans take psychoactive drugs for many reasons, including relief from withdrawal, direct hedonic effects, performance enhancement, and mood alteration.[1] Although abused drugs come from different pharmacological classes (e.g. opiates, psychostimulants, alcohol, and barbiturates) and produce physiological and behavioral effects that are unique to their class (e.g. analgesia, constipation, paranoia, and sedation), research over the past quarter-century suggests that their reinforcing properties are linked to common neuroanatomical and neurochemical systems.[2,3] In addition to a putative common neurobiological linkage, another hallmark of human drug abuse is the high recidivism rate when abstinence is attempted. For example, within 6 months of attempting to quit cigarette smoking, more than 95% of individuals return to regular smoking.[4] In spite of extensive fundamental insight into the cellular and molecular mechanisms of action of drugs of abuse from preclinical animal and in vitro models,[5,6] such knowledge has been difficult to translate into more successful behavioral and/or pharmacotherapeutic treatments. In part, this may reflect the fact that human drug abuse, although based on the interaction of drugs acting at specific molecular binding sites, is more than a simple pharmacological disease. Rather, these drugs, both acutely and in the long term, ultimately interact in complex and still poorly understood ways with specific cognitive subsystems.

NEUROPSYCHOLOGY OF ADDICTION

Drug addiction has been viewed as a disease of pathological drive and compulsive behavior.[7] The key symptoms of drug addiction in humans are compulsive drug intake and the intense drive to take the drug at the expense of other behaviors and in the face of negative consequences.[8] Following this concept, the acute reward/pleasure produced by drug intake per se cannot account for the compulsive nature of the behavior. Indeed, many abused drugs produce both pleasure and dysphoria, suggesting that the simplistic notion of 'drug reward' does not accurately explain their addictive properties. For example, acute cocaine intake induces a complex pattern of subjective effects that include a brief intense euphoria or 'rush' immediately followed by an extended period of alertness, increased confidence and strength, heightened sexual feelings, and indifference to concerns and cares.[9] However, not only does the rush rapidly dissipate, but also the general behavioral state reverses, despondency, dejection, and despair being hallmarks of a post-cocaine state. Euphoria returns with the next dose of the drug. It is this rapid alternation between 'pleasure' and 'dejection' that has been postulated to lead to the 'binge' pattern of cocaine use, in which the drug is used repeatedly at short intervals until either the supply or the user is exhausted.[10]

Rather than the acute pleasure or euphoria that appears to drive the early use of illicit

drugs, it is the long-term progressive effects that are likely to underlie many of the physiological and psychological pathologies linked to substance abuse.[11,12] In searching for those circuit(s) involved with addiction, it has been postulated that intermittent dopamine (DA) release secondary to repeated drug use leads to disruption of the orbitofrontal cortex (OFC) via a striatothalamic–orbital (STO) circuit.[11] A range of pathologies linked to the OFC supports its central role in regulating drive and obsessive–compulsive disorders, which share with addiction a compulsive behavioral quality.[13] The hypothesis that dysfunction of the STO circuit results in compulsive behavior in addictive subjects was originally corroborated by positron emission tomography (PET) studies showing disruption of striatal, thalamic, and orbitofrontal brain regions in drug abusers.[14,15] More recently, functional magnetic resonance imaging (fMRI), with its superior temporal and spatial resolution, has reinforced and greatly extended our understanding of the reward and STO circuits in humans that are believed to be at the forefront in drug addiction. This chapter will first briefly review the neurobiology of drug abuse and then discuss in greater, although non-exhaustive detail, the application of various MRI-based (and, to a more limited extent, PET) techniques to study the disease in human drug addicts.

NEUROBIOLOGY OF DRUG ABUSE

By the early 1990s, extensive converging preclinical evidence suggested that many (if not all) drugs of abuse act through mechanisms involving the mesocorticolimbic (MCL) DA pathways, a system long identified as the major neural substrate subserving motivational and stimulus-reinforcing properties.[6,16–19] At its simplest, the MCL system consists of dopaminergic neurons within the brainstem mesencephalic ventral tegmental area (VTA) and their target neurons in forebrain regions, including the nucleus accumbens (NAc), medial prefrontal cortex (MPFC), and amygdala.

While abused drugs apparently all induce a net increase in VTA neuronal firing to elevate extracellular terminal field DA levels,[20–22] each class of agents seems to do so via a different cellular mechanism. For example, cocaine and amphetamine elevate DA levels by blocking DA reuptake (and, in the case of amphetamine, also increasing DA release),[23–24] while nicotine acts via presynaptic cholinergic receptors on DA terminals in the NAc and olfactory tubercle and on DA cells in the VTA,[25–26] where it activates DA neurons projecting to NAc and increases the concentration of extracellular DA in the NAc.[27–29] In contrast, opiates (e.g. heroin and morphine) activate DA neurons via disinhibiting inhibitory γ-aminobutyric acid (GABA)ergic interneurons in the substantia nigra and VTA.[24,30] Phencyclidine (PCP) blocks excitatory, descending glutamate inputs onto NAc medium spiny neurons.[31] Other drugs of abuse, such as ethanol, barbiturates, benzodiazepines, and cannabinoids, also increase DA release in the NAc, possibly via GABAergic disinhibition of VTA DA neurons.[32,33] Importantly, descending forebrain excitatory glutamatergic efferent fibers are known to modulate both VTA and NAc output neurons.[34]

The vast majority of human imaging studies have investigated brain mechanisms underlying nicotine and cocaine abuse. Thus, a brief overview of these agents is provided. Cocaine is a short-acting psychostimulant that produces marked physiological and behavioral alterations in both experimental animals and humans. Acutely, cocaine increases heart rate (HR), blood pressure (BP), stereotypy, and locomotion, increases attention and arousal, decreases fatigue, and produces a profound euphoria.[35] The MCL and nigrostriatal DA systems are thought to be principally involved in the reinforcing and motor activating properties, respectively, of cocaine,[2,3] while the NAc is suggested to lie at the limbic–motor interface[36] involved in the reinforcing and locomotor effects of both drugs.[37]

Nicotine is capable of producing tolerance and physical dependence,[38] and acutely increases HR and BP.[38,39] While the casual user

often reports such negative sensations as lightheadedness, nausea, respiratory distress, sweating, and feelings of fear or loss of control,[40] experienced nicotine users report profound behavioral effects, including memory facilitation, locomotor activation, antinociception, mild calming, and appetite suppression.[41,42] Further, cigarette smokers report intravenous (IV) nicotine as pleasant, preferring it to cigarettes.[43] Although nicotine and cocaine have very different mechanisms of action, they appear to share many behavioral properties and neuroanatomical loci.[20] For example, cocaine abusers identify IV nicotine as similar and, in many cases as identical to IV cocaine,[40,44] while nicotine can substitute for self-administered cocaine in the rat.[45] Further, self-administration of either drug increases glucose metabolism in identical limbic regions in the rat,[46] while a nicotine patch increases cue-induced cocaine craving in cocaine addicts.[47] Like cocaine, nicotine is thought to interact with DA in the MCL system, although the neurobiological mechanisms of nicotine reinforcement are less well understood.[48,49] Additional targets have also been proposed for the action of nicotine on the central nervous system (CNS), including the brainstem pedunculopontine tegmental nucleus and laterodorsal tegmental nucleus.[50]

In addition to behavioral studies (for review, see Xi and Stein[51]), invasive animal model imaging techniques (mostly autoradiographic metabolic studies of regional cerebral glucose metabolism ($rCMR_{glc}$) and cerebral blood flow (rCBF) and in vitro receptor autoradiographic studies) have also pointed towards selective increases in MCL regional activity following acute drug administration.[52–56] These studies have served as the bases for the few published human fMRI and PET experiments reviewed below.

HUMAN IMAGING STUDIES

Non-invasive brain imaging has opened an especially rich field of inquiry and provides the best opportunity to study the neurobiological mechanisms associated with human drug abuse in vivo. At least two main classes of experiments and approaches have been employed to address the problem. These include pharmacological challenge studies, where (generally) drug-experienced individuals receive an injection of their principal drug of choice, and cognitive/affective neuroscience experiments, where specific constructs hypothesized to be involved in the disease are probed during image acquisition. Several design variations, especially for the latter, are possible, including between-group (target and control populations) and/or within-group designs (e.g. with and without treatment, in the presence or absence of acute or chronic drug administration, during withdrawal, etc.). Additionally, depending upon the specific hypothesis to be tested and whether it includes 'state' or 'trait' characteristics, dependent imaging measures might include magnetic resonance spectroscopy (MRS), blood oxygen level-dependent (BOLD), or other indirect markers of neuronal activity (e.g. arterial spin labeling (ASL), cerebral blood volume (CBV), and cerebral metabolic rate of oxygen ($CMRO_2$)), and anatomically based methods such as diffusion tensor imaging tractometry (DTI), voxel-based morphometry (VBM), and region of interest (ROI)-based volumetric analyses. Finally, a few studies have looked at 'resting-state' BOLD signal alterations between groups.

Pharmacological challenge studies

Cocaine and other psychostimulants

That cocaine-induced euphoria might be associated with a decrease in cerebral metabolism was first suggested by London et al,[57] who demonstrated a global decrease in $rCMR_{glc}$ in experienced polydrug users following an acute 40 mg cocaine injection. This group has gone on to hypothesize that other abused drugs, including morphine and nicotine, share a common property of reducing cerebral metabolism.[58,59] These pioneering studies using [^{18}F]fluorodeoxyglucose (FDG)-PET gave impetus for today's fMRI pharmacological examinations.

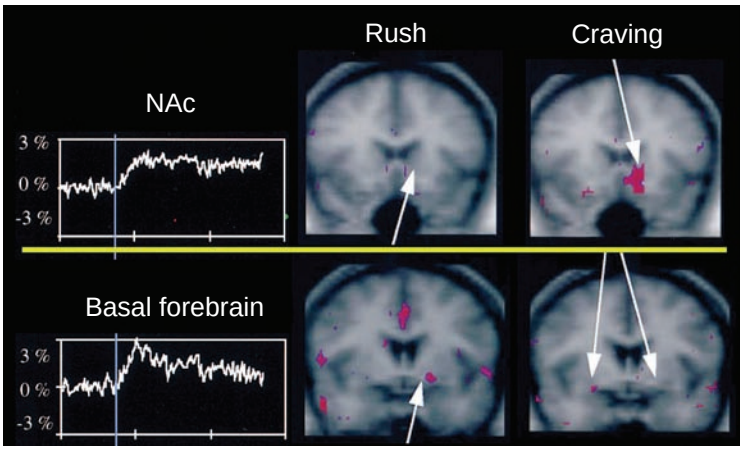

Figure 4.1 Effects of acute cocaine administration in a group of experienced cocaine users. The BOLD signal time courses on the left illustrate the mean signal from the nucleus accumbens (NAc) and basal forebrain before and after a single injection of 40 mg cocaine (drug injection at vertical line). When each subject's behavioral ratings of 'Rush' and 'Craving' were used as an input vector in a cross-correlation analysis with that subject's BOLD signal time course, the NAc activity correlated with 'Craving', while the basal forebrain activity only correlated with 'Rush'. White arrows indicate regions of interest, Adapted from Breiter et al.[65]

The rapidly emerging field known as pharmacological MRI (phMRI) has, to date, been applied mostly in animal experiments.[60–64] However, several groups have used BOLD imaging to determine the acute effects of abused drugs in humans. In an early application, Breiter et al[65] administered a single dose of cocaine to a group of experienced cocaine users. They reported mostly BOLD signal increases in multiple brain regions, including the NAc, basal forebrain, basal ganglia, insula, VTA, and various frontal and other cortical regions; a signal decrease was seen in the amygdala. Subjects reported a rapid, drug-induced rush followed by a more delayed feeling of drug craving during the experiment. When these self-reports were correlated with the subjects' BOLD signals, transient activation was seen in the VTA, basal forebrain, thalamus, caudate, and lateral prefrontal and cingulate cortices during the rush, whereas activation in the NAc and parahippocampal gyrus and deactivation in the amygdala correlated with drug craving (Figure 4.1).

It is not clear why acute cocaine administration caused mostly positive valence effects in the study by Breiter et al,[65] while resulting in mostly metabolic reductions using FDG-PET. It is possible that the very different timescales of the two measures (30–45 min for FDG and several seconds for BOLD fMRI) and different metabolic coupling mechanisms might explain these differences (i.e. glial cells are thought to represent the highest metabolic driver of glucose metabolism secondary to glutamate recycling and gycolysis,[66] while BOLD is thought to reflect changes in local CBF, CBV, and oxygenation.[67]). It should be noted that most rat,[54–56] but not primate,[68] studies have demonstrated increases in metabolic markers of activity following acute cocaine. While it is possible that the cerebral cortex is functionally different or utilizes and/or couples energetics with neuronal activity differently across these species, it is equally likely that different behavioral and pharmacological histories in humans compared with drug-naive animals, or other methodological distinctions inherent in FDG and BOLD measurement assumptions, are responsible for these distinct drug responses.[69] For example, Volkow et al[70] reported that while the effect of a single acute methylphenidate (Mph) injection was to reduce metabolism, repeated injections tended to increase metabolism, especially in the frontal, parietal, and occipital cortices and the hippocampus.

Correlations in spontaneous resting fMRI signal fluctuations, which are thought to be physiologically driven, have been posited to represent functional connectivity within and between cortical areas.[71,72] To determine if cocaine alters low-frequency fluctuations and functional connectivity, Li et al[73] administered cocaine and saline to a group of cocaine

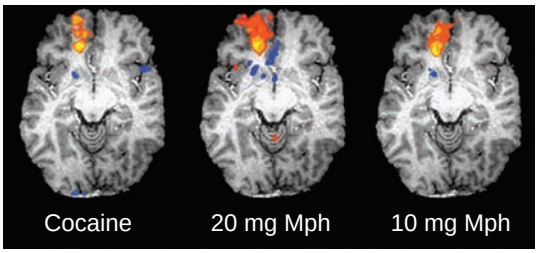

Figure 4.2 Effects of cocaine and methylphenidate on changes in BOLD signal. Superimposed on the T1 axial images (at the level of the nucleus accumbens (NAc)) are the results from *t*-tests against the null hypothesis of no change. Maps were thresholded at $p<0.02$ and 500 µl volume. Illustrated are the group maps following 20 mg cocaine ($n = 13$), 20 mg methylphenidate (Mph) ($n = 13$) and 10 mg Mph ($n = 11$) conditions. Note the strong left lateralization of drug activation of the orbitofrontal cortex and deactivation of the NAc as well as the remarkable overlap of the activation map regions. Adapted from Dirckx et al.[74]

users. Cross-correlation maps were constructed using the synchronous low-frequency signal from voxel time courses after filtering out respiratory, cardiac, and other physiological noise. Using a spatial correlation coefficient (SCC) analysis, a marked 50% reduction in SCC values in primary visual cortex and a 43% reduction in primary motor cortex was observed after cocaine administration. The significant reduction in SCC values in these cortical regions is likely a reflection of changes in neuronal activity, suggesting that BOLD signal time courses become more random following drug administration. These changes in low-frequency components during a resting, no-task situation may also serve as a baseline reference source when assessing the effects of cocaine on task-driven activation (see below).

We have performed a direct within-subject comparison of IV Mph (10 and 20 mg/70 kg) and cocaine (20 mg/70 kg) in a group of cocaine-addicted subjects.[74] Common areas of activation included the anterior cingulate, insula, caudate, and ventral medial frontal gyrus, while the NAc and the inferior frontal gyrus were deactivated. For reasons that are still unclear, the dominant effect was seen on the left side of the brain in this group of right-handed, drug-experienced subjects (Figure 4.2). In all instances, the Mph response lasted significantly longer than that of cocaine. However, despite such common activation patterns, these two pharmacologically similar drugs (both are DA transporter reuptake inhibitors) possess very different abuse liability, suggesting that distinct pharmacodynamic and/or pharmacokinetic properties may be more or as important as the sites or cellular mechanisms of action driving drug use, which at this level of analysis are not easily differentiated. A generally similar story has emerged from the extensive work of Volkow et al,[75] who, using PET, reported increases in activation in OFC and basal ganglia in both healthy controls and cocaine addicts after acute Mph challenge. Interestingly, and perhaps a bit surprisingly when using the relatively long time window of FDG, Volkow et al[76] have reported that expectancy and anticipation significantly modulate the pharmacological effects of Mph, suggesting the important role of cognitive evaluation in the manifestation of 'drug responses'.

To date, virtually all human drug challenge studies have, for ethical and safety reasons, employed subjects who were well experienced with the drug under investigation. However, this has also led to the question of whether the data reflect a drug effect within a brain compromised (neuronal and/or vascular) by years of repeated and often varied, drug administration. A study by Vollm et al[77] has addressed this question by administering methamphetamine (0.15 mg/kg, IV) to drug-naive subjects during fMRI acquisition. Consistent with previous human studies, they observed activation within the OFC, anterior cingulate (subgenu and rostral regions), and dorsal and ventral striatum. Time-course data confirm the observation by Breiter et al[65] of an increase in BOLD signal following stimulant administration and suggest that whatever effects chronic stimulant administration has in the CNS, at this level of analysis the response to an acute drug challenge remains relatively stable over the course of the disease.

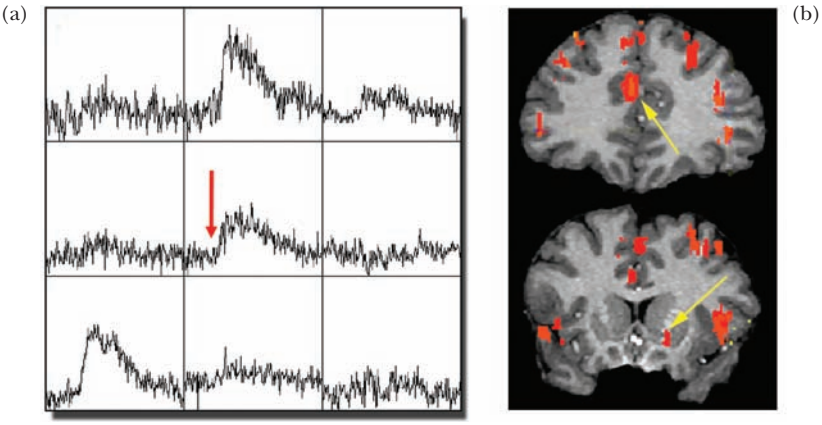

Figure 4.3 Response to a single intravenous injection of nicotine in a group of heavy (>1 pack/day) cigarette smokers. (a) Nine independent BOLD signal time courses taken from the posterior cingulate of a single subject. Nicotine (1.5 mg/70 kg) was administered over a 1 min period 4 min into a 20 min scan (at red arrow). Note the rapid rise and exponential return of the signal back to baseline within approximately 15 min. Note also that only three of the nine contiguous voxels showed an apparent drug effect. (b) Results from a group analysis using a pharmacokinetic analysis model[85] illustrating significant effects of a single nicotine injection (2.25 mg/70 kg). Yellow arrows point to the medial frontal gyrus (top) and nucleus accumbens (bottom). Adapted from Stein et al.[82]

Nicotine

Several PET studies have mapped the acute pharmacological effects of nicotine using metabolic and blood flow markers. Consistent with their observations following acute cocaine[57] and morphine[59] administration, Stapleton et al[58] found reductions in glucose metabolism in almost all of the 30 brain regions measured. In contrast, Zubieta et al[78] reported a CBF reduction in the anterior temporal cortex and an increase in the anterior thalamus following intranasal nicotine, while Domino et al[79,80] observed increases in the thalamus, visual cortex, and cerebellum and decreases in the hippocampus. Rose et al[81] also reported a decrease in normalized amygdala CBF and an increase in the left frontal cortex after acute nicotine administration.

Using a cumulative dosing, within subjects designed study, we reported selective increases in fMRI BOLD signal after acute nicotine administration within such cortical limbic regions as the cingulate, dorsolateral prefrontal cortex (DLPFC), OFC, and MPFC (Figure 4.3).[82] Additional MCL activation in the amygdala and NAc was also seen. These areas of activation are consistent with the behavioral profile seen after IV nicotine[42,83] and the distribution of nicotinic receptors in humans.[84] Further, many of the activated regions have also been implicated in the reinforcing properties of both cocaine and nicotine in animal experiments.[2,20,54]

As for the cocaine studies discussed above, it is again unclear why the various studies and methods employed have failed to yield consistent areas and valence of activation. While the sample of published studies is still modest and additional experiments may ultimately generate a consensus, it is also likely that differences in imaging modality, route, dose and rate of administration, subject selection, and analysis methods can explain the greatest portion of the variance.

Nevertheless, taken together, these acute drug studies highlight the importance of the MCL DA system, traditionally associated in animal experiments with reward behaviors, as also mediating the acute effects of abused drugs in humans. In addition, they illustrate how the fMRI time-course data can help dissociate brain mechanisms associated with temporally discrete affective responses to

drugs, including the initial rush and delayed and sustained craving responses.

Data analysis issues surrounding phMRI brain mapping

Before the advent of fMRI, little was known regarding the real-time dynamic properties of psychoactive substances in the human brain. Early PET studies allowed for only a single (in the case of $rCMR_{glc}$) or at best a few (in the case of rCBF) measurements that averaged together the entire acute drug effect. In contrast, the temporal resolution of fMRI permits rapid, continuous brain measurements. As such, the 'gold standard' of what form a drug-induced signal response might take was unknown. The first study to apply fMRI to a pharmacological challenge in humans[65] was analytically agnostic to the response profile and applied a non-parametric, pre-post injection *t*-test analysis (Kolmogorov–Smirnov, KS) to determine whether the signal after drug administration differed significantly from that in the period immediately prior to the injection. The valence, shape, and magnitude of the signal were lost in this analysis.

Several years ago, we proposed an alternative method to identify significant BOLD signal changes after an acute drug injection.[85] Reasoning that the acute drug effect should follow single-dose pharmacokinetics, we developed a binary decision-making technique based on signal template matching. The BOLD signal was required to conform to certain rise-time and fall-time characteristics while also reaching statistically different peak levels (either positive or negative) and time values in order to be considered a candidate activation site. Specific parameters are chosen based on both published values and empirical observations. A significance level is determined by performing an identical analysis following saline administration, with the hypothesis that any voxels that survive the template matching after saline are noise. Unlike the KS test, this method retains the extensive temporal information available in the full BOLD time series data.

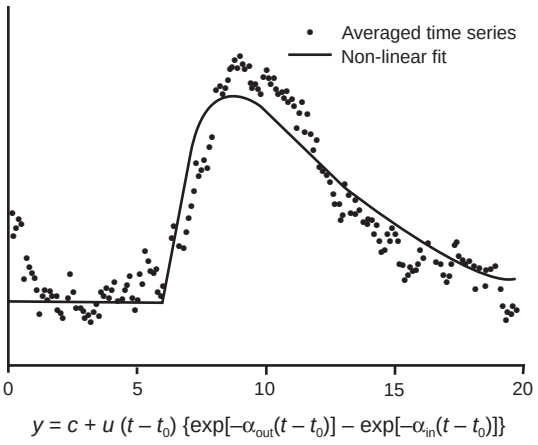

Figure 4.4 The pharmacokinetic model used for the non-linear regression of the BOLD signal (shown in Figure 4.2), expressed as the difference of two exponentials, where t_0 is the onset time, α_{out} is the elimination rate constant, α_{in} is the absorption rate constant, c is the offset relative to a constant fit of the data (–1000 to +1000), and $u(k)$ is the Heaviside unit step function ($u = 0$ if $x<0$ and $u = 1$ if $x>0$). This function has the effect of 'turning on' the function after t_0. Values for α_{out} and α_{in} were varied for methylphenidate and cocaine, according to their known pharmacokinetics. The model allows for both positive and negative changes. The signal change can be expressed as percentage area under the curve. Adapted from Ward et al.[86]

More recently, we have refined this procedure to include formal parametric pharmacokinetic modeling.[86] In this case, the BOLD signal in each voxel is fitted to a difference of two exponents function with an *F*-test performed on the goodness of model fit in each voxel (Figure 4.4). This method has the added advantage of reporting such pharmacokinetically important derived features as magnitude, time to reach peak signal, and duration of effect (i.e. time to reach half maximum, half-return to baseline, etc.). With this information at hand, one can now create brain maps not simply of activated voxels, but rather those with the most rapid signal rise or longest duration of action or largest signal.

Sensory and motor system activity after drug administration

A number of investigators have also employed fMRI to determine the effects of acutely

administered abused substances on various sensory and motor processes. Using an animal somatosensory model, Devonshire et al[87] reported that acute cocaine administration increases the BOLD signal response to vibrissae movement in whisker barrel cortex. Gollub et al[88] and Rao et al[89] argued that their findings of no drug-induced attenuation in, respectively, visual cortex activity after cocaine or motor cortex activation after Mph suggest that the BOLD signal transduction process is unchanged after acute drug administration, allowing these and similar manipulations to serve as bioassay control procedures when performing phMRI studies (see the section below on control procedures).

In contrast, Sell et al[90] reported a decrease in visual activation in human primary visual cortex after acute heroin administration. Acute alcohol intake also produced similar attenuated visual[91] and primary auditory cortex responses.[92] Uftring et al[93] reported specific amphetamine-induced increases in the number of active voxels following a tone discrimination task, as well as during a finger-tapping task, suggesting specific drug-induced neuronal enhancements. Interestingly, caffeine increased visual cortex activation in proportion to the amount consumed.[94] However, this drug-induced enhanced BOLD signal has been attributed not as a consequence of drug-induced neuronal alterations but rather a reduction in baseline BOLD signal, once again without altering the signal transduction processes.[95] As such, caffeine has been suggested to serve as a potential signal contrast booster.

Cognitive imaging studies of human drug abuse

It is becoming increasingly clear that, rather than psychoactive drugs acting in isolation, their effects depend upon the 'baseline' cognitive and affective state of the individual. Notably, such 'baseline' states, especially in individuals who are chronic drug abusers, do not remain constant. Rather, changes in duration, pattern, and amount of drug use are well known to induce neuronal plasticity, which can ultimately alter behavior, either permanently or transiently.[5,6,96] Additionally, whatever neuroplasticity becomes manifest during chronic drug use may reverse, or undergo further adaptive plasticity, during drug withdrawal and abstinence. Drug-induced cognitive impairment (both while under the influence of acute intoxication and during short- and long-term abstinence) is an important avenue for investigation for several reasons. First, such underlying alterations may contribute to or exacerbate cognitive dysfunctions including decision making, reward perception, episodic memory,[97,98] stimulus response-learning or habit learning,[99,100] arousal and attention,[101] and response inhibition[13] – any or all of which may help to perpetuate addiction. Of course, it is equally likely that multiple cognitive subsystems are altered, permanently or transiently, by chronic drug intake.[102] Finally, such putative impairments could limit the efficacy of behavioral treatment modalities, thus enhancing the prospect of recidivism. As such, the interaction of abused drugs with various cognitive constructs is a potentially important research area that might help shed light on the nature of addiction as well as pointing to novel therapeutic directions.

Application of fMRI enables determination of whether an affected cognitive process can be ascribed to a specific brain region(s). However, it is not necessarily the case that an impaired process can be attributable to impaired activation of a structure that mediates that process; instead, performance may be altered by interference from other ongoing processes that occupy separate neuroanatomical spaces. Conversely, neurological impairment that may be detectable by functional imaging may not have readily observable behavioral sequelae. For example, Parkinson's disease can be asymptomatic even with extensive (up to 90%) striatal damage.[103] It may only be through functional activation that neuroadaptive subtleties are best observed. Even with changes in performance, it is not always clear whether brain activation changes are due to changes in attention,

motivation, or central executive systems. Imaging studies may provide a neuroanatomical foundation that will inform, and be informed by, the functional/cognitive effects of abused drugs, and should help explain hypothesized cognitive alterations that are accentuated or attenuated after acute drug administration.

It has been suggested that cognitive functions such as working memory (WM),[104] inhibitory control,[105,106] aspects of decision-making,[107] initiation of goal-directed behavior,[108] concept shifting,[46] and selective attention[109] may reside in the frontal lobes. The frontal cortex is a large and heterogeneous cortical region made up of a variety of functionally distinct subregions. In the context of this chapter, the most important frontal lobe divisions include the DLPFC (Brodmann (BA) areas 9, 10, and 46), the anterior cingulate (BA 12, 24, and 32), and the OFC (BA 11 and 13) (for a review, see Rolls[110]). As most drugs of abuse enhance (among others) DA mechanisms,[2] the ways in which brain regions activated by tasks thought to depend, in large part, on intact frontal functions are altered during and after drug delivery may yield insights into the cognitive profile of dependence. DA dysregulation in drug dependence has been emphasized, as DA has been shown to play an important role in frontal lobe functions, with DA depletion disrupting[111] and DA iontophoresis improving[112] task performance.

Neurobehavioral consequences of chronic cocaine administration

Chronic cocaine use has been linked to cerebral atrophy[113] and hypoperfusion in the frontal, periventricular, and/or temporal–parietal areas.[114–116] Use of cocaine has also been associated with cerebral stroke and hemorrhage (for a review, see Kosten[117]), which likely contribute to the deficits in cerebral perfusion and may underlie at least some of the reported cognitive impairments (see below). In vivo biochemical studies suggest possible long-term cerebral dysfunction in humans, including low glucose metabolism,[57,118] phospholipid metabolism,[119] and adenosine triphosphate (ATP) levels.[120] Prolonged cocaine use may also induce a reduction in endogenous opioid transmission, resulting in an upregulation of μ opioid receptors in the frontal and temporal cortex, anterior cingulate and amygdala that persists for at least 4 weeks of abstinence.[121] Administration of buprenorphine, an agonist at the μ opioid receptor, may normalize opioid neurotransmission and help reduce cocaine intake.[122] Functional consequences of these neuroadaptive properties suggest compromised attention, problem solving, WM, and abstract thinking in chronic cocaine users,[123–126] although inconsistent improvements in reaction time, attention, and learning task performance have also been reported.[127–129]

While drug-free alcohol abusers perform more poorly on neuropsychological tasks of attention and executive function than cocaine addicts,[130] both groups performed similarly poorly (although not as severely) compared with frontal lobe patients on gambling tasks that depend on, and activate, the OFC and amygdala.[14,98,131,132] Both drug addicts and frontal lobe patients show slowed decision making and choose the riskier, ultimately less advantageous, option. This behavioral profile can also be induced in non-drug-users by reducing serotonergic transmission, which putatively causes hypoactivity in the OFC.[131] These findings are consistent with the reductions in OFC serotonergic transmission reported in methamphetamine users,[133] and with abnormal OFC function in cocaine and alcohol abusers.[11]

The loss of control that often accompanies human drug addiction suggests that disrupted executive functioning, including impaired behavioral inhibition arising from altered frontal cortical function, including anterior cingulate and OFC, may be one component of addiction. Patients with lesions in this region are unable to suppress interference from external stimuli;[134] they are impulsive, hyperactive, and distractible, and demonstrate mood lability. Successful behavioral

inhibitions in healthy controls performing a go/no-go paradigm are associated with right-hemispheric activations in ventromedial and dorsolateral frontal, anterior insula, and inferior parietal cortical regions.[135] However, when active cocaine users and non-users completed a similar go/no-go task, the users not only made significantly more commission and omission errors than non-users (suggesting that they did not maintain the task set throughout the entire session), but also showed significantly less activation for successful inhibitions in the right superior temporal gyrus and the anterior cingulate – a region that has been implicated in error detection.[136,137] For unsuccessful inhibitions, users showed hypoactivity relative to non-users in the cingulate, left insula, left inferior frontal gyrus, and right medial frontal gyrus (Figure 4.5). Notably, no between-group differences were found for other regions previously suggested to be important for inhibitory control.[138] A very similar attenuated anterior cingulate response in opiate addicts has been reported.[139] Together, these findings may represent a unique dysexecutive functional profile for drug users in an inhibitory task, and suggest a dysexecutive sequelae of drug abuse such that while drug users are able to perform inhibitory control tasks, task maintenance and error detection may be impaired.

Long-term, chronic drug use is associated with changes in brain function, notably decreases in baseline frontal cortical activity and blunted responses to acute drug administration. Some of these alterations show normalization during detoxification, but others persist, suggesting that cocaine use can permanently alter the brain. For example, during abstinence (1 week to 4 months), frontal cortical rCBF is reduced in the OFC and cingulate gyrus of cocaine abusers, and this decrease correlates with persistent reductions in D2 receptor availability.[140,141] In addition, decreased metabolism in the dorsomedial prefrontal cortex and DLPFC has been reported in cocaine users who were up to 4 months abstinent.[118] Evidence also points to persistent reductions in D2 receptors in alcoholic individuals,[142] although the glucose metabolism deficits seen in alcoholics, particularly in frontal regions, show some recovery during abstinence.[143]

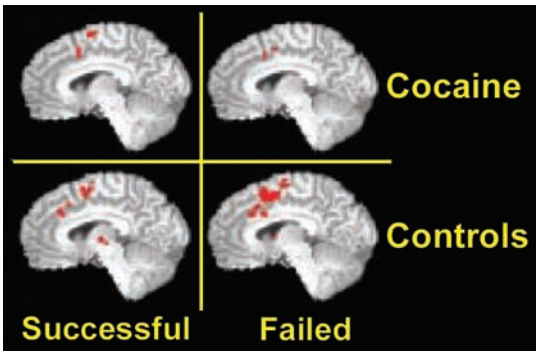

Figure 4.5 Sagittal sections showing midline regions involved in performing the inhibitory control task. Examination of successful inhibitions (left column) and failed inhibitions (right column) between cocaine-using subjects (upper row) and control subjects (bottom row) demonstrates consistent regions of activation for both groups. However, smaller volumes of activation survive thresholding for cocaine subjects for these regions, consistent with significant hypoactivity for cocaine users in midline structures, notably the anterior cingulate. Adapted from Kaufman et al.[138]

Neurochemical consequences of chronic cocaine administration

Proton (^{1}H) MRS, an MRI technique that allows in vivo measurement of brain chemistry, has recently been employed in several drug abuse studies. Lactate can provide information on the level of aerobic and anaerobic metabolism and has been used to examine the acute effects of caffeine.[144] Caffeine is known to stimulate glycolysis and can reduce CBF via its action on adenosine receptors. Global and regional increases in lactate were seen in caffeine-intolerant individuals and regular caffeine users 1–2 months abstinent, but not in current, heavy caffeine users. Regions of increased lactate in response to caffeine included the insula, temporal lobe, frontal cortex, thalamus, and cingulate, with abstinent users showing lactate increases in a broader range of areas.

Similarly, Christensen et al[145] reported dose-dependent increases in choline and *N*-acetyl-aspartate (NAA) in the basal ganglia following an acute cocaine injection. They noted that these changes could indicate cocaine-induced osmotic modulation, leading to the signal change, and/or could indicate increased phospholipid turnover with acute cocaine injection. MRS can also be used to measure brain levels of certain drugs whose spectra can be discerned. For example, several investigators have used ^{1}H MRS to determine brain alcohol levels.[146,147]

NAA has been used as a marker of neuronal viability.[148,149] When compared with non-using control subjects, a reduction in NAA has been seen in the thalamus (but not basal ganglia)[150] and frontal lobes[151,152] in chronic cocaine abusers. Increases in creatine (Cr) and myoinositol (MI) in temporoparietal white matter and a trend toward increased Cr in mid-occipital gray matter have also been reported in abstinent cocaine users,[153] again compared with non-drug-using controls. A similar increase in MI was seen in abstinent users of 3,4-methylenedioxymethamphetamine (MDMA, 'ecstasy') in white matter.[154] It thus appears that MRS can be used to localize areas of possible neuronal damage or dysfunction as a consequence of long-term drug exposure.

Although still somewhat controversial, animal research suggests possible neurotoxic effects of MDMA to serotonergic neurons.[155] A PET study in abstinent MDMA users corroborated the animal findings by revealing decreased serotonin transporter binding that correlated with previous MDMA use.[156] Several fMRI studies support an MDMA-induced neurotoxicity. For example, Jacobsen et al[157] reported a failure to activate the hippocampus in adolescent MDMA users during a high load verbal memory task, while Daumann et al[158] report that heavy and moderate Ecstasy users show stronger parietal activation and weaker temporal pole and frontal regions than controls in a WM task. That they saw no change in task performance in the face of these activation changes suggests that brain changes may precede the behavioral manifestations of possible neuronal injury and neurotoxicity.

Drug interactions with cognitive imaging

An emerging class of experiments examines the acute and/or chronic administration of an abused drug during the performance and imaging of a specific cognitive task in order to address hypotheses related to the mechanistic underpinnings of addiction. For example, Willson et al[159] reported that amphetamine decreased both the number of activated voxels and the BOLD signal magnitude in non-drug-users during performance of WM and spatial attention tasks, while having no effects on a motor task. Similarly, Knutson et al[160] reported that amphetamine reduced the ventral striatal signal during reward outcome anticipation. Presumably it was the increase in DA that accounted for the changes in task performance and signal alterations.[161] In contrast, Mattay et al[162] reported that the effects of amphetamine on WM task performance and brain activation were not obligatory, but were related to the WM capacity of the individual.

However, not all abused drugs are necessarily associated with cognitive deficits. Nicotine, which stimulates DA and cholinergic neurotransmission (among other transmitters), has been shown to enhance cognitive performance in humans and animals,[83,163] particularly in tests of sustained and visuospatial attention. Such cognitive improvements could contribute to the maintenance of smoking behavior in addicted individuals. Indeed, smokers often report that a cigarette helps them concentrate.[164] In an attempt to elucidate the neural substrates of the cognitive effects of nicotine, Ghatan et al[165] observed that acute IV nicotine administered to abstinent smokers and non-smokers enhanced rCBF in parieto-occipital regions during performance of a complex spatial attention maze test. Similarly, nicotine gum enhanced prefrontal and parietal cortex rCBF in non-smokers performing a two-back WM task,[166] although no behavioral improvement

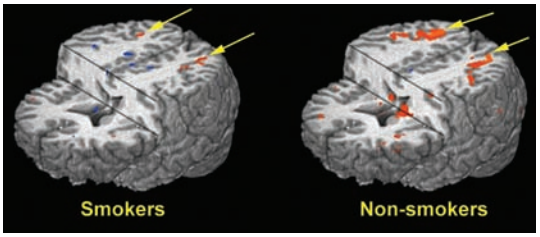

Figure 4.6 Task-induced activation in smokers relative to non-smokers. Activated (red) clusters represent the activation difference from baseline between rapid visual information processing (RVIP) and control task in smokers who received placebo during their first scan session (n = 8) and in non-smokers (n = 7) (cuts were made at 40 mm and 11 mm superior to and 2 mm anterior to the anterior commissure). Note the significantly attenuated BOLD response in the posterior parietal cortex (yellow arrows) during RVIP task performance in smokers wearing a placebo patch compared with the response in the group of matched non-smokers. Adapted from Lawrence et al.[167]

was reported in either study. In contrast, Lawrence et al[167] found a significant improvement in performance on a test of visual sustained attention in mildly abstinent smokers wearing a nicotine, but not a placebo patch, which was accompanied by enhanced activation in several task-related (parietal, thalamic, caudate, and occipital) areas. When compared with non-smokers performing the same attention task, smokers with a placebo patch showed regional hypoactivity in parietal cortex and caudate, along with mild behavioral impairment in mood and performance (Figure 4.6). As nicotine replacement in smokers led to identical task-induced brain activation and behavioral responding compared with non-smokers, the authors suggested that nicotine brings smokers up from a hypoactive to a normal baseline level of mood and cognition.[168]

A second experimental approach employs pharmacological modulation of specific neurochemical systems that are also altered by various abused drugs. These studies, generally performed in healthy, non-drug-using volunteers, enables the examination of specific neurochemical manipulations on cognitive task performance and brain imaging. Detailed discussion of these studies is beyond the scope of this chapter, which emphasizes imaging and drug dependence. Several examples from this class of experiments include DA receptor activation,[169] cholinergic activation,[170] and noradrenergic activation and arousal.[171]

ANATOMICAL STUDIES OF DRUG ABUSE

While much of the emphasis on using MRI to study drug abuse has focused on functional studies, with the advent of newer MRI-based anatomical techniques, there has been an emergence of interest in structural alterations as a consequence of chronic drug use. Early structural studies using computed tomography (CT) scans suggested that chronic use of alcohol was associated with enlarged ventricles,[172] although this may normalize with prolonged abstinence.[173] While still difficult to fully interpret, a voxel-based morphometry (VBM) study has pointed to a spectrum of structural abnormalities compared with matched controls in a group of chronic marijuana users, including a decrease in gray matter density within the parahippocampal gyrus but an increase near the precentral gyrus and thalamus, while also seeing white matter density decreases in the parietal lobe and increases in the parahippocampal gyrus.[174]

In cocaine addicts, cocaine-induced euphoria is lower in individuals with larger ventricles, suggesting that tolerance may develop following reduced periventricular gray matter.[175] A structural MRI study also pointed to reduced prefrontal gray matter in cocaine abusers, with larger reductions in addicts reporting more years of use.[122] Reductions in multiple frontal gray matter regions (Figure 4.7) have also been seen in chronic cocaine abusers using VBM and other structural tools.[176–178]

That white matter integrity may also be associated with prolonged cocaine use has been suggested by the presence of T2-signal white matter hyperintensities, predominantly in anterior cortical (mostly frontal)[179–181] and

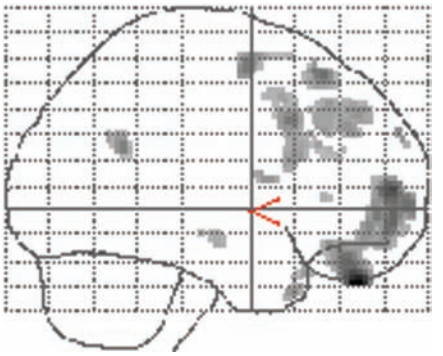

Figure 4.7 Voxel-based morphometric (VBM) analysis displayed by a 'glass brain' (maximum-intensity) projection in the sagittal orientation showing the voxels where there was higher gray matter concentration in non-drug-users compared with those individuals who abused cocaine. Non-users had significantly higher gray matter tissue concentration than cocaine abusers, primarily in the frontal cortex. The red cursor is placed at the image origin – the anterior commissure. Adapted from Matochik et al.[178]

temporal[182] areas. It has been suggested that such hyperintensities may be secondary to the potentially disruptive cerebrovascular actions of cocaine in reducing CBF,[183,184] – a phenomenon that could be related to the prolonged hypometabolism reported in abstinent cocaine abusers.[118] It should be noted, however, that volumetric abnormalities in medial temporal regions including the hippocampus and amygdala have not been universally identified.[185]

While these and other anatomical data are intriguing and are consistent with functional[11,14] and cognitive[98,186] studies demonstrating cocaine-induced frontal deficits, a consistent profile of structural abnormalities, has not yet emerged. Methodological differences across studies as well as the potential low sensitivity of structural studies (most of which are incapable of identifying changes on the cellular or small-regional level) may account for these disparities. Clearly, additional work is needed to relate these changes to cellular, functional, and cognitive phenotypes and specific polymorphism genotypes related to chronic illicit drug dependence.

AFFECT AND LEARNING (CUE CONDITIONING)

It has been hypothesized that one reason individuals take drugs is for their positive affective value and/or to relieve the negative state associate with withdrawal, drug craving, or other dysphoric states.[187] Relapse to drug use is more likely in situations that cue negative emotional reactions,[188] while cue-induced craving appears to be modulated by mood state.[188–191] Based mostly on animal models of addiction, Koob and LeMoal[192] hypothesized that affective dysregulation both leads to and is a consequence of repeated use. It has been proposed[193] that a negative affect state is at least as potent as external cues in cocaine craving and may in fact be sufficient to induce craving. Cigarette smokers report that they feel calmer, more relaxed, contented, friendlier, and happier after smoking, and smoke more when they are worried and angry.[194]

A corpus of neuroimaging research over the past few years has focused on brain activity underlying craving – operationally defined as the intense desire or powerful motivational state that often precedes drug seeking and taking. The rationale for this area of research is that a better understanding of the neurobiological mechanisms underlying craving may help minimize, control, or even eliminate this state, thereby preventing or reducing drug seeking and taking and minimize recidivism.[195] A preliminary model of the brain circuitry involved in craving suggested dysfunction in the ventral STO loop.[196] This hypothesis followed observations that this circuitry shows abnormalities in obsessive–compulsive disorder patients,[197] and is activated during symptom provocation,[198,199] which, like craving, is associated with intrusive thoughts and intense urges to carry out ritualized behaviors in response to certain internal or external cues.

Craving for drugs has been induced using a number of methods – videotapes of simulated drug taking and drug-related paraphernalia, directed recall of past experiences via mental imagery, and low doses of pharmacological stimulants (i.e. drug-induced drug craving). In addition, since craving putatively directs the patient into a certain affective/motivational state, studies have examined differences in more general affective processing in drug addicts. One principal goal of these studies is to determine if affective responses to drug cues are exaggerations of normal emotions or new pathological brain responses. To this end, in order to isolate brain regions specifically involved in drug craving in addicts, studies have typically compared the brain activation response to drug-related cues and other affectively charged stimuli with that to neutral cues in both drug addicts and non-drug-using controls. In general, evidence largely supports increased activation of the ventral striatum–NAc, caudate nucleus, thalamus, and OFC as the principal brain circuitry underlying craving. In addition, a number of regions associated with learning, memory, and emotional arousal, such as the amygdala, parahippocampal gyrus, and DLPFC are also generally activated in response to visually presented drug-related cues. In general, these regions are consistent with those implicated in normal human emotional processes.[200–203]

Most craving studies have examined the response to cocaine-related visual cues in cocaine addicts undergoing treatment and in withdrawal,[204–206] or cocaine-free but not withdrawn,[97,206–208] compared with control subjects. Brain areas demonstrating increased metabolism, rCBF, or BOLD response in cocaine addicts in response to cocaine videotapes include the OFC, DLPFC, anterior cingulate, parietal and medial temporal cortex, amygdala, insula, and cerebellum.[97,204,207,208] Reports of craving in addicts correlated with dorsolateral and medial temporal cortex and cerebellar metabolism,[97] and with anterior cingulate[205,207] and left DLPFC BOLD increases.[206] Using guided imagery, Kilts et al[209] have reported reduced amygdala, insula, OFC, and cingulate activation in a population of female cocaine addicts compared with male abusers, suggesting gender specific cue associated and emotional processing. Except for that by Garavan et al,[208] none of these studies showed increases in basal ganglia or thalamic metabolism during craving, although Childress et al[204] reported a decrease in basal ganglia rCBF.

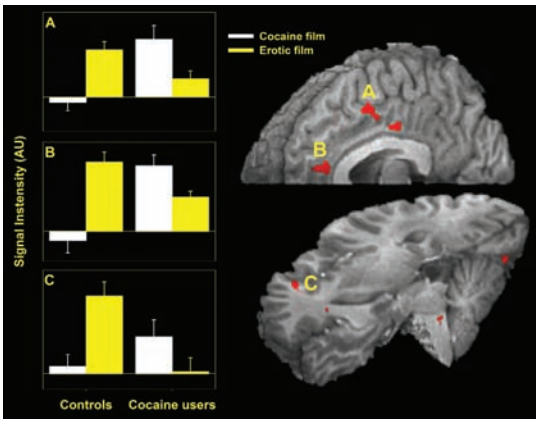

Figure 4.8 Illustration of the results of a two-way ANOVA of population (cocaine users and controls) by film type (cocaine use and erotic film). All three areas illustrated (A, cingulate; B, anterior cingulate; C, inferior frontal gyrus) demonstrated a similar pattern of effects from viewing of the two films. While the control subjects gave a larger response to the erotic film than the cocaine use film, the cocaine addicts showed the opposite pattern, i.e. a larger response to the cocaine than to the erotic film. Notably, the addicts' response to the erotic film was smaller than that of the controls watching the same film. Adapted from Garavan et al.[208]

Interestingly, Garavan et al[208] showed that many of the cortical activations evoked by a cocaine film in cocaine addicts were also induced by an explicit sexual film in both addicts and healthy controls, implying that cocaine craving may be subserved by the same brain regions and mechanisms that respond to 'naturally' rewarding, evocative stimuli. However, the cocaine users showed a blunted activation response to the sexual film when compared with healthy controls, suggesting a diminished capacity to crave and possibly

appreciate 'natural' rewards in favor of a stronger desire for drugs (Figure 4.8). Similarly, Wexler et al[205] observed that cocaine addicts show different temporal dynamics of brain activation in response to tapes inducing happy and sad moods when compared with controls, suggesting general affective dysregulation in chronic cocaine users. Of particular interest were findings of increased activation in 'sad' mood areas in cocaine users following the onset of sad feelings, and in response to the cocaine film, pointing to an association between cocaine use and dysphoric mood, which is borne out by the high incidence of depression in cocaine users.[210]

In addition to a limited number of cortical regions, studies investigating drug-induced drug craving have revealed activation in more subcortical sites than the above using visual drug cues. Hence, small doses of alcohol elicited craving in alcoholics, which correlated with increased rCBF in the right caudate nucleus.[211] A more recent fMRI study of craving in 1-week abstinent alcoholics found increased craving along with right amygdala and cerebellar activation in response to ethanol odor, which normalized following a 3-week recovery program.[212] As mentioned in the preceding section, Breiter et al[65] reported that NAc and parahippocampal gyrus activation correlated with cocaine-induced cocaine craving, while craving induced by Mph administration to cocaine addicts is associated with increased metabolism in the right OFC and right caudate nucleus,[75] and increased DA release in the thalamus.[213] Therefore, it seems that the compulsive desire to take drugs can be triggered by at least two distinct neurobiological mechanisms – a more cognitive cortical circuit and a more affective, limbic–subcortical circuit.

Activation of cortical areas associated with forms of explicit and implicit memory (episodic, working, and emotional) is triggered by presentation of visual cues related to drug use, suggesting that craving occurs due to the activation of autobiographical memories of previous drug-taking experiences,[97] leading to heightened attention towards drug-related stimuli and thoughts.[208] In fact, increased metabolism in the insula, OFC, and cerebellum,[214] and increased rCBF in the amygdala, insula, anterior cingulate, NAc, and subcallosal cortex[206] have been observed during script-guided recall of previous drug-taking experiences in cocaine users. Similarly, heroin addicts listening to audiotapes of personalized craving scripts showed increased rCBF in the anterior cingulate, basal ganglia, insula, cerebellum, and parahippocampal gyrus.[215] In contrast, pharmacological induction of craving appears to act via a more striatal–basal ganglia–thalamic mechanism, possibly by generating the expectation of further reinforcement.[216] Both mechanisms of craving appear to involve the activation of a learnt association or memory, prompting the suggestion that possible pharmacotherapeutic interventions in drug addiction might involve the development of agents that selectively block the formation of or reduce already-formed memories of associations between drug cues and reward.[217] However, it is difficult to envisage pharmacotherapies that could selectively alter drug-related associations and memories, as drugs appear to activate mechanisms also involved in learning about 'natural' reinforcers.

The neuronal sites activated during drug craving outlined above seemingly converge in the anterior cingulate and OFC regions. Anterior cingulate activation may arise from the powerful motivational states elicited by drug-related cues, or alternatively as a consequence of individuals' attempts to inhibit drug craving and drug taking, since the anterior cingulate is often activated by conflicting stimuli.[218,219] In addition, the anterior cingulate seems to be involved in the inhibition of externally triggered automatic behavior.[219] OFC activation could generate the anticipation of reward and result in compulsive seeking and taking of a drug. The functional significance of changes in OFC and anterior cingulate function in chronic drug users are areas of active exploration.

TECHNOLOGICAL LIMITATIONS AND CONTROL PROCEDURES FOR fMRI STUDIES OF DRUG ADDICTION

Detailed discussions of issues related to employing neuroimaging to study acute drug effects on the brain, subject safety concerns, drug-induced motion, and the effects of drugs on the physiological variables underlying the BOLD signal have been reviewed.[220,221] Subject selection, while a critical issue in all human neuroimaging research, becomes even more challenging when working with a vulnerable population and especially when protocols call for administering a drug known to have addictive properties. It is generally agreed that it is unethical to administer highly addictive and potentially neurotoxic substances to non-drug-using individuals. Thus, direct comparisons of drug-induced activations in healthy controls and chronic users are limited to a few substances. This makes isolating causation from consequences of drug use difficult if not impossible. Some also find it questionable on ethical grounds or safety concerns to administer abused drugs to any individual, even those with long histories of choosing to self-administer the drug. The former concern may be addressable with analogy to a disease-state model, i.e. it is impossible to study a disease in its absence. As to the latter, the burden is clearly on the investigators to utilize rigorous safety measures in order to preclude using individuals of questionable health to ensure minimal complications and/or side-effects. On a positive note, several groups have reported that cocaine administered in a laboratory environment to active cocaine users does not increase their illicit drug use after discharge from the study.[222,223]

Secondly, head movement in fMRI studies is always a critical issue, as movement of a millimeter or so is equal to the spatial resolution of most modern fMRI studies. Rapid IV drug administration is likely to exacerbate head movement, even in the most compliant of subjects and even with the best head restraint system. Further, even the most effective post hoc motion-correction algorithms cannot generally compensate for signal alterations due to movement-induced shim inhomogeneities.[224] It is thus probably fair to assume that successful scan sessions will be significantly less frequent than in non-drug experiments.

Since the BOLD signal is an indirect marker of neuronal activity,[67] factors other than changes in action potentials and post-synaptic potentials could give rise to changes in the fMRI signal. At least two transduction processes must be considered when interpreting BOLD signals after a drug challenge: first, the physiological transduction processes that couple electrical activity with changes in CBF and metabolism and, second, the biophysical processes that couple this hemodynamic response with the measured fMRI signal. Interpretations are made more difficult by the fact that, at present, both transduction processes are still incompletely understood.[225]

A number of drugs and other manipulations can potentially disrupt this hemodynamic coupling and/or cerebral hemodynamics. For example, DA can directly influence vascular diameter,[226] and most abused drugs either directly or indirectly alter synaptic DA levels.[3] Additionally, hypercapnia-related increases in resting CBV can reduce the activation-induced BOLD response in the primary motor cortex, although motor performance and, presumably, underlying neural activity remain unchanged.[227] If the BOLD response is to be used to measure drug-induced changes in neural circuitry, it is imperative to demonstrate that the drug does not also alter hemodynamic coupling or have direct vasoactive properties – either of which could lead to data misinterpretation. For example, Terborg et al[228,229] demonstrated acute hemodynamic alterations after cigarette smoking.

For these reasons, it is critical to ensure similarities between rCBF/BOLD changes and changes in metabolic rate (e.g. $CMRO_2$, which is not as vulnerable to such confounding variables) and/or to perform control

experiments to delineate any non-specific drug effects on CBF and BOLD. These control procedures include use of alternative fMRI pulse sequences in addition to the commonly used echo-planar BOLD signal, such as ASL, vascular space occupancy (VASO),[230] or the injection of contrast agents such as gadolinium to measure CBF or CBV.

Several studies have used controlled visual sensory or finger-tapping motor activation in the presence and absence of acute drug as a positive control procedure. No alterations in BOLD response to visual stimulation were seen after IV cocaine administration,[88] even in the face of a tonic 10% decrease in CBF, while Jacobsen et al[231] and Stein[232] likewise reported no changes after IV nicotine. Similarly, Rao et al[89] found no changes in BOLD response to paced finger tapping after 20 mg oral Mph. Since dopaminergic terminals are found in many cortical regions, including the prefrontal and motor regions,[233] and have been shown to directly modulate local CBF,[226] and since Mph raises local DA concentration,[234] a global or local effect on cerebral perfusion or activation–flow coupling is theoretically possible. That no changes in either CBF or BOLD signal were seen suggests that enhanced extracellular DA levels does not alter local neural–hemodynamic coupling or directly influence the vasculature (at least of this level of resolution). Another argument for the fidelity of BOLD signal changes after drug administration can be made when region specific changes in CBF are seen, especially when both increases and decreases in flow are reported (as by Devous et al[235]), as it is unlikely that the drug or ancillary changes in perivascular DA levels would be expected to have a regional, rather than a global, effect on CBF. In a technically demanding and elegant study, Schwarz et al[236] reported that following acute cocaine administration in rats, the relationship between DA content and BOLD signal was complex, although the direct vasoaction of DA was unlikely to be a dominant factor driving the CBV signal. Further, a study in humans[237] has demonstrated that DA does not alter the stimulus–response power function using either BOLD or evoked potential measures, suggesting that drug-induced changes in local DA concentration are not likely to alter BOLD coupling. Taken together, these results support the use of fMRI to study the neural mechanisms and sites involved in drug-induced pharmacological changes.

Another concern specific to experiments using subjects with long histories of drug abuse is the possibility of vascular insult that may, in turn, alter baseline CBF and/or vascular reactivity to cognitive or pharmacological challenges. Once again, control procedures such as CO_2 administration or sensory/motor stimulation across populations are recommended. The argument made for these studies is that blood vessels and their innervations appear to be relatively brain-region- and structure-independent; thus, vascular reactivity or BOLD response coupling should be relatively homogeneous. If one sees global increases in CBF with CO_2 or unaltered motor cortex activity after finger tapping in a particular patient population or in an individual taking a drug, then one could infer that the consequences of long-term drug use were relatively benign on these underlying mechanisms. Thus, any drug-induced or cognitive task-induced alterations in fMRI signal could then be inferred to be due to the disease or the drug effects on neuronal processes and not via an indirect effect on cerebral blood vessels.

Finally, many abused drugs, when administered acutely, alter such physiological parameters as BP, HR, and respiration. Transient changes in one or more of these parameters could independently alter the BOLD signal in ways that might be easily confused with a neuronal effect. Alternatively, such direct autonomic nervous system (ANS) actions could confound BOLD data interpretation. For example, opiates are known to depress respiratory rate and thus increase pCO_2 levels, which could increase vasodilation and global CBF. The net effect would be to depress a task- or drug-induced BOLD response.[63] Alternatively, cocaine and other stimulants

enhance BP and HR,[35] and could lead to increases in CBF and BOLD signal that could be confused with the kinetics of a direct drug effect. However, autoregulation appears to occur relatively rapidly, and is mostly completed within a minute or so.[238] It is thus important to demonstrate regionally specific fMRI responses that are within well-defined anatomical borders, have a time course distinct from peripheral autonomic drug responses, and are consistent with the localization of transmitters and receptors thought to mediate the particular drug effect. Global change in BOLD signal is taken to more likely reflect a global ANS or vascular-mediated effect. (However, it should be noted that several studies in rats and humans[239,240] have manipulated BP and have reported region-specific changes in BOLD signal, suggesting that the relationship between BP and BOLD signal may be heterogeneously driven by differences in vascular density, further justifying the need to tightly maintain and/or control for physiological variables.)

Finally, it is important to consider that drug administration to both experienced and drug-naive individuals will likely cause both the desired cognitive and/or affective response plus a host of other effects that are either indirect or non-specific. For example, nicotine administration in very light or non-smokers is likely to cause significant gastrointestinal distress and nausea along with mild hypertension.[42,163] These 'side-effects' could alter the emotional state of the subject, independent of the cognitive constructs under investigation such as vigilance, attention, and memory. Thus, one must be cognizant of measuring or controlling for 'ancillary' affective and emotion-inducing effects of the drug that might interfere with the measure of interest.

CONCLUSIONS

In conclusion, appropriate control procedures (physiological, affective, and biophysical), tasks, and pulse sequences need to be used when one performs experiments on this group of volunteers to help disambiguate specific pharmacological effects from other physiological and affective processes that could change secondary to drug administration. That having been said, the application of modern fMRI tools to the study of human drug abuse, while still in its very early stages, promises to yield unique insights into the etiology, neuronal toxicity, cognitive impairments, treatment matching, and outcome predictions for this disease, which has such devastating personal and societal consequences.

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Dyslexia

5

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INTRODUCTION

Developmental dyslexia is characterized by an unexpected difficulty in reading in children and adults who otherwise possess the intelligence and motivation considered necessary for accurate and fluent reading. More formally, 'Dyslexia is a specific learning disability that is neurobiological in origin. It is characterized by difficulties with accurate and/or fluent word recognition and by poor spelling and decoding abilities. These difficulties typically result from a deficit in the phonological component of language that is often unexpected in relation to other cognitive abilities and the provision of effective classroom instruction.'[1] Dyslexia (or specific reading disability) is the most common and most carefully studied of the learning disabilities, affecting 80% of all individuals identified as learning-disabled. This chapter reviews recent advances in our knowledge of the epidemiology, etiology, cognitive influences, and neurobiology of reading and dyslexia in children and adults.

Historically, dyslexia in adults was first noted in the latter half of the 19th century and developmental dyslexia in children was first reported in 1896.[2] Our understanding of the neural systems for reading had its roots as early as 1891, when Dejerine[3] suggested that a portion of the posterior brain region (which includes the angular gyrus and supramarginal gyrus in the inferior parietal lobule, and the posterior aspect of the superior temporal gyrus) is critical for reading. Another posterior brain region, this more ventral in the occipitotemporal area, was also described by Dejerine[4] as critical in reading.

EPIDEMIOLOGY

Recent epidemiological data indicate that, like hypertension and obesity, dyslexia fits a dimensional model. In other words, within the population, reading ability and reading disability occur along a continuum, with reading disability representing the lower tail of a normal distribution of reading ability.[5,6] Dyslexia is perhaps the most common neurobehavioral disorder affecting children, with prevalence rates ranging from 5% to 17.5%.[7,8] Longitudinal studies, both prospective[9,10] and retrospective,[11–13] indicate that dyslexia is a persistent, chronic condition – it does not represent a transient 'developmental lag' (Figure 5.1). Over time, poor readers and

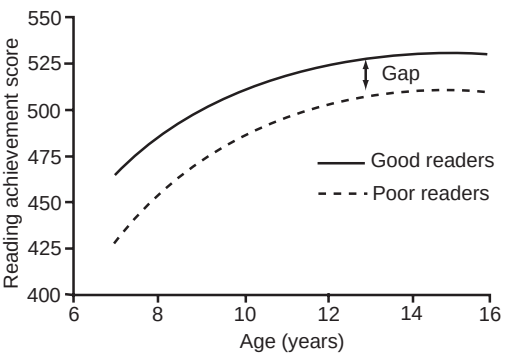

Figure 5.1 Trajectory of reading skills over time in non-impaired and dyslexic readers. The ordinate shows the Rasch score (*W* score) from the Woodcock–Johnson reading test[134] and the abscissa is the age in years. Both dyslexic and non-impaired readers improve their reading scores as they get older, but the gap between the dyslexic and non-impaired readers remains. Thus, dyslexia is a deficit and not a developmental lag. Derived from data from Francis et al[9] and reprinted from Shaywitz[45] with permission.

good readers tend to maintain their relative positions along the spectrum of reading ability.[9,14]

ETIOLOGY

Dyslexia is both familial and heritable.[15] Family history is one of the most important risk factors, with 23% to as much as 65% of children who have a parent with dyslexia reported to have the disorder.[13] A rate among siblings of affected persons of approximately 40% and among parents ranging from 27% to 49%[15] provides opportunities for early identification of affected siblings and often for delayed but helpful identification of affected adults. Replicated linkage studies of dyslexia implicate loci on chromosomes 2, 3, 6, 15, and 18.[16] Whether the differences in the genetic loci represent polygenic inheritance, different cognitive paths to the same phenotype, or different types of dyslexia is not clear.

Reading difficulties are commonly observed in children with known genetic abnormalities, particularly those involving sex chromosomes. Thus, reading difficulties are noted in 50–75% of boys with Klinefelter syndrome (reviewed by Geschwind et al[17]). Neuropsychological deficits in neurofibromatosis 1 were originally believed to affect non-verbal domains, but more recent evidence indicates that problems in reading are observed in more than half of affected children.[18,19] Individual word reading is usually normal in girls with Turner syndrome, although a report of difficulties in oral fluency suggests that reading fluency should be examined in this group of children.[20]

Reading difficulties have been purported to occur in association with a range of insults, although, in general, these associations occur in only a very small proportion of children presenting with reading disability. Data are strongest for the association between exposure to lead and decline in academic functioning, including reading. Recent data support the belief that what had been considered relatively 'safe' blood levels (i.e. lead levels <10 μg/dl) are associated with reading problems. Thus, every 1 μg/dl increase in blood lead concentration was associated with a one-point decrement in mean reading scores.[21–23] Academic difficulties, including reading problems, are frequently reported in children with congenital heart disease, particularly cyanotic congenital heart disease.[24–26] More recently, Bellinger et al,[27] using a randomized clinical trial of two methods of vital organ support within a longitudinal prospective design, have examined the neurodevelopmental consequences of one type of cyanotic congenital heart disease, transposition of the great vessels. Follow up at 8 years of age indicated that the most prominent deficits affected motor function and visuospatial skills, although academic difficulties, including reading problems (particularly reading fluency) were noted in many children. Cognitive problems, including problems in academic achievement such as reading, are reported more frequently in children with epilepsy than in non-impaired groups, although the prevalence of reading problems in different types of epilepsy is not known. Furthermore, studies in children have not differentiated the relative contributions of the seizures, the underlying disorder, or the contributions of the anticonvulsant agents used to treat seizures in children with epilepsy.[28] Because nearly all children with seizure disorders are receiving antiepileptic medications, any cognitive or behavioral difficulties attributed to the seizure disorder could as easily be attributed to medication effects. These questions are difficult to resolve. Farwell et al[29] suggested that phenobarbital may lower intelligence quotients in 2- to 3-year-old children given the medication to prevent febrile seizures. Such findings lend support to the suggestion that long-term phenobarbital therapy to prevent seizures should be used judiciously.[30] A report that followed children exposed to phenobarbital in utero was reassuring in indicating normal reading at age 7 years compared with placebo controls.[31] Although the question of a relationship between epilepsy and reading difficulties remains a difficult one, the

question of whether chronic otitis media with effusion results in reading problems appears to have been resolved. Using a prospective longitudinal design, Roberts et al[32] demonstrated that there was no significant relationship between a history of early otitis media with effusion and later problems in reading.

COGNITIVE INFLUENCES: THEORIES OF DEVELOPMENTAL DYSLEXIA

A number of theories of dyslexia have been proposed, including: the phonological theory,[33,34] the rapid auditory processing theory,[35–37] the visual theory,[38,39] the cerebellar theory,[40,41] and the magnocellular theory.[39,42–44] Ramus et al[34] have reviewed and provided a critique of the various theories.

Among investigators in the field, there is now a strong consensus supporting the phonological theory. This theory recognizes that speech is natural and inherent, while reading is acquired and must be taught. To read, the beginning reader must recognize that the letters and letter strings (the orthography) represent the sounds of spoken language. In order to read, a child has to develop the insight that spoken words can be pulled apart into the elemental particles of speech (phonemes) and that the letters in a written word represent these sounds; [45] such awareness is largely missing in dyslexic children and adults.[11,45–50] Results from large and well-studied populations with reading disability confirm that in young school-age children[46,51] as well as in adolescents,[52] a deficit in phonology represents the most robust and specific correlate of reading disability.[34,53] Such findings form the basis for the most successful and evidence-based interventions designed to improve reading.[54]

IMPLICATIONS OF THE PHONOLOGIC MODEL OF DYSLEXIA

Reading comprises two main processes – decoding and comprehension.[55] In dyslexia, a deficit at the level of the phonological module impairs the ability to segment the spoken word into its underlying phonological elements and then link each letter(s) to its corresponding sound. As a result, the reader experiences difficulty – first in decoding the word and then in identifying it. The phonological deficit is domain-specific; that is, it is independent of other, non-phonological, abilities. In particular, the higher-order cognitive and linguistic functions involved in comprehension, such as general intelligence and reasoning, vocabulary,[56] and syntax,[57] are generally intact. This pattern – a deficit in phonological analysis contrasted with intact higher-order cognitive abilities – offers an explanation for the paradox of otherwise-intelligent, often gifted, people who experience great difficulty in reading.[45,58]

According to the model, a circumscribed deficit in a lower-order linguistic function (phonology) blocks access to higher-order processes and to the ability to draw meaning from text. The problem is that the affected reader cannot use his or her higher-order linguistic skills to access the meaning until the printed word has first been decoded and identified. Suppose, for example, an individual knows the precise meaning of the spoken word 'apparition;' however, she will not be able to use her knowledge of the meaning of the word until she can decode and identify the printed word on the page, and it will appear that she does not know the word's meaning.

NEUROBIOLOGICAL STUDIES OF DYSLEXIA

To a large degree, these advances in understanding the cognitive basis of dyslexia have informed and facilitated studies examining the neurobiological underpinnings of reading and dyslexia. Thus, a range of neurobiological investigations using postmortem brain specimens,[59] and, more recently, brain morphometry[60–62] and diffusion tensor magnetic resonance imaging (MRI)[62] suggests that there are differences in the temporoparieto-occipital

brain regions between dyslexic and non-impaired readers. While the focus of this chapter is on functional brain imaging, particularly functional MRI (fMRI), these other brain imaging studies are also discussed in more detail below.

Functional brain imaging – general issues

Rather than being limited to examining the brain in an autopsy specimen, or measuring the size of brain regions using static morphometric indices based on computed tomography (CT) or MRI, functional imaging offers the possibility of examining brain function during the performance of a cognitive task. We use the term 'functional imaging' to refer to technologies that measure changes in metabolic activity and blood flow in specific brain regions while subjects are engaged in cognitive tasks. The principles of fMRI depend on the principle of autoregulation of cerebral blood flow. When an individual is asked to perform a discrete cognitive task, that task places processing demands on particular neural systems in the brain. To meet those demands requires activation of neural systems in specific brain regions, and these changes in neural activity are, in turn, reflected by changes in brain metabolic activity, which, in turn, are reflected, for example, by changes in cerebral blood flow and in the cerebral utilization of metabolic substrates such as glucose. The term 'functional imaging' has also been applied to the technology of magnetic source imaging using magnetoencephalography (MEG), an electrophysiologic method with strengths in resolving the chronometric properties of cognitive processes.[64] Studies employing MEG are discussed following the studies using positron emission tomography (PET) and fMRI.

PET

Some of the first functional imaging studies of dyslexia used PET.[65,66] In practice, PET requires the administration of a radioactive isotope to the subject so that cerebral blood flow or cerebral utilization of glucose can be determined while the subject is performing the task. Positron-emitting isotopes of nuclei of biological interest have very short biological half-lives and are synthesized in a cyclotron immediately prior to testing, a factor that mandates that the time course of the experiment conform to the short half-life of the radioisotope. Rumsey et al[67] noted that adult dyslexic readers failed to activate the left parietal and left middle temporal regions in response to an aurally presented rhyming task; no differences were found between dyslexic and control adult readers on an aurally presented semantic judgment task.[68] Paulesu et al,[69] using a visually presented single-letter rhyming task, reported a disconnection between the anterior and posterior language regions – a theory supported by their finding of underactivation in the insula in a small group of compensated dyslexic university students. Rumsey et al[70] noted that dyslexic readers demonstrated reduced blood flow in temporal cortex and inferior parietal cortex, especially on the left, during both pronunciation and decision-making tasks.

fMRI

fMRI promises to supplant other methods for its ability to map the individual brain's response to specific cognitive stimuli. Since it is non-invasive and safe, it can be used repeatedly – this makes it ideal for studying humans, especially children. In principle, the signal used to construct MRI images changes by a small amount (typically of the order of 1–5%) in regions that are activated by a stimulus or task. The increase in signal results from the combined effects of increases in the tissue blood flow, volume, and oxygenation, although the precise contributions of each of these are still somewhat uncertain. MRI intensity increases when deoxygenated blood is replaced by oxygenated blood. A variety of methods can be used to record the changes that occur, but one preferred approach makes use of ultrafast imaging, such as echo-

planar imaging, in which complete images are acquired in times substantially shorter than a second. Echo-planar imaging can provide images at a rate fast enough to capture the time course of the hemodynamic response to neural activation and to permit a wide variety of imaging paradigms over large volumes of the brain. Details of fMRI have been reviewed by Anderson and Gore,[71] Frackowiak et al,[72] and Jezzard et al.[73]

fMRI has proven to be a powerful tool for understanding the brain organization for reading. Studies have examined a number of domains, each of which are detailed below.

Identification and localization of specific systems and their differences in good and poor readers

A number of research groups, including our own, have used fMRI to examine the functional organization of the brain for reading in non-impaired and dyslexic readers. We studied 61 right-handed adult subjects, 29 dyslexic readers (14 men and 15 women, aged 16–54 years) and 32 non-impaired readers (16 men and 16 women, aged 18–63 years),[74] focusing on those brain regions that previous research had implicated in reading and language.[75–77] We found significant differences in brain activation patterns between dyslexic and non-impaired readers – differences that emerged during tasks that made progressive demands on phonological analysis. Thus, during non-word rhyming in dyslexic readers, we found a disruption in a posterior region involving the superior temporal gyrus and angular gyrus, with a concomitant increase in activation in the inferior frontal gyrus anteriorly.

When studying adults with dyslexia, there is always the concern that the findings may represent the consequences of a lifetime of poor reading, and so it is important to study children in order to examine the neural systems for reading during the acquisition of literacy. We used fMRI to study 144 right-handed children, 70 dyslexic readers (21 girls and 49 boys, aged 7–18 years, mean age 13.3 years) and 74 non-impaired readers (31 girls and 43 boys, aged 7–17 years, mean age 10.9 years) as they read pseudowords and real words.[78] This study was designed to minimize some of the problems encountered in previous studies, and thus we examined a large sample, particularly for a functional imaging study; we included a broad age range and studied both boys and girls. We found significant differences in brain activation patterns during phonological analysis in non-impaired compared with dyslexic children. Specifically, non-impaired children demonstrate significantly greater activation than do dyslexic children in predominantly left-hemisphere sites (including the inferior frontal, superior temporal, parietotemporal, and middle temporal–middle occipital gyri) and a few right-hemisphere sites (including an anterior site around the inferior frontal gyrus and two posterior sites – one in the parieto-temporal region, the other in the occipitotemporal region) (Figure 5.2). These data converge with reports from many investigators using functional brain imaging that show a failure of left-hemisphere posterior brain systems to function properly during reading[67,78–86] as well as during non-reading visual processing tasks,[87,88] and indicate that dysfunction in left-hemisphere posterior reading circuits is already present in dyslexic children and cannot be ascribed simply to a lifetime of poor reading.

Compensatory systems in dyslexic readers

The study design also allowed for the examination of compensatory systems that develop in dyslexic readers. Two kinds of information were helpful in examining this issue. One involved the relationship between brain activation and age. During the most difficult and specific phonological task (non-word rhyming), older compared with younger dyslexic readers engaged the left and right inferior frontal gyrus, in contrast to non-impaired readers, where few differences emerged between older and younger readers. Another clue to compensatory systems comes from the findings of the

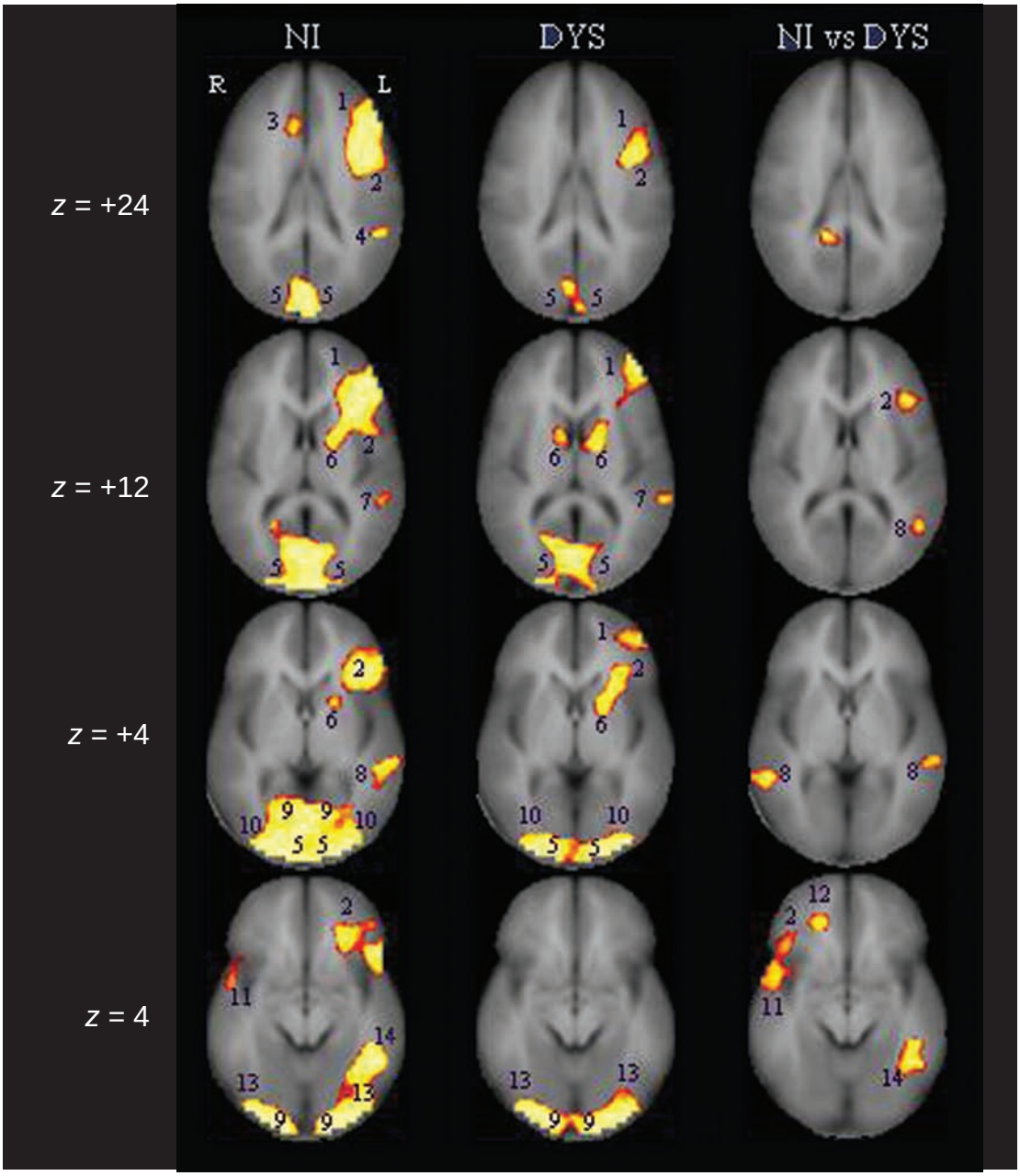

Figure 5.2 Composite maps (columns 1 and 2) demonstrating brain activation in non-impaired (NI) and dyslexic (DYS) readers as they determined whether two pseudowords rhymed (NWR, non-word rhyme), and composite contrast maps (column 3) directly comparing the brain activation of the two groups. In columns 1 and 2, red–yellow indicates areas that had significantly greater activation ($p = 0.05$) in the NWR task compared with the line task, and in column 3, red–yellow indicates brain regions that were more active in NI compared with DYS during the NWR task. The four rows of images from top to bottom correspond to $z = +23$, +14, +5, and –5 in Talairach space.[135] Key to regional brain activation: (1) middle frontal gyrus; (2) inferior frontal gyrus; (3) anterior cingulate gyrus; (4) supramarginal gyrus; (5) cuneus; (6) basal ganglia; (7) superior temporal gyrus; (8) superior temporal sulcus and posterior aspect of superior and middle temporal gyri; (9) lingual gyrus; (10) middle occipital gyrus; (11) anterior aspect of superior temporal gyrus; (12) medial orbital gyrus; (13) inferior occipital gyrus; (14) posterior aspect of middle temporal gyrus and anterior aspect of middle occipital gyrus. From Shaywitz et al[78] with permission from The Society of Biological Psychiatry.

relationship between reading skill and brain activation, where a significant positive correlation was noted between reading skill and activation in the left occipitotemporal word-form area. We also found a negative correlation between brain activation and reading skill in the right occipitotemporal region; that is, the poorer the reader, the greater the activation in the right occipitotemporal region. Thus, compensatory systems seem to involve areas around the inferior frontal gyrus in both hemispheres, and perhaps the right-hemisphere homologue of the left occipitotemporal word-form area as well.

Computational roles of the component systems

These data from laboratories around the world indicate that there are a number of interrelated neural systems used in reading – at least two in posterior brain regions, as well as distinct and related systems in anterior regions. The two posterior systems appear to parallel the two systems proposed by Logan[89,90] as being critical in the development of skilled, automatic reading. One system involves word analysis, operates on individual units of words such as phonemes, requires attentional resources, and processes relatively slowly. It is reasonable to propose that this system involves the parietotemporal posterior reading system. As noted previously, as early as 1891, Dejerine[3] suggested that a portion of the posterior brain region (which includes the angular gyrus and supramarginal gyrus in the inferior parietal lobule, and the posterior aspect of the superior temporal gyrus) is critical for reading. Since that time, a large literature on acquired inability to read (acquired alexia) describes neuroanatomical lesions most prominently centered about the angular gyrus as a region considered pivotal in mapping the visual percept of the print onto the phonological structures of the language system.[91–93] Thus, it is reasonable to suggest that this temporoparietal reading system may be critical for analyzing the written word, that is, transforming the orthography into the underlying linguistic structures.

Perhaps of even greater importance to reading is the second system proposed by Logan – a system that operates on the whole word (word form), an obligatory system that does not require attention, and one that processes very rapidly. This system has historical roots that were also described by Dejerine[4] – a system located in another posterior brain region, the occipitotemporal area. Converging evidence from a number of lines of investigation indicates that the left occipitotemporal area is critical for the development of skilled reading and functions as an automatic, instant word recognition system, the visual word form area.[94–96] Not only does brain activation in this region increase as reading skill increases[78] (Figure 5.3), this region responds preferentially to rapidly presented stimuli,[97] responds within 150 ms after presentation of a stimulus,[83] and is engaged even when the word has not been consciously perceived.[98] Still another reading-related neural circuit involves an anterior system in the inferior frontal gyrus (Broca's area) – a region that has long been associated with articulation and also serves an important function in silent reading and naming.[72,99]

Plasticity of neural systems for reading

Given the converging evidence of a disruption of posterior reading systems in dyslexia, an obvious question relates to the plasticity of these neural systems, that is, whether they are malleable and can be changed by an effective reading intervention. We have hypothesized that the provision of an evidence-based, phonologically mediated reading intervention would improve reading fluency and the development of the neural systems serving skilled reading.[100] The experimental intervention was structured to help children gain phonological knowledge (develop an awareness of the internal structure of spoken words) and, at the same time, develop their understanding of how the orthography represents the phonology.[101] Children in the community intervention received a variety of interventions within the school setting.

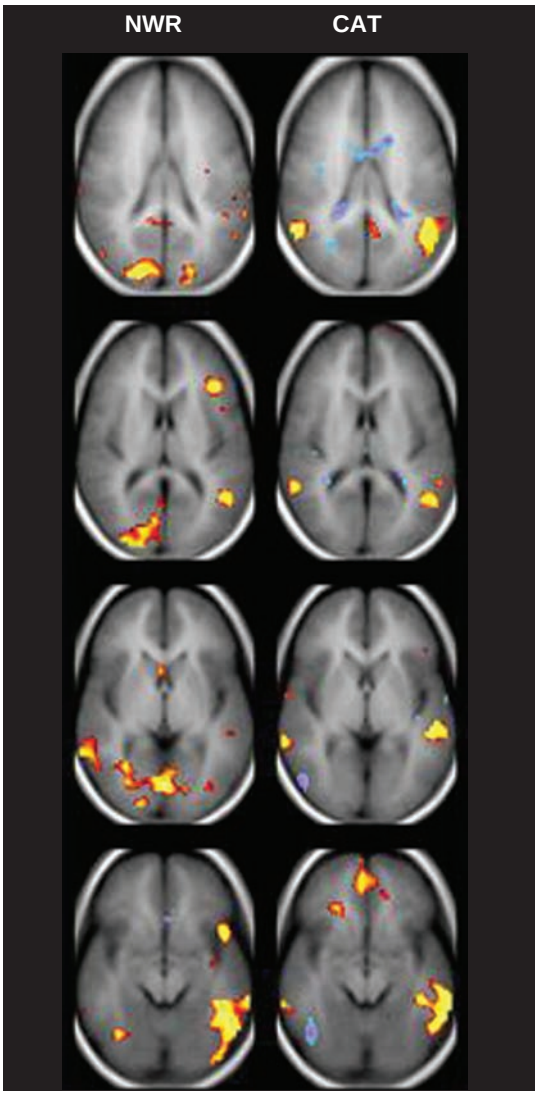

Figure 5.3 Correlation map between reading skill as measured by the Word Attack reading test[134] performed out of magnet during two activation tasks: judging whether two pseudowords rhymed (NWR) and judging whether two real words were in the same category (CAT). At each voxel, a Pearson correlation coefficient (r) was calculated, with age included as a covariate; a normal distribution test was used.[136] Areas in yellow–red show a positive correlation of in-magnet tasks with the out-of-magnet reading test (threshold, $p<0.01$). The four rows of images from top to bottom correspond to $z = +23, +14, +5$ and -5 of the Talairach atlas. Strong correlation was found in the inferior aspect of the occipitotemporal region (fourth row), in the more superior aspect of the occipitotemporal region (second and third rows), and in the parietal region (top row). From Shaywitz et al[78] with permission from The Society of Biological Psychiatry.

Seventy-seven right-handed children, aged 6.1–9.4 years, were recruited for three experimental groups: experimental intervention (n = 37); community intervention (n = 12), and community controls, i.e. non-impaired readers (n = 28). Children in the community intervention met criteria for reading disability and received a variety of interventions commonly provided within the school; specific, systematic, explicit phonologically based interventions comparable to the experimental intervention were not used in any of reading programs that were provided to the community group. The experimental intervention provided second- and third-grade poor readers with 50 minutes of daily, individual tutoring that was explicit and systematic and focused on helping children understand the alphabetic principle (how letters and combinations of letters represent the small segments of speech known as phonemes) and provided many opportunities to practise applying the letter–sound linkages taught. Children were imaged on three occasions: preintervention, immediately postintervention, and 1 year after the intervention was complete.

Children who received the experimental intervention improved their reading accuracy, reading fluency, and reading comprehension. Compared with community intervention, both community control and experimental intervention groups showed increased activation in left-hemisphere regions, including the inferior frontal gyrus and the posterior aspect of the middle temporal gyrus. One year after the experimental intervention had ended (Figure 5.4), compared with their preintervention images, children in the experimental intervention group were activating bilateral inferior frontal gyri, the left superior temporal sulcus, the occipitotemporal region (involving the posterior aspects of the middle and inferior temporal gyri and the anterior aspect of the middle occipital gyrus), the inferior occipital gyrus, and the lingual gyrus.

These findings indicate that the nature of the remedial educational intervention is critical to successful outcomes in children with reading disabilities and that the use of an

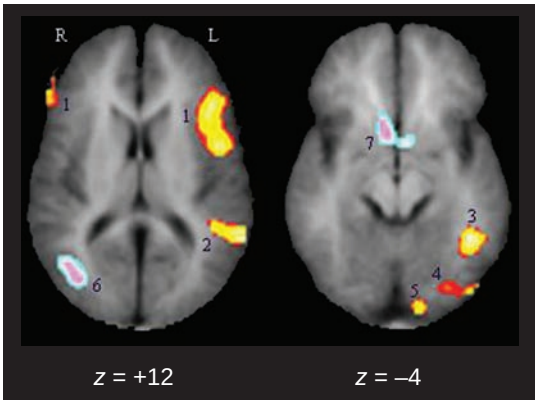

Figure 5.4 Composite maps indicating the difference in activation between year 3 and year 1 in the experimental intervention (EI) study group (n = 25). Red–yellow indicates brain regions that were more active (p = 0.05) in the third year; blue–purple indicates brain regions that were more active (p = 0.05) in the first year. The slice locations are 12 and –4 in Talairach space. The brain regions (with Talairach (x,y,z) coordinates shown in parentheses) more active in the third year compared with the first were as follows: (1) bilateral inferior frontal gyri (±41, 23, 12); (2) the left superior temporal sulcus (51, –42, 12); (3) the occipitotemporal region, involving the posterior aspects of the middle and inferior temporal gyri and the anterior aspect of the middle occipital gyrus (42, –49, –4); (4) the inferior occipital gyrus (34, –71, –4); (5) the lingual gyrus (13, –88, –4). The brain regions more active in the first year compared with the third were as follows: (6) the right middle temporal gyrus (–35, –69, 12); (7) the caudate nucleus (–7, 10, -4). From Shaywitz et al[100] with permission.

evidence-based reading intervention facilitates the development of those fast-paced neural systems that underlie skilled reading. Our findings indicate that a phonologically based reading intervention leads to the development of neural systems both in anterior (inferior frontal gyrus) and posterior (middle temporal gyrus) brain regions.

This is the first imaging study of a reading intervention in either children or adults that has reported its effects on reading fluency, a critical but often neglected reading skill.[54] It is also the largest imaging study of a reading intervention and the first report of the effects of a reading intervention on fMRI in children that examined not only reading-disabled children who received an experimental reading intervention but also reading-disabled children who did not receive such an intervention. Previous studies on the effects of a reading intervention on neural systems in reading disability were informative but were limited to smaller studies in adults and MEG and magnetic resonance spectroscopy (MRS) in children and an fMRI study in solely reading-disabled children without a non-experimental comparison group. Two studies from the same investigative group have used fMRI to examine the effects of a commercial reading program (Fast Forword) first in adults and then in children with dyslexia. Their first study examined three adults with dyslexia who received Fast Forword training during a task requiring that subjects respond to a high-pitched stimulus. Following 33 training days, two of the three subjects demonstrated greater activation in the left prefrontal cortex after training compared with before training, and these two adults also showed improvements in both rapid auditory processing and auditory language comprehension after training; the one adult who did not show a change in fMRI after training failed to show behavioral changes.[86] In a more recent study, immediate short-term improvement in reading accuracy and brain activation changes were observed in 20 children with dyslexia – changes that included the areas observed in our study, as well as in the right hemisphere and cingulate cortex.[102] Richards et al[103] used proton MRS to measure brain lactate concentrations at two time points, 1 year apart, in eight dyslexic and seven control boys before and after 3 weeks of a phonologically based reading intervention. Before treatment, the dyslexic boys demonstrated increased lactate concentration (compared with controls) in the left anterior quadrant during a phonological task. After treatment, brain lactate concentrations were no different in the dyslexic and control boys, and reading improved after treatment. More recently, this same group reported fMRI changes in areas similar to those reported here following 28 hours of an intensive phonological and morphological reading intervention.[104]

Simos et al[105] used MEG in eight children with dyslexia and eight controls before and after 8 weeks of a phonologically based reading intervention. Prior to intervention, the dyslexic readers demonstrated little or no activation of the posterior portion of the superior temporal gyrus. After intervention, reading improved and activation increased in the left superior temporal gyrus.

Eden et al[106] examined brain activation in adults with dyslexia on an oral language task before and after an 8-week intervention designed to improve phonological skills. Intervention-related increases in brain activation were observed in the left parietal cortex and left fusiform gyrus, as well as in right-hemisphere parietotemporal regions.

The findings here with a reading intervention suggest plasticity of the neural systems for reading in children and parallel those observed after a variety of therapies in individuals with stroke[107] and after surgical removal of a hemisphere in a child with Rasmussen syndrome.[108] It is reasonable to suppose that these differences in plasticity reflect the view of Gilbert et al[109] that the 'ability of a given brain structure to participate in alteration of topography depends on a preexisting framework of connections' and that this framework changes with maturation. Importantly, the effects of the experimental intervention, both on promoting skilled reading and on the activation of the occipitotemporal word-form area shown to be critical for skilled reading,[78] are similar to the co-occurrence of visuospatial proficiency and cortical specialization reported in adults. Thus, Gauthier and coworkers have demonstrated a progressive increase of activation of the right-hemisphere fusiform face area and right lateral occipital cortex with increasing proficiency in identifying novel face-like stimuli, which they called 'Greebles'.[110,111] The current findings suggest that, as in recognition of Greebles, an intervention that improved proficiency in reading was the most important element in functional reorganization of the neural systems for reading. Such findings have important implications for understanding the effect on neural systems of phonologically based reading programs for young children that have been shown to be effective in the educational equivalent of clinical trials.[54]

In summary, these data demonstrate that an intensive evidence-based reading intervention brings about significant and durable changes in brain organization so that brain activation patterns resemble those of typical readers, with the appearance of the left occipitotemporal area and improvement in reading fluency. These data have important implications for public policy regarding teaching children to read: the provision of an evidence-based reading intervention at an early age improves reading fluency and facilitates the development of those neural systems that underlie skilled reading.

Types of reading disability

Using data from participants in a longitudinal, epidemiological study, we examined the neural systems for reading in two groups of young adults who were poor readers as children, a relatively compensated group, and a group with persistent reading difficulties, and compared them with non-impaired readers.[85] In addition, we wanted to determine if there were any factors distinguishing the compensated from persistently poor readers that might account for their different outcomes. To this end, we took advantage of the availability of a cohort who are participants in the Connecticut Longitudinal Study, a representative sample of now young adults who have been prospectively followed since 1983, when they were 5 years old, and who have had their reading performance assessed yearly throughout their primary and secondary schooling.[52,112,113]

Three groups of young adults, aged 18.5–22.5 years, were classified as follows: (1) persistently poor readers (PPR, $n = 24$) met criteria for poor reading in second or fourth grade and again in ninth or tenth grade; (2) accuracy (but not fluency)-improved (compensated) readers (AIR, $n = 19$) satisfied criteria for poor reading in second or fourth

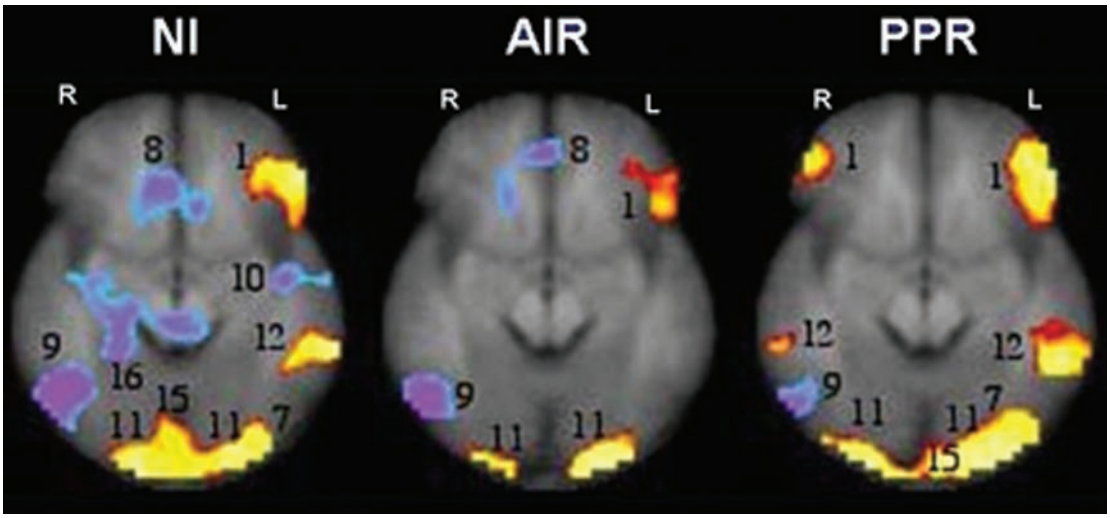

Figure 5.5 Composite maps demonstrating brain activation in non-impaired (NI), accuracy-improved (AIR), and persistently poor (PPR) readers when judging whether two simple real words were in the same category. Red–yellow indicates areas that had significantly greater activation ($p = 0.05$) in the reading task compared with the line task. Blue–purple indicates areas that had significantly greater activation ($p = 0.05$) in the line task compared with the reading task. The slice locations correspond to a z level of –4 in the Talairach and Tournoux atlas.[135] Following standard MRI nomenclature, the right side of the axial slice corresponds to the left hemisphere. Key to regional brain activation: (1) inferior frontal gyrus; (2) precentral gyrus; (3) insula; (4) superior temporal gyrus and superior temporal sulcus; (5) middle temporal gyrus and superior temporal sulcus; (6) cuneus; (7) middle occipital gyrus; (8) anterior cingulate sulcus and adjacent aspects of the cingulate gyrus and superior frontal gyrus; (9) posterior middle temporal gyrus and anterior middle occipital gyrus; (10) anterior aspect of superior temporal gyrus; (11) inferior occipital gyrus; (12) middle temporal gyrus; (13) superior frontal gyrus; (14) posterior cingulate gyrus; (15) lingual gyrus; (16) medial occipital temporal gyrus (parahippocampal region); (17) basal ganglia. Modified from Figure 1 in Shaywitz et al[85] with permission from The Society of Biological Psychiatry.

grade but not in ninth or tenth grade; (3) non-impaired readers (NI, $n = 27$) were selected on the basis of (a) not meeting the criteria for poor reading in any of the second to tenth grades; (b) having a reading standard score over 94 (above the 40th percentile) to prevent overlap with the PPR and AIR groups; (c) having average full-scale IQ lower than 130 to avoid a supernormal control group. Findings during pseudoword rhyming in both groups of poor readers (AIR and PPR) were similar to those observed in previous studies; that is, a relative underactivation in posterior neural systems located in the superior temporal and the occipitotemporal regions. But when reading real words, findings were quite surprising. Brain activation patterns in the AIR and PPR groups diverged. As they had for non-word rhyming, compared with the NI group, the AIR group demonstrated relative underactivation in left posterior regions (Figure 5.5, column 2). In contrast, during real word reading PPR subjects activated posterior systems (Figure 5.5, column 2); thus, there was comparable activation in the NI and PPR subjects in the posterior reading systems – findings that were both new and unexpected. Despite the significantly better reading performance in the NI compared with the PPR group on every reading task administered, left posterior reading systems were activated during reading real words in both NI and PPR groups.

We hypothesized that the PPR subjects were reading real words very differently from NI readers, reading the very simple real words primarily by memory. Support for this belief came from their performance on a word

pronunciation task out of magnet. PPR subjects were accurate while reading high-frequency words, but far less accurate when reading low-frequency and unfamiliar words. Further support for this hypothesis comes from a functional connectivity analysis. This strategy involves interrogating a 'seed voxel' (in this case, a voxel in the left occipitotemporal region), determining those regions most functionally related to the seed voxel.[114,115] We hypothesized that in NI readers, the occipitotemporal region processes print in a linguistically structured manner and should interact with other areas implicated in orthographic and phonological processing. We further hypothesized that in PPR subjects, the occipitotemporal area serves as a visually based memory system and should interact with other areas implicated in memory retrieval. Results indicated that NI readers demonstrated connectivity between the left occipitotemporal seed region and the left inferior frontal gyrus, a traditional language region (Figure 5.6, column 1). In contrast, PPR subjects (Figure 5.6, column 2) demonstrated functional connectivity between the seed region and right prefrontal areas often associated with working memory and memory retrieval[116,117] – a finding consistent with the hypothesis that in PPR subjects the occipitotemporal area functions as a component of a memory network.

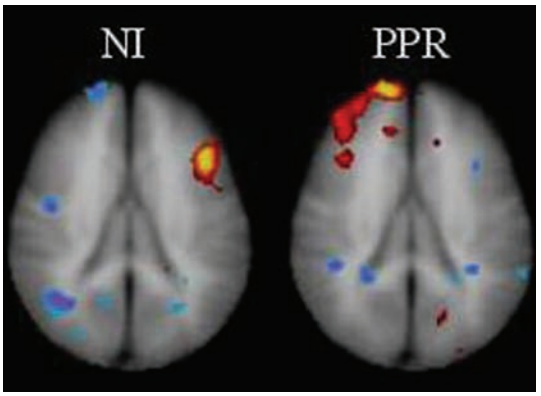

Figure 5.6 Group connectivity profiles between the 'seed voxel' in the left occipitotemporal region (Talairach coordinates (–55, –36, –5)) and other brain regions during the category (real-word) reading task. Red–yellow indicates significant positive correlations (p <0.02); blue–purple indicates negative correlation. The images correspond to z = +24 in Talairach space. In the non-impaired readers (NI), a strong positive correlation is observed between the left occipitotemporal region and the left inferior frontal gyrus (Broca's area), a traditional language region. In contrast, for persistently poor readers (PPR), the occipitotemporal region is correlated with regions in the right superior, middle, and inferior frontal gyri, brain regions believed to play a role in attention and memory. From Shaywitz et al[85] with permission from The Society of Biological Psychiatry.

Insight into some of the factors responsible for compensation on the one hand and persistence on the other comes from an examination of early childhood measures. The two groups of disabled readers (AIR and PPR) began school with comparable reading skills, but with the PPR subjects having poorer cognitive ability compared with the AIR subjects and tending to attend more disadvantaged schools. These findings suggest that the PPR group may be doubly disadvantaged in perhaps being exposed to a less rich language environment at home[118] and then less effective reading instruction at school. In contrast, the presence of compensatory factors such as stronger cognitive ability allowed the AIR subjects to minimize, in part, the consequences of their phonological deficit so that as adults they were indistinguishable from NI readers on a measure of reading comprehension and a measure of prose literacy. These findings are consonant with a large body of evidence indicating that the impact of dyslexia can be modified by the availability of compensatory resources, for example, semantic knowledge,[119] use of context,[120,121] and verbal ability[122] to compensate for phonological deficits. In adults, verbal abilities, as measured by verbal IQ, directly predict reading accuracy, with phonological factors influencing reading indirectly through their effects on verbal IQ.[123] The current study extends such findings by demonstrating that childhood cognitive ability may be an important influence on the development of reading skills in later childhood and into adult life. Beginning reading is most related to phonological skills, and within a few years, other

language skills (e.g. semantic knowledge), gain in importance. The current findings suggest that greater cognitive abilities may provide some degree of compensation for a reading difficulty; intuitively, this makes sense since a larger vocabulary and better reasoning skills are helpful when a struggling reader is trying to decipher unknown words. If the word is in his spoken language vocabulary, the beginning reader may recognize the word even if he can only partially sound it out. Strong reasoning abilities also help this reader to use the context around an unknown word to figure out its meaning. The imaging findings noted earlier that demonstrate a greater number of ancillary systems in AIR compared with PPR subjects may represent the neural correlates of this compensation.

Finally, for the first time, results from functional brain imaging studies distinguish two potential types of reading disability. These are consistent with Olson's suggestion of two possible etiologies for childhood reading disability: a primarily genetic type with IQ scores over 100 and a more environmentally influenced type with IQs below 100.[124–126] Although genetic and environmental factors clearly play a role in reading in all children, it is intriguing to speculate that the AIR subjects may represent a predominantly genetic type while the PPR group, with significantly lower IQ and a trend to come from lower SES families and to attend more disadvantaged schools, may represent a more environmentally influenced type of dyslexic reader. Another possibility is that both types of disabled readers (AIR and PPR) have a genetic predisposition, but in the case of AIR, the genetic predisposition is modified somewhat by positive environmental influences and higher cognitive ability. We speculate that in young adults, the neural system differences between these groups may not have been recognized before because previous functional imaging studies have generally focused on the compensated dyslexics, who, with appropriate accommodations, are more successful academically and are able to enter university,[79,82] while the environmentally influenced poor readers rarely attend university and may not readily come to the attention of investigators.

These findings have important educational implications and are of special relevance for teaching children to read. Consistent with our knowledge of the components of reading, children need to be able to sound out words in order to decode them accurately, and then they need to know the meaning of the word – to help decode and comprehend the printed message. Both the sounds and the meanings of words must be taught. These findings suggest that it may be beneficial to provide early interventions aimed at stimulating both phonological and verbal abilities in children at risk for reading difficulties associated with disadvantage.

Magnetoencephalography

MEG, also referred to as magnetic source imaging (MSI), has also been used to study reading and dyslexia. In principle, MEG depends on measuring the evoked fields produced in response to a stimulus, and then estimating the activity sources for the evoked fields. Compared with fMRI, which has good spatial resolution but is somewhat insensitive to the time course of events, MEG is most useful in examining the chronometry of cognitive processes, that is, the sequence of activation in millisecond resolution. In a series of experiments in adults and typically reading children, Papanicolaou and co-workers have described a sequence of brain activation profiles in aurally and visually presented word recognition tasks. Papanicolaou et al[64] have reviewed these studies, and only a brief summary is included here. This pattern consists of an initial engagement (within the first 100–150 ms) of primary sensory cortices (the floor of the Sylvian fissure for aurally presented words and the occipital cortex for written words). Next to be activated (150–250 ms) is the posterior portion of the left superior temporal gyrus for aurally presented words and the left fusiform and lingual gyri for written words. These activations are followed by activations in the left superior

temporal gyrus and inferior parietal regions (including the angular and supramarginal gyri), as well as the inferior frontal cortex, including Broca's area. The last structures to be activated (250 ms and later) include the hippocampus and middle temporal gyrus. When the visual stimuli are pseudowords rather than real words, the left superior temporal, left inferior parietal, and left inferior frontal regions are activated primarily, and the middle temporal and hippocampus do not activate. The principal difference observed in dyslexic children is activation of right temporal and right temporoparietal systems, rather than the typical left-hemisphere activation. These hemispheric differences are observed as well in even younger children at risk for reading problems. Provision of an effective intervention program resulted in significant increase in activity in the left superior temporal and left inferior parietal regions.[64]

Postmortem studies of dyslexia

As noted above, postmortem studies of adults who suffered acquired alexia suggested two posterior brain regions influential in the reading process. Using traditional neuropathological methods, Galaburda et al[59] were able to examine the neurobiological underpinnings of developmental dyslexia more than two decades ago. Subjects were adults with a childhood history suggestive of reading difficulties, who had died suddenly, usually in automobile or motorcycle accidents. Galaburda et al[59] described a pattern consisting of symmetry of the planum temporale, rather than the asymmetric pattern of larger left planum observed in adults who were assumed to be non-reading-impaired. In addition, affected individuals exhibited gray matter heterotopias most commonly observed along the left Sylvian fissure.

Structural MRI studies of dyslexia

Building on the postmortem findings, a number of structural MRI studies have attempted to demonstrate the asymmetric planum in dyslexic individuals. Earlier MRI studies of dyslexia have assessed asymmetries in such measures as gross regional volumes[127] and the lengths of various posterior temporal regions such as the planum temporale.[128] We have examined this issue and discussed this early literature previously, and the reader is referred to that paper for more details.[129] Other studies have demonstrated a reduction in temporal lobe volume, particularly on the left side, in adult right-handed dyslexic men,[61] and localized to temporal lobe gray matter.[62] A more recent study examining children indicates, in dyslexia, smaller right anterior lobes of the cerebellum, pars triangularis, and total brain volume.[130] These studies have not supported the postmortem findings. Advances in computer technology now allow a much more detailed examination of brain cortical changes. For example, Sowell et al[131] have used such technology to map cortical change across the lifespan and to map the sulcal pattern asymmetry in vivo. Such studies are currently underway in dyslexic and typically reading children in our laboratory in collaboration with Dr Sowell.

Reading and dyslexia in languages other than English

Phonological deficits characterize dyslexia in individuals whose native language is not English but who use an alphabetic script. Thus, Paulesu et al[82] noted a comparable disruption to native English speakers in posterior reading systems in college students with dyslexia in Italy and in France. Recent studies have begun to examine dyslexia in Chinese readers. Siok et al[132] suggest that in non-impaired readers, the left middle frontal gyrus is critical for skilled Chinese reading. This region appears to be critical in processing syllables, while the left inferior frontal gyrus mediates the processing of phonemes. This pattern of findings offers compelling evidence for distinct cortical areas relevant to the representation of syllables and phonemes. Siok et al[133] found that dyslexic Chinese children demonstrated a reduction in activa-

tion of the left middle frontal gyrus with increased activation in the left inferior frontal gyrus – presumably a compensatory activation. Brain imaging during a word recognition task indicated that dyslexic Chinese children showed reduced activation in both left and right middle frontal gyri, left and right inferior frontal gyri, and left fusiform gyrus. Dyslexic readers demonstrated increased activation in the right occipital cortex. Thus, in a pattern similar to that seen in dyslexic English readers, dyslexic Chinese children exhibit reduced activation in left frontal and left occipitotemporal regions. However, in contrast to dyslexic American children, no differences were observed in parietotemporal regions.

CONCLUSIONS AND FUTURE DIRECTIONS

Within the last two decades, overwhelming evidence from many laboratories has converged to indicate the cognitive basis for dyslexia: dyslexia represents a disorder within the language system and more specifically within a particular subcomponent of that system, phonological processing. Recent advances in imaging technology and the development of tasks that sharply isolate the subcomponent processes of reading now allow the localization of phonological processing in the brain, and, as a result, provide for the first time the potential to elucidate a biological signature for reading and reading disability. Converging evidence from a number of laboratories using functional brain imaging indicates a disruption of left-hemisphere posterior neural systems in child and adult dyslexic readers while performing reading tasks, with an additional suggestion of an associated increased reliance on ancillary systems (e.g. in the frontal lobes and right-hemisphere posterior circuits). The discovery of neural systems serving reading has significant implications. At the most fundamental level, it is now possible to investigate specific hypotheses regarding the neural substrate of dyslexia, and to verify, reject, or modify suggested cognitive models. From a more clinical perspective, the identification of neural systems for reading offers the promise of more precise identification and diagnosis and more targeted, effective treatment of dyslexia in children, adolescents, and adults.

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Epilepsy

6

Jeffrey R Binder, Manoj Raghavan

INTRODUCTION

Brain surgery is an effective treatment for individuals who suffer from medically intractable epilepsy.[1–5] Of the over 2 million Americans with epilepsy, 30–40% continue to have seizures despite optimal anticonvulsant treatment.[6–8] Of these, it is estimated that at least 30%, or over 200 000 individuals in the USA, would be candidates for epilepsy surgery.[8–10] Determination of the appropriateness of surgery requires identification of a brain locus of seizure origin as well as evaluation of the surgical risks. Functional magnetic resonance imaging (fMRI) can potentially contribute to this process in several ways. First, by determining the location of important brain functions, fMRI can help predict the risk of postoperative language, memory, and motor deficits, and during the surgical procedure can be used to minimize such deficits. Second, asymmetries in temporal lobe functional activation can identify diseased brain tissue in which seizures are inferred to originate. Third, techniques for detecting ictal or interictal hemodynamic changes can be used to directly localize epileptic foci.

Traditional techniques for presurgical functional mapping include the intracarotid amobarbital (Wada) test,[11,12] subdural grid cortical stimulation mapping,[13] intraoperative stimulation mapping,[14] and positron emission tomography (PET).[15] These methods, while very useful, are generally invasive, costly, or not widely available. Despite use of these techniques, demonstrable language or memory decline occurs in 40–60% of patients undergoing dominant-hemisphere temporal lobe surgery for epilepsy.[16–21] Methods for locating epileptogenic foci continue to improve, yet uncertainty about localization in individual patients continues to be a major problem affecting surgical eligibility and outcome.[22–27] A significant proportion of patients require invasive or semi-invasive recording techniques, adding to the cost and risk of a surgical approach.[28–30]

Compared with these traditional techniques, fMRI offers a number of well-known advantages. First, and most importantly, the technique is safe, requiring no invasive procedures or radiation exposure. The safety of fMRI allows activation protocols to be thoroughly tested in normal volunteers prior to clinical use, enables collection of large datasets in individual patients with resultant enhancement of statistical power, and permits studies to be repeated if necessary without additional risk. Second, the relatively small size of fMRI voxels (typically 2–4 mm) provides excellent spatial resolution. Functional data can be registered with higher-resolution structural images acquired at the same brain locations in the same session, permitting functional loci to be identified more precisely with specific anatomical loci. Third, a large number of activation procedures can be performed in each subject during a single session, enabling localization of a wide variety of cognitive processes and systems. Fourth, fMRI can be implemented on the MRI scanners already in place at most medical facilities and requires no costly radioisotopes or surgical procedures.

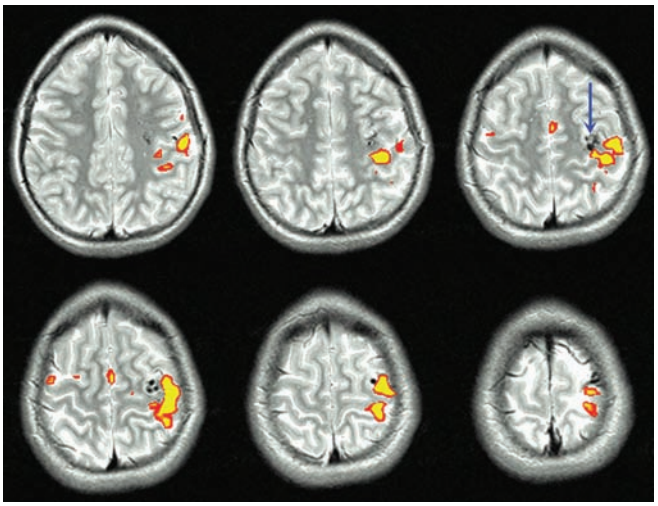


Figure 6.1 Preoperative fMRI during right hand finger movements in a patient with seizures secondary to a left precentral gyrus arteriovenous malformation (blue arrow). Close proximity of the motor cortex activation to the AVM resulted in a decision to forego endovascular and surgical considerations in favor of gamma knife therapy. Figure courtesy of John Ulmer, MD, Medical College of Wisconsin.

PREOPERATIVE MAPPING OF SENSORIMOTOR CORTEX

Motor activation

Many fMRI studies have focused on activation of primary motor cortex along the central sulcus.[31–35] Because movement provides tactile and proprioceptive sensory input, activation is not confined to the motor cortex (the anterior bank of the central sulcus), but involves both primary motor and sensory areas. Several imaging studies have confirmed the well-known somatotopic organization of this region.[36–38] Finger movements are used most commonly in fMRI studies, since face or proximal limb movements increase the likelihood of unacceptable movement artifacts. The magnitude of activation in primary motor cortex depends on the rate of movement.[39,40] Complex, sequential movements produce additional activation in associated regions such as premotor cortex, supplementary motor area, and postcentral sulcus bilaterally.[33,41] Thus, the activation pattern depends strongly on the particular body part, type of movement, and movement parameters selected for the activation task. Common procedures include simple repetitive tapping of a single finger, sequential opposition of each finger to the thumb, and repetitive opening and closing of the fist.

Such tasks reliably activate sensorimotor cortex in the central sulcus and have been used in a number of patient studies (Figure 6.1).[42–54] The clinical utility of such maps is in functional localization prior to surgery in this region for tumor or seizure focus resection. When the lesion is in close proximity to primary sensorimotor cortex along the central sulcus, precise localization of the activated region relative to the lesion could potentially help predict whether a sensorimotor deficit is likely to occur from lesion resection. It might also be possible to minimize any resulting deficit by purposefully sparing activated and immediately surrounding regions, although no quantitative studies have verified the effectiveness of such an approach. fMRI information is perhaps particularly useful when anatomical structures are distorted by mass effects, making it difficult to ascertain the location of the central sulcus with certainty (Figure 6.1). Motor cortex localization with fMRI has generally been highly concordant with intraoperative electrocortical stimulation mapping.[42–44,48,51–54]

Because motor tasks often produce activation in bilateral premotor and sensory association regions, it can be difficult in some cases to distinguish primary motor cortex from these other areas. One solution to this problem is to contrast movements of one hand with

movements of the other hand, rather than with a resting baseline.[53] In addition to activating contralateral primary sensorimotor cortex, both of these conditions activate premotor, postcentral, and supplementary motor areas bilaterally. When the conditions are contrasted, these bilateral activations are subtracted away, leaving only activation in the contralateral central sulcus. This protocol successfully identified the central sulcus in 82% of 50 patients with brain tumors.[53] Failure to activate the central sulcus was associated with pre-existing paresis of the contralateral hand, older age, and head motion. Correct localization by fMRI was confirmed in all of the 22 patients studied with intraoperative cortical stimulation.

Activation of motor cortex in patients with severe contralateral paresis is an important problem, since these patients are likely to have lesions in or near the motor strip and so have the greatest need for preoperative mapping. One approach to this problem is to activate the premotor area by movement of the ipsilesional (unimpaired) hand, from which the location of the central sulcus can then be estimated.[55] Another problem encountered in motor studies is that performance of a motor task may cause the patient to move the body and head slightly, resulting in false-positive signals in the fMRI data, referred to as task-correlated motion artifacts.[56] Careful instruction and training of the patient, measures to comfortably restrict head motion, use of small rather than large movements for the activation task, and proximal fixation of the limb to be moved should minimize such artifacts.[57]

Somatosensory activation

Somatosensory cortex has been the focus of many fMRI studies.[58–73] Stimuli have included light touch with air puffs or other tactile stimuli,[59,61,62,68] scratching of the palm,[57] vibration,[60,61,73] electrical stimulation,[58,63,65,66,71,72] noxious stimuli,[64,69] and proprioception induced by passive joint movement.[62] Activated areas usually include primary somatosensory cortex (SI) along the central sulcus and postcentral gyrus, and secondary cortex (SII) in the parietal operculum, insula, and more posterior ventral parietal areas (PV). Many studies have demonstrated somatotopic organization in primary somatosensory cortex, whereas association areas are not clearly somatotopic.[58–61,67,71] As with the motor system, unilateral stimulation activates primary cortex only in the contralateral hemisphere but secondary areas bilaterally.[63,66,70]

It is still uncertain what stimulus is the most effective, although indications are that pain stimuli are somewhat less reliable for evoking SI activation than more dynamic stimuli.[69] Activation magnitude in SI depends on the intensity of stimulation,[65,71] the size of the stimulated body surface,[64,69] and the rate of stimulation.[72] Responses in secondary areas seem to be less influenced by these variables, but are probably more dependent on the level of attention paid to the stimulus[66] and on whether stimulation is delivered unilaterally or bilaterally.[70]

Somatosensory activation can be used to localize the central sulcus preoperatively and is applicable even in patients with severe hemiparesis, unless they also have severe hemianesthesia. Sensory activation also has the advantage of not requiring movement that could cause artifacts. One study of 94 brain tumor patients found a lower incidence of severe movement artifacts with a somatosensory paradigm (repetitive brushing of the palm) compared with a motor paradigm, but significantly higher percent signal increases with the motor paradigm.[57] The authors concluded that somatosensory paradigms are less sensitive than motor paradigms, but it is unclear whether repetitive brushing of the palm represents an optimal sensory stimulus.

PREOPERATIVE MAPPING OF LANGUAGE SYSTEMS

The aim of localizing language functions preoperatively is to minimize postoperative language deficits, such as anomia, that can result from epilepsy surgery.[17,19–21,74] By determining the location of important language

Table 6.1 Some task contrasts used for language mapping and the regions in which robust activations are typically observed

	Ventrolateral prefrontal	*Dorsal prefrontal*	*Superior temporal*	*Ventrolateral temporal*	*Ventral occipital*	*Angular gyrus*
Hearing words vs rest			B			
Hearing words vs non-speech sounds			L > R			
Word generation vs rest	L > R			L > R	B	
Word generation vs reading	L					
Object naming vs rest	B			L > R	B	
Semantic decision vs sensory discrimination	L	L	L > R	L		L
Semantic decision vs phonological decision		L		L		L
Reading sentences vs letter strings	L > R		L > R	L > R		

L, left hemisphere; R, right hemisphere; B, bilateral.

functions, fMRI techniques might help predict the risk of postoperative language deficits. During the surgical procedure itself, functional maps might be used to minimize such deficits by avoiding important functional areas.

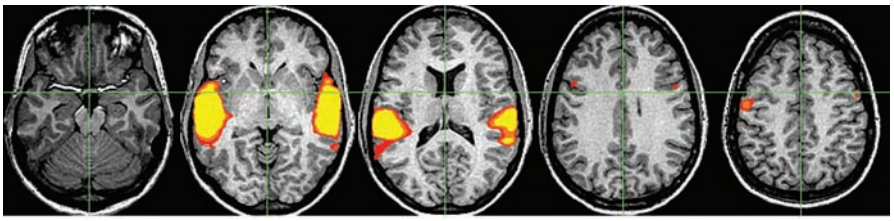
Language activation protocols

Although fMRI and PET have been used extensively to study normal language processing, the areas identified in different studies have varied markedly, likely owing to the use of different language activation tasks, control tasks, imaging techniques, and data-processing methods.[75] Language is not a single process, but rather involves specialized sensory systems for speech, text, and object recognition; access to word meaning; processing of syntax; and multiple mechanisms for written and spoken language production. Neuropsychological studies suggest a certain modularity of organization of these language subsystems,[76] and it is unlikely that any single activation procedure could identify all of them. Some commonly used task combinations and the brain regions that they typically 'activate' are shown in Table 6.1.

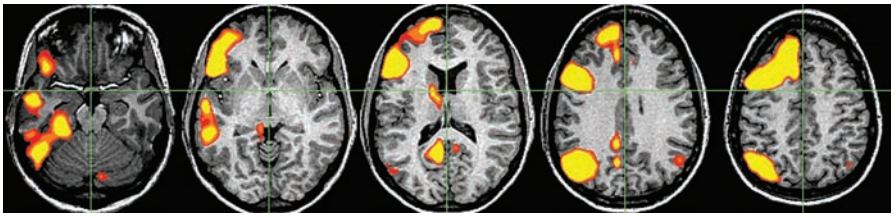
A few examples may be illustrative of some main issues in task design. Numerous studies over the past decade have shown that hearing words – whether the task involves passive listening, repeating, or categorizing – activates the superior temporal gyrus bilaterally when compared with a resting state (Figure 6.2a).[77–80] The symmetry of this activation may be surprising, but a consideration of the task contrast (complex sounds compared with no sounds) reveals that the 'rest' baseline contains no controls for primary or secondary auditory processes that engage auditory cortex in both superior temporal gyri.[81] Thus, much of the activation produced by contrasting word listening with no sound could be due to prelinguistic auditory processing. These activation patterns bear almost no relationship to language dominance measured by Wada testing.[82] Another problem in using such a paradigm for language mapping is that left-lateralized brain areas associated with semantic processing are probably active during the 'rest' state.[83] Thus, any activity in these regions during the word-listening task would be difficult to detect when compared with 'rest'.

Similar problems occur in designs that contrast reading or naming tasks with a resting or visual fixation baseline. The resting condition contains little in the way of controls for prelinguistic visual form recognition processes in ventral occipitotemporal regions, which thus dominate the activation map. Benson et al[84] found that such procedures do not reliably produce lateralized activation and do not correlate with language dominance measured by Wada testing.

More widely used than listening, repeating, reading, and object naming tasks are 'word



(a)



(b)

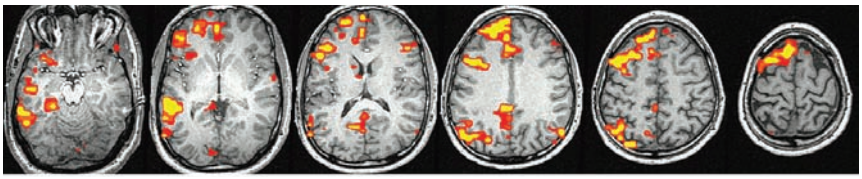
Figure 6.2 Group-average fMRI activation patterns in neurologically normal, right-handed volunteers during two language paradigms. (a) Listening to spoken words contrasted with resting (28 subjects). Superior temporal activation occurs bilaterally. (b) Semantic decision on auditory words contrasted with a tone decision control task (30 subjects). Activation is strongly left-lateralized in multiple prefrontal and sensory association areas. The images are serial axial sections spaced at 15 mm intervals through stereotaxic space, starting at $z = -15$. The left hemisphere is on the reader's left. Green lines indicate stereotaxic x and y axes. Reproduced from Binder et al[301] with permission from Blackwell Publishing.

generation' tasks (also called fluency tasks) that require word retrieval in response to a verbal cue. Subjects are given a beginning letter, a semantic category, or a word, and must retrieve a phonologically or semantically associated word. This task strongly activates the dominant inferior and dorsolateral frontal lobe, including prefrontal and premotor areas.[77,85–87] Posterior language areas such as the middle and inferior temporal gyri, fusiform gyrus, and angular gyrus are only weakly activated by the word generation task compared with a resting state or a word reading control.[77,85–87]

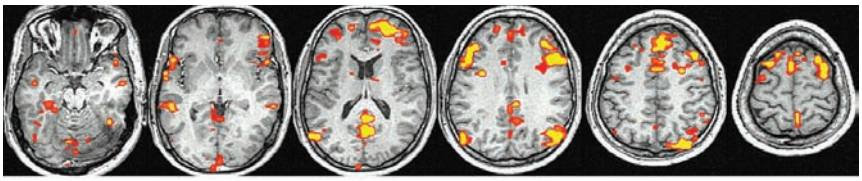
Another approach involves pairing a word comprehension task with a non-linguistic sensory discrimination task.[88–94] These tasks can be given in either the visual or auditory modality. The sensory discrimination task controls for primary sensory, attentional, working memory, and motor aspects of the language task. The resulting activation pattern is strongly left-lateralized and involves both prefrontal and posterior association areas (Figure 6.2b). An attractive feature of these paradigms is that measured behavioral responses, consisting of simple button presses for stimuli that meet response criteria, permit task performance to be quantified.

Normative studies of language lateralization

Several language mapping protocols have been carried out in relatively large samples of normal participants.[95–100] All of these procedures produced left-lateralized activation patterns in groups of right-handed subjects, although the degree of lateralization at the individual level varies along a continuum (Figure 6.3). Lateralization has often been quantified using the left–right difference in the number of activated voxels (difference in activation volume), normalized by the total number of activated voxels: i.e. $(L - R)/(L + R)$. This index varies from –1 (all activated voxels in the right hemisphere) to +1 (all activated voxels in the left hemisphere).



(a)



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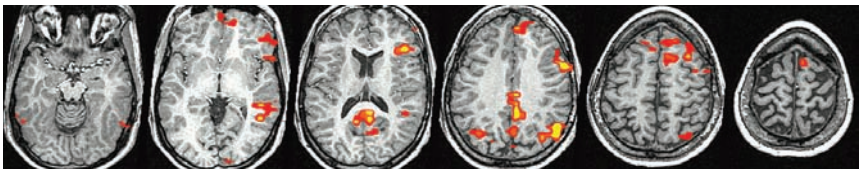

(c)

Figure 6.3 Examples illustrating variation in language dominance. The activation protocol used a contrast between semantic decision and sensory discrimination tasks (see Figure 6.2b). The images are serial axial sections spaced at 15 mm intervals through stereotaxic space, starting at $z = -15$. The left hemisphere is on the reader's left. (a) Typical strong left lateralization (LI = 0.73) in a healthy right-handed man, age 31. (b) Bilateral, slightly right-lateralized activation (LI = –0.23) in a healthy left-handed man, age 32. (c) Right-lateralized activation (LI = –0.61) in a 28-year-old left-handed woman with epilepsy.

This type of index depends on the statistical threshold used to identify voxels as 'active', and tends to increase with increasingly stringent thresholds due to the elimination of false-positive voxels in both hemispheres.[101,102] Others have advocated measures based on magnitude rather than volume of activation.[84,103] The lateralization index (LI) can be computed for the entire hemisphere or for homologous regions of interest (ROIs). Focusing on language-related ROIs avoids the problem of non-specific or non-language activation in bilateral sensory, motor, and executive systems that is characteristic of some task contrasts.[101]

Language lateralization in right-handed adults, as measured by fMRI in several large samples, ranges from strong left dominance (LI near +1) to roughly symmetrical representation (LI near 0)[96,97] (Figure 6.4). As expected, moderate to strong left dominance is typical, with only 4–6% falling in the symmetric range (e.g. LI = –0.2 to 0.2).[96,97] As a group, left-handed and ambidextrous subjects show a relative rightward shift of language functions compared with right-handed subjects.[97,99,104] This difference reflects a group tendency only: most left-handed and ambidextrous subjects are, like right-handers, left-dominant for language, but a larger minority (20–25%) are symmetrical or right-dominant. These estimates of language dominance in normal subjects agree very well with earlier Wada language studies in patients with late-onset seizures.[96,105,106]

Sex differences in language lateralization were reported in a few fMRI studies.[95,98,107,108] Other PET,[109,110] fMRI,[97,99,100,111] and functional transcranial Doppler[112] studies, together involving over 600 normal subjects, have

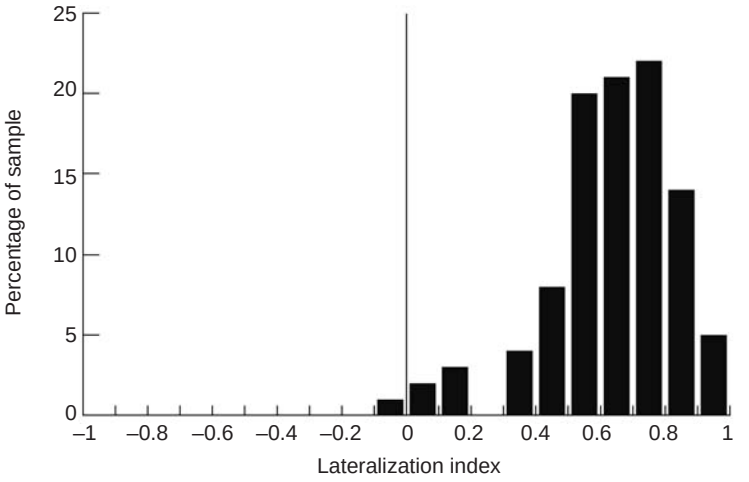

Figure 6.4 Frequency distribution of fMRI language lateralization index (LI) in a sample of 100 healthy right-handed adults.[96] The activation protocol used a contrast between semantic decision and sensory discrimination tasks (see Figure 6.2b). Positive LI values indicate left lateralization, negative values indicate right lateralization. The mean LI for the group is 0.63.

failed to find differences between men and women in lateralization of language functions.[113] Two studies reported age effects on language dominance in adults, manifested as a decline in the LI (greater symmetry of language processing) with increasing age.[96,99] Similar declines in hemispheric specialization have been observed for other cognitive domains,[114,115] and may reflect recruitment of homologous functional regions as compensation for age-related declines in neural functional capacity. Level of education had no effect on LI in the one study in which it was assessed.[96]

Two fMRI studies directly compared LIs from a sample of normal adults with LIs from patients with epilepsy.[96,102] Both studies included only right-handed individuals to avoid confounding effects of handedness. Patients with epilepsy had a higher incidence of atypical (symmetric or right-lateralized) language dominance; this was particularly true for patients with left-sided seizure foci.[102] In one study, there was a clear relationship between LI and age of onset of seizures (r = 0.50, p <0.001), with language tending to shift more toward the right hemisphere with earlier onset[96] (Figure 6.5). These effects are in agreement with Wada studies showing effects of side of seizure focus and age at onset on language lateralization,[105,106,116,117] attesting to the general validity of the fMRI measures.

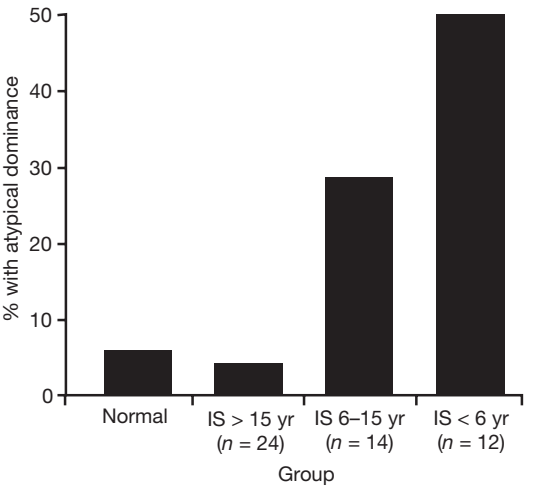

Figure 6.5 Frequency of 'atypical' language dominance (defined as LI ≤ 0.2) in 100 normal right-handed adults and 50 right-handed epilepsy patients. Epilepsy patients are divided into three groups with age at onset of intractable seizures (IS) after 15 years old, between 6 and 15 years old, and before 6 years old. Atypical dominance increases markedly with earlier seizure onset. Reproduced with permission from Springer et al.[96]

Wada test comparisons

Preliminary results suggest a high level of agreement between fMRI and Wada tests on measures of language lateralization (Table 6.2).[82,84,92,93,102,118–126] Most of these studies, however, involved relatively small sample sizes

Table 6.2 Wada–fMRI language lateralization comparisons

Ref	*n*	*Language task*	*Control task*	*Result*
118	7	Semantic decision (visual words)	Orthographic decision	100% concordance
119	22	Semantic decision (auditory words)	Tone monitoring	100% concordance, $r = 0.96$
120	7	Covert phonological word generation	Rest	100% concordance
121	6	Covert or overt word generation	Rest	100% concordance
128	12	Covert phonological word generation	Rest	56% concordance
122	13	Covert phonological word generation	Rest	100% concordance, $r = 0.91$
84	12	Covert verb generation	Fixation	100% concordance
		Covert object naming	Fixation	NS lateralization
		Covert word reading	Fixation	NS lateralization
82	10	Covert semantic word generation	Rest	$r = 0.88$ for a frontal ROI
		Covert sentence repetition	Rest	NS correlation
		Passive story listening	Non-word listening	NS correlation
123	8	Rhyme decision (visual words)	Shape decision	100% concordance
127	49	Semantic decision (auditory words)	Tone monitoring	98% concordance
92	10	Semantic/syntactic decision	Sensory discrimination	90% concordance
93	13	Semantic matching (visual words)	Color matching	100% concordance frontal ROI
125	18	Covert verb generation	Shape detection	72% concordance verb generation
		Covert semantic word generation	Rest	83% combining all tasks
		Covert object naming	Shape detection	n.s. concordance for others
		Covert sentence reading	Shape detection	
102	19	Covert phonological word generation	Rest	100% concordance
124	20	Covert semantic word generation	Rest	95% concordance
126	94	Covert word generation	Rest	91% concordance

NS, non-significant; ROI, region of interest.

(7–20 patients) and relatively few crossed-dominant individuals. A variety of task contrasts have been employed, including semantic decision versus sensory discrimination,[92,93,119,127] semantic decision versus orthographic decision,[118] word generation versus rest,[82,84,102,120–122,124–126] rhyme decision,[123] object naming,[84,125] and word or sentence reading.[84,125]

Semantic decision and word generation paradigms generally produce high (90–100%) concordance rates (although see Worthington et al[128]). Results from several other protocols, including sentence listening versus rest,[82] object naming versus rest,[84] and object naming versus sensory discrimination,[125] were not concordant with Wada results. Lack of concordance probably stems from the fact that these latter contrasts produce strong activation in auditory and visual sensory systems that are not strongly lateralized, and only weak activation in prefrontal or posterior association cortex language areas.

Word generation tasks produce strong frontal activation but relatively weak temporal and parietal activation. The most concordant results obtained with word generation tasks are thus based on activation in a frontal ROI. This characteristic of the word generation task is potentially problematic for clinical applications in patients with temporal lobe pathology, for two reasons. First, it is possible that language lateralization in such cases could differ for the frontal and temporal lobes, and it would be preferable to know the dominance pattern in the region in which surgery is to be undertaken. Second, if the goal is not simply to determine language dominance but rather to detect language-related cortex with optimal sensitivity for surgical planning, then lack of dominant temporal or parietal lobe activation represents a clear failure of the task paradigm. Another major limitation of the word generation task is that it requires spoken responses for scoring, which produce movement

artifacts and are difficult to record in fMRI studies. As a result of these difficulties, all of the cited studies have used 'covert' responding, in which subjects are asked simply to 'think of' words. The absence of behavioral confirmation of task performance is not a problem if the goal is simply to calculate an LI in the setting of at least some measurable activation. If, on the other hand, there is little or no activation, or the goal is to localize activation with optimal sensitivity, it can never be known whether lack of activation implies lack of cortical function or is simply an artifact of poor task compliance.

Comparisons with cortical stimulation mapping

A number of studies have compared fMRI language maps with language maps obtained from cortical stimulation mapping.[84,92,129–136] These studies are of interest because they permit a test of whether fMRI activation foci represent 'critical' language areas. Some regions activated during language tasks may play a minor, supportive role rather than a critical role, and resection of these active foci may not necessarily produce clinically relevant deficits. The assumption underlying the cortical stimulation technique is that temporary deactivation induced by electrical interference can specifically identify critical areas.

Published results on this topic have been mostly encouraging. These reports involved relatively small samples (<15 patients). Methods for comparing the activation maps have tended to be qualitative and subjective rather than quantitative and objective, with a few exceptions.[129,136] Fitzgerald et al[129] reported, in 11 patients, an average sensitivity of 81% and specificity of 53% when using fMRI to predict 'critical' language sites on intraoperative cortical stimulation mapping, employing a criterion that the fMRI focus in question spatially overlap the stimulation site. When the criterion was loosened to include instances in which the fMRI focus was within 2 cm of the stimulation site, the sensitivity improved to 92% but the specificity was 0%.

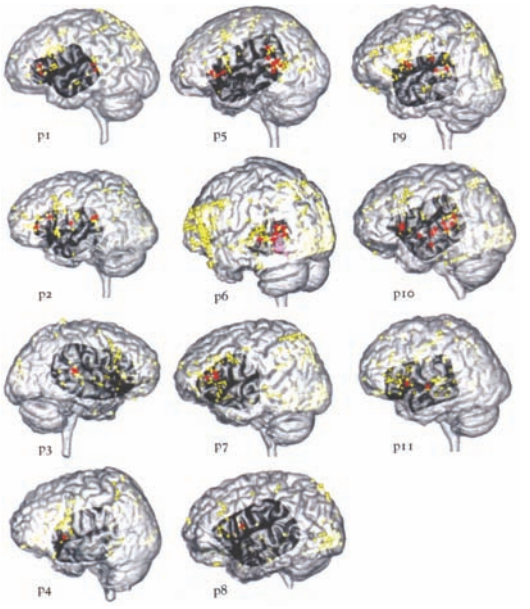

Figure 6.6 Cortical surface renderings of 11 patients studied with language fMRI and intraoperative cortical stimulation mapping. Foci of significant activation by fMRI are shown in yellow and foci identified by stimulation mapping during picure naming are shown in red. The surgically exposed cortical region is indicated with darker shading. fMRI maps were derived by combining activations from four protocols (silent verb generation vs shape discrimination, silent word fluency vs rest, picture naming vs shape discrimination, and sentence reading vs shape discrimination). Reproduced with permission from Rutten et al.[136]

Sensitivity and specificity were highly variable across subjects. Rutten et al[136] found an average sensitivity of 92% and specificity of 61% in using fMRI to predict temporal lobe language sites on cortical stimulation mapping (Figure 6.6). Only about half of the fMRI activation sites were found to be 'critical' on stimulation mapping. Given that 3 of the 11 patients showed no temporal or parietal lobe language sites on stimulation mapping, this low positive predictive value may have resulted from a lack of sensitivity of the stimulation technique rather than low specificity of the fMRI method.

Several factors make these comparisons particularly difficult to carry out. One problem is in matching the task characteristics

across the two modalities. fMRI studies usually employ controls for non-linguistic aspects of task performance, whereas this is typically not true of stimulation mapping studies. For example, stimulation studies often focus on speech arrest, which can result from disruption of motor or attentional systems as well as language systems.[137] A second difficulty concerns the potential for lack of sensitivity of the stimulation technique. Stimulation mapping protocols are usually brief, especially when carried out intraoperatively, limiting the number of language functions that can be assessed. One study showed dramatically different results depending on the type of stimulus used for naming during stimulation mapping.[138] Many fMRI activation foci lie buried in the depths of sulci, which are not available for stimulation mapping. Thus, it is reasonable to expect that many foci of activation observed by fMRI simply will not be tested adequately during cortical stimulation mapping. Finally, the assumptions forming the basis of the cortical stimulation technique have yet to be adequately tested. There is, for example, very little evidence that resection of 'critical' areas detected by cortical stimulation necessarily leads to postoperative language deficits or that cortical stimulation mapping has any effect on preventing language decline.[74] One study, in fact, showed that the likelihood of finding 'critical' foci in the left anterior temporal lobe was higher among patients with poor language function, even though these patients are less likely to show language decline after left anterior temporal lobectomy.[139,140]

Prediction of language outcome

It could be argued that neither the Wada test nor cortical stimulation mapping constitutes an ideal 'gold standard' against which to judge fMRI language maps. Both of these tests have recognized limitations, and both differ sufficiently from fMRI in terms of methodology and level of spatial detail that it is probably unreasonable to expect strong concordance with fMRI maps. A more meaningful measure of the validity of fMRI language maps is how well they predict postoperative language deficits. The purpose of preoperative language mapping, after all, is to assess the risk of such deficits and to minimize their severity. If fMRI can predict postoperative language deficits as well as, or better than, the Wada test, then what need is there to compare fMRI directly with the Wada test?

Sabsevitz et al[21] assessed the ability of preoperative fMRI to predict naming decline in 24 consecutively encountered patients undergoing left anterior temporal lobe resection (ATLR). fMRI employed a semantic decision versus sensory discrimination protocol. All left ATLR patients also underwent Wada testing and intraoperative cortical stimulation mapping, and surgeries were performed blind to the fMRI data. Compared with a control group of 32 right ATLR patients, the left ATLR group declined postoperatively on the 60-item Boston Naming Test ($p < 0.001$). Within the left ATLR group, however, there was considerable variability, with 13 patients (54%) showing significant declines relative to the control group and the remainder no decline. An LI based on fMRI activation in a temporal lobe region of interest was strongly correlated with outcome ($r = -0.64$, $p < 0.001$), such that the degree of language lateralization toward the surgical (left) hemisphere was related to poorer naming outcome, whereas language lateralization toward the non-surgical (right) hemisphere was associated with less or no decline (Figure 6.7). Of note, an LI based on a frontal lobe ROI was considerably less predictive ($r = -0.47$, $p < 0.05$), suggesting that an optimal LI is one that indexes lateralization in or near the surgical resection area. The fMRI temporal lobe LI showed 100% sensitivity, 73% specificity, and a positive predictive value of 81% for predicting significant decline. By comparison, the Wada language LI showed a somewhat weaker correlation with decline ($r = -0.50$, $p < 0.05$), 92% sensitivity, 43% specificity, and a positive predictive value of 67%.

These results suggest that preoperative fMRI could be used to stratify patients in

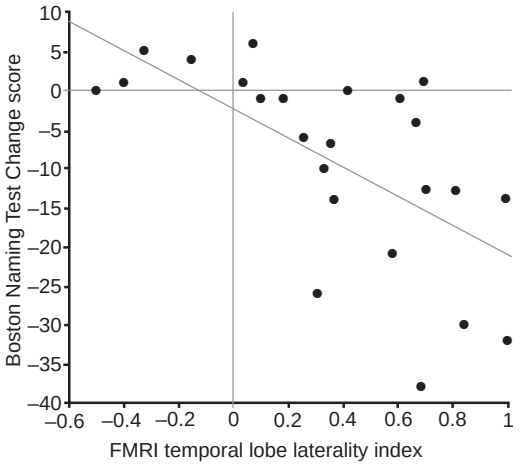

Figure 6.7 Scatterplot depicting the relationship between preoperative lateralization of language-related brain activation in a temporal lobe region of interest and postoperative decline in confrontation naming performance. Reproduced with permission from Sabsevitz et al.[21]

terms of risk for language decline, allowing patients and physicians to more accurately weigh the risks and benefits of brain surgery. It is crucial to note, however, that these results hold only for the particular methods used in the study and may not generalize to other fMRI protocols, analysis methods, patient populations, or surgical procedures. Future studies should not only confirm these results using larger patient samples, but also test their generalizability to other protocols.

'Tailoring' resections

It is not yet known how useful fMRI language activation maps will be for precise planning of surgical resections. At least three significant problems complicate progress: (i) inconsistencies in language maps produced by different activation protocols; (ii) the failure to date to find an activation protocol that reliably activates the anterior temporal lobe where the majority of epilepsy surgeries are performed; (iii) an inadequate understanding of the specificity (i.e. predictive value) of fMRI activations.

As indicated earlier, different fMRI language protocols produce markedly different patterns of activation.[75,141,142] Notably, none of the activation protocols currently in common use is associated with robust anterior temporal lobe activation. Because the dominant anterior temporal lobe is known to contribute to language processes,[78,138,143–147] and left anterior temporal lobectomy not infrequently results in language decline,[17,19–21,148,149] it follows that these protocols are simply not detecting critical language areas. Clearly, further language activation task development is needed. It may also be necessary, as some have suggested,[125,141] to combine multiple activation protocols to obtain a complete picture of the language zones in a given individual.

In addition to these issues concerning the sensitivity of the activation protocol, it is conceivable that some regions activated during language tasks may play a minor or non-specific role rather than a critical role in language. Resection of these 'active' foci may not necessarily produce clinically relevant or persisting deficits. Thus, those who would use fMRI activation maps to decide which brain regions can be resected in an individual patient run two risks: (i) resection of critical language zones that are 'not activated' due to insensitivity of the particular language activation protocol employed, resulting in postoperative language decline; (ii) sparing of 'activated' regions that are actually not critical for language, resulting in suboptimal seizure control. Only through very carefully designed studies – in which resections are performed blind to the fMRI data, standardized procedures are used for assessing outcome, and quantitative measures are made of the anatomical and functional lesion – will the usefulness of fMRI language maps for 'tailoring' surgical resections be determined.

PREOPERATIVE MAPPING OF MEDIAL TEMPORAL LOBE MEMORY SYSTEMS

Role of the medial temporal lobe in memory

The hippocampus and surrounding medial temporal lobe (MTL) structures, including

the parahippocampus, entorhinal cortex, perirhinal cortex, and their efferent and afferent projections, play a pivotal role in supporting memory.[150–153] Recent models propose that the MTL coordinates unimodal and multimodal association cortex activity during perception, comprehension, and response to a stimulus event, or 'episode'. Coordination of activity in these systems creates a complex, unique representation of the event 'configuration', composed of the salient stimulus elements (including the environment or context in which the stimulus occurs), stored knowledge (e.g. semantic or spatial information) associated with these elements, and behavioral responses by the subject to the stimulus, creating a unitary representation of the episode for later retrieval from long-term memory.[153–158] Although memory encoding studies in humans often involve tasks with explicit instructions to 'memorize', it is important to note that episodic memory storage occurs relatively continuously and effortlessly during daily existence, as demonstrated by the fact that we remember much of what we experience without explicitly trying to do so.

Episodic memory can be conceptualized as involving several stages or components. Although several theoretical schemes have been offered, most acknowledge a stage called encoding, in which sensorimotor events are perceived and processed. Neural activation during encoding is believed to depend on both 'depth of processing' and stimulus 'modality'. Events that activate associative and conceptual knowledge are more thoroughly encoded and better remembered than events that do not.[159,160] Information that is verbally encoded primarily engages the left MTL system, while nonverbal or spatial information depends more heavily on the right MTL.[151,161–164] Following initial encoding, there is a stage of consolidation, in which the encoded information is gradually entered into long-term storage involving cortical regions outside the MTL. A third component is retrieval, which allows the stored experience to be brought back to consciousness. The degree of involvement of MTL structures at each of these stages remains uncertain, although some recent evidence links the hippocampus more closely to encoding and consolidation than to retrieval processes.[165–167] Complicating attempts to disentangle these processing stages is the fact that all retrieval tasks are episodic events and therefore also engage encoding processes.[168]

Applications of MTL imaging in epilepsy

Structural and functional abnormalities in the MTL can provide important evidence for localizing a seizure focus. Pathological changes in these structures, including progressive sclerosis and asymmetric volume loss, are a common feature of temporal lobe epilepsy (TLE) and can be detected with good sensitivity and specificity using structural MRI.[169–172] PET may reveal interictal hypometabolism and associated hypoperfusion in the MTL of patients with TLE.[173–175] The memory portion of the Wada test, which assesses episodic encoding during unilateral cerebral anesthesia, can detect asymmetric dysfunction of the MTL, which is used to infer the laterality of a seizure focus.[176–179] One potential application of fMRI, therefore, is to provide evidence about seizure focus laterality by measuring asymmetry of activation in the MTL. In addition to assisting in seizure focus identification, asymmetry of activation might be useful for predicting seizure outcome after surgery. When functional asymmetry consistent with the side of seizure focus is demonstrated on PET or on the Wada memory test, for example, seizure control is better than when no asymmetry or reversed asymmetry is observed.[173,175,177,180–183]

An equally important application of MTL assessment is in predicting memory outcome after dominant anterior temporal lobe surgery. Decline in verbal memory performance is a frequent finding after left ATLR.[184–189] Memory decline is more likely when Wada testing shows lateralization of

memory toward the left hemisphere.[188–192] Similarly, the degree of lateralization of activation in the MTL on fMRI might predict the likelihood and the degree of verbal memory decline in patients considering left ATLR.

MTL imaging with fMRI

MTL activation during memory encoding and retrieval tasks has been the subject of intense research with fMRI (for which there are several excellent reviews[165,166,193,194]). Of the dozens of MTL imaging studies, only a few have reported activation of the hippocampus proper, and this activation is typically small and highly dependent on the tasks and imaging parameters used.[167,195–206] Several factors could affect the sensitivity of functional imaging techniques to MTL activation. The hippocampal formation is relatively small in comparison with the volume elements (voxels) used in functional imaging. Within-voxel averaging of signals from active and inactive structures may thus impair detection of hippocampal activity when larger voxels are used. Loss of signal occurs near air–tissue interfaces on T2*-weighted images (such as those used for detecting blood oxygen level-dependent (BOLD) contrast) due to macroscopic field inhomogeneities. One brain region often affected by this phenomenon is the ventral–medial temporal pole, including in some cases parts of the amygdala and anterior entorhinal cortex.[75,198,207] Finally, the 'baseline' state employed in subtraction analyses is probably of critical importance, in that detection of MTL activation will be difficult if MTL activity continues to occur during the baseline. Some neurophysiological evidence suggests that hippocampal encoding processes continue beyond the duration of the stimulus or event.[154] In addition, there is reason to suspect that, in humans at least, episodic memory encoding, consolidation, and retrieval processes continue to occur even during 'rest' states or states with ostensibly minimal task requirements.[83,197,203,208] Stark and Squire,[203] for example, demonstrated that the hippocampus and parahippocampus both show higher BOLD signals during 'rest' than during active perceptual discrimination tasks. Activation of these MTL regions during encoding of pictures was detected using the perceptual discrimination tasks as a baseline, but not when 'rest' was used as a baseline.

As with language imaging studies, a large variety of task contrasts have been used to elicit MTL activation. In one commonly used paradigm, subjects are presented with either novel or repeating stimuli and perform tasks designed to elicit encoding. Previous electrophysiological studies have shown that the hippocampus responds more strongly to novel than to repeated stimuli;[209–212] thus, the contrast between novel and repeated stimuli is expected to show hippocampal activation. The encoding task itself might involve explicit memorization for later retrieval testing or a conceptual judgment designed to produce implicit encoding. Examples of such tasks include judging whether a complex environmental scene is indoors or outdoors, whether a word is concrete or abstract, or whether a face is male or female. Activation has been consistently observed in bilateral MTL regions in these novelty contrasts, although more often in the posterior parahippocampus and adjacent fusiform gyrus than in the hippocampus proper.[195,200,203,207,213–215] These results suggest that the posterior MTL plays a role in encoding novel visual stimuli. Because the novel and repeating conditions differ in terms of perceptual priming and attentional demands, however, it is not yet clear whether these posterior MTL activation differences are necessarily related to episodic memory processes per se.[216,217]

Because TLE often arises from the hippocampus, particularly the anterior hippocampus,[218–220] clinical assessment of MTL function should ideally focus on the hippocampus and anterior MTL. One MTL activation strategy that seems to show promise in this regard involves manipulating the degree of 'relational processing' that occurs during encoding. In this paradigm, rather

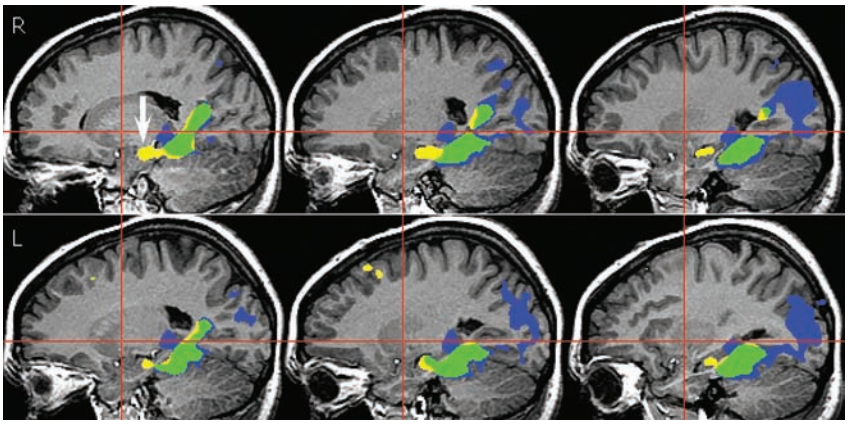

Figure 6.8 A direct comparison of MTL regions activated in a novelty contrast (novel vs repeating pictures) and a relational processing contrast (novel pictures vs scrambled pictures) in 32 healthy adults. The composite image shows voxels with reliable novelty effects (blue), relational processing effects (yellow), or both (green). Top row: right-brain slices through the hippocampus at $x = +18$, +22, and +26. Bottom row: left-brain sagittal slices through the hippocampus at $x = -21$, −25, and −29. Red lines indicate the stereotaxic y and z axes. A functional dissociation is observed between anterior hippocampus (white arrow), which is modulated by relational processing demands, and posterior hippocampus, which is modulated by novelty. Reproduced from Binder et al[234] with permission from Blackwell Publishing.

than contrasting novel with repeated stimuli, the contrast of interest is between episodes that require integration of stimuli with a semantic or situational context versus those that do not. The theory underlying this approach is that the main role of the hippocampus is to bind simultaneously occurring visual, auditory, somatosensory, and olfactory sensory events as well as conceptual and emotional states triggered by these sensory inputs. Storing the unique configuration of these co-occurring neural events results in storage of the episode in memory. The hippocampus, which receives inputs from widespread sensory association and limbic areas funneled through perirhinal and entorhinal mesocortex, is uniquely situated to serve this configural binding function.[221–224] According to this model, hippocampal activity depends on how much co-occurring neural activity is elicited by an episode, i.e. how complex the episode is in terms of evoked sensory and associative processing.[153] Stimuli that evoke elaborative associative processing by virtue of being recognizable and meaningful should therefore elicit greater hippocampal activation than nonsense stimuli that cannot be deeply processed; and tasks that require activation of such associations (e.g. conceptual, associative, or semantic tasks) should elicit stronger hippocampal activation than tasks that do not.

Support for this model of hippocampal function comes from a large number of imaging studies showing stronger MTL activation for meaningful relative to meaningless stimuli and associative/semantic relative to non-semantic tasks.[83,90,91,167,201,202,204–206,225–234] Examples of task contrasts used in these studies include processing of complex visual scenes versus unrecognizeable 'scrambled' versions of the same scenes, processing object pictures versus meaningless shapes, processing words versus non-words, performing semantic judgments versus phonological or orthographic judgments, and learning new associations between stimuli. Although the precise location of these MTL activations is still under investigation, results from our laboratory[91,227,233,234] and many others[90,167,201,205,206,225,226,230–232] suggest greater involvement of the anterior compared with the posterior MTL in relational processing contrasts (Figure 6.8). In a meta-analysis of episodic encoding studies, Schacter and

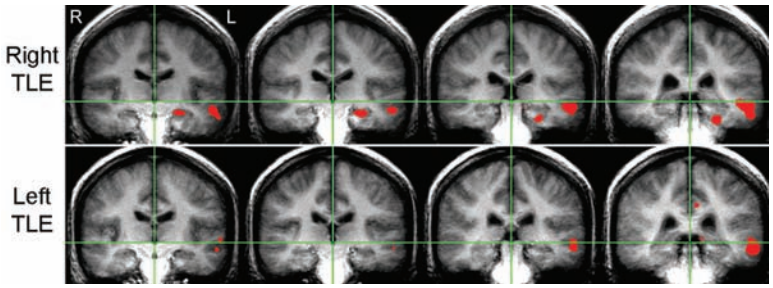

Figure 6.9 Dependence of left MTL activation on the side of seizure focus in two groups of temporal lobe epilepsy (TLE) patients. Activations were obtained using a semantic word encoding task contrasted with a sensory decision task (see Figure 6.2b). Reproduced with permission from Bellgowan et al.[227]

Wagner[165] also suggested that MTL activations tend to be more anterior when stimulus and task contrasts emphasize differences in the degree of relational processing.

Other variables affecting MTL activation include the type of stimulus material presented and whether or not the material is encoded sufficiently to support later recall. Activation of the MTL is left-lateralized for word stimuli and generally symmetric for pictorial stimuli.[91,197,201,227,233–237] The strength of encoding has been measured directly in a number of studies by testing item recognition after scanning.[168,196,198,200,201,204,229,238,239] Recognition performance (either accuracy or confidence ratings) can then be used to model the event-related BOLD response during scanning. These studies consistently show greater MTL activation during subsequently remembered stimuli compared with subsequently forgotten stimuli, although the precise MTL regions showing such modulation have varied considerably. Applied in general to all MTL activation protocols, this technique could in theory improve sensitivity by accounting for additional variance in the MTL response, resulting in improved detection of hippocampal activation.

fMRI of the MTL in epilepsy

Testing of fMRI methods to study MTL function in epilepsy remains at a somewhat preliminary stage. The basic premise that TLE results in impaired functional activation of the MTL was tested by Bellgowan et al,[227] using a semantic decision task known to activate the left anterior hippocampus and parahippocampus in normal subjects.[91] Similar to normal controls, a group of 14 patients with right temporal seizure foci showed anterior left MTL activation. In contrast, a closely matched group of 14 patients with left temporal foci showed no activation in this region (Figure 6.9). Interestingly, no compensatory activation of the right MTL was observed in the left TLE group, suggesting that verbal memory functions may reorganize primarily within the left hemisphere in left TLE rather than shifting to the right MTL. This latter finding is currently in dispute, however, as Richardson et al[240] subsequently showed reorganization of MTL activity to the right MTL in a group of 24 patients with left TLE. This study benefitted from greater statistical power due to the larger subject sample and the use of an ROI analysis, so the apparent discrepancy may simply be due to a difference in methodology.

A few preliminary studies have compared MTL activation asymmetry with Wada memory asymmetry in patients with TLE. Detre et al[241] used an environmental scene-encoding task in which subjects were asked to memorize each stimulus. In the baseline condition, subjects passively viewed a repeating nonsense stimulus (a spatially scrambled picture). This protocol therefore includes both a new–repeated (novelty) contrast and a meaningful–meaningless (depth-of-processing) contrast. One potential problem with this design is that the passive viewing baseline is similar to a resting condition, which some authors believe is associated with conceptual processing, memory encoding, and memory retrieval processes that

activate the hippocampus.[83,197,203,208] This may account for the MTL activation pattern observed by Detre et al,[241] which involved primarily the posterior parahippocampus. An ROI was created using the average activation map from a normal subject group, and an LI was computed for this ROI in each epilepsy patient. fMRI results agreed with qualitative Wada memory asymmetry in all nine patients, including two with paradoxical memory lateralization toward the side of the seizure focus.

Golby et al.[242] compared fMRI and Wada memory asymmetry in another small sample of patients. The main contrast was between novel and repeated stimuli, and this contrast was performed with four different types of verbal and non-verbal visual stimuli (words, objects, scenes, and visual patterns). fMRI lateralization indexes were computed for an ROI that included hippocampus and parahippocampus. Wada and fMRI lateralization scores were concordant in six of seven patients, and were judged to be concordant in another two cases despite incomplete Wada exams.

In the largest comparison study to date, Rabin et al[243] examined Wada and fMRI memory asymmetry in 27 patients with TLE. Although the fMRI methods were identical to those used in the earlier report by Detre et al,[241] the authors found a relatively weak correlation of 0.385 between fMRI MTL asymmetry and Wada memory asymmetry. Mean fMRI asymmetry scores did not significantly differ between the patients with left versus right Wada memory dominance, nor in a subgroup of 16 patients with left versus right seizure foci who were seizure-free at 1 year after ATLR.

Several preliminary studies have tested the ability of fMRI to predict side of temporal lobe seizure focus based on MTL activation asymmetry in patients with unilateral TLE.[242,244,245] Binder et al[244] contrasted indoor/outdoor judgment of visual scenes with perceptual discrimination of meaningless, scrambled versions of the same stimuli. Bilateral activation occurred throughout the posterior and anterior MTL (see Figure 6.8). Activation asymmetry was examined in several ROIs, including anterior hippocampus, posterior hippocampus, and parahippocampus. Only the anterior hippocampal asymmetry was correlated with side of seizure focus. Activation asymmetry in this ROI was concordant with seizure side in 86% of the 22 patients studied. Jokeit et al[245] used a task in which subjects were asked to imagine navigating familiar routes, thereby engaging retrieval of visual and spatial memories. This was contrasted with a control task requiring silent counting. Activated voxel counts in an ROI encompassing the MTL were entered in a discriminant analysis, which correctly predicted the side of seizure focus in 90% of the 30 patients. Finally, Golby et al[242] reported decreased activation ipsilateral to the seizure focus in eight of nine patients with TLE.

One preliminary study examined prediction of seizure outcome using fMRI. Killgore et al[183] found that combining the results of Wada memory testing with fMRI MTL imaging enabled prediction of seizure outcome in TLE. Either measure used alone correctly predicted outcome in six of the eight patients (five were seizure-free at 1 year and three had persistent seizures). For both tests, freedom from seizures was associated with lateralization of MTL function away from the seizure focus. Combining the two measures in a discriminant analysis produced correct predictions in all cases. These results suggest that Wada and fMRI measures of MTL asymmetry may capture independent sources of variance. Consistent with this interpretation, the measures were found to be uncorrelated ($r = 0.11$). If substantiated in larger samples, these results would suggest the need to combine fMRI and quantitative Wada scores to obtain the best prediction of seizure outcomes.

Finally, Rabin et al[243] found that fMRI of the MTL can predict memory decline after ATLR. They used the scene-encoding paradigm of Detre et al[241] during fMRI, and tested delayed recognition of the same pictures immediately after scanning. Delayed picture recognition was then tested again

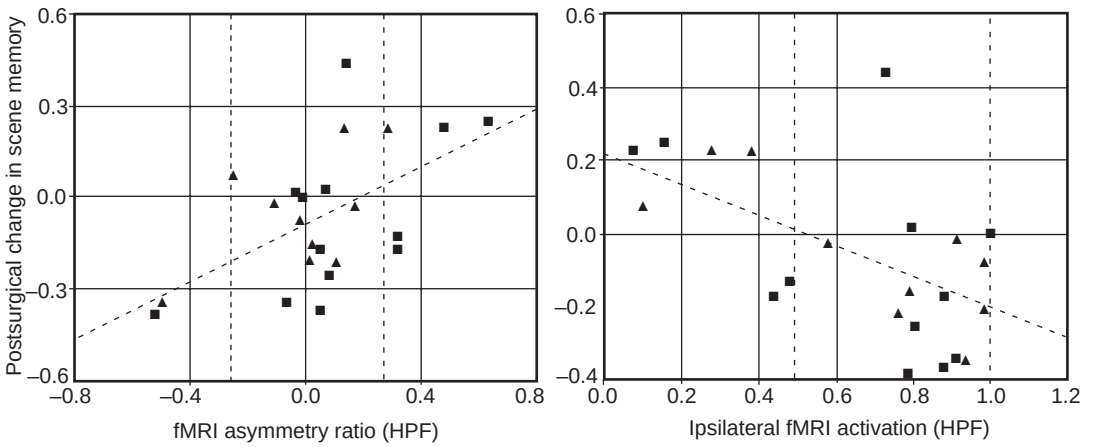

Figure 6.10 Prediction of postsurgical change in visual scene memory using preoperative fMRI activation in a hippocampal–parahippocampal–fusiform (HPF) region. (a) Relationship between memory change and asymmetry ratio calculated from the fMRI data ($r = 0.55$, $p = 0.007$). (b) Relationship between memory change and the degree of activation ipsilateral to the planned surgery, expressed as the proportion of voxels in the region with positive activation values ($r = 0.56$, $p = 0.005$). Plot symbols differentiate left (triangles) and right (squares) TLE patients. Vertical dotted lines indicate the mean ± 2SD range for the fMRI measures in a sample of normal controls. Reproduced with permission from Rabin et al.[243]

after surgery, and the change on this recognition task was used as the primary memory outcome variable. About half of the 23 ATLR patients (10 left and 13 right) declined on this measure, and declines were observed regardless of side of surgery. Preoperative fMRI activation asymmetry toward the side of surgery was correlated with decline (Figure 6.10a), as was the extent of activation on the side of surgery (Figure 6.10b). Although these results are promising, the relationship between the picture recognition test used by Rabin et al[243] and standard tests of memory is unclear. By far the most clinically important neuropsychological risk in ATLR is decline in verbal memory after left ATLR. In the left ATLR patients studied by Rabin et al,[243] neither Wada memory nor fMRI activation asymmetry predicted verbal memory decline as measured by standard psychometric tests.

In summary, there is preliminary evidence that fMRI of the MTL may provide information concerning side of seizure focus, seizure outcome after ATLR, and memory outcome after ATLR in patients with TLE. These are the three clinical applications for which fMRI would need to be validated before considering replacing the Wada test with fMRI. Despite some initial small series suggesting a close correspondence between the two tests,[241,242] more recent studies show a relatively weak correlation,[183,243] suggesting that current Wada memory and fMRI MTL activation protocols may not be measuring the same phenomena. Most clinicians regard prediction of verbal memory decline to be the most important goal of Wada testing, yet fMRI has not been shown to be capable of such prediction, nor has it been compared with the Wada test in this regard. There is clearly a need for further development and testing of fMRI MTL activation protocols in patients with TLE, including optimization of image acquisition methods,[198,207] optimization of task protocols, assessment of test–retest reliability,[246] optimization of data analysis strategies,[247] and clinical testing with larger patient samples.

HEMODYNAMIC IMAGING OF ICTAL AND INTERICTAL EPILEPTIC DISCHARGES

Non-invasive localization of epileptic foci in partial epilepsy remains an elusive goal in the application of neuroimaging techniques to epilepsy. The surgical remediation of medically refractory epilepsy relies heavily on the ability to identify areas of the cortex involved in producing seizures, referred to as the 'epileptogenic zone'. Conventional MRI has proven very useful for identifying subtle structural abnormalities in the neocortex or in the medial temporal structures. The presence of structural abnormalities that are concordant with non-invasive physiological localization of the epileptic focus typically predicts a good surgical outcome. When conventional MRI shows the presence of medial temporal sclerosis, seizures almost invariably arise from the MTL structures,[248] and resective surgery can be a curative procedure in close to 80% of such patients. However, structural abnormalities are not present in a substantial proportion of patients with focal epilepsy. Furthermore, even in the presence of structural abnormalities, seizures typically arise from the vicinity of the lesions but not necessarily from the lesions themselves. With large lesions, the spatial uncertainty as to the location of the epileptogenic zone is proportionately greater.

Scalp-recorded ictal and interictal electroencephalographic (EEG) data very often lack the spatial resolution required to identify the surgical target, especially when tailored resections that respect adjacent functional cortex are indicated. In the absence of well-localized lesions that clearly correlate with non-invasive physiological data, neuroimaging techniques such as [^{18}F]fluorodeoxyglucose (FDG)-PET and ictal single photon emission computed tomography (SPECT) are often helpful in delineating the cortical region of interest.[249–253] Both of these techniques have relatively low spatial resolution and do not directly capture correlates of epileptic discharges. Reversible T2 signal abnormalities on MRI associated with epileptogenic cortical areas have been noted after partial seizures or status epilepticus,[254–257] but are too inconsistent a finding to be of routine clinical value. As a high-resolution tool capable of imaging hemodynamic correlates of brain activity, there are strong incentives to apply fMRI to localizing the generators of epileptic activity.

Spike-triggered fMRI

Hemodynamic changes that are most likely to correspond to the epileptogenic zone would be those associated with the onset of seizures. The unpredictability of seizures, their relative infrequency compared with interictal discharges, the associated motor manifestations, and the higher likelihood of capturing propagated effects rather than primary generators make ictal fMRI relatively impractical, except in rare instances in which a patient is experiencing frequent focal electrographic events unaccompanied by motor manifestations.[258–261] These limitations do not apply to hemodynamic responses that follow interictal epileptiform discharges or spikes. The cortical areas that generate interictal spikes, often referred to as the 'irritative zone', are usually closely related to the epileptogenic zone,[262] and their identification can be of enormous value in pre-surgical evaluation.[263]

The capacity to record EEG continuously in the MRI scanner is essential to imaging the hemodynamic correlates of EEG events. EEG recording in the scanner poses several technical challenges related to the quality of EEG, the quality of MRI images, and patient safety. The presence of artifacts related to static and dynamic magnetic fields, and ballistocardiographic artifacts related to pulsatile blood flow, can severely degrade the quality of EEG recordings in an MRI scanner. Incremental technical improvements over the last decade have made it feasible to record high-quality EEG during MRI without compromising the quality of the images acquired. Early implementations demonstrated the feasibility of obtaining usable EEG tracings by a careful

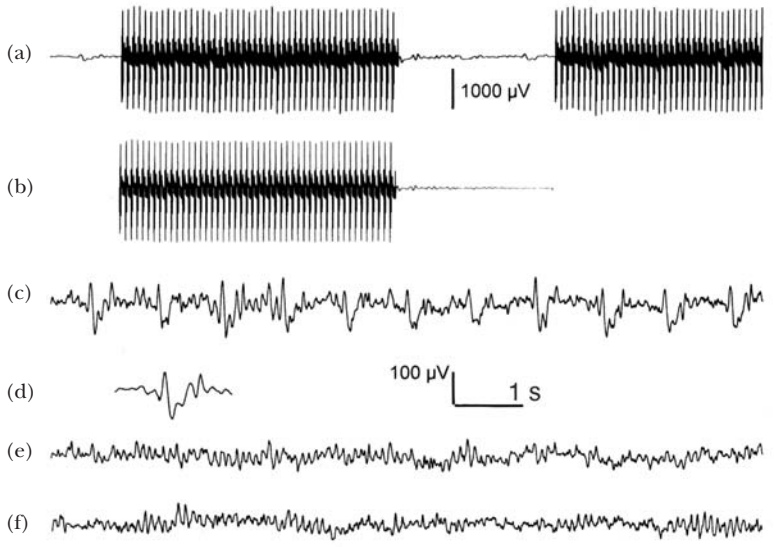

Figure 6.11 EEG waveforms (C4–A1) before and after imaging and pulse artifact subtraction. The bandwidth was 0.45–50 Hz. (a) The raw EEG during periodic fMRI. A large artifact is apparent during the 4 s of imaging (one volume), completely obscuring the EEG. The EEG during the 2 s gap between volume acquisitions appears to be relatively free of imaging artifact. (b) The averaged imaging artifact. (c) The result of subtracting the averaged imaging artifact in (b) from the EEG in (a), followed by downsampling and ANC. Pulse artifact is now clearly present and imaging artifact is difficult to discern. The display scale has been increased from that in (a) and (b). (d) The averaged pulse artifact from (c) (not to scale). (e) Result of subtracting the averaged pulse artifact in (d) from the EEG in (c). A 10.5 Hz signal is apparent in this trace, and this frequency matches that of this subject's alpha rhythm. (f) The EEG from the same subject, recorded outside the scanner, i.e. free of imaging and pulse artifact. The character of this EEG appears to match closely the artifact-corrected trace in (e). Reprinted with permission from Allen et al.[302] Copyright (2000) with permission from Elsevier.

choice and arrangement of telemetry equipment.[264] Subtraction techniques, in which the averaged electrocardiographic artifact is subtracted from the recorded EEG signal,[265] can significantly attenuate ballistocardiographic artifacts and increase the odds of reliably identifying epileptiform activity. Further refinements of artifact subtraction techniques to remove EEG signal distortions that result from magnetic field gradients have been shown to dramatically improve the quality of recordings[266–271] (Figure 6.11). Electromagnetic noise emanating from the EEG recording equipment and magnetic susceptibility artifacts related to recording electrodes can degrade the quality of the MRI images, although these problems can be eliminated by appropriate shielding.[272] Patient safety is another major concern. Possible heating of scalp electrodes during MRI and exposure of the patient to currents induced in the recording wires are preventable by using current-limiting resistors fitted to each recording electrode.[273]

Since the mid-1990s, many studies have examined BOLD signal changes related to interictal epileptiform spikes by triggering echo-planar image acquisitions at some fixed time interval after a spike has been detected in the EEG trace.[274–287] The acquisitions are typically manually triggered within 3–5 s after a spike has been identified by an experienced electroencephalographer. Using echo-planar imaging, multislice data can be acquired within 2 s of being triggered. This is much briefer than typical hemodynamic responses following spikes.[282] Control states for comparison are typically acquired at points in time

well separated from spike events by durations of at least 10–20 s.

Cortical locations showing significant fMRI activations during spikes correlate approximately with alternative means of locating spike generators, such as EEG dipole modeling[275,288] and intracranial EEG recordings.[258,279,284,286] Direct comparison of EEG dipole models with fMRI activations may show a separation of over 1.5 cm between the inferred dipoles and the nearest fMRI activations.[288] Such disparity may derive from several sources, including differences in the underlying neurophysiological basis of the two measurements, limitations of the dipole source modeling technique, effects of scanner field strength,[289] and physiological noise from cortical processes unrelated to spikes. The reported correlations between fMRI activations and intracranial EEG recordings have generally been good, although a careful analysis of false-positive findings remains to be done. There is also some evidence suggesting that areas that are primary generators of interictal spikes may show a different hemodynamic response compared with areas of spike propagation: lateralized fMRI activations have been found in instances where EEG shows bilateral spikes.[290]

Ideal candidates for spike-triggered fMRI localization are those patients with relatively frequent interictal spikes. Even after excluding patients with infrequent spikes, the percentage of EEG spike locations for which cortical fMRI activation can be detected varies considerably, ranging from 40% to 70%. In other words, spike-associated fMRI activations are absent in a substantial proportion of patients who have clearly defined epileptiform discharges on the EEG record.[284,286,287,290] On the other hand, fMRI activations have been demonstrated after single spike events without averaging.[277] The reasons for failure to detect fMRI activations are not yet entirely clear. Spike-triggered fMRI relies on the ability to trigger image acquisitions based on the identification of EEG events, and therefore on the quality of the EEG signal. The presence of EEG artifacts could result in image acquisitions based on spurious spike detections, thereby introducing noise and lowering the sensitivity of the technique. With the current techniques available for ballistocardiographic artifact subtraction, however, this is unlikely to be a major reason for failure to demonstrate fMRI activations. Signal loss due to susceptibility artifacts in the temporal lobe may also contribute to the less than ideal yield of spike-triggered fMRI.[286]

The model assumed for the hemodynamic response function (HRF) following a spike event could affect the ability to detect fMRI activation. Statistical analyses typically assume a standard HRF model. If the time course of the BOLD signal changes is different from that assumed by the model, the mismatch between model and data could result in a loss of sensitivity. Available data on the HRF for interictal spikes suggests marked variability across spike locations and a lack of correlation between BOLD signal and electrographic spike amplitudes.[282] Even with careful evaluation of the HRF model on an individual basis, however, fMRI activations may not be identified in over 35% of cases.[286] The use of patient-specific HRF models does, however, result in an increase in the spatial extent of fMRI activations[291] (Figure 6.12).

At the cellular level, epileptiform discharges seen on EEG correlate with phenomena known as paroxysmal depolarizing shifts,[292] which represent giant excitatory postsynaptic potentials,[293] and not necessarily neuronal firing. Neuronal firing may or may not be associated with specific spike instances. Hemodynamic changes are presumably greater when neurons fire, and may not accompany membrane potential shifts that are not accompanied by neuronal firing. This may be another reason for the observed inconsistency of fMRI activations in response to spikes.

Spike localization with continuous fMRI

The BOLD response to cortical events typically lasts longer than 10 s, yet acquisition of a single image after each spike provides no opportunity to track the entire hemodynamic

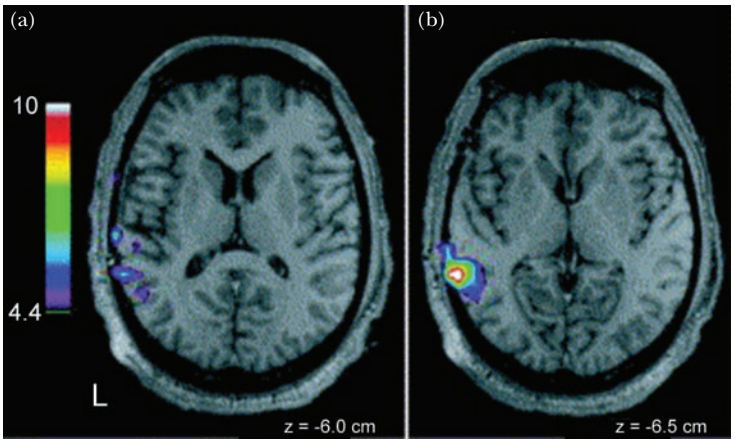

Figure 6.12 Comparison between spike-related fMRI activations obtained with a standard HRF (a) and the patient-specific HRF (b). This patient showed a left posterior temporal activation in both analyses, but results with the patient-specific HRF showed higher *t*-scores and a larger activation area than that with the standard HRF. Reproduced with permission from Kang et al.[291]

response nor to optimize statistical power by averaging several acquisitions after each spike. An alternative method is to acquire fMRI data continously. Only recently, however, have methods been developed that are capable of removing MRI radiofrequency pulse artifacts from the EEG. With high-quality EEG recordings, continuous fMRI and simultaneous EEG recording has been shown to have higher sensitivity than spike-triggered fMRI, requiring fewer spikes to demonstrate activations[284] (Figure 6.13). Another advantage of this method is that offline analysis of the EEG can be performed to more accurately separate the acquired images into active and control groups.

Current clinical utility of fMRI for localizing seizure foci

At its current state of development, fMRI of epileptic activity suffers from several limitations that compromise its appeal in the routine evaluation of patients for epilepsy surgery.[284,286,290] The long duration of the hemodynamic response, compared with the

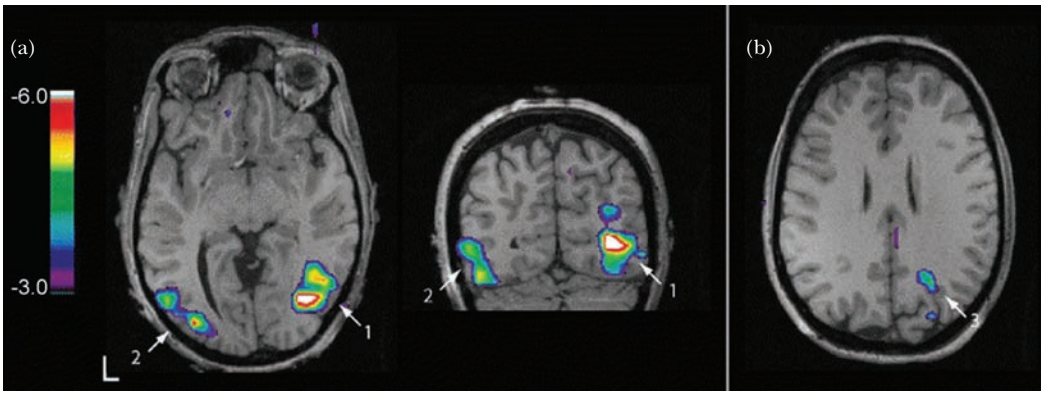

Figure 6.13 Map of spike-related activation obtained using continuous fMRI, superimposed on high-resolution T1-weighted anatomical MRI. The color scale indicates the values of the *t*-statistic. Three sites of blood oxygen level dependent (BOLD) response are seen: (a) in the right and left posteroinferior temporal and occipital junctions, in agreement with the ictal and interictal EEG abnormalities and ictal single photon emission computed tomography (SPECT); (b) in the depth of a sulcus in the right parietal lobe. The responses were all negative, indicating spike-induced decreases in the BOLD signal relative to baseline. Reproduced from Al-Asmi et al[284] with permission from Blackwell Publishing.

timescale over which neuronal events transpire, implies that imaging based on the BOLD signal may not have the temporal resolution to distinguish between areas that are sequentially activated over a few seconds.[290] Sensitivity across a variety of partial epilepsy types is a primary concern. The dependence on spikes that are identifiable on scalp EEG restricts its use to patients with abundant and well-defined spikes. Epileptiform spikes in partial epilepsies are state-dependent, with marked increases during non-REM sleep and relative paucity during REM sleep or wakefulness.[294] Spikes also vary greatly in frequency in any given physiological state.[295] Infrequency of spikes during the period of the MRI study makes spike-triggered fMRI infeasible. On the other hand, spikes that are too frequent can also be a limiting factor, since this can prevent acquisition of sufficient control states that are well separated from spike events within a reasonable scan time. As noted earlier, imaging spike generators also have the inherent limitation, shared with magnetoencephalography (MEG) and interictal EEG source localization techniques, of identifying 'irritative zones' rather than locating the 'epileptogenic zone'.

From the perspective of epilepsy surgery, functional neuroimaging tools for localizing epileptic dysfunction in the cortex are useful only to the extent that they provide additional information beyond what can be learned from more traditional non-invasive methods such as EEG analysis, structural imaging, analysis of seizure semiology, and ictal SPECT. In TLE with structural MRI evidence of medial temporal sclerosis, concordant ictal scalp EEG, and behavior consistent with a MTL focus, localization of epileptiform spikes to the MTL structures using fMRI is unlikely to be of additional value. However, fMRI could potentially have a role in identifying epileptogenic areas in neocortical TLE, especially in the dominant hemisphere, where proximity of language areas often demands tailored resections.

TLE and epilepsy associated with structural lesions tend to be associated with a relatively high prevalence of spikes on scalp EEG. Spikes may be rare or absent on scalp recordings in non-lesional extratemporal epilepsies, which are also the most challenging in terms of localizing the epileptogenic zone.[296,297] The lower success rate of surgery in patients with extratemporal epilepsy may well be attributable, to a large extent, to the lower accuracy with which the epileptogenic zone can be identified in these cases. Invasive intracranial EEG studies are almost always necessary in extratemporal epilepsy if surgical treatment is to be pursued. In the presence of multifocal epileptic spikes on scalp EEG, fMRI evidence of spike activity could potentially be useful for identifying the generators and guiding the placement of intracranial electrodes. EEG or MEG dipole localization methods can yield similar information with a higher temporal resolution, although with lower spatial accuracy.[298]

Spikes generated from deep cortical locations or with dipoles that are unfavorable for scalp recording may often be apparent on intracranial recordings but undetectable on scalp EEG. Spike-dependent fMRI techniques cannot be applied in these instances. For such cases, alternative techniques will be needed that allow focal epileptic dysfunction to be imaged without relying on spikes evident on scalp EEG. Functional imaging of focal slow waves has been shown to produce a stronger and more widespread BOLD signal activation that overlaps with the area identified by spike-triggered fMRI.[299] One study has also demonstrated a technique in which resting fMRI in patients with partial epilepsy is analyzed using temporal clustering techniques to localize areas of epileptic dysfunction without the need for simultaneous EEG recordings.[300] It remains to be determined if the fMRI activations produced by this technique are related to spikes or to some other aspect of cortical activity in the epileptogenic cortex.

CONCLUSIONS AND FUTURE DIRECTIONS

fMRI is likely to have a profound impact on the surgical treatment of epilepsy. Clinical

issues related to epilepsy surgery are complex, mandating cautious patient selection based on careful assessment of risks and benefits. fMRI of the somatosensory and motor systems can assist in the precise localization of these sensitive areas of cortex. Further studies are needed to determine optimal activation strategies in patients with hemiparesis due to lesions near the central sulcus; these are typically the patients in greatest need of motor cortex mapping. fMRI of language processing is an area of intense ongoing research. A number of fMRI language mapping protocols can provide information comparable to that provided by the Wada test, and one protocol has been shown to predict language outcome from left temporal lobectomy. Much more work is needed, however, to clarify the organization of phonological, semantic, and syntactic systems in the normal brain, and to distinguish critical cortical regions from those that play a minor supporting role in these processes. Caution is urged in using language activation maps to guide surgical resections, as currently very little is known regarding the consequences of resecting either 'non-active' or 'active' areas. fMRI of the MTL could in theory assist in seizure focus identification, seizure outcome prediction, and prediction of memory outcome. Studies of the clinical value of MTL fMRI are still at an early stage, however, and optimization of protocols for detecting hippocampal activation will require further research. Finally, a variety of fMRI techniques are currently under investigation for localization of ictal and interictal epileptiform activity. While many of the basic methodological problems of concurrent EEG and fMRI have been solved, the ultimate clinical utility of these techniques remains a topic for future research.

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Mood and anxiety disorders

7

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INTRODUCTION

Neuroimaging research has emerged as a powerful force in shaping neurobiological models of psychiatric disorders. In this chapter, functional neuroimaging findings pertaining to mood and anxiety disorders are reviewed. We will review studies using functional magnetic resonance imaging (fMRI) as well as those using other functional neuroimaging techniques (e.g. positron emission tomography (PET) and single photon emission computed tomography (SPECT)) to delineate the neurocircuitry involved in mood and anxiety disorders. This review extends previous ones that we have written, together with our colleagues, on these and related topics.[1–3]

Contemporary models of mood disorders (unipolar depression and bipolar disorders), integrate a wide variety of findings from animal, human lesion, and postmortem studies, as well as structural and functional neuroimaging studies. They emphasize that mood symptoms arise from disruptions in the interactions of widely distributed neural networks involved in emotional and cognitive processing.[4–6] Symptoms of depression and mania are viewed as the result of disturbances in functions normally subserved by these networks, such as regulating emotions, attention and memory. In addition, these models assign some regional specificity in that dysfunction in certain portions of these networks are associated with cognitive, vegetative, or emotional features of depression (or mania). For example, Mayberg's limbic–cortical model of depression (Figure 7.1)[5,6] involves three compartments, each responsible for some portion of the constellation of symptoms associated with depression. The dorsal compartment, including the dorsolateral prefrontal cortex (DLPFC) and dorsal anterior cingulate cortex (dACC), parietal lobe, and posterior cingulate, is postulated to be principally involved with attentional and

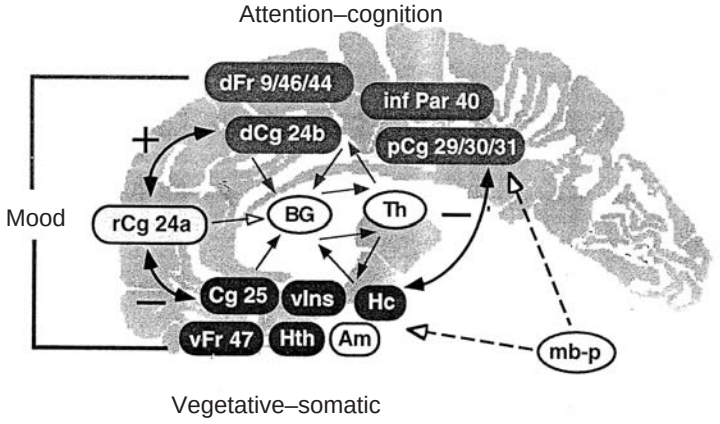

Figure 7.1 Mayberg's model of depression.[5] This involves three compartments: a dorsal compartment, including dorsolateral prefrontal cortex (dFr), inferior parietal cortex (inf Par), dorsal anterior cingulate (dCg), and posterior cingulate (pCg); a ventral compartment, including subgenual prefrontal cortex (Cg 25), ventral anterior insula (vIns), hippocampus (Hc), ventral frontal cortex (vFr), and hypothalamus (Hth); a rostral compartment, consisting of rostral anterior cingulate (rCg), midbrain pons (mb-p), and basal ganglia (BG); thalamus (Th); amygdala (Am). Numbers are Brodman designations.

cognitive disturbances in depression (e.g. concentration difficulties, explicit memory impairment and impairments in executive functions). The ventral compartment, consisting of paralimbic cortical, subcortical, and brainstem regions, is postulated to mediate vegetative and somatic features, including disruptions in sleep and appetite. In addition, ventrolateral prefrontal and orbitofrontal cortex (OFC) components of the ventral compartment have been suggested to contribute to maladaptive emotional, cognitive, and behavioral responses.[5,6] Finally, the rostral compartment (the rostral anterior cingulate cortex (rACC), corresponding to Brodmann area (BA) 24a; Figure 7.1) has connections to both the dorsal and ventral compartments and may play an important 'regulatory' role in the overall network.

Limbic and paralimbic circuits also play an important role in mediating anxiety. The posterior medial OFC, anterior temporal cortex, anterior cingulate cortex (ACC), and insular cortex (i.e. the paralimbic cortex) are linked to cortical regions subserving higher-level cognition and sensory processing with deep limbic structures, such as the amygdala and hippocampus.[7] Contemporary models of threat assessment and the normal fear response focus on the role of the amygdala.[8,9] The amygdala receives input regarding the environment directly from the thalamus, as well as from sensory cortex. The functions of the amygdala include preliminary threat assessment and facilitation of fight-or-flight responses, as well as enhancement of arousal and plasticity, so that the organism can learn from current experience in order to guide responses in future similar situations. Conversely, the medial frontal cortex (i.e. ACC and OFC) provides important feedback to the amygdala and critical 'top-down' governance over the amygdala.[8,9] More specifically, the medial frontal cortex appears to enable attenuation of the fear response once danger has passed or when the meaning of a potentially threatening stimulus has changed. The hippocampus provides important information about the context of a situation (based upon information retrieved from explicit memory stores), and corticostriatothalamic circuits mediate 'gating' at the level of the thalamus, thereby regulating the flow of incoming information that reaches the amygdala. The activity within each of these various brain areas is influenced by neuromodulators, as well as the interactions among the nodes of the entire system outlined above. Ascending projections from the raphe nuclei (serotonin), and the locus ceruleus (norepinephrine), as well as widespread local γ-aminobutyric acid (GABA)ergic neurons, are perhaps most relevant to the physiology of anxiety.[10–12] These transmitter systems likely serve as the principal substrates for contemporary anxiolytic medications, including serotonin reuptake inhibitors, monoamine oxidase inhibitors, and benzodiazepines.

DEPRESSION

Resting-state PET and SPECT studies in patients with unipolar depression and bipolar disorder provide support for prefrontal and limbic–paralimbic abnormalities involved in depressive episodes. Most consistently, studies have found decreased frontal lobe function.[13–15] This includes decreased regional cerebral glucose metabolism (regional cerebral metabolic rate for glucose, $rCMR_{glu}$) and decreased regional cerebral blood flow (rCBF) in the DLPFC[6,13] and the dorsomedial and dorsal anterolateral prefrontal cortex (PFC), as well as in the dACC.[13,16] Increases in $rCMR_{glu}$ and rCBF have been found in the ventral PFC (i.e. ventrolateral and ventromedial cortex and OFC), the pregenual ACC located anterior to the genu of the corpus callosum, and the subgenual PFC.[5,17,18] Limbic–paralimbic increases in $rCMR_{glu}$ and rCBF involve the amygdala and anterior temporal and insular cortex, as well as decreased $rCMR_{glu}$ in the posterior cingulate. In addition, altered basal ganglia (e.g. ventral striatum) and thalamic function has also been reported (for reviews, see Drevets[4,19] and Mayberg[5]).

One strategy for developing a better understanding of the observed frontal limbic–para-

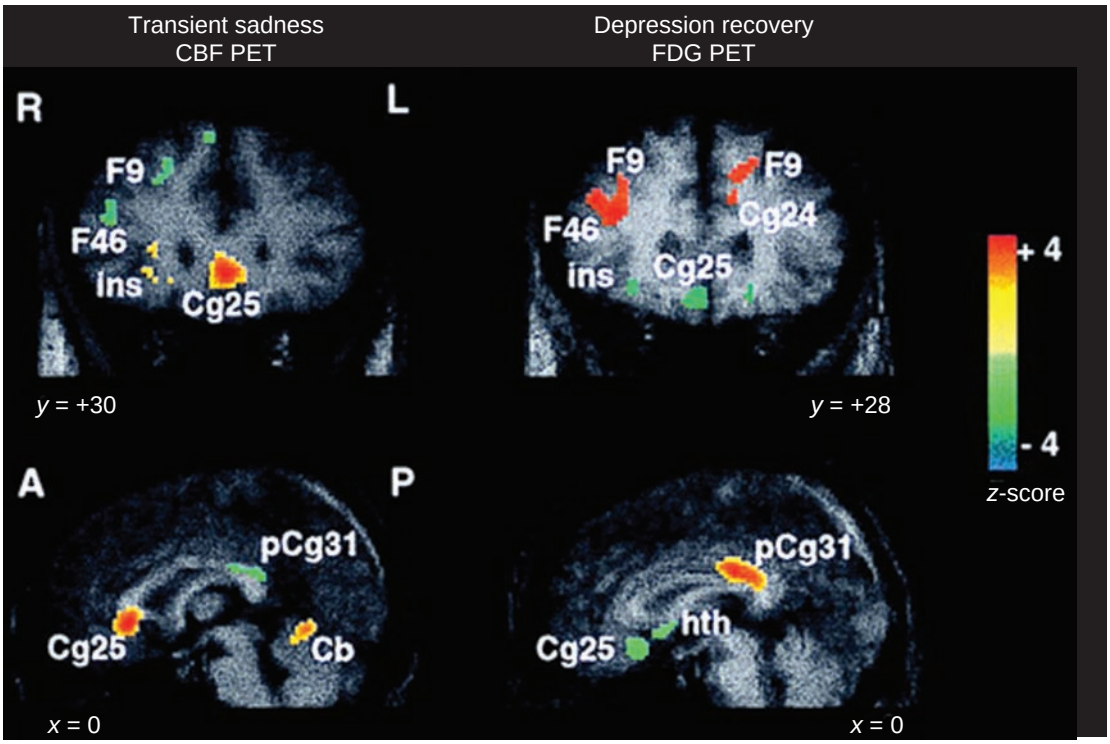

Figure 7.2 Changes in glucose metabolism and regional cerebral blood flow (as assessed by PET) associated with recovery from major depression and transient sadness in healthy control subjects.[6] The left-hand images display changes in regional cerebral blood flow with $H_2{}^{15}O$-PET associated with transient sadness in eight healthy volunteers (coronal image top, sagittal view bottom). The right-hand images show changes in regional glucose metabolism with FDG-PET after 6 weeks of fluoxetine treatment in eight unipolar depressed patients. Sadness is associated with increases in ventral paralimbic regions and decreases in dorsal frontal regions. With recovery from depression, the reverse is seen: ventral decreases and dorsal cortical increases. Slice locations are shown in millimeters relative to the anterior commissure. Numbers are Brodmann area designations. R, right; L, left; A, anterior; P, posterior; F, prefrontal; ins, anterior insula; Cg24, dorsal anterior cingulate; Cg25, subgenual cingulate; pCg, posterior cingulate; Cb, cerebellum; hth, hypothalamus. Color scale: red indicates increases and green indicates decreases in flow or metabolism.

limbic changes during depressive episodes has been the use of mood challenge paradigms. Such paradigms applied in healthy volunteers help to delineate the brain systems that mediate normal mood and affect. In these paradigms, subjects undergo transient periods of sadness and control states, by recalling sad or neutral autobiographical events while brain activity is recorded using PET, SPECT, or fMRI. Comparison between rCBF changes during sad versus neutral conditions in healthy volunteers enables investigators to draw conclusions about alterations in the brain systems that mediate mood and affect regulation. Such challenge paradigms revealed changes in prefrontal and limbic–paralimbic areas associated with the induction of sad mood in healthy volunteers, many of which correspond to areas of alterations observed in resting-state studies in depression. More specifically, in healthy volunteers, increases in rCBF during sadness (vs neutral state) have been found in the subgenual PFC, pregenual ACC, insula, and ventral PFC,[6,20,21] whereas decreased rCBF associated with sad mood has been reported for DLPFC, dACC, and inferior parietal and inferotemporal cortex[6,20,21] (Figure 7.2). Pretreatment abnormalities in $rCMR_{glu}$ and rCBF in prefrontal limbic–paralimbic areas

appear to normalize with recovery from depression (Figure 7.2). Changes in cortical (prefrontal, ventral prefrontal and parietal), limbic–paralimbic (cingulate, amygdala and insula) and subcortical (caudate/pallidum) areas have been described after various treatments, including medication, psychotherapy, sleep deprivation, electroconvulsive therapy (ECT), transcranial magnetic stimulation (TMS), and ablative surgery.[6,22–34] Perhaps the best-replicated finding is a normalization of frontal hypometabolism.[13,16,23–25] For remitted patients with major depression, changes in glucose metabolism from pre to post treatment involve neocortical and limbic–paralimbic sites involved in induced transient sadness (Figure 7.2). The direction of change from pre to post treatment reflects a reversal of the pattern seen with provoked sadness in mood challenge studies in healthy volunteers[6,27–29] (Figure 7.2). More specifically, successful treatment has been characterized by increases in regional glucose metabolism in the DLPFC, dACC, posterior cingulate, and parietal cortex, as well as decreases in ventral PFC, subgenual PFC, insula, and medial temporal lobe (including the amygdala, hippocampus, and parahippocampal gyrus).[6,27–29,35,36]

HYPOMANIA/MANIA

Regional involvement in hypomania/mania in bipolar disorder is less well described than alterations during depressive states. Functional imaging studies in mania, including studies of resting metabolic rate, rCBF, and cognitive activation paradigms, have demonstrated altered functioning in frontal and temporal cortex as well as in basal ganglia.[18,37–46] Decreased rCBF is found in the ventromedial cortex/OFC,[37] whereas increases are found in the dorsal anterior cingulate[39,41] extending to the pregenual ACC[39] and subgenual PFC.[18] Several cognitive activation PET and fMRI studies have provided evidence for altered ventral prefrontal and dorsolateral prefrontal functioning during mania.[38,39,42,47] For example, Rubinsztein et al,[42] using fMRI, found impaired probability-based decision making in manic patients for more complex/difficult choices (possibly reflecting increased impulsivity or reduced cognitive processing). This was associated with reduced activation in the ventrolateral PFC (BA 47) and decreased frontal polar cortex (BA 10) activation, but increased activation in the dACC. Elliot et al[47] found evidence for enhanced responses in DLPFC (BA 9/46) and ventrolateral and medial PFC (including BA 44/45: subgenual PFC extending to medial OFC) in response to emotionally valenced stimuli during a go/no-go task in manic individuals, but attenuated function in response to neutral stimuli. Blumberg et al,[38,40] using fMRI, reported decreased activation in the ventral PFC and frontal polar cortex (BA 10) during a word fluency and Stroop task.

Increased activation during mania has also been reported in the basal ganglia, including the head of the nucleus caudate[39] and the ventral striatum.[48] In addition, there is evidence for involvement of the temporal cortex in mania as well, although findings are variable. Decreased right basotemporal activity has been reported, with a trend towards a negative correlation between mania ratings and right basotemporal rCBF.[43] On the other hand, increased right temporal activity[44–46] and decreased amygdala activity[44] have also been reported. Right temporal increases in activity have been shown to correlate positively with mania scores.[46]

FUNCTIONAL NEUROANATOMY OF MOOD DISORDERS

In summary, there is converging evidence from functional neuroimaging studies for involvement of the PFC, limbic–paralimbic, and subcortical regions in the pathophysiology of depression and mania. Below, we selectively review some of the functions of these relevant brain structures in more detail.

Dorsolateral prefrontal cortex (DLPFC)

Prefrontal hypometabolism and decreased rCBF during depression have been linked to

impairments in psychomotor speed and executive functions (higher-level planning and problem-solving skills).[49] Among other regions, executive functions rely on the integrity of the DLPFC. Cognitive activation paradigms in healthy volunteers have shown DLPFC involvement in tasks of working memory, encoding, and retrieval processes in episodic memory tasks, as well as tasks of forward planning and problem solving.[50–52] DLPFC activations during working and episodic memory tasks reflect the use of executive control processes such as monitoring, updating and manipulating information held in working memory.[50–52] These processes contribute to a variety of complex cognitive skills, including the ability to organize information during learning (encoding) as well as forward planning and problem solving. For example, in depressed patients with major depression, Elliot et al[49] investigated rCBF using PET in depressed patients using a Tower of London forward planning task. In healthy subjects, the task engaged a network of DLPFC (BA 9/46/10) and dACC, as well as posterior cortical areas and subcortical structures, including striatum, thalamus, and cerebellum. Depressed patients showed attenuated DLPFC and posterior cortical activation and failed to show significant activation in the ACC and striatum.

Although 'resting-state' metabolic and blood flow abnormalities during depression have been shown to normalize with symptom remission, MRI and postmortem studies in unipolar depression and bipolar disorder suggest pervasive structural and volumetric changes in the DLPFC.[53–58] This includes reduced PFC volume[53–55] and reduced density of neuronal and glial cells, reduced neuronal size, or reduced density in oligodendroglial cells in the DLPFC in bipolar disorder.[56–58] In addition, several functional imaging studies in remitted patients suggest that DLPFC functioning does not return to normal during remission. For example, Winsberg et al,[59] using in vivo proton magnetic resonance spectroscopy (MRS), found that euthymic (neither depressed nor manic), non-medicated patients with bipolar disorder exhibited reduced *N*-acetylaspartate (NAA) creatine/phosphocreatine (Cr/PCr) ratios bilaterally in the DLPFC. A PET study by our group[60] linked abnormal DLPFC CBF to persistent learning and memory impairment found in euthymic/remitted patients with bipolar disorder.[61–63] Compared with healthy control participants, euthymic remitted patients with bipolar I disorder had difficulties learning a word list during PET scanning, and, compared with controls, exhibited blunted activation during encoding (learning).

Anterior cingulate

Structural and functional abnormalities in the ACC have been reported for both unipolar depression and bipolar disorders. During episodes of depression, the region of the ACC that shows decreased $rCMR_{glu}$/CBF is the dACC, whereas increased activation during depression has been reported for the pregenual rACC and subgenual PFC.

The dACC maintains strong reciprocal interconnections with DLPFC, parietal cortex, premotor, and supplementary motor areas.[64] Converging data indicate that this region is involved in cognition and motor control.[65] For example, in functional neuroimaging studies, the dACC has been activated by tasks that involve target and motor response selection,[66–70] error detection and performance monitoring,[71,72] novelty detection,[73] competition monitoring,[74–76] motivational valence assignment,[77] and reward-based decision making.[78] Overall, this suggests that the dACC is part of a distributed attentional network.[77] Activity in the dACC has been consistently observed during Stroop or Stroop-like tasks, suggesting that one of the functions supported by the dACC is selection of information when faced with competing input streams (i.e. inhibition of irrelevant stimuli). These functions closely parallel clinical symptoms of depression and mania, which include difficulties in concentrating, distractability, and flight of ideas. It has been reported that individuals with attention

deficit/hyperactivity disorder fail to activate the dACC during Stroop test performance.[79] Studies employing the Stroop test and Stroop-like tasks on depressed and manic subjects have repeatedly demonstrated impaired performance.[80–87] Consistent with these findings, George et al[88] reported blunted activation of the dACC in a PET Stroop study in depressed individuals. In addition, there is growing evidence that attentional impairments remain, at least in part, when bipolar patients are euthymic/remitted.[89–91]

The rACC has extensive connections with limbic regions (including the amygdala and hippocampus) and the brainstem.[92–94] Regional glucose metabolism appears to be increased in depressed individuals who subsequently respond to antidepressant treatment.[36,95,96]

In functional neuroimaging studies, induction of emotional states[97–104] as well as procaine-induced fear and euphoria[105–107] in healthy individuals are associated with activations in the vicinity of the rACC. The rACC has also been activated by affectively related tasks used in psychiatric populations, including obsessive–compulsive disorder (OCD),[108,109] simple phobia,[110] post-traumatic stress disorder (PTSD),[111] and depression.[112] Current theories of emotional dysregulation have focused on the interactions of the ACC and the amygdala, suggesting that the amygdala and connected structures are involved in driving emotional responses, while the ACC regulates such responses[113–115] in a top-down manner. Consistent with this notion, connections between the ACC and the amygdala have demonstrated importance in regulating amygdala responsivity.[116–120] Whalen et al[121] reported activation in the vicinity of the rACC in healthy individuals using the emotional counting Stroop task. Their results suggest that the rACC is a regulatory area that inhibits affectively valenced information in order to facilitate cognitive processing. Consistent with this view, individuals with PTSD are known to disproportionately attend to threat-related information[122,123] and fail to activate the rACC when confronted with combat-related negative information in the emotional counting Stroop task.[124] In depression or mania, 'offline' information processing studies using emotional Stroop or emotional Stroop-like tasks have found that depressed or manic individuals disproportionately attend to negative (depression) or positive (mania) aspects of emotional stimuli.[87,125–129]

Morphometric MRI assessments of the subgenual prefrontal cortex have demonstrated mood state-independent reductions of gray matter volume.[18] Postmortem analysis of the subgenual PFC has demonstrated a mood state-independent reduction in glia, without loss of neurons of increased neuronal density in both unipolar depression and bipolar disorder.[130] When reduced $rCMR_{glu}$ reported for depression is corrected for gray matter reductions, $rCMR_{glu}$ in the subgenual PFC appears to be increased – not decreased – in depressed individuals,[4] and metabolism decreases to normative levels during effective treatment in individuals with major depression.[4,6] Metabolic decreases in the subgenual PFC with antidepressant treatment in depressed individuals with unipolar disorder may be limited to individuals who respond to treatment and remain improved at 6-month follow-up.[29] The subgenual PFC (among other connections) has extensive reciprocal connections with the ventromedial (orbitofrontal) cortex, amygdala, and hypothalamus. In rats, lesions in the homologue of the primate subgenual PFC attenuate or increase sympathetic autonomic arousal and corticosterone responses to stress.[131] Thus, as suggested by Drevets,[4] altered $rCMR_{glu}$ in the subgenual PFC during depression (or mania) may contribute to increased sympathetic and hypothalamus–pituitary–adrenal axis arousal and thereby to the altered neuroendocrine and autonomic function observed during mood episodes.[132–134] In addition, it has been hypothesized that the subgenual PFC is involved in evaluating reward-related significance of stimuli and disturbances of hedonic perception and motivated behavior in mood disorders[4] (see also below).

Ventral prefrontal cortex

Mood state-dependent increases in rCBF and $rCMR_{glu}$ in the ventrolateral and ventromedial PFC (including the OFC) during depression (and mania) appear to normalize with successful treatment or remission. Metabolic alterations in these regions are not unique to depression or mania, but have also been observed in OCD and phobias. The animal literature has implicated the OFC in operations underlying the motivational control of goal-directed behavior.[135] This includes stimulus–reward reversal and monitoring the incentive value of potential reinforcers.[136,137] For example, Tremblay and Schultz[135] found that OFC neurons in monkeys responded differentially based on the animals' preference among reinforcers, as reflected in their ultimate behavioral choice, rather than the physical properties of the reinforcers (liquid or food). These processes appear to be especially important early on in learning and conditioning. For instance, Dias et al[136] reported that OFC lesions in monkeys impaired stimulus–reward reversals – but only during the first reversal trial. Furthermore, studies of odor discrimination learning in rats have shown that OFC neurons fire in anticipation of rewarding and aversive outcomes, early in the course of training, before reliable behavioral discriminations have developed.[138,139] These and other animal studies implicate the OFC in early processes guiding behavior based on anticipation of future events[138] as well as being involved in redirecting behavior based on changes in reward contingencies.[140,141]

Functional imaging studies specifically targeting the OFC found that OFC activation was associated with conditions in which subjects had to inhibit previously learned stimulus–response associations on a test of visuospatial orientation.[142] This finding is consistent with other evidence in humans that the OFC mediates the ability to inhibit previously reinforced responses and shift mental set.[143] The OFC has also been implicated in 'guessing' operations on a task, based on the Bechara/Damasio gambling paradigm, in which subjects were instructed to make their best educated 'guess' regarding the upcoming card suit or color.[144] Specifically, OFC activation was associated with increased guessing demands, as subjects had to factor in past instances of success and failure over a number of trials to predict what the next card would be. Rogers et al[145] reported results of a PET study using a computerized 'risk-taking' task, modeled very closely after the Bechara/Damasio gambling paradigm. During scanning, subjects had to choose small, high-probability rewards over large, low-probability rewards. The authors found activations in right orbital and inferior PFC as subjects resolved conflicts between these competing choices. Taken together, these studies indicate that the OFC mediates the early inhibition of automatic behavior in favor of developing a plan for future action, especially in novel or ambiguous situations. In depression, ventrolateral and ventromedial PFC abnormalities may reflect endogenous attempts to break (reverse or inhibit) perseverative patterns of self-depreciative and non-rewarding thought and emotion.[146] In mania, functional alterations in the ventrolateral and medial PFC are associated with impairments in reward-based decision making,[42] as well as enhanced responsivity to emotionally valenced versus neutral stimuli,[47] which may reflect some of the core features of mania (increased orientation towards pleasant activities, risky, impulsive decisions, disregard of social cues, etc.). Recent findings suggest involvement of the ventromedial PFC in inhibiting anger (or impulsive anger outbursts) in a subgroup of patients with major depression with anger attacks.[147] Compared with depressed patients without anger attacks and healthy control subjects, depressed patients with anger attacks appear to be characterized by reduced ventromedial PFC blood flow (as assessed with PET) when anger was provoked using script-driven imagery.

Amygdala

Amygdala metabolism and rCBF have been documented to correlate positively with the severity of depression.[17,148] In addition, left

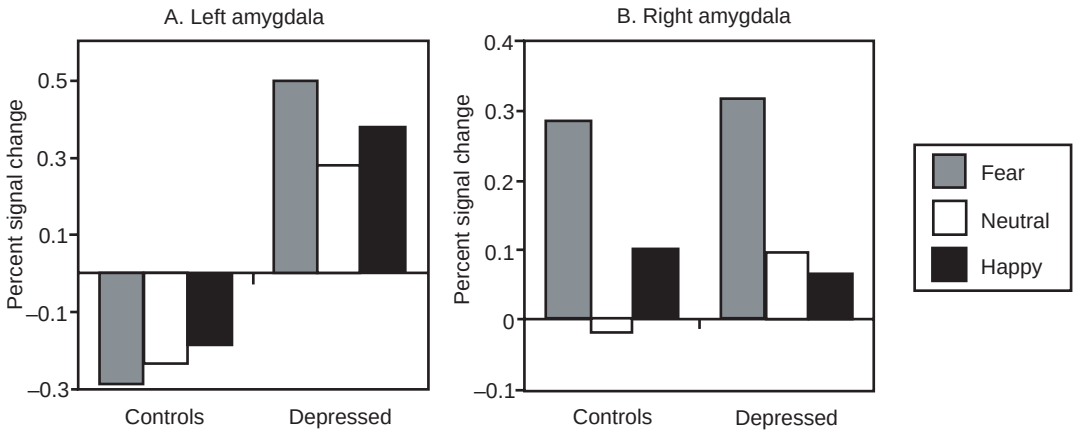

Figure 7.3 Amygdala activations in response to masked fearful faces in an fMRI study by Sheline et al.[35] Depressed subjects had significantly greater left amygdala activation to fearful faces than control subjects. Data reflect the percentage change in MRI (BOLD) signal for the left and right amygdala.

amygdala metabolism is positively correlated with plasma cortisol levels in individuals with unipolar and bipolar depression.[149] This positive correlation between activity in the amygdala and severity of depression may reflect the role of the amygdala in organizing multiple aspects of emotional and stress responses.

Cognitive activation studies probing amygdala functioning suggest sustained exaggerated amygdala responses to emotionally valenced (sad or fearful) stimuli in individuals with major depression compared with normal controls. For example, Sheline et al[35] found exaggerated amygdala activation during fMRI in response to masked emotional (fearful versus neutral) faces in individuals with major depression compared with normal control participants (Figure 7.3).

Siegle et al,[150] using fMRI, showed sustained amygdala responses to negative, self-referential stimuli in subjects with major depression compared with never-depressed individuals. Subjects were presented with personally relevant negative, positive, or neutral words on a computer screen. For never-depressed individuals, amygdala responses to all stimuli decayed within 10 s, whereas depressed individuals displayed sustained amygdala activations to negative words. Although amygdalar hyper-responsivity (and resting $rCMR_{glu}$) appear to resolve with antidepressant treatment,[29,35] there is some evidence that amygdala $rCMR_{glu}$ may remain abnormally elevated in asymptomatic individuals with major depression who are not taking antidepressant medication,[17] potentially reflecting susceptibility to recurrence of depressive episodes. Consistent with this view, Bremner et al[151] found that increased amygdala metabolism following tryptophan depletion in remitted patients predicted relapse. In this study, remitted patients who had responded to fluoxetine or paroxetine treatment underwent tryptophan depletion. Patients who subsequently relapsed (i.e. showed an increase in depressive symptoms following tryptophan depletion) were characterized by higher amygdala glucose metabolism compared with patients who did not show an increase in depressive symptoms following tryptophan depletion.

ANXIETY DISORDERS

Below, we summarize the imaging data pertinent to anxiety disorders, including PTSD, OCD, specific phobias (SpP), social phobia

(SoP – also called social anxiety disorder), and panic disorder (PD). Patients with anxiety disorders typically either suffer exaggerated fear responses to relatively innocuous stimuli (e.g. SpP) or spontaneous fear responses in the absence of true threat (e.g. PD). Thus, it is important to consider the mediating functional neuroanatomy of normal threat assessment and the fear response. Contemporary models focus on these systems as candidate neural substrates for the anxiety disorders.

Post-traumatic stress disorder (PTSD) – amygdalocentric neurocircuitry model of PTSD

A previously presented neurocircuitry model of PTSD by our group[3] focused on the central role of the amygdala and its interactions with the hippocampus and medial PFC, as well as other heteromodal cortical areas that mediate higher cognitive functions. This model postulates hyper-responsivity within the amygdala to threat-related stimuli combined with inadequate top-down governance over the amygdala by the medial PFC (specifically, the affective division of the ACC[152]) and the hippocampus. In this model, symptoms of hyper-arousal result from amygdala hyper-responsivity, which explains the indelible quality of the emotional memory for the traumatic event; deficits in habituation to threat-related stimuli are attributable to inadequate influence by the ACC, and failure to identify safe context (as well as explicit memory difficulties) is mediated by decreased hippocampal function.[153] In addition, the model proposes that, in threatening situations, patients with PTSD exhibit an exaggerated reallocation of resources to regions that mediate fight-and-flight responses, and reallocation away from widespread heteromodal cortical areas, as a neural substrate for dissociation.

Morphometric MRI studies have found reduced hippocampal volumes in PTSD in Vietnam combat veterans as well as in PTSD resulting from childhood abuse.[153–155] Hippocampal volume abnormalities were associated with cognitive deficits (explicit memory impairment)[153] as well as PTSD symptom severity.[155] Although the extent of traumatic exposure may be correlated with hippocampal volume, it appears that hippocampal volume abnormalities between PTSD and control groups cannot be explained by traumatic exposure alone.[155] In addition, alterations in hippocampal volume may not (yet) be evident in samples of children/adolescents or in samples of subjects with relatively recent traumatic exposures.[156] Abnormal hippocampal volume in PTSD has been hypothesized to result from stress and prolonged exposure to glucocorticoid hormones.[157] However, it should be noted that that cortisol levels are characteristically reduced, rather than elevated, in PTSD.[158] One theory suggests that patients with PTSD suffer hypersensitivity to glucocorticoids, resulting in both reduced levels of cortisol (due to accentuated feedback inhibition) and reduced hippocampal volume.[158]

Consistent with the proposed neurocircuitry model of PTSD, functional neuroimaging studies using PET and fMRI in individuals with PTSD have found evidence for alterations in rCBF or BOLD signal in OFC, ACC, anterior temporal cortex, and amygdala.[152,159–167] For example, Rauch et al[160] investigated rCBF during script-driven imagery (a method for inducing symptoms) using PET in a mixed-gender cohort of subjects with PTSD. In the comparison between provoked versus control imagery condition, patients exhibited increased rCBF within ACC, right OFC, insula, anterior temporal and visual cortex, and right amygdala. rCBF decreases occurred within left inferior frontal (Broca's area) and left middle temporal cortex. In a follow-up study, using a similar paradigm, Shin et al[161] compared women with childhood sexual abuse-related PTSD and trauma-exposed control subjects without PTSD. In the traumatic versus neutral scripts comparison, both groups exhibited anterior paralimbic activation. Control participants showed greater rCBF increases within the ACC than PTSD participants in the comparison between

traumatic and neutral script, whereas the PTSD group showed significantly greater rCBF increases within the anterior temporal cortex and OFC compared with controls.

Decreases in rCBF in the medial PFC and ACC were found by Bremner et al[163] in PTSD Vietnam veterans in response to trauma-related pictures and sounds compared with Vietnam veterans without PTSD. Liberzon et al,[165] comparing combat sounds and white noise using SPECT in Vietnam veterans with and without PTSD and healthy non-veterans, found that all three groups showed activation in ACC/medial PFC, but only the PTSD group exhibited activation in the left amygdaloid region.

Shin et al[166] compared patients with combat-related PTSD and trauma-exposed control subjects without PTSD in the context of a PET cognitive activation paradigm. Participants were required to make judgments about three types of pictures (neutral, general negative, and combat-related) in two types of conditions: one involved responding while actually seeing the pictures (perception); the other entailed responding while recalling the pictures (imagery). In the combat imagery versus control conditions, the PTSD group exhibited rCBF increases in right amygdala and ventral anterior cingulate gyrus, and rCBF decreases in the left inferior frontal gyrus (Broca's area). Rauch et al[167] found an increase in amygdala activation during the exposure of combat veterans with PTSD to masked fearful faces in comparison with healthy combat veterans. The magnitude of amygdala activation was correlated with PTSD severity. Taken together, data from neuroimaging studies are consistent with our neurocircuitry model of PTSD that emphasizes the aberrant functional relationship between the amygdala, hippocampus, and medial PFC.

Obsessive–compulsive disorder (OCD) – cortico-striatal model of OCD

One current neuroanatomical model of OCD focuses on corticostriatothalamocortical circuitry.[2,168] According to this model, the primary pathology lies within the striatum (specifically, the caudate nucleus). This leads to inefficient gating at the level of the thalamus, which results in hyperactivity within the OFC (associated with intrusive thoughts) and the ACC (corresponding to anxiety, in a non-specific manner). Compulsions are viewed as ritualistic behaviors that are performed to recruit the inefficient striatum so as to ultimately achieve thalamic gating, and hence neutralize the unwanted thoughts and anxiety. Overall, MRI studies in OCD suggest abnormal caudate nucleus volume, although the nature of the observed abnormalities (i.e. increase or decrease) is inconsistent.[169–173]

Neutral-state paradigms employing PET and SPECT have most consistently indicated that patients with OCD exhibit increased regional brain activity within the OFC and ACC in comparison with normal control subjects.[174–179] Observed differences in regional activity within the caudate nucleus have been less consistent.[174,178] Studies comparing individuals with OCD pre and post treatment[180–185] have reported attenuation of abnormal regional brain activity within the OFC, AFC, and caudate nucleus following treatment using both pharmacological and behavioral therapies.[180,184] Some treatment studies suggest that lower pretreatment glucose metabolic rates in the OFC predict better response to serotonin reuptake inhibitors.[179,186,187] Symptom provocation studies employing PET[188,189] as well as fMRI[190] have also most consistently shown increased brain activity within anterior/lateral OFC, ACC, and caudate nucleus during the OCD symptomatic state (Figure 7.4).

Some cognitive activation studies using PET and fMRI have probed the functional integrity of the striatum in OCD.[191,192] In these studies, patients with OCD performed an implicit (i.e. non-conscious) learning paradigm shown to reliably recruit striatum in healthy individuals.[193,194] In both studies, patients with OCD failed to normally recruit striatum, and instead activated medial temporal regions that are typically associated with

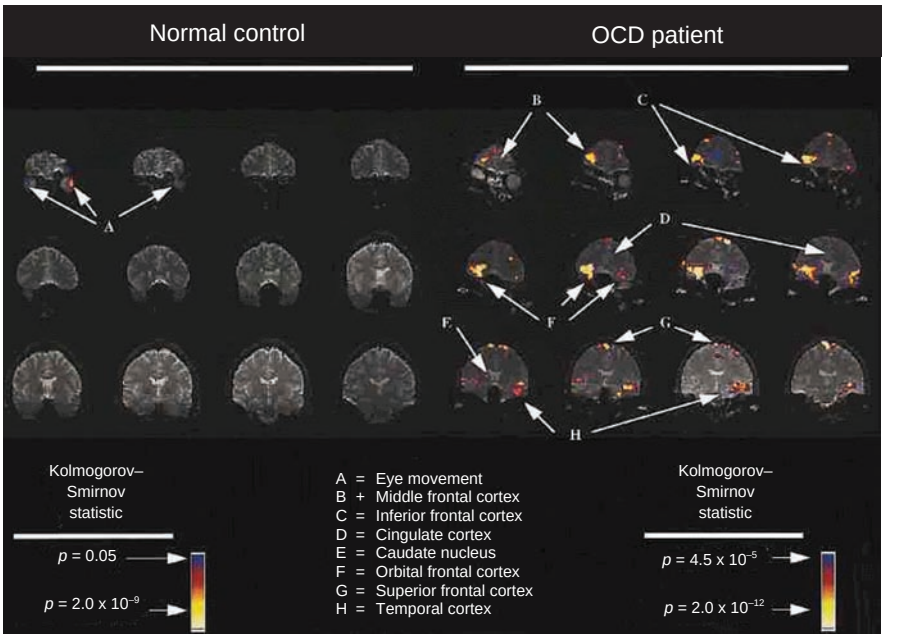

Figure 7.4 Activations in response to symptom provocation in a patient with obsessive–compulsive disorder (OCD) compared with a normal control subject as assessed with fMRI in a study by Breiter et al.[108] The functional data are shown as a probability map in color, superimposed over structural MRI scans. The threshold for the control subject is shown at a lower level to emphasize the absence of activation, while the patient's threshold was held to a more stringent significance level ($p < 10^{-7}$).

conscious information processing and involved in episodic/explicit memory.

Consistent with the these findings, MRS studies comparing NAA concentrations in patients with OCD versus healthy comparison subjects found reduced NAA levels in the striatum and ACC in OCD.[195,196] MRS has also been used to demonstrate elevated glutamatergic concentrations within the striatum of a child with OCD.[197] Glutamate is the principal transmitter mediating frontostriatal communication. Elevated striatal glutamate levels were attenuated toward normal following successful pharmacotherapy. These findings suggest that orbitofrontal hyperactivity in OCD may be mirrored by elevated glutamate at the site of orbitofrontal ramifications in the striatum, and that treatment-related attenuation of orbitofrontal activity may be accompanied by decreased glutamate concentration within the striatum.

Panic disorder (PD) – neuroanatomical models of PD

Neurobiological models of PD have emphasized a wide range of disparate elements.[198] Spontaneous panic attacks are the defining feature of PD, and satisfactory models of PD must account for these. Spontaneous panic attacks may correspond to a normal physiological anxiety response that is mediated by intact fear/anxiety circuits but, due to homeostatic deficits, occurs in inappropriate, threat-free situations. This view is consistent with theories such as the suffocation false alarm model, which proposes hypersensitivity to CO_2 at the level of the brainstem, as well as theories regarding abnormalities in monoaminergic regulation. It is also possible that panic attacks emerge in the context of what should be considered minor anxiety episodes because of failures in the systems

responsible for limiting such normal responses. In this context, hippocampal deficits may provide insufficient inhibition of anxiety responses. Finally, spontaneous panic episodes (i.e. without reportable or identifiable precipitants) could reflect anxiety responses to stimuli that are not processed at the conscious (i.e. explicit) level, but instead recruit anxiety circuitry without awareness (i.e. implicitly). In this context, it is important to consider evidence that the amygdala can be recruited in the absence of awareness that a threat-related stimulus has been presented.[152] By this view, PD would be characterized by fundamental amygdala hyper-responsivity to subtle environmental cues, triggering full-scale threat-related responses in the absence of conscious awareness.

Resting-state neuroimaging studies suggest abnormal hippocampal activity in PD. Symptom provocation studies have revealed reduced activity in widespread cortical regions, including PFC, during symptomatic states. For example, in a PET neutral state study, Reiman et al[199] found that patients with PD, vulnerable to lactate-induced panic, were characterized by abnormally low left/right ratios of parahippocampal blood flow. DeCristofaro et al[200] used SPECT to measure rCBF at rest and found that treatment-naive PD subjects compared with age-matched healthy control subjects were characterized by elevated left occipital but bilaterally reduced rCBF. Similarly, Nordahl et al[201] showed lower left/right hippocampal $rCMR_{glu}$ in individuals with PD compared with normal control subjects during an auditory continuous performance task. A follow-up study[202] using [^{18}F]fluorodeoxyglucose (FDG)-PET found a rightward shift in symmetry of $rCMR_{glu}$ within hippocampus and posterior inferior frontal cortex in imipramine-treated subjects with PD. Compared with an untreated group of subjects with PD, the imipramine-treated group exhibited $rCMR_{glu}$ decreases in posterior OFC. On the other hand, Bisaga et al,[203] using FDG-PET, found elevated $rCMR_{glu}$ in the left hippocampus and parahippocampal area in a cohort of women with PD compared with control subjects.

Symptom provocation studies of PD have been conducted using pharmacological and hyperventilation challenges. For example, Stewart et al[204] found that PD subjects who experienced lactate-induced panic attacks following lactate induction displayed global cortical CBF decreases. Woods et al,[205] using SPECT, found that increased anxiety in subjects with PD following yohimbine infusion was associated with decreased rCBF in bilateral frontal cortex. In a PET study, Reiman et al[206] measured rCBF during lactate infusions in patients with PD and normal control subjects. The eight patients who suffered lactate-induced panic episodes exhibited rCBF increases in bilateral temporopolar cortex and bilateral insular cortex/claustrum/putamen. Healthy control subjects and PD patients who did not experience lactate-induced panic attacks did not exhibit such rCBF changes. The temporopolar findings were subsequently questioned as possibly reflecting extracranial artifacts from muscular contractions.[207,208] Dager et al[209] used MRS to measure brain lactate levels during a hyperventilation challenge in treatment-responsive patients with PD compared with healthy comparison subjects. The PD group showed a significantly greater rise in brain lactate compared with control participants in response to the same level of hyperventilation. Dager et al[210] also used MRS to measure brain lactate levels during lactate infusions in subjects with PD and healthy comparison subjects. The PD group exhibited a significantly greater brain lactate level during lactate infusion, consistent with the interpretation of reduced clearance, rather than higher production, of lactate in PD.

In summary, consistent with prevailing neurobiological models of PD, it is possible that fundamental abnormalities in monoaminergic neurotransmitter systems, originating in the brainstem, underlie the abnormalities of metabolism and hemodynamics found in widespread cortical territories. Furthermore, regional abnormalities within the medial temporal lobes provide some support for theories regarding hippocampal or amygdala dysfunction in PD.

Social and specific phobias (SoP and SpP)

Currently, to our knowledge, there are no cohesive neuroanatomically based models for the phobias.[211,212] Phobic symptoms may reflect dysregulated systems for detecting potentially threatening stimuli or situations. That is, if humans have evolved a neural network designed to assess social cues for threatening content, and another to assess threat from small animals, etc., these might represent the neural substrates for the pathophysiology underlying phobias. Alternatively, it is also possible that phobias are learned, and hence reflect another example of fear conditioning to specific stimuli or situations.

Studies of SpP to date have almost exclusively employed PET symptom provocation paradigms, and have reported somewhat inconsistent results. For example, Mountz et al[213] found increases in heart rates and respiratory rates and subjective reports of anxiety during exposure to phobic stimuli in individuals with small-animal phobias, although no changes in rCBF measurements were observed. In a study performed by Wik et al,[214] exposure of snake-phobic individuals to snakes was associated with rCBF increases in the secondary visual cortex and rCBF decreases in the PFC, posterior cingulate cortex, anterior temporopolar cortex, and hippocampus. These findings were similar to that of two other phobia studies from the same laboratory.[215,216] Using in vivo exposure and PET, Rauch et al[217] studied rCBF in subjects with a variety of small-animal phobias. In the exposure-provoked versus control condition, subjects with phobias exhibited rCBF increases within multiple anterior paralimbic territories (i.e. right anterior cingulate, right anterior temporal pole, left posterior OFC, and left insular cortex), left somatosensory cortex, and left thalamus.

In SoP, several recent fMRI studies have advanced our knowledge of the involved neurocircuitry. For example, Birbaumer et al,[218] using fMRI, compared SoP subjects with healthy control subjects during exposure to slides of neutral human faces or aversive odors. In comparison with the control group, the SoP group exhibited hyper-responsivity within the amygdala that was specific to the human face stimuli. In a follow-up study, Schneider et al[219] used fMRI and a classical conditioning paradigm to study SoP subjects and healthy control subjects. In this paradigm neutral face stimuli served as conditioned stimuli and odors (negative odor and odorless air) as the unconditioned stimuli. In response to conditioned stimuli associated with the negative odor, the SoP group displayed signal increases within amygdala and hippocampus, whereas healthy comparison subjects displayed signal decreases in these regions.

In summary, although relatively few neuroimaging studies of SpP have been conducted, findings from existing research suggest activation of anterior paralimbic regions and sensory cortex corresponding to stimulus inflow associated with a symptomatic state. Although these findings are consistent with a hypersensitive system for assessment of or response to specific threat-related cues, they do not provide clear anatomical substrates for the pathophysiology of SpP. Cognitive activation neuroimaging studies of SoP reveal exaggerated responsivity of medial temporal lobe structures to human face stimuli, possibly reflecting a neural substrate for social anxiety in SoP.

CONCLUSIONS AND FUTURE DIRECTIONS

Neuroimaging research is helping to advance neurobiological models of mood and anxiety disorders. At the current early stage of this scientific enterprise, there is evidence of commonalities such as prefrontal and limbic–paralimbic abnormalities involved in both mood and anxiety disorders, although disorder-specific features are beginning to emerge. For further advances in detecting disorder-specific features of different mood states (i.e. depression vs. mania) and between different disorders (e.g. depression versus

anxiety disorders), it will be critical to explore the specificity of initial findings by conducting studies with psychiatric comparison groups in addition to healthy control subjects. Common etiological or vulnerability factors may have corresponding pathophysiological profiles that are independent of our current diagnostic scheme. For example, the relationship between early or chronic life stress and hippocampal structure and function may well span anxiety, mood, and even psychotic disorders. In this light, longitudinal and developmental studies might be of particular importance in elucidating the neural correlates and consequences of stress. Similarly, genetic studies in animals and humans will benefit from neuroimaging methods that can illuminate the bidirectional link from behavior to brain structure, function, and chemistry.

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Neurological recovery after stroke 8

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INTRODUCTION

Stroke is the leading cause of disability in western societies and the third cause of mortality. Stroke-related disability is steadily increasing as mortality decreases because of better interventions at the acute stage. Each year about 700 000 people suffer a stroke, of whom about half remain paralyzed on one side, one-fourth have difficulty with speech, and between one-fifth and one-third suffer deficits of attention and perception. These deficits carry a high price in terms of disability and burden to society. The estimated costs per year from stroke-related disability and loss of revenue in the USA are about 6.3 billion dollars (www.americanheart.org).

It is a common observation that most patients improve their neurological function within 3–4 weeks up to 6–12 months after a stroke.[1] For example, although at onset 80–90% of all stroke patients have motor deficits, only 40–60% of them will have a persistent hemiparesis at 6 months to 1 year. Similar degrees of recovery occur for language and visuospatial perception.[2,3]

Whereas early (1–3 days) recovery may be explained by vascular changes, such as early canalization of an obstructed vessel or reduction in the amount of edema surrounding an ischemic area, recovery that occurs in the weeks and months following the stroke must be explained by different mechanisms. Today, we know that central nervous system injuries including strokes and trauma trigger a series of events at different levels: brain networks, individual areas, neurons, connections, molecules, and even genes.[4–6] However, most of these changes are unlikely to be related to recovery of function, rather they represent 'housekeeping' operations after injury. For instance, in the area of ischemic damage, an inflammatory reaction is mounted that leads to the elimination of vascular and cellular debris, which eventually leaves a hole in the brain. Similarly, at the level of brain networks, damage to one area will lead to synaptic adjustments in distant areas that no longer receive inputs from the damaged area. For example, damage to the frontal lobe is known to cause a relative decrement in the baseline neuronal function of the connected contralateral cerebellum (so-called 'diaschisis').[7] Whether these adjustments have any relation to observed behavioral deficits or to recovery of function is currently unknown. Therefore, current neurobiological research on recovery of function has two main goals. The first goal is 'to separate the wheat from the chaff' – that is, determine what changes are triggered by brain injury and which of those changes are actually related to behavioral recovery. Secondly, if that goal is achieved, it should then be possible to use that information to categorize patients based on mechanisms, predict outcome, and potentially monitor the efficacy of interventions (rehabilitation or drugs). The final goal would be the development of a mechanistic theory of recovery of function so that one could directly manipulate one or more of the said mechanisms to improve function.

This research program is hampered by incredible theoretical and pragmatic challenges. We can visualize the problem, shown in Figure 8.1, as a multidimensional space. One dimension is the brain with its different levels of organization (molecules to

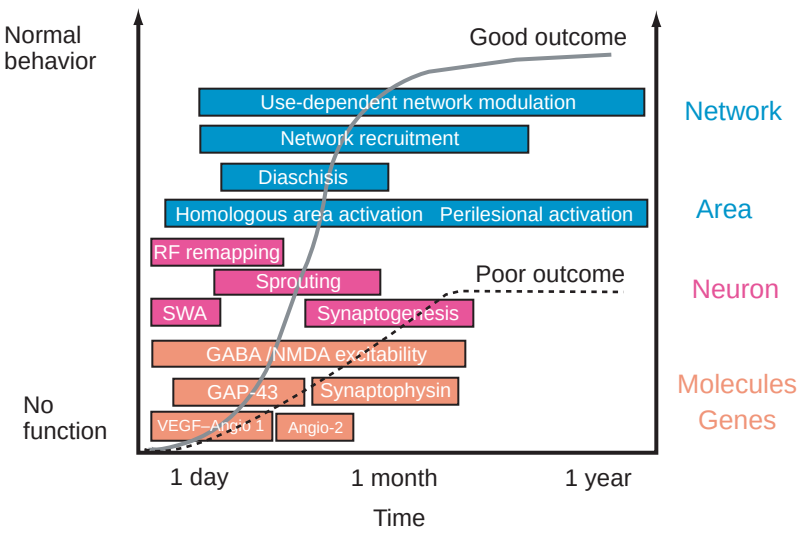

Figure 8.1 Three-dimensional problem space for studying recovery of function. RF, receptive field; SWA, slow-wave activation; GABA, γ-aminobutyric acid; NMDA, *N*-methyl-D-aspartate; GAP-43, growth-associated protein 43; VEGF, vascular endothelial growth factor; Angio-1/2, angiopoietin-1/2.

networks), where changes putatively related to recovery occur at different levels, but must be related across levels to be helpful. For instance, going from brain to molecules, we would like to understand how changes recorded at the level of brain networks (e.g. the motor system) relate to changes recorded from single neurons near the lesion, and how in turn these neuronal changes are related to upregulation or downregulation of certain neurotransmitters. Conversely, going from molecules to brain, we would like to understand how the activation of certain genes causes the formation of molecules that promote synaptic sprouting, leading to the formation of new connections that change the pattern of activity in certain areas. A second dimension is the timing of these changes and how it relates to the timing of recovery of function. Ideally, one would like to concentrate on mechanisms that have a temporal profile matching or paralleling the time course of recovery. A final important and critical dimension is the behavioral relevance of these mechanisms. How do these mechanisms relate to good or poor overall level of function? How do they relate to the extent of recovery – that is, the amount of change from acute to chronic? A related issue is whether these mechanisms are mediating the original behavior or a compensated version of it – a behavior similar to the original one, but generated through compensatory strategies (e.g. a grasping movement that uses shoulder elevation more than normally).

NEUROIMAGING SIGNALS TO VISUALIZE RECOVERY OF FUNCTION AFTER STROKE AND THEIR PITFALLS

In this review, we will concentrate on changes that occur at the level of brain networks and individual areas (Figure 8.1) that have been recorded mainly using functional neuroimaging techniques (positron emission tomography (PET) and functional magnetic resonance imaging (fMRI). These techniques allow the in vivo visualization of regional metabolic signals (blood flow, oxygen metabolism, glucose metabolism, and oxygen concentration) that are indirectly related to the level of neuronal activity within an area.[8] While the cellular mechanisms linking neuronal activity to metabolic changes are not fully understood, the current theory is that task-related changes in blood flow or oxygen concentration are mainly related to the sum of the excitatory and inhibitory inputs to and within an area, and much less to the output from that area.[9,10] This fact has been directly established by simultaneous recording of blood oxygen level-depen-

dent (BOLD) signals (a measure of blood oxygenation) with fMRI and electrical recordings (single- and multi-unit, and local field potential) in anesthetized monkeys.[9] These studies have shown that the local BOLD signal (and therefore local blood flow) is best correlated with the local field potential, a weighted measure of the electrical potentials generated by both excitatory and inhibitory inputs, and less well correlated with single-unit activity, a more direct measure of the neuronal output. It is assumed that most of the metabolic demands within a cortical area depend on the local integration of information, which in turn suggests that the hotspots localized by neuroimaging mainly reflect local neuronal processing. Therefore, functional neuroimaging methods are ideally suited to monitor brain activity in patients recovering from stroke and to identify recovery-related changes at the level of areas or brain networks.

Unfortunately, several factors related to stroke may change the physiological relationship between neuronal activity and hemodynamic (blood flow and oxygenation) signals – so-called 'neurovascular coupling'.[11] One factor is the effect of aging on blood vessels. Aging may influence the structure of blood vessels, interfere with signaling underlying neurovascular coupling, or directly impair neuronal function. For example, we know that older adults tend to activate the brain in a more widespread and less selective fashion than younger adults, and that this more widespread activation may correlate with cognitive compensation.[12,13] Similarly, widespread and less specific activations have been reported in recovering stroke patients (see below), in whom their relationship to recovery of function must be differentiated from the effect of aging.

Atherosclerosis may also change the structure of the brain blood vessels and impair neurovascular coupling. In patients with transient ischemic attacks (TIAs), the blood flow response to a stimulus may be suppressed even when behavior is normal, and neuronal activity is present.[14–16] In vessels distal to a carotid stenosis, the shape and temporal dynamics (onset and offset) of the BOLD response recorded with fMRI may be abnormal.[11] Finally, BOLD responses to a stimulus may be abnormal for several weeks after a stroke in the hemisphere contralateral to the lesion, despite a normal electromagnetic response.[17]

A third factor is the potential effect of angiogenesis.[18] Angiogenesis defines a sequence of events including vascular permeability, extravasation of plasma proteins, destabilization of mature vessels, endothelial cell division and budding, the formation of a new vascular tree, and finally new patterns of local blood flow. These changes have been documented in the perilesional area in the first 1–2 weeks after a stroke. Sites of angiogenesis in the perilesional area are where synaptic sprouting and the poststroke stem cell response occurs. A common concern in neuroimaging studies of stroke recovery is that task-induced blood flow or BOLD signals may be weak or not present at the subacute stage (3–4 weeks), and become more detectable at the chronic stage (3–6 months).[19] Although these results are considered evidence of local neural reorganization, it is possible that, at the acute stage, neuronal activity in the perilesional area may be present but not detectable with neuroimaging because of lack of a mature vascular system capable of sustaining a normal neurovascular coupling.

A final factor to consider is the effect of diaschisis on task-evoked BOLD or blood flow signals. Diaschisis is defined as a decrement in neuronal activity and metabolism within an area produced by lack of excitatory input from a connected area that is injured.[20–22] For example, a stroke in the frontal lobe may cause decreases in baseline blood flow and glucose metabolism, and presumably neuronal activity, in the contralateral cerebellum due to a decrement of neuronal traffic in corticopontocerebellar connections. Diaschisis can occur in cortex after thalamic or basal ganglia lesions, in homologous areas of the contralesional hemisphere via callosal connections; and in distant areas within the same hemisphere through long-range corticocortical connections. Figure 8.2(a) shows diaschisis in the

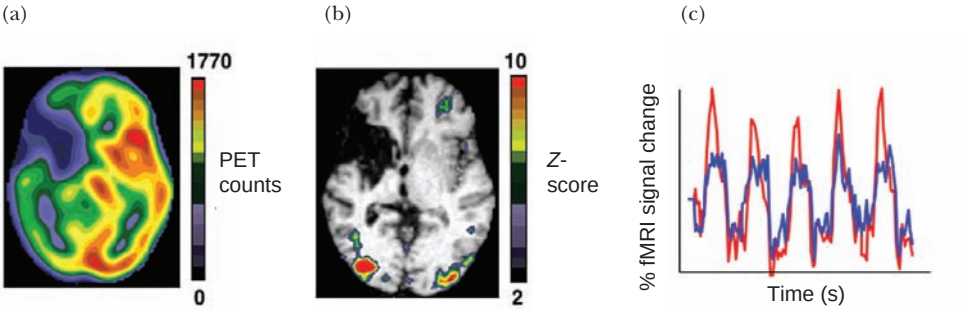

Figure 8.2 (a) PET blood flow scan of patient with left frontal stroke. Note the decreased blood flow from the damaged area (blue) and structurally normal temporal and occipital lobes of the damaged hemisphere. (b) Corresponding slice from anatomical MRI on which fMRI responses during a visually cued word generation task are mapped. Note the responses in the diaschitic occipital lobe. (c) BOLD signal time course from left (red) and right (blue) occipital lobe activations.

occipitotemporal lobe at 6 months post onset after a stroke in the frontal lobe.

It is unknown whether changes of the neuronal and metabolic baseline of an area affect stimulus- or task-evoked activity. This is a critical issue for validating the use of neuroimaging signals to track brain activity in recovering stroke patients, and has not been satisfactorily addressed to date. Figure 8.2(b) shows the BOLD response evoked within the area of diaschisis in occipital cortex by the presentation of a word on a computer screen during a word generation task. The shape of the BOLD response is similar to that in the normal hemisphere – an indication of normal neurovascular coupling. The magnitude of the response, however, is twice as large as normal. This may be related to lack of inhibitory input from the damaged frontal lobe, which is known to have a regulatory function (mostly inhibitory) on behavior.[23] Correspondingly, patients with frontal lobe lesions have higher than normal sensory evoked potentials in the hemisphere ipsilateral to the lesion, consistent with the sensory gating hypothesis.[24]

NEURAL CORRELATES OF MOTOR RECOVERY

The large majority of patients with a stroke invariably show some degree of recovery, ranging from minimal to complete.[1] The degree of recovery depends on initial severity, being more complete in patients with milder deficits at onset, and occurs largely in the first 3 months post stroke, tapering off by about 6 months. Importantly, the recovered movements are not identical to the original movements in terms of dynamics (speed, accuracy, and trajectories) and thus pattern of muscle recruitment, even when the lesions are circumscribed to parts of sensorimotor cortex.[25] It is therefore more correct to define motor recovery as 'motor reorganization' – a definition that highlights the fact that recovered movements are actually mediated by reorganized neural mechanisms.

Against this background, neuroimaging studies are providing information about neural mechanisms of motor recovery at the level of areas and brain networks (systems) (Figure 8.1). Some studies have also addressed the relationship between these mechanisms and functional outcome. Finally, we are just beginning to use imaging to monitor the effect of drugs and rehabilitation. Two main mechanisms have been identified in studies of motor recovery using neuroimaging: (1) hyperactivation and bilateral recruitment of motor, premotor, and attention-related areas; (2) topographic shifts in the distribution of activity in primary sensorimotor cortex in the affected hemisphere.

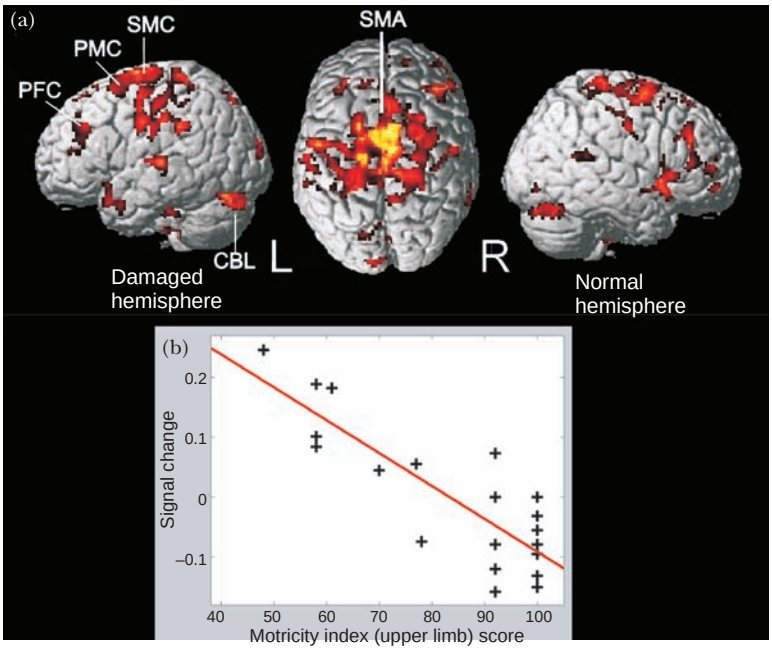

Figure 8.3 (a) Brain regions in which there is a negative correlation between the magnitude of the change in BOLD signal during hand grip and upper limb motor recovery scores (as measured by the upper limb portion of the motricity index), in chronic stroke patients with right-hemisphere subcortical infarcts. Results are surface-rendered onto a canonical brain, which is shown (from left to right) from the left side, from above and from the right. PFC, prefrontal cortex; PMC, premotor cortex; SMC, primary sensorimotor cortex; SMA, supplementary motor area; CBL, cerebellum; (b) Correlation plot between motricity index and BOLD signal change in the supplementary motor area. Kindly provided by Nick Ward.

Hyperactivation and bilateral recruitment of motor, premotor, and attention-related areas

Many neuroimaging studies (PET and fMRI) have documented the normal pattern of brain activation during simple and complex movements.[26,27] During an automatized simple motor sequence (e.g. repetitive finger opposition), a relatively small number of areas are active, including the contralateral sensorimotor cortex, contralateral premotor and supplementary motor area, contralateral thalamus, and ipsilateral cerebellum. When the task becomes more attention-demanding, as during a sequence of finger movements, or when a movement is selected from among many possible movements, or when the movement is unskilled, the basic contralaterally organized sensorimotor circuit is activated more strongly and is integrated with bilateral prefrontal and parietal cortices that control, monitor, and correct performance.

Chronic stroke and relationship to outcome

In stroke patients, a number of early studies demonstrated a relative overactivation, as compared with control subjects, of motor-related regions during movements of the affected upper extremity.[28–31] Specifically, recruitment of the sensorimotor cortex ipsilateral to movements of the recovered arm and the contralateral cerebellum were described. In addition, greater than normal activation was also reported in premotor (dorsal, ventral, and insula) and attention-related areas (prefrontal and parietal), making the pattern of motor activation more bilateral, even for simple tasks. These early studies suggested that recovery of motor function was mediated by the recruitment of ipsilateral motor systems that 'take over' functions originally limited to the contralateral damaged motor system, as well as the recruitment of intention–attention mechanisms.

However, several subsequent studies have shown that a more bilateral (and overactive) pattern of motor activation correlates with a less complete recovery of motor function. Patients with no residual impairment tend to have relatively normal maps of motor activation, whereas patients with lesser recovery tend to activate more strongly and more bilaterally the motor system.[32–35] This observation was

most convincingly demonstrated in a cross-sectional study by Ward et al[35] of 20 patients with mixed strokes (cortical, internal capsule, thalamus, and pons) at least 3 months after onset who had varied outcomes. Outcome was measured with 20 different measurements, including general outcome (Barthel and Rankin), tests of arm function (ARA and 9-hole peg test), and grip strength. A composite score was generated that was highly representative of the 20 measures. During the imaging session, subjects performed a hand grip task while brain activity was measured with BOLD fMRI. The main finding was that the degree of activation in the motor system correlated negatively with outcome: high activity during the hand grip task occurred in those patients with less complete recovery. Figure 8.3(a) shows areas of the damaged (right) and undamaged (left) hemisphere where the magnitude of the BOLD signal correlated negatively with level of function. Note that this inverse relationship was not limited to motor areas (primary sensorimotor cortex and cerebellum), but extended to premotor areas (premotor and supplementary motor cortices) and attention-related areas of the frontal and parietal lobe (prefrontal cortex). Figure 8.3(b) shows the correlation between BOLD signal change during the hand grip task in the supplementary area and the motricity index for the upper extremity. Note that patients with high signal change had low motricity scores, and vice versa. All of these patients were studied more than 6 months after their stroke at a time when their clinical recovery was deemed complete.

Longitudinal changes and relationship to motor recovery

Cross-sectional studies provide information about neural correlates of recovery at one point in time, but do not provide information about how the brain is changing while it is recovering from an injury. Ideally, we would like to know whether neural correlates of functional outcome (performance level at the chronic stage) are the same as or different from those that mediate changes in performance from the acute to the chronic stage of recovery. With this information in hand, it would be theoretically possible to develop formal predictive models of recovery of function that could be used to stratify patients at the acute stage into those likely to recover a great deal of function and those likely to recover little function based on expected outcome.

Some of the earlier longitudinal studies reported an initial increase in activity early on after stroke, followed by a decrease in task-related activity several months later, but failed to establish a quantitative relationship with recovery of function.[33,36] Other studies did not find a consistent relationship between pattern of activation and measures of recovery.[37,38] Ward et al,[39] however, used a parametric longitudinal design in which patients were studied multiple times in the first month and a half post stroke, and again at 3, 6, and sometimes 12 months. This powerful design allowed them to establish a very convincing inverse relationship between recovery of function and brain activity in motor, premotor, parietal, prefrontal, and subcortical areas. Patients who recovered more on a composite measure of motor recovery showed more task-related decreases than patients who recovered less. Importantly, this relationship was independent of the rate of recovery or the initial severity of the deficit. These results are consistent with other studies showing that recovery is associated with a 'focusing' of motor-related activity within the affected hemisphere, and a restriction of activation in the undamaged hemisphere and in areas outside of the motor system.

In conclusion, both cross-sectional and longitudinal brain imaging studies show that task-related hyperactivity and recruitment of additional motor (contralesional M1), premotor (premotor and supplementary), and attention-related (prefrontal and parietal) areas are a common response after stroke, and that the persistence of hyperactivity and bilateral hemispheric recruitment at the chronic stage tends to correlate with poor recovery. In contrast, normalization of task-related hyperactivity and refocusing of activity

to contralateral premotor and motor networks is associated with better recovery and final outcome.

Behavioral and anatomical factors may underlie hyperactivity and recruitment

What factors can explain the association among hyperactivity, bilateral hemispheric recruitment, and motor recovery? An important behavioral variable to consider is the effect of attention and effort. Patients with lesser recovery may require more effort or pay more attention than patients with greater recovery to maintain the same level of performance. Attention and effort boost neuronal activity and, secondarily, hemodynamic signals.[27,34] Specifically, attention to movement modulates activity in several sensorimotor areas (premotor, cingulate, supplementary motor area, and insula), including the primary motor cortex. It is possible that diminished activity associated with motor recovery in those with good outcome reflects progressively more automaticity in performing the same movements than individuals with poorer recovery perform with effort.

While attentional factors are difficult to control, effort has been controlled in some studies by manipulating task performance while keeping effort constant, or vice versa by keeping performance constant while leaving effort unchecked. At least in one study, these factors did not modify the negative relationship between hyperactivity and functional outcome.[35]

Another important variable is learning, as in the course of recovery patients relearn to perform movements with the affected arm. Motor learning is associated with neural changes at the level of single neurons, areas, and brain networks.[40] Neuronal firing becomes more selective, and decreases in magnitude. The topography of motor areas changes with the expansion of the representation dedicated to the trained movements.[41,42] Finally, learning tends to focus the pattern of activation across areas, restricting activity to sensorimotor circuitries while recruiting attention-related areas in prefrontal or parietal cortex less and less as learning proceeds.[43] Since normal learning-related modulations closely mimic some of the changes observed in recovering stroke patients, it is possible that some of those changes also reflect learning effects in the context of poststroke recovery.

Hyperactivity and recruitment may also depend on anatomical factors, such as the parallel connectivity of the motor system with the spinal cord. The traditional view of a single descending motor output pathway from the primary motor cortex has been replaced by a more parallel view of cortical motor output.[44,45] At least three motor fields (M1 or primary motor cortex, supplementary motor area/cingulate, and premotor) send descending fibers via the pyramidal tract to the spinal cord. While the output from M1 may be especially important for mediating articulated finger movements, it appears that more proximal movements can be achieved through a more parallel combination of signals. The hypothesis is then that, when a stroke disrupts the normal pattern of descending motor activation, accessory motor fields in premotor, supplementary motor area, cingulate cortex become active when trying to overcome the deficit. This activation may be enhanced by attention. Recruitment of the accessory motor system plus or minus attentional boosting lead, in turn, to the observed hyperactivity and recruitment of motor and non-motor areas. That hyperactivity correlates inversely with functional recovery may actually depend on the fact that accessory motor pathways (e.g. premotor cortex) are less effective in generating movements. For instance, in primates with a limited M1 lesion, transient or permanent damage of the ipsilateral premotor cortex disrupts motor recovery of hand function;[46,47] however, the dynamics of hand movements are permanently altered after M1 lesions, even in the presence of a functioning premotor area.[25]

The recruitment of the ipsilateral hemisphere, opposite the lesion, may also depend on the disinhibition triggered by damage of callosal connections.[48,49] For instance, in the case of a motor cortex lesion, the motor area in the opposite hemisphere

may show abnormally high activity or decreased inhibition because of missing inhibitory callosal input from the damaged cortex. An important question debated in the literature is whether activity in the hemisphere opposite the lesion is detrimental to recovery, contributes to recovery, or is just epiphenomenal. Studies that show an inverse relationship between hyperactivity and recruitment (even of the normal hemisphere) and recovery of function are supportive of the first interpretation.[35,39] Similarly, transcranial magnetic stimulation (TMS) studies show that the ability to record motor potentials in the affected limb evoked from the damaged motor cortex correlates with good recovery, whereas recording of motor potentials evoked from the undamaged motor cortex (ipsilateral pathways) correlates with poor outcome.[47,50]

Conversely, clinical data suggest that a second stroke in the hemisphere opposite to that damaged by a first stroke can reinstantiate a hemiparesis in a person who is recovering strength.[51] Moreover, some recent TMS data show that inactivation of the ipsilesional dorsal premotor cortex selectively slows the latency of simple movements performed by a recovered hemiparetic arm, and that this effect is particularly strong in patients with strong ipsilateral activations and relatively poor recovery.[52] These findings are consistent with a compensatory role of ipsilateral activity.

At this stage, a reasonable summary of the current evidence is that the heightened and bilateral activation of the motor system in recovering stroke patients allows the execution of movements of the hemiparetic arm. However, these movements are typically abnormal, as they involve compensatory dynamics. As the recovery process tends to approach normality, so does activity in the brain, with a pattern that becomes more contralateral and more normal in terms of range of activation.

Shifts in the topography of sensorimotor activity

A separate mechanism of functional reorganization observed in patients with motor deficits is a relative shift of the topography of activation in the sensorimotor cortex.[29,33,53,54] Normally, during the execution of finger movements, activity is centered in the hand representation of sensorimotor cortex. In patients with subcortical strokes and recovered upper extremity function, some studies have reported a ventral shift toward the face representation, while other studies have reported a posterior shift toward the postcentral gyrus (primary somatosensory cortex). It should be noted, though, that in normal subjects there is considerable variability in the topography of motor activations.[55] These shifts in topography of task-related activity (or 'remapping') are not unique to stroke patients, but have been observed in patients with peripheral deafferentation such as limb amputees or patients with spinal cord injury.[56–58] Figure 8.4 shows the cortical activation map of a patient with tetraplegia from a C2–C4 traumatic injury while he is moving his left index finger. Activity in sensorimotor cortex is widespread and involves both the hand and face representations; in contrast, in a control subject, the response is more restricted to the hand representation.

In patients with limb amputation or sensory deafferentation, cortical remapping is related to anatomical changes at the subcortical and thalamic levels, with rerouting of inputs from the deafferented limb to relay nuclei that code inputs from the face.[59,60] In the case of cortical lesions, remapping may be related to local sprouting and a change in the organization of intra-area connections.[18] At the physiological level, Nudo et al[41,61] have discovered that after small lesions in the somatosensory or motor cortex, monkeys recover the use of the injured fingertips. In parallel, there is a re-emergence of the injured fingertip representation in the territory adjacent to the lesion. Furthermore, the representation of spared fingers adjacent to a lesion can undergo a significant reduction in cortical representation, but this functional reorganization is avoided if the animal undergoes daily physical training. These neuronal changes might be the basis of the topographical shifts observed in functional neuroimaging

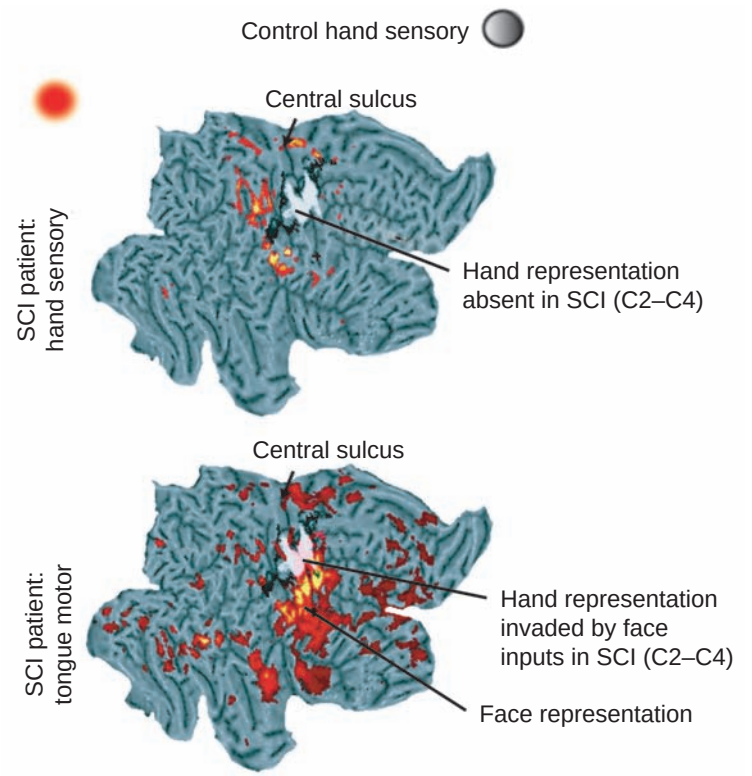

Figure 8.4 Flat map of atlas brain on which activations for control (gray scale) and spinal cord injury (SCI) patient (red–yellow) are superimposed. Control activation marks the location of the normal hand representation in sensorimotor cortex localized using a vibratory stimulus. (a) Lack of hand response in SCI patient. (b) Invasion of hand representation by movements of the tongue that selectively activate the face representation in controls (not shown).

experiments in stroke patients. It remains unknown what determines the variability of shift direction (dorsoventral or anteroposterior), and whether these shifts have any behavioral consequence in terms of recovery or final outcome.

NEURAL CORRELATES OF APHASIA RECOVERY

Similar to the motor system, functional neuroimaging has been used to map regions of the brain involved in the production and comprehension of spoken and written language (for a comprehensive review, see Demonet et al[62]). Likewise, imaging has been used to examine patterns of brain activity in patients who have aphasia after stroke to determine the neural mechanisms that correspond to behavioral recovery of language, although much less is known about aphasia recovery than motor recovery.

As in individuals with motor deficits, the majority of aphasic patients show some degree of recovery, ranging from minimal to complete.[63] The extent of the lesion through the language regions of the brain and the degree to which white matter is affected are important in determining the degree of recovery that patients experience. The time course for language recovery, however, is more protracted than for motor recovery. Language recovery is largely complete by 1 year post onset, with a diminished rate of recovery by the 2-year mark.[63–65] It remains an open question whether recovered language is performed in the same way as the original language was produced or comprehended in individuals with good recovery. Clearly, in individuals who have poorer recovery, language production is not identical to the original output; articulation is of poorer quality, grammatical structures are not well preserved, and word choice is affected.

Recruitment of right hemisphere in language recovery

Two general theories have been proposed to explain the recovery of aphasia. One theory, originally proposed by Gowers and Wernicke, suggests that activity in the right hemisphere plays a major role in allowing the return of language. There is considerable support for this view. Some recovery occurs in patients with very large lesions of the left hemisphere.[66] Patients with a left-hemisphere lesion who have recovered some language function can become aphasic after a second lesion in the right hemisphere.[67] Electrophysiological and early blood flow studies with xenon methods reported 'abnormal' right-hemisphere activity in recovered aphasics during language tasks.[68] Several functional activation studies have also reported recruitment of right-hemisphere regions homologous to those active during language processing in the left hemisphere in healthy adults,[69–78] although right-hemisphere recruitment may depend on the extent of the lesion in critical language structures in the left hemisphere. For example, Blank et al[79] have shown in a PET study that patients with lesions including the left pars opercularis activate the right hemisphere during propositional speech, whereas patients with left-hemisphere lesions that did not encompass the pars opercularis activated regions in the left hemisphere surrounding their lesion. Figure 8.5 shows the normal pattern of frontal activation in a group of control subjects during a word generation task. The activation moves to the homologous area in the right hemisphere in a group of chronic aphasics (>6 months post onset) with damage of the left inferior frontal gyrus and surrounding cortex and white matter.

As in the case of motor recovery, the role of ipsilateral activity (right-hemisphere after left-hemisphere stroke) in aphasia recovery is not well understood. Some patients with excellent recovery of language after left frontal cortex stroke show abnormally strong activation of the homologous regions in the right inferior frontal gyrus while performing flawlessly word generation tasks at the chronic stage[71] – a result consistent with compensation. However, in other studies, the magnitude of right-hemisphere activations during language tasks across patients did not correlate with language performance;[75] and several other studies suggest that exclusively right-hemisphere activation may not be associated with good language recovery.[19,69,73,77]

Left-hemisphere activation in language recovery

A second theory proposes that recovery of aphasia is mediated by regions in the left hemisphere. Some support comes from studies that have combined neuropsychological testing and resting/activation measurements of regional glucose metabolism ($rCMR_{glu}$).[80–84] These studies have demonstrated that hypometabolism of regions in the left hemisphere measured within 2–3 weeks from the onset of the stroke correlates with the rate of improvement on selected language scales. For example, low acute $rCMR_{glu}$ in the left superior temporal gyrus predicted poor performance on a follow-up test of auditory comprehension.[80] These findings have been confirmed with PET activation methods. Figure 8.2 shows an example of left-hemisphere hypometabolism (in this case low blood flow) at rest after a stroke in the frontal lobe. A longitudinal PET activation study by Heiss et al[19] showed that favorable recovery of auditory comprehension in frontal–subcortical patients was correlated with activation of the right superior temporal gyrus and right inferior frontal gyrus at baseline, followed by activation of the left superior temporal gyrus at follow-up during auditory word repetition. Unfavorable outcome was associated with persistent activity in the right frontal gyrus. This study provides the best evidence to date that recovery of language is mediated by regions in the left hemisphere.

Both hypotheses, then, for right- and left-hemisphere mechanisms in aphasia, seem to find some support in the current data, and each remains an active area of investigation.

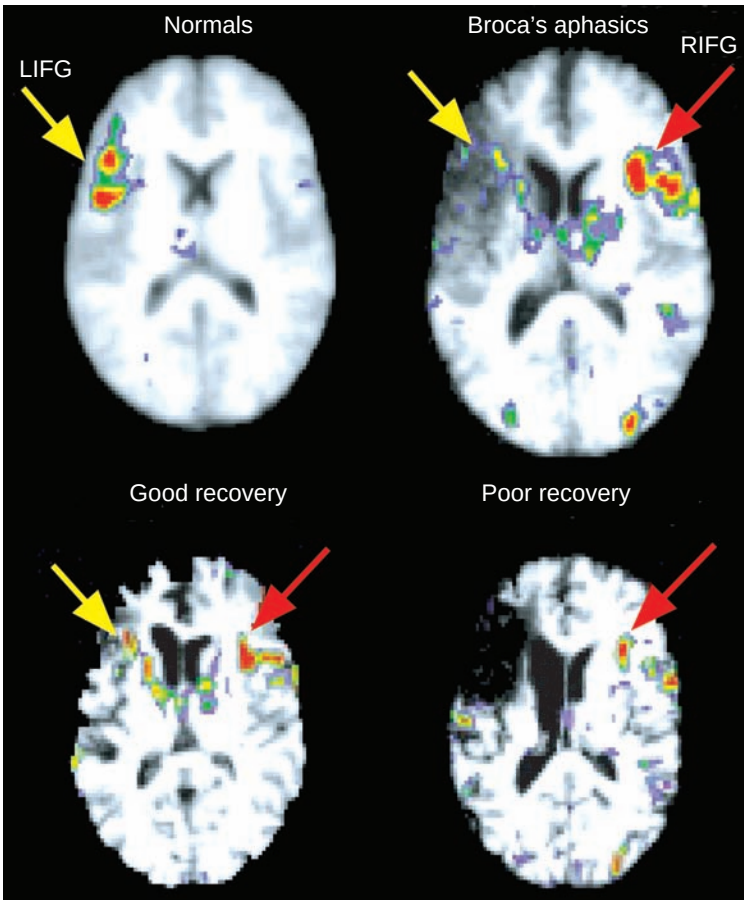

Figure 8.5 Top: group-averaged data in controls and Broca's aphasics at the chronic stage. Yellow arrow: left inferior frontal gyrus (LIFG) activity. Red arrow: compensatory right inferior frontal gyrus (RIFG) activity. Bottom: individual subjects with respectively small (left) and large (right) LIFG stroke. Note the perilesional activation in the LIFG in the patient with a smaller lesion and good recovery.

Factors that may be important in determining the role of right- and left-hemisphere mechanisms of recovery may be the nature of the language task that is attempted (verbal production, auditory comprehension, reading, or writing), the integrity of the remaining language regions of the brain and their white matter connections, the time post stroke when brain functioning is evaluated, and the nature of the speech therapy given during the recovery process.

Although left- and right-hemisphere hypotheses are presented as separate in the literature, in reality both types of mechanisms coexist in individual patients and likely represent a continuum. If one considers a group of patients with relatively well-defined lesions to one of the language areas (e.g. Broca's area in the left frontal lobe) and maps language-related activity at the chronic stage, patients with small lesions show activation both near the lesion and in the right hemisphere, whereas patients with larger lesions have activation only in the right frontal cortex.[75] Interestingly, in experimental animals, the ratio of contralateral to ipsilateral activation is inversely correlated with lesion size and with level of neurological function.[85,86] Although this relationship has not been clearly demonstrated in patients with aphasia, the current evidence resembles that in the motor system, whereby the degree of ipsilateral (right-hemisphere) recruitment correlates with the extent of damage to language areas in the left hemisphere, and correlates inversely

with recovery of function. Optimal recovery will occur when the lesion allows less reactivation of left-hemisphere mechanisms, while lesser recovery may be expected when only right-hemisphere mechanisms are available. This rule may apply especially for functions such as articulation that are strongly lateralized to the left hemisphere,[87] but may not generalize to processes that are more bilaterally represented, such as sentence comprehension.[88] The bottom part of Figure 8.5 shows two patients: one with both perilesional and right frontal responses, had very good recovery and performed well on a word generation task that requires the selection of a word based on phonological–orthographic cues; the other, with a larger lesion and activation only in the right frontal cortex, had much less recovery, and performed less accurately on the word generation task.

TREATMENT AND FUNCTIONAL IMAGING

Human and animal studies have shown that poststroke experience can strongly modify the degree of recovery: enriched environment, training of the affected limb, amphetamine therapy coupled with training, and nerve growth factors (NGFs) have improved recovery of sensorimotor function in experimental animals (for a review, see Nudo[5]). Therefore, there seems to be an important clinical role for behavioral (rehabilitation) and chemical (drugs and molecules) modulation of recovery of function.

Neuroimaging studies can provide three different types of clinically relevant information. First, they could theoretically be used to predict outcome and stratify patients early on with good and poor recovery. Outcome prediction has not been very successful using either anatomical or clinical information; it is possible that a complex model in which functional, anatomical, and behavioral information are used jointly may stand a better chance of becoming a useful clinical tool. For example, if the notion that hyperactivity is correlated negatively with motor recovery is confirmed in other studies and generalized to other conditions such as aphasia and visuospatial perception deficits, it should be possible to develop a clinically relevant cutoff of hyperactivity that separates patients into levels of likely recovery with reasonable specificity and sensitivity. Different therapeutic interventions could then be targeted at patients with different levels of likely recovery.

Second, neuroimaging studies will be important to guide interventions. Patients with similar behavioral profiles at the acute stage may recover differentially, relying on different mechanisms. For instance, patients with small lesions may rely more on remapping mechanisms and recruitment of perilesional areas, whereas patients with larger lesions may rely more on ipsilateral hemispheric mechanisms. Correspondingly, different interventions may be appropriate. For instance, remapping mechanisms may be modulated more by constraint-induced therapies that seem to work by enhancing local plasticity.[89,90] Conversely, therapies aimed at decreasing hyperactivity may work best by regulating mechanisms in distant areas or in the opposite hemisphere.

Third, neuroimaging studies will be important to monitor the efficacy of therapies. While behavioral measurements remain the gold standard for assessing recovery of function or performance, many times clinical measurements are not sensitive enough to capture therapeutic effects, particularly early on in the treatment. An example case is what has happened in multiple sclerosis research, where for many years the efficacy of novel drug treatments was tested using clinical scales. In the last decade, however, the advent of MRI scans and their capability to directly measure the impact of the disease on the brain (e.g. by measuring the number of plaques on T2-weighted scans) has created a true paradigm shift. Today, new treatments are evaluated against clinical evidence as well as MRI evidence of disease.[91,92]

Last, but not least, neuroimaging studies will advance our understanding of how interventions modulate neural mechanisms related to recovery of function and will help

clarify which of these mechanisms are indeed behaviorally relevant. This is the area in which most progress can be expected in the next decade and to which most effort is being applied.

Modulation of motor recovery by rehabilitation

An important advance in neurorehabilitation sciences in the last decade has been the development of the theoretical framework for constraint-induced interventions.[93] Constraint-induced rehabilitation methods include a variety of treatments based on the principle that behavioral deficits post injury are partly supported by learned non-use. Everyday difficulties in using a hemiparetic arm leads to the progressive non-use of the affected arm, and a parallel increase in compensatory use of the unaffected arm. These behavioral changes lead to structural and physiological changes in the brain that worsen function of the affected arm. The intervention is based on two principles: (1) constraining the unaffected arm to decrease non-use of the affected arm; (2) retraining and shaping movements of the affected arm through a series of goal-directed activities.

There is some molecular and cellular evidence supporting this theoretical framework (for reviews, see Nudo,[5] Carmichael,[18] and Schallert et al[94]). An injury in rat somatosensory cortex or middle cerebral artery occlusion causes a phase of dendritic overgrowth followed by a phase of pruning and increasing synaptogenesis in the cortex opposite the lesion. These changes depend on the increased use of the unimpaired forelimb, since constraining the limb prevents dendritic overgrowth. Correspondingly, structural and physiological changes, including neural sprouting, synaptogenesis, and remodeling of physiological representations, in the cortex near the lesion occur as function of practice.

Since the original studies by Taub and colleagues, numerous groups have now demonstrated that motor constraint-induced therapy (CIT) improves motor function by producing a relative expansion of the motor cortex representation in the damaged hemisphere.[89,90,95–98] This expansion may be related to recruitment of ipsilateral premotor cortex and supplementary motor areas, as suggested by the neuroimaging studies reviewed earlier. Interestingly, there is direct evidence for CIT-induced changes in fMRI activity during motor tasks, although the direction of those changes varies across studies.[98,99] Some studies have reported increases in fMRI activation, while other groups have reported decreases. An important factor may be the site of injury, which may have differential effects on cortical excitability and thus affect transcranial magnetic stimulations and fMRI measurements.[99]

A few studies have begun to compare the behavioral and physiological effects on brain activity of different rehabilitative interventions[100] – an important step toward eliminating differences in motivation, effort, and expectation between treated and placebo groups.

Modulation of motor recovery by drugs

Another exciting development has been the observation that the administration of drugs can modulate functional recovery and neuroimaging measures of task-related activity. Animal studies have consistently shown that amphetamines[101] and NGFs[102] can improve recovery. More recently, neuroimaging studies have shown selective increases of the BOLD signals in motor cortex of stroke patients after administration of single doses of selective serotonin reuptake inhibitors.[103,104] At least in one study, the effect of medication also changed motor behavior. These experiments provide proof in principle that it will be possible to use neuroimaging to monitor the effect of medications on recovery of function.

Modulation of aphasia recovery by rehabilitation

Speech therapy has been the primary tool to aid rehabilitation of language. Many treatment approaches are based on psycholinguistic

theory, with training being aimed at restoring a particular aspect of language impaired in a particular patient. For instance, a patient with impairment in constructing a sentence may be treated with an intervention designed to train production of these linguistic structures.[105] Patients with impairment of semantic knowledge may be trained in making semantic discriminations.[106] Treatments have also been targeted at particular language behaviors (e.g. verbal production) and modified through training by rewarding successive approximations to the behavioral goal – an approach similar to CIT for motor recovery. For instance, constraint-induced aphasia therapy has been shown to increase the amount of verbal output of chronic aphasic patients.[107]

A few studies have attempted to examine how intense practice of the kind administered during CIT modulates activity in regions recruited in functional imaging studies. Musso et al[108] repeatedly measured regional cerebral blood flow (rCBF) in four Wernicke's aphasics. Between scans, they were given brief, intense comprehension training. Changes in blood flow in the right superior temporal gyrus and left precuneus correlated with changes in Token Test performance. Blasi et al[70] examined changes in brain regions during practice with repeated word stem completion. When control subjects were repeatedly exposed to the same set of word stems and were asked to generate a response to each item, vocal reaction times sped up over list repetitions and selection of words become more stereotypical. These behavioral changes were accompanied by functional response decrements in left inferior frontal gyrus and left occipitotemporal cortex. Behaviorally, aphasic patients performed similarly to controls, although with more errors. In patients, the right inferior frontal gyrus and right lingual and fusiform gyri were modulated in a manner analogous to that observed in the left inferior frontal and fusiform gyri of controls, suggesting that practice-related changes were now occurring in the opposite hemisphere than in controls (Figure 8.6). Overall, these results suggest that reorganized activity in the right hemisphere of aphasic individuals is amenable to modification by practice in the laboratory setting – a possible analog of changes induces by speech therapy in the clinical setting. That these changes occur in the right hemisphere suggests that this activity may be compensatory, although there are other non-linguistic factors (attention and sensorimotor associations) that could be modified by practice.

A number of studies have tested more directly the effect of speech therapy on brain activations. Belin et al[69] studied the effect of melodic intonation therapy (a well-established technique for the rehabilitation of productive deficits), and found a relative shift of activity from right hemisphere before training, to left hemisphere post-training. Peck et al[109] examined BOLD signal in three patients during a word generation task over an 8-week treatment interval. They found that the difference in latency of the BOLD signal between auditory and motor areas decreased in the right hemisphere of two patients who underwent treatment. No change was measured in the left hemisphere. Another treatment study[110] used a variant of magnetoencephalography (MEG) called abnormal slow-wave mapping (ASWAM), to map regions of cortex surrounding a cerebral infarct that may be active but unable to support language function. The goal was to determine if intensive language training could cause changes in the intensity or distribution of abnormal slow waves. The study examined 28 chronic patients before and after one of two intense, brief, language treatments. In 26 of these patients, significant delta-wave activity was found in the left hemisphere near the patients' lesion. After training, 16 patients showed a decrease in left-hemisphere delta activity, and a parallel behavioral improvement; conversely, 12 patients who did not show decreases in delta also did not show a significant behavioral change. The magnitude of behavioral language change was correlated with change in left-, but not right-hemisphere, delta activity. The authors interpret their

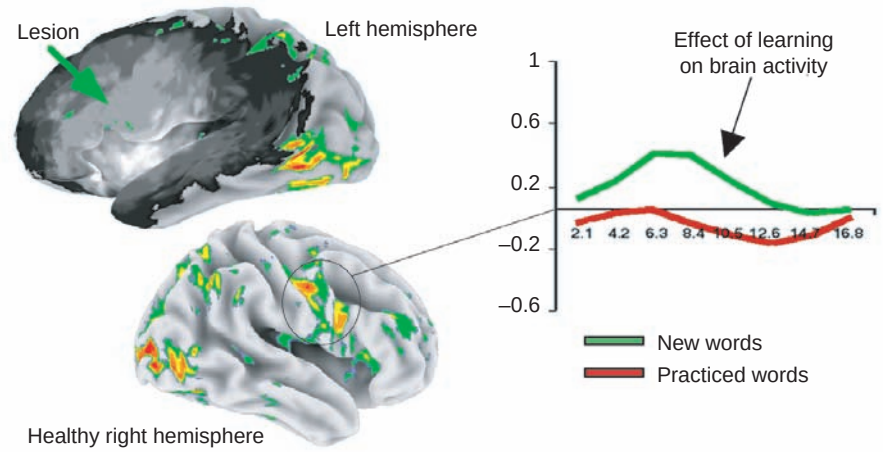

Figure 8.6 Effects of verbal practice on brain activity. Group-averaged anatomical and functional images during word generation in a group of chronic aphasics with left inferior frontal gyrus (IFG)/insula damage (top left; white indicates the center of mass of the averaged lesion). Note the activation in homologous areas in the right inferior frontal gyrus (left bottom). The level of activation in right IFG is modulated by practice, i.e. repetition of the word generation task on the same list of words four times.

findings as support for a left-hemisphere reorganization of language abilities with training. Clearly, more studies of aphasia recovery with multiple imaging techniques need to be conducted to shed light on the nature of recovery due to treatment.

Finally, imaging has begun to be used as a tool to examine both the need for intervention and the basis of intervention. Hillis and colleagues have been at the forefront of using neuropsychological performance on language tests coupled with perfusion-weighted imaging (time-to-peak (TTP) maps) to make decisions regarding acute stroke intervention – see e.g. Hillis et al.[111] Hillis has focused on individuals with behaviorally evident language impairments who have ischemic lesions with a lesion penumbra encroaching on classic language cortex. She has shown that increasing perfusion through drug or intravenous fluid administration improves language performance in these patients. She advocates the use of perfusion-weighted imaging to determine if elevating blood pressure can salvage ischemic, but not yet infarcted, tissue.

In summary, the application of neuroimaging to investigations of aphasia and its treatment has made significant progress, but is still in its infancy. Moreover, we know little about the recovery of other cognitive abilities such as visuospatial, memory, and executive functions. In the field of aphasia, from the viewpoint of prognosis, there is no clear association to date between measures of functional outcome or recovery and a specific neural correlate of compensation or reorganization in the brain. We need more longitudinal studies in which precise, and functionally significant, behavioral measures are compared longitudinally with measures of neural activity. Likewise, treatment studies, although they have provided some information about the relative contribution of left- versus right-hemisphere mechanisms, have been complicated by a lack of a clear-cut mechanistic hypothesis about the underlying neural mechanism. An exception in this regard is the work of Naeser et al,[112] who have begun to use TMS based on the theoretical notion that individuals with poor outcome have hyperactivity in the right frontal areas. They have had early success in dampening this abnormally high activity to improve picture naming.

CONCLUSIONS

Significant advances have been made in understanding the mechanisms of recovery of function by using neuroimaging methods. However, a major goal for future research will be linking these observations at the level of brain networks and areas, with information at the neuronal, connectional, and molecular level of analysis. In no small part, difficulties in advancing this field have been related to the lack of animal models of human cognitive functions, as well as major differences in the spatiotemporal scale used to study these mechanisms across levels, i.e. neuroimaging to investigate brain networks and areas in humans versus electrophysiology and anatomical methods to study cellular and molecular mechanisms in experimental animals.

A potential breakthrough is offered by novel combined behavioral and fMRI studies of recovery of function in rats with poststroke injuries.[85,86] Surprisingly, the phenomenology of fMRI patterns in these studies is very similar to that observed in patients with either motor or language deficits. Early after damage, task-evoked activity is present predominantly in the opposite normal hemisphere, whereas task-evoked activity reappears at the chronic stage in the damaged hemisphere. This is very significant, since, independently of function (sensorimotor versus language) or species (rat versus humans), similar patterns of activity are observed. Necessarily, then, patterns of neural activations must be limited by connectivity constraints that may be similar across species. If that is true, then it will be possible to use animal models to generate predictions about human data, and vice versa, in terms of both mechanisms and interventions. Linking information across levels is critical to generate a brain theory of recovery of function that hopefully will be helpful for improving human health.

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Pain

9

Martin Ingvar

INTRODUCTION

Moving from tools for scientific exploration into clinical practice necessitates adjustments. The clinical perspective is the wellbeing of the individual patient. The scientific perspective is that of extraction of knowledge on the group level for subsequent application in clinical practice. This is not a trivial difference, as the statistical basis for interpretation of results from any intervention is far more disadvantageous when based on individual measurements as opposed to group level studies.

Pain is a clinical entity but also an everyday experience, where it represents a major protective system to teach us to avoid harmful exposure in the external world. Translational research involves the application of previously exploratory methods from research in clinical practice. In this transition, the perspective is often moved from strict statistically based determinations to multidimensional subjective determinations of normality versus pathology. Hence, the leap is often much larger than realized. In pain, the leap is even greater, given that pain is a subjective entity, based on an often ill-determined stream of nociceptive input. It is therefore a formidable task to write a text on clinical functional magnetic resonance imaging (fMRI) of pain. This task becomes even more daunting considering that clinical pain syndromes represent something very different from pain evoked in an experimental situation. The vast majority of studies in functional imaging and pain have been made in experimental manipulations of pain in otherwise-healthy volunteers. The wide definition of pain recognizes that the experience of pain is modulated by a complex set of emotional, environmental, and psychophysiological variables.[1,2] Pain can therefore be expected to influence brain processing on many levels. This influence is expressed not only in terms of pain processing proper but also by competition for central mechanisms of consciousness such as attention, information selection, learning, avoidance, and anticipation. This complexity represents a challenge in that most neuroimaging has a modular approach where isolation of singular cognitive components is sought.

The definition of pain is given by the International Association for the Study of Pain (IASP). Pain is an unpleasant sensory and emotional experience associated with actual or potential tissue damage, or described in terms of such damage. Pain is always subjective. It is individual not only in terms of experience but also in the way it is described to others. Each individual learns the application of the word through experiences. There is unquestionably a sensory component as part of most pain experiences, but it is also always unpleasant and therefore also an emotional experience. Experiences that resemble pain but are not unpleasant (e.g. pricking), should not be called pain. Unpleasant abnormal experiences (dysesthesias) may also be pain – but are not necessarily so, because, subjectively, they may not have the usual sensory qualities of pain. Many people report pain in the absence of tissue damage or any likely pathophysiological cause; usually, this happens for psychological

reasons. There is usually no way to distinguish their experience from that due to tissue damage if we take the subjective report. If they regard their experience as pain and if they report it in the same ways as pain caused by tissue damage, then it should be accepted as pain. This definition avoids tying pain to the stimulus. Activity induced in the nociceptor and nociceptive pathways by a noxious stimulus is not pain, which is always a psychological state, even though we may well appreciate that pain most often has a proximate physical cause.

The intensity and unpleasantness of a painful experience is often conceptualized to correlate with the degree of noxious stimulation. However, the perception of pain is not a linear phenomenon, reflecting the signal from the peripheral neuron. Rather, the noxious input may be modulated at every level of the neural axis. One of the most potent sources of modulation is the brain. Supraspinal modulatory influences involve both lower-order automatic processes and higher-order cognitive mechanisms. It may be suggested that this organizational pattern has developed as an evolutionarily driven adaptation, in which both fast hardwired responses and slower dynamic responses increased the chance for survival. As in all other neuronal processing, time is of essence and effective throughput of information is vital. While pain experience is a higher-order central nervous system phenomenon, pain modulation starts peripherally and occurs throughout the entire neural axis. The first station is supraspinal, and this initial processing includes instigation of autonomic responses, defense reactions, and analgesia by descending mechanisms.[2] The gate theory of Wall and Melzack that suggested lower-order mechanisms on the spinal level has been supplemented with an abundance of data showing multilevel modification of the pain experience. In fact, the perception of pain is now considered to be composed of sensory–discriminative, affective–motivational and cognitive–evaluative dimensions with a multilevel regulatory mechanism[3] (Figure 9.1).

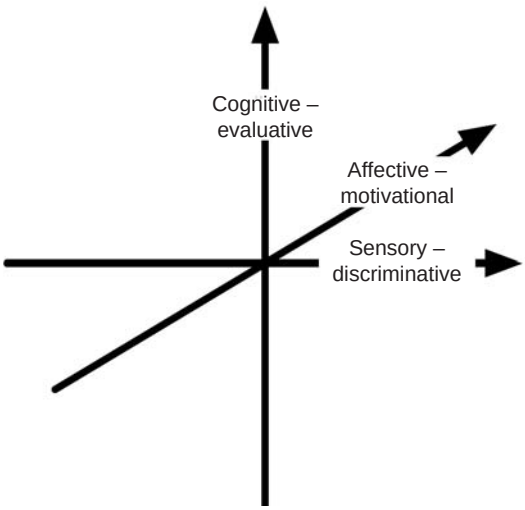

Figure 9.1 The major dimensions of pain according to the IASP classification.

Recently, higher-order regulatory mechanisms have come into focus. Also, placebo manipulations of the pain experience have been informative.[4]

METHODOLOGICAL CONSIDERATIONS

Pain estimates

The time domain is of essence. In functional imaging, the sensitivity varies depending on the dynamics of the studied event. Whereas events on a timescale of seconds to minutes are easily imaged, sensitivity decreases rapidly when trying to reflect changes with faster or slower time properties. Experimental pain paradigms usually assess rapid-onset, repeatable, and transient events, whereas chronic pain is represented in slow events with minor fluctuations. A major advantage of functional magnetic resonance imaging (fMRI) is its ability to follow transitions between states, and it is therefore well suited for the study of experimental pain. The sensitivity of fMRI is low for interindividual comparisons other than interaction-type analyses and factorial analyses (intermittent pain stimulus by

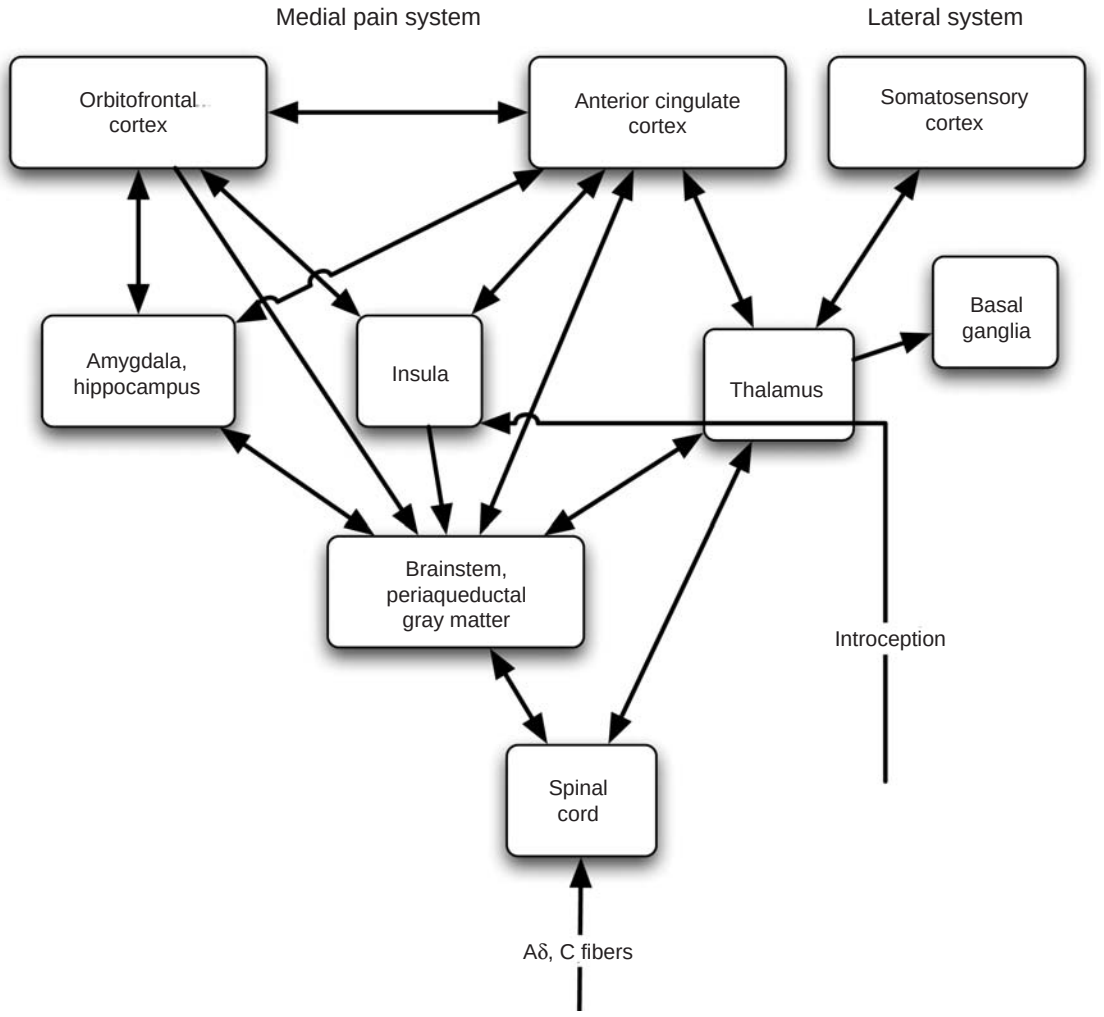

Figure 9.2 Schematic showing the functional anatomical substrate for pain processing of ascending stimuli.

group). Static differences in pain are very difficult to assess with fMRI.

As pain syndromes must be characterized in many dimensions, many methods for pain assessment have been developed. The pain experience is subjective in nature, and therefore the gold standard for pain intensity determination in experimental subjects and in patients is the visual analog scale (VAS). With easy applicability and reasonable intra-individual reproducibility, its poor inter-individual stability is less of a problem. It should be noted that *immediate* reports are necessary, as retrospective accuracy is very low.[5] Other forms of descriptional notation of pain have not been proven to carry any advantage. In functional imaging, the intensity of the experience translates directly into activity changes in some regions, but not in others (see below).

Pain multidimensionality

The multidimensionality of pain is poorly reflected by simple VAS estimates. Different extensions with other verbal descriptions have

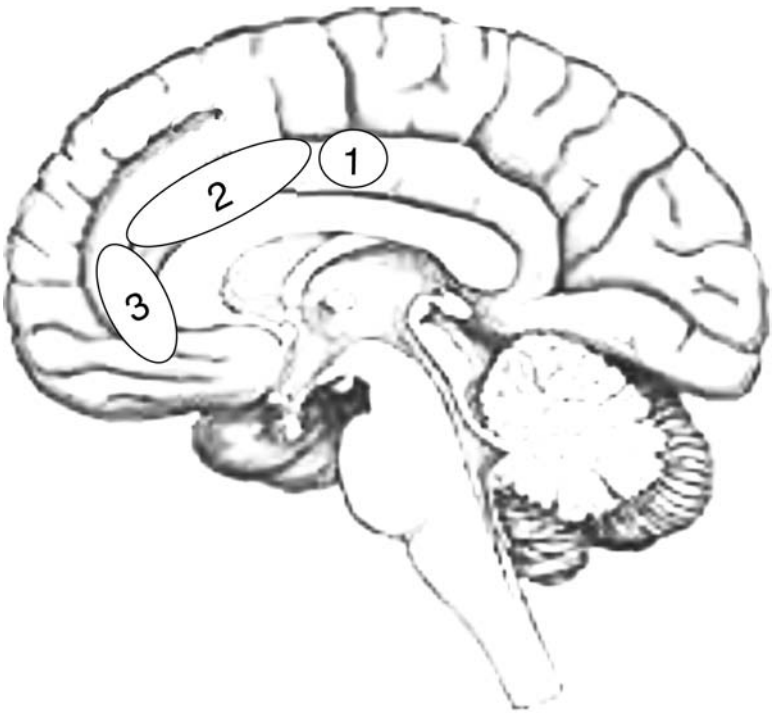

Figure 9.3 The anterior cingulate cortex has subsections[38] and is involved in several aspects of pain processing. The posterior dorsal region (1) is associated with coding of the aversive experience of pain, the midsection (2) is associated with cognitive/attention/experience coding, and the rostral component (3) participates in pain affect/regulatory processing.[7]

been used, but the stability of such instruments has been shown to be limited. fMRI, and previously positron emission tomography (PET), have been used successfully in the characterization of different dimensions of the pain experience. Early on, the sensory discriminative components were accessed together with affective motivational parts.[6] Over the last few years, the cognitive and regulatory systems have been successfully investigated. Only through successful developments in paradigm design has this become possible.[7]

The multidimensionality of pain is also reflected in functional anatomy (Figure 9.2). The lateral system appears to be more closely involved in the sensory discriminative dimension, whereas the medial system is related more to the affective motivational dimension. Several clinical pain entities have exhibited an association between activity in this region and symptom severity.[8–10] Neuroimaging studies have demonstrated activations in the anterior cingulate cortex (ACC) related to the affective component of pain, but less to stimulus intensity (Figure 9.3). Buechel et al[11] investigated the central pain response in the dimensions of stimulus intensity and stimulus awareness (i.e. pain-unrelated) responses within the ACC in volunteers. Pain-related regions in the ventral posterior ACC showed stimulus intensity-related response. Regions in the dorsal anterior ACC along the cingulate sulcus that differentiated between not-perceived and perceived stimulations exhibited no additional signal increase with increased intensity; these regions were associated with stimulus awareness and probably with cognitive processing. Most importantly, Buechel et al[11] confirmed the existence of a region in the dorsal posterior ACC showing a response that discriminated for pain but without intensity coding. Stimulus-related activations were all located adjacent to the cingulate motor area, highlighting the strategic link between stimulus processing and response generation in the posterior ACC.

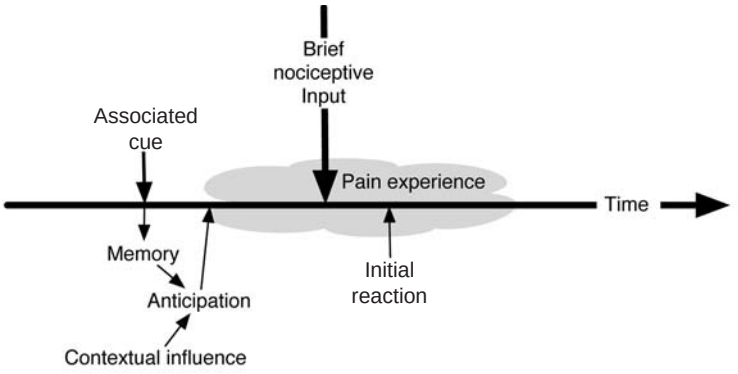

Figure 9.4 Anticipation of a painful event regulates both the acute experience and coping strategy.

DYNAMIC NATURE OF THE PAIN EXPERIENCE

There is much more to a pain experience than the painful event. Both the cognitive–evaluative and affective–motivational domains have prominent dynamic characteristics (Figure 9.4). The initial response to pain is influenced by a number of mechanisms, such as the element of surprise, the subjective sense of security, controllability, etc. In experimental studies of pain, the components of threat, insecurity, expectation, fear, etc. have all been demonstrated to influence the pain experience. Simple contextual manipulations can influence the way in which we handle the upcoming pain.

The establishment of an association between a non-aversive cue and a painful or aversive stimulus can be established very quickly. We have shown that a neutral visual cue can be rapidly associated with an aversive sensory stimulus. Following an initial period of establishment of the association, a previously non-aversive visual cue can lead to changes in activity in the primary and secondary cortices, even in absence of somatosensory input.[12] In more general terms, such associative learning can be seen as part of a necessary adaptive processing that we possess.

Contextual information is part of our pain processing. All clinicians are aware that small changes in the ambient surroundings can influence the results of a clinical intervention. Context is directly related to a patient's expectations regarding an upcoming painful event. The involvement of the antinociceptive descending systems can be influenced by a simple manipulation. The amygdala has been implicated in fundamental functions related to survival of the organism, such as fear and pain. In accord with this, several studies have shown increased amygdala activity during fear conditioning and the processing of fear-relevant material in human subjects. In contrast, functional neuroimaging studies of pain have shown decreased amygdala activity.[13,14] It has been proposed that the observed deactivation of the amygdala in these studies indicates a cognitive strategy to adapt to a distressful but (in the experimental setting) unavoidable painful event. In one study,[15] simple contextual manipulation, immediately preceding a painful stimulation, that increased the anticipated duration of the painful event led to a decrease in amygdala activity and modulated the autonomic response during the noxious stimulation. The subjects in this study were informed that the upcoming pain stimulus would last either 1 or 2 minutes. The imaging was performed only during the first minute of pain. In the 2-minute context, there was suppression of activity in the amygdala (Figure 9.5). On a behavioral level, 7 of the 10 subjects reported that they used coping strategies more intensely in this context. The altered activity

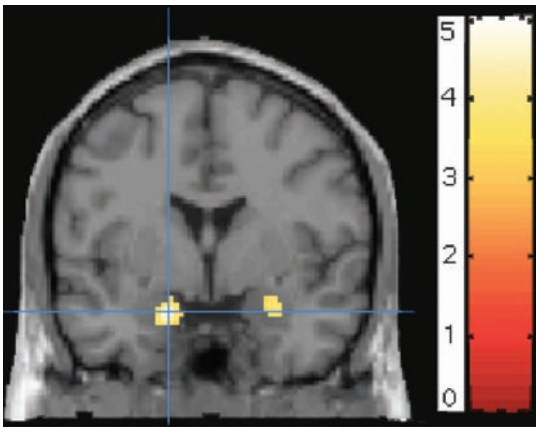

Figure 9.5 Decreased activity in the amygdala during the first minute (in a 2-minute context) of pain stimulation as a result of a contextual manipulation. Data from Petrovic et al.[15]

in the amygdala may be part of a mechanism to attenuate pain-related stress responses in a context that is perceived as being more aversive. The study also showed increased activity in the rostral part of the ACC in the same context in which the amygdala activity decreased, further supporting the idea that this part of the cingulate cortex is involved in the modulation of emotional and pain networks.

There are many factors that influence the experience of pain, each with its own time frame (Figure 9.6). Genetic differences between individuals probably play an important role – albeit one that has not yet been investigated in detail. Other measurable traits in personality and attitude seem to be of importance in the prediction of long-term outcome in pain syndromes.[16] fMRI still has some way to go before its usefulness in the prediction of outcome can be established. There are several studies under way where genetic traits are being studied in relation to pain sensitivity. While still in their infancy, receptor studies may provide key insights into what determines pain sensitivity.[17,18] The combination of behavioral studies in genetically characterized subjects with advanced fMRI and PET methods has a lot of promise for the future.

THE DIFFERENCE BETWEEN CLINICAL PAIN AND THE EXPERIMENTAL SITUATION

There are a number of differences between the experimental situation and clinical pain (Table 9.1). The major complaint from patients with chronic pain pertains not only to the experience of pain itself but also to issues of controllability, and to side-effects on cognition, attention, and mood. In the experimental situation, these are factors outside the scope of the studies (mainly due to ethical considerations). For good reasons, and according to statutory regulations, the subject is always left in control of the situation and can discontinue participation at any time. The intensity of pain must be controlled, and must be guaranteed never to surpass an intensity that is unbearable or that can cause tissue

Table 9.1 Differences between experimental studies in healthy subjects and clinical pain.

Factor	*Experimental situation*	*Clinical situation*
Duration	Short, phasic, or tonic	Often chronic
Intensity	Within subject manipulability	Difficult to manipulate
Nociceptive input	Known fiber types	All fiber types
Central pain	No good models	Varying basis for symptoms
Controllability	Yes	No
Anticipation	Well-instructed subject in control	Out of control
Comorbidity	Subjects with comorbidity deselected for participation	Psychological/psychiatric comorbidity common
Data loss	Preselected cases that accept fMRI procedure	More common with unwillingness to participate
Medication	Rarely a problem	Major problem

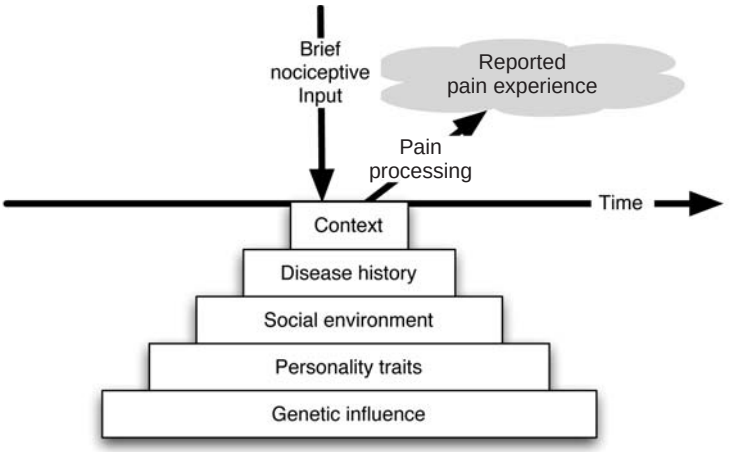

Figure 9.6 Factors with different time bases influencing individual pain experience. All of these factors will influence the results of fMRI studies unless taken into account.

damage. The subject must remain still for the fMRI session and not use common everyday strategies such as moving a limb to alleviate pain.

The emotional context in clinical pain is that of tissue destruction and uncontrollability whereas issues of location and precise timing are of less importance. This makes the clinical situation radically different from the experimental situation. Experimental studies in chronic pain have, in spite of their differences, shown important similarities. As predicted, the lateral pain system, including S1 and S2, is less involved. Chronic nociceptive input leads to changes in activity in the thalamus[10] and posterior ACC,[8–10] as well as other parts of the medial system. With regard to pain sensitivity, on provocation in patients with increased sensitivity, there is a pathologically increased response in the pain system in those regions that are expected to be involved.[14,19]

NOCICEPTION VERSUS PAIN EXPERIENCE

The idea of competition and local regulation of nociception that was advanced in the mid-1960s by Melzack and Wall[20] was a great step forward in the understanding of nociceptive mechanisms. The extension of the gate theory is obvious in that every step along the neuroaxis has regulatory power. Also, consideration of the role of descending analgesic mechanisms has shown that nociceptive input is always accompanied by descending analgesic outflow.[21] It is now known that descending modulation of spinal nociceptive processing can be either inhibitory or facilitatory. Accumulating evidence suggests that descending facilitatory influences may contribute to the development and maintenance of hyperalgesia and thus contribute to chronic pain states.[22]

PAIN AND PAIN-EVOKED ANALGESIA – CONTROLLING PAIN

In the majority of cases, clinical pain syndromes are not so much a problem of nociceptive input, but rather seem to be dependent on failure of pain control mechanisms. Behavioral treatment in chronic pain has moved towards affective/mood therapy and cognitive–behavioral therapy.

LOWER-ORDER CONTROL MECHANISMS

As already mentioned, there are many mechanisms on the spinal cord level that are suited to the control of nociception. The gate control hypothesis served to integrate the body of literature suggesting that processing of nociceptive information is subject to

dynamic regulation. This provided a theoretical framework for processes leading to hyper- as well as hypo-algesia. The localization of the suggested gating mechanism was in the spinal dorsal horn. Subsequent work on the pharmacology of spinal systems has served to emphasize the importance of this spinal regulatory process. The complexity of these spinal systems has led to significant advances in our understanding of the transmission systems by which these gating systems function. This has had the practical consequence of providing important therapeutic modalities serving to control pain processing originating from both tissue and nerve injury by drugs that are limited in their distribution to the spinal cord.[23] The brainstem region stands out as an important origin of descending paths.[24] The initial demonstration of analgesia has been complemented by knowledge that descending pathways may also facilitate nociceptive input and hence may be part of what can develop into a clinical pain syndrome.[22] The brainstem has in numerous studies proven to be activated as a result of experimental pain.

The periaqueductal gray matter (PAG) and the nucleus raphe magnus and adjacent structures of the rostral ventromedial medulla (RVM), with their projections to the spinal dorsal horn, constitute the 'efferent channel' of a pain control system that descends from the brain into the spinal cord. Considerable evidence has recently emerged regarding the participation of this system in persistent pain conditions such as inflammation and neuropathy.[25] Possibly, this inhibition is different for different components of pain. In models of inflammation, descending inhibition predominates over facilitation in pain circuits with input from the inflamed tissue, and thus attenuates primary hyperalgesia, while descending facilitation predominates over inhibition in pain circuits with input from neighboring tissues, and thus facilitates secondary hyperalgesia. Both descending facilitation and inhibition mainly stem from the RVM. The (primary) hyperalgesia and allodynia of the neuropathic syndrome are facilitated from the RVM. Simultaneously, there is an inhibition of secondary neuronal pools that is partly supported from the PAG. Because in all of these models of peripheral damage, descending facilitation and inhibition are triggered simultaneously, it is important to elucidate why inhibition predominates in some neuronal pools and facilitation in others. fMRI, with the use of parallel imaging whereby an increased spatio-anatomical resolution of the functional signal may be achieved, will prove to be of importance for this.

HIGHER-ORDER CONTROL MECHANISMS

Cognitively based control mechanisms are less well characterized. In spite of this, there seems to be ample evidence that the orbitofrontal cortex, the rostral ACC, and the anterior insulae are of importance for such descending mechanisms.[7] In different models of pain control, invoked by cognitive mechanisms, by distraction, or by hypnosis, increases in activity have been noted in these regions.[7,26,27] Descending fibers project to the above-mentioned brainstem areas, and different forms of correlation analysis have indicated that the causality that has been shown in animal studies regarding coupling between the forebrain and the brainstem may also hold in humans. A future important area of study is to further develop methodology in order to use fMRI in a manner whereby the differences in network properties of pain protecting systems can be revealed in patient populations.

THE LATERAL ORBITOFRONTAL CORTEX

The lateral orbitofrontal cortex (OFC) has shown relatively increased activity in several studies involving modulation of pain. There are several lines of evidence that implicate the lateral OFC in modulating distant neural activity in emotional contexts. The OFC is involved in response suppression when a value-based stimulus–response association has to be suppressed.[28] This mechanism may be depen-

dent on a representation of the magnitude of punishment in the lateral OFC.[29] The region is also involved in depression. Although both the amygdala and the lateral OFC show increased activity during major depression, only the activity of the amygdala correlates with the severity of the disease.[30] In contrast, the activity of the lateral OFC is inversely related to several indices of depression. Drevets and colleagues have therefore suggested that the lateral OFC is involved in suppressing a network (possibly including the amygdala) that has a pathologically increased activity. Thus, the lateral OFC is probably involved in modulating value-based processes in emotional networks or response systems. The lateral OFC may represent a source of cognitive modulation of emotional components that are produced by or interact with pain processing.

THE LIMBIC SYSTEM

As noted above, the posterior part of the anterior cingulate seems to encode pain affect.[9,31] Also, the rostral ACC, with its close relation to the limbic system, is strongly associated with pain regulation. The role of the limbic system as a conveyor of emotional information from external and internal sources is well established. In most experimental pain studies, the decrease of activity in the limbic system can be viewed as a down-regulation enabling the subject to succumb to the experimental situation. As mentioned above, we have demonstrated how a manipulation of information can lead to a change of activity in the amygdala as a sign of top-down control. Although different interpretations may be applied to these results, they corroborate previous results indicating that a well-controlled experimental situation of no-escape is associated with down regulation of activity in the limbic system. These findings, together with the known projections of the amygdala to other regions important in regulation of pain (e.g. the brainstem and hypothalamus), suggest that an intense study of these mechanisms may provide insights into chronic pain.

CENTRALIZED PAIN

A rather dramatic change of concept has emerged from the work of Craig[32] in his shift of focus from pain as a perception towards the view of pain as an emotion. While most people have understood pain as a system that provides input to motivational mechanisms, the inclusion of pain in the set of basic emotions that we possess provides a better understanding of the commonalities between pain and other emotions. Also, the systematic understanding of internal monitoring of homeostatic mechanisms provide a basis for explaining the experience of pain in the absence of sensory input. As pointed out by Craig, homeostatic emotions drive behavior. The affect (i.e. pleasantness or unpleasantness) that we feel with an innocuous thermal cutaneous stimulus is the perceptual correlate of thermoregulatory motivation. Pain normally originates from a physiological condition in the body that automatic (subconscious) homeostatic systems alone cannot rectify, and it comprises a sensation and a behavioral drive with reflexive autonomic adjustments. It is an important observation that pain evokes a motivational state that drives the individual into adjustments. The clarification of the importance of the primary interoceptive pathways has been useful in the understanding of the anatomical and thereby the functional mechanisms of pain syndromes from sources other than the somatosensory system. Understanding the mechanisms underlying the augmentation of activity in the polymodal nociceptive channel could be particularly fruitful for identifying new therapies for chronic pain. Lastly, it remains to be seen how endogenous homeostatic control mechanisms provide integrated modulation of the afferent activity that produces the emotion of pain, and how these might best be engaged by clinical intervention. Not least, the undestanding of interoceptively generated pain has recently reached a higher level through the application of fMRI.[33]

The issue of centralization of pain, i.e. going from dependence on external input to

independence, is not well understood. This may be one of the very few areas where animal fMRI may provide real insight.[34] The ability to perform serial studies over time during the development of central pain is an important challenge. In pathological pain, evidence is accumulating that hyperalgesia is accompanied by an increased response in the known pain matrix.[14,35] However, few studies have provided mechanistic data indicating a change in functional connectivity or similar differences.

PLACEBO AND ANTICIPATORY MECHANISMS OF PAIN

With pain being viewed as an emotion, its dependence on nociceptive input is less evident. Hence, the experience of pain may be evoked simply from anticipatory mechanisms.[13] In behavioral experiments and in imaging findings are parallel, with suggestions of an upcoming lower-intensity stimulation resulting in a lower grading of the event.[36] Just as it is possible to influence emotional affect with suggestions, this can also be done for pain. Importantly, suggestability seems to be highly sensitive to conditioning (learning). A previously tested successful drug treatment seems to predict a better response to a placebo manipulation.[37] These conditioning/learning mechanisms are of interest, as they may provide a clue to the understanding of how pain can become less dependent on external perception. We have tried a placebo manipulation in experimental pain and have demonstrated how the intrinsic mechanisms for pain regulation could be influenced, as discussed above. A strong case has been built suggesting that central opioid pathways are of importance for the placebo effect. Our findings have been confirmed and extended with fMRI, where it has been shown that the placebo mechanisms can actually be demonstrated to precede the painful stimulus.[26] No doubt, fMRI will play an important role in the further elucidation of the mechanisms of behavioral therapy that is successful in pain treatment.

Along the same lines, it is important to note that an fMRI investigation itself can provide a strong manipulation that may, in certain situations, be perceived as a placebo (although, given the size and complexity of MRI scanners, this is hardly a practical proposition for patients suffering everyday chronic pain).

CONCLUSIONS AND FUTURE DIRECTIONS

fMRI holds promise of providing important information on the clinical entity of chronic pain. The concepts and methods need further development. There are a number of important questions awaiting answers. For example, are there genetic traits connected to activity in different receptor systems that predict which patients will develop chronic pain? Can we develop postlesion diagnostic tools that will provide predictive information at an individual level? Are there differences in the functional connectivity during evoked pain in patients with clinical pain as opposed to control subjects? Can we build models of how central pain develops that can inform us how to construct fMRI studies of clinical pain? These questions represent the quantum steps that need to be taken if we are going to move away from what the Nobel Laureate Lord Rutherford characterized as stamp collection in science into clinically useful development of fMRI as a tool for studying pain.

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Presurgical planning of neoplasms and arteriovenous malformations

10

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INTRODUCTION

Non-invasive mapping of 'eloquent' brain regions prior to surgical resection of brain neoplasms, arteriovenous malformations (AVMs), or ictal foci has been strongly advocated for many years. This is particularly relevant if the surgery is elective or the lesions are nonmalignant.

A major reason to perform mapping is to limit the extent of brain resection while maximizing a successful response to treatment. The situations in which this is most applicable has been for delineating the brain regions that subserve motor, as well as language, memory and other cognitive domains in relation to seizure foci being considered for resection, and/or neighboring brain lesions (typically AVMs and brain tumors) that require surgical intervention. Given that a subset of these procedures is elective and another subset is for treatment of benign or likely slowly growing tumors, successful removal of the lesion with minimal resultant postoperative morbidity (and seizure reduction if indicated) is considered of paramount importance. Being able to delineate brain regions that are associated with essential cognitive or motor functions that are neighboring, or even supported/encoded in, the lesion, allows the patient and physician to intelligently determine (a) what likely postoperative impairments may occur if resection of specific brain regions becomes necessary as part of the surgical procedure, (b) what eloquent regions should be avoided in a resection of a lesion or surrounding areas, and (c) where neural localizations of a function may have shifted due to the presence of a lesion, and thus allowing for safer surgical manipulation of a region that typically encodes for the cognitive functions in question. This localization of functions is invaluable for successful surgical planning, and to this point has been unavailable without invasive mapping or at the level of anatomic resolution of magnetic resonance imaging (MRI).

A variety of invasive techniques have been applied during the past quarter-century to address the issues delineated above. These techniques have benefited from being rather specific (direct cortical stimulation) or sensitive (intracarotid amobarbital injection), and the majority of them create temporary lesions to determine if a brain area is necessary for performing that particular cognitive function. However, the invasive nature of these procedures, the risk of morbidity and mortality, and in some cases their lack of reliability render these approaches less than optimal.

The most widespread of these mapping procedures has been the intracarotid amobarbital injection (IAI) for determination of the right- versus left-hemisphere laterality of cognitive operations. These IAI procedures were initially adopted to determine language laterality,[1] as evidence from lesion studies had suggested that language and/or speech processing was predominantly lateralized to one hemisphere in the brain (typically the left). The use of these IAI procedures as a guide has led to relatively successful temporal lobe resections for epileptic foci, without the production of significant aphasia following surgery.[2] However, while there was a lack of profound aphasic syndromes following

surgical resection, there were a significant number of patients with selective naming and new learning deficits, compared with their own preoperative performance, suggesting that the IAI may not be entirely adequate to assess temporal lobe functions. This is not surprising given the vascular anatomy of the branches that arise from the internal carotid artery and their variable supply to the medial temporal lobe structures. Jeffery et al,[3] using single photon emission computed tomography (SPECT) in conjunction with IAI, demonstrated that intracarotid amobarbital injection leads to medial temporal lobe perfusion in only 29% of the injections.[3,4] Thus, nearly two-thirds of the injections may not deliver adequate amobarbital to the medial temporal lobe to deactivate it. While there is the distinct possibility that it is not necessary to perfuse the medial temporal lobe to determine if removal of this structure would lead to a deficit (e.g. the IAI may still isolate or disconnect the region by deactivating the areas surrounding it), the persistent deficits in new learning that occur postoperatively suggest that the IAI technique may not be sensitive enough.

As a result, functional MRI (fMRI) has been considered to play a significant role in the future for more detailed and non-invasive mapping of cognitive functions preoperatively. The work of Binder et al (see Chapter 6) has shown that fMRI is valuable for preoperative planning for surgical resection of epileptic foci.[5–8] These investigators have demonstrated the usefulness of the technique for determining language laterality preoperatively and have validated these findings with standard invasive techniques.[5–8]

The use of fMRI for medial temporal lobe assessment has been limited for several reasons. First, the structures in question are relatively small. In addition, neuropsychological tests that were previously found to effectively interrogate functions of the hippocampal region were not initially found to elicit medial temporal lobe signal changes during fMRI. Potentially, this could be attributed to the hippocampus being one of the most electrically and subsequently neuronally active regions in the brain, and thus incremental changes in regional metabolism with transient activation may be relatively smaller than they are in other parts of the brain. The situation is also complicated to some degree by the proximity of the ventral temporal lobes to structures (sphenoid sinus, greater wing of the sphenoid bone, and petrous ridges) that cause MRI signal-dephasing artifacts in adjacent brain parenchymal structures. Such artifacts can and often do markedly impede the ability to detect the relatively small-amplitude fMRI signal changes induced by memory-related behavioral tasks.

Investigators have recently been able to demonstrate medial temporal lobe activation for tasks of new learning in normal subjects. As opposed to learning simple figures, which had not been found consistently to evoke medial temporal lobe activation, Brewer et al[9] showed that reliable medial temporal lobe activation could be obtained using stimuli consisting of complex, color photographs. For lesions related to epilepsy or tumor, being able to assess the fullest extent of cortical brain regions and cognitive functions provides a flexible investigative tool that can be generally applied to brain mapping for preoperative evaluation. fMRI is thus evolving into such a tool, as there are few brain regions and cognitive functions that cannot be interrogated with the technique. The accuracy of the functional localizations provided by fMRI has been confirmed by comparison of the findings from fMRI with more standard lesion-based but invasive techniques, such as intraoperative or postoperative cortical stimulation (see below). As these lesion-based techniques are invasive and have not been used extensively at multiple centers (but see Ojemann,[10] Morris et al,[11] and Lesser et al[12]), a non-invasive, readily available investigative brain mapping tool such as fMRI can have widespread utility. Below, we review some of the studies using fMRI in preoperative evaluations of brain AVMs and neoplasms to delineate regions of critical cognitive functions neighboring areas where surgical resections are planned to occur.

PRESURGICAL EVALUATION OF AVMS

There were an estimated 35 000–53 000 individuals with AVMs in the USA in 2000.[13] Early reports of the use of functional imaging to map a lesion and related cortex engaged in a neurologic function involved the use of two oxygen-15 (^{15}O) positron emission tomography (PET) scans to (1) localize an AVM to the precentral gyrus and (2) map associated somatosensory cortices.[14] These findings were later verified by intraoperative cortical mapping. While these studies demonstrated the usefulness of the techniques, the use of radiation with PET, the limited availability of the technique at that time, and the need for invasive procedures for validation studies to be performed in multiple patients all limited the more extensive development of the technique as an investigative clinical tool. Baumann et al[15] used three modalities of functional imaging (fMRI, PET, and magnetoencephalography (MEG)) to identify sensory and motor cortices in a single subject, demonstrating that fMRI and PET converged in terms of localization of eloquent cortices, which was confirmed on postoperative evaluations. These sort of findings supported the notion that fMRI could be as accurate as PET in terms of localization, with the added value that exposure to ionizing radiation is not a factor in fMRI.

Maldjian et al[16] used fMRI in a group study of six patients with AVMs to localize cortical function. Twenty-three studies were performed on these six patients to assess discrepancies between fMRI data in the same patient with a vascular lesion. Considering that the signal changes in fMRI that are the basis for localization of cognitive measures reflect changes in blood flow associated with task performance, patients with AVMs could present the most daunting technical challenges due to the nature of these vascular lesions: (1) abnormal vascular architecture, (2) siphoning of cerebral blood flow by some AVMs, and thus (3) the possible invalidation of some of the general assumptions underlying fMRI statistical analyses (levels of significant differences, 'rest' state blood flow assessment, relative equivalence across all voxels, etc.). This study demonstrated that 21 of the 23 scans were without motion artifacts and could be analyzed, with all of the 21 showing activity as would be expected for the paradigms. Additional regions were detected that appeared to represent regions likely associated with relocated functions, perhaps due to the brain's plasticity in the face of AVMs that had presumably been present since early life, when the brain appears to have the greatest capacity for reorganization. The study not only showed the feasibility of using fMRI for presurgical mapping in AVM patients, but also the reproducibility of the results over multiple sessions in these patients.

The issue of brain plasticity and lesions provoking transfer of cognitive functions to brain regions not typically associated with those functions has been further addressed with fMRI in patients with AVMs.[17] The investigations were performed to assess whether occlusion of AVM branches would result in cognitive deficits. Using language function tasks, selective amobarbital injections into branches of the left middle cerebral artery feeding the left frontal brain regions demonstrated no language deficits, suggesting that the typical frontal regions associated with language (e.g. Broca's area) no longer supported these functions. fMRI of related language functions (specifically verbal fluency associated with the left frontal lobe) showed that analogous regions in the right frontal lobe were now associated with this function. This supports the notion of interhemispheric transfer of language functions and neural reorganization in the face of a chronic lesion. This finding was supported by a similar study in five more patients with AVMs in the perisylvian area; [18,19] but see Seghier et al[20] to observe that right-hemisphere dominance overall does not seem to shift with an AVM to the left hemisphere.

A region that is often in question with regard to AVM resections is the motor cortex,

with the possibility of a hemiparetic deficit if essential cortex is resected. Neural plasticity plays a major role in determining the degree to which the surgeon can resect AVMs in this area, and there are often shifts in the localization of motor function that will allow for lower-risk resection of tissue that had previously subserved the function in question. Alkadhi et al[21] evaluated nine patients with AVMs using fMRI to localize the hand and foot primary motor areas bilaterally to see if there was a difference in location of primary motor area on the lesion side versus the unaffected side. The AVMs were located primarily in the rolandic area, with six near the hand region and three near the foot. Of the six patients with AVMs in the hand area, four showed functional displacement of the motor area on the affected side compared with the unaffected side in the same individual (Figure 10.1). The relocated function appeared to remain in the same hemisphere as the typical, expected localization, usually within another region of the motor cortex. In one of the other two patients, there was no contralateral signal change in the expected hand motor area where the lesion was located, but there was ipsilateral (to the moving hand) signal change related to hand movement. Of the three patients with foot area AVMs, two showed no contralateral activation in the motor area, but activation in the ipsilateral area. These findings showed the value of the technique to detect shifting localizations, but has also shed light on the issues of plasticity and shifting localization of functions. It would appear from this limited study that motor cortices supporting hand function are more likely to shift within the same hemisphere, while those of foot function are more likely to shift to the other hemisphere. This shift of foot function to the opposite hemisphere could be attributable to the proximity of the foot area in the superior frontal lobe to the area supporting foot motor function of the opposite hemisphere, while the hand motor area in one hemisphere is a considerable distance from the homologous region in the opposite hemisphere. Further studies of the patterns of displacement and the 'distance' hypothesis proposed are indicated to verify if these two claims are valid.

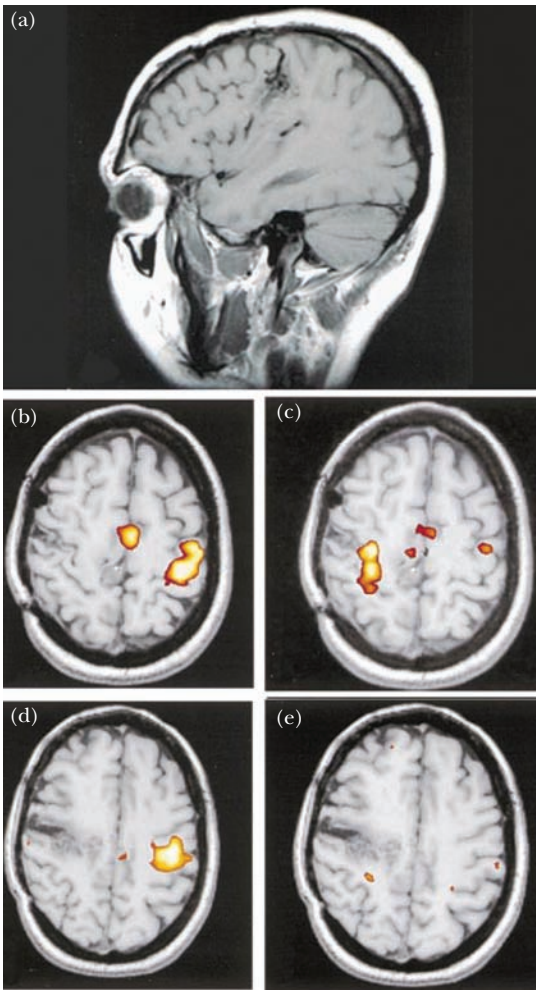

Figure 10.1 (a) Sagittal T1-weighted image of a patient with an AVM in the right precentral gyrus, in the general region where the hand region is typically represented. (b–e) fMRI of a hand motor task in the unaffected left hemisphere (b, d) and the affected right hemisphere (c, e) (radiological convention). The hand representation in the right hemisphere is displaced medially in the precentral gyrus (best seen in image (c), with little activation at the level of (e)). Adapted from Alkadhi et al.[21]

fMRI has been applied to cortical mapping in pediatric cases with lesions in regions near eloquent cortex, including those with AVMs.[22]

Localization of function using fMRI was correlated in cases with cortical stimulation and somatosensory evoked potentials/electrocorticography (SSEP/ECoG) in these pediatric cases and found to be concordant. Long-term follow-up in these patients with seizures, including venous malformations and tumors, showed that 13 of 14 were improved at 12 months after surgery, further supporting the indication for fMRI in the pediatric population.

Ozdoba et al[23] performed multiple fMRI studies in patients with AVMs in different parts of their motor systems (cortical, basal ganglia, and cerebellum), who were undergoing endovascular treatments for their lesions. Their findings not only indicate that spatial shifts in function can occur in motor-related structures other than primary motor cortex, but also demonstrated how fMRI can be utilized in concert with other investigative techniques. In this study, the authors combined fMRI and selective amobarbital injections, and interventional endovascular procedures to perform the safest treatments possible at the time. As endovascular interventions become more prevalent and sophisticated,[24] there is an increasing need for more detailed and less invasive functional mapping. Neural reorganization to support cognitive operations in the presence of a lesion is a reason to advocate the implementation of individual mapping. It is also the main reason that mapping must be precise to be useful in integrated investigations of AVMs for treatment decisions. With the accuracy of MRI localization of lesions, non-invasive fMRI that can be co-localized with these lesions is a valuable adjunct, particularly considering that in the case of AVMs, it can be an asset to surgical resection, endovascular treatments, and radiation therapy. In addition, even with validation of fMRI findings with techniques such as amobarbital injections and cortical interference, there is a continued role for combining an activation technique such as fMRI with these lesion/subtractive techniques to determine if a region is safe to be resected without major concern for postresection deficits.

PRESURGICAL EVALUATION OF BRAIN NEOPLASMS

The most extensive use of fMRI for clinical evaluations, in terms of both the number of patients studied and validation of the technique, is in preoperative evaluations to identify cortical regions mediating motor, language, or cognitive operations in patients with brain tumors. In a study of 41 neurosurgical patients with intracranial tumors but no neurological deficits, preoperative fMRIs were performed on a 1.5 T magnet using finger-tapping tasks to identify motor cortex and a semantic test for correlation between word pairs to assess speech/language-related areas.[25] Thirty-eight of the patients had increased signal in the cortical region for finger movement contralateral to the moved extremity. These images thus allow the surgeon to perform preoperative assessment of the distances between the tumor and activated regions associated with motor function. In this same fashion, similar measurements were conducted between the tumors and regions associated with language-related activation, producing preoperative maps of tumor location and language cortices. Of the five patients who underwent both Wada testing and fMRI, there was agreement between language laterality as determined by Wada and the dominant laterality of the frontal activation on the fMRI language task. In the one patient also undergoing intraoperative cortical stimulation, there was similar localization between fMRI and cortical interference in a speech region adjacent to the tumor. Overall, the high spatial resolution of the anatomical regions of interest and extent of the tumor, coupled with the ability to superimpose the patterns of task-related signal change, is one of the fundamental values that fMRI provides to surgical planning. This is particularly relevant given the non-invasive nature of the technique, and its potential repeatability, if necessary.

Lee et al[26] addressed the use of the technique to assess the risk and feasibility of surgery, in planning the procedure to be

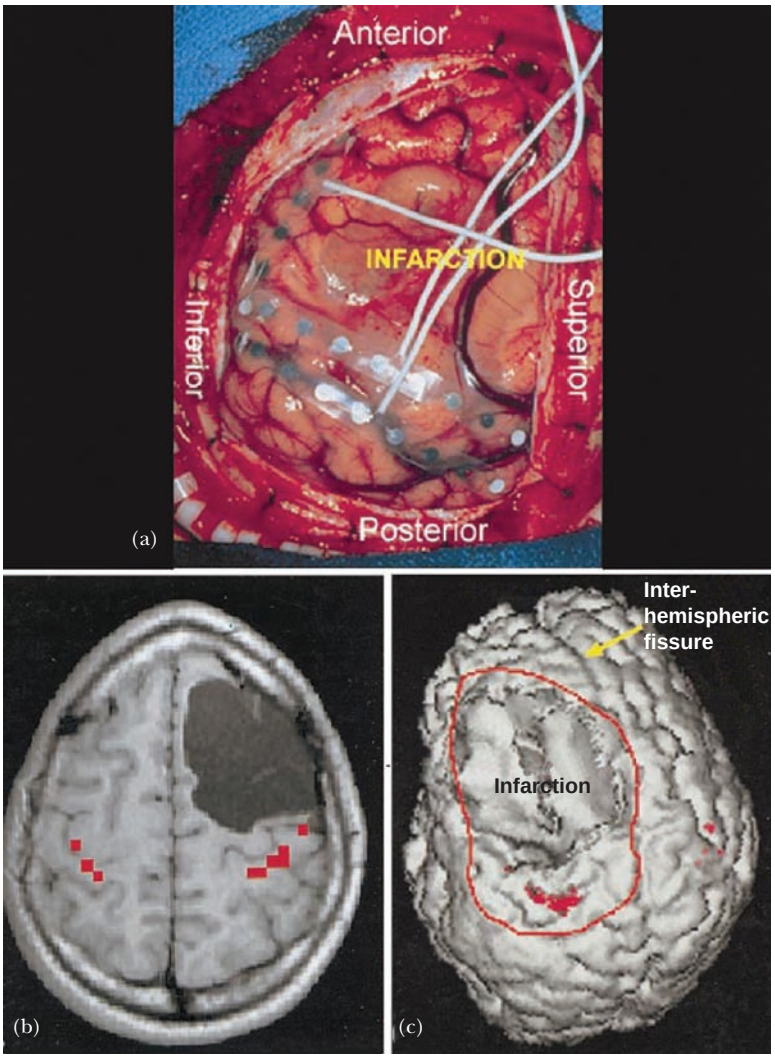

Figure 10.2 Images of the brain of an 18-year-old boy with a medically intractable seizure disorder due to a perinatal hemorrhage. (b) fMRI activation in square voxels that were associated with sensorimotor hand function in relation to the posterior aspect of the lesion. (c) Three-dimensional rendering of the lesion and activation. The fMRI activation pattern was used to guide placement of electroencephalogram (EEG) strips to ensure that the functional hand area was covered by the subdural strips for the purpose of performing extraoperative cortical interference mapping (a). Extraoperative EEG–video recording and interference mapping localized the functional hand to the region that coincided with the fMRI localization. Adapted from Lee et al.[26]

performed, and in deciding whether invasive mapping was going to be necessary for a safe resection. They studied 46 patients in whom resection of either epileptic focus or tumor was being contemplated (Figure 10.2). fMRI was successful in 32 of the subjects. In the others, motion artifact rendered the data unusable. Motor (finger tapping or sponge squeezing), or sensory (vigorous brushing of the palms) activations, or both, were used as the functional tests. fMRI was successful in identifying primary somatomotor regions, and their relationship to the central sulcus, in all 32 of the patients. Overall, it was determined that (1) fMRI was useful in assessing surgical feasibility even when no visible anatomical abnormality was present on structural MRI scan in identifying the functional hand area to aid placement of implanted grid/strips, (2) in placing the craniotomy flap to ensure proper exposure for cortical stimulation mapping, and (3) in identifying which patients needed invasive functional mapping done. With regard to the degree to which presurgical fMRI fulfilled the criteria of usefulness defined by the authors, the technique fulfilled the three purposes and was useful in 89% of tumor patients and 91% of epilepsy surgery patients.

In addition to its use in defining regions to avoid during surgical resection, fMRI may be used to predict outcomes from surgical procedures. Haberg et al[27] studied 25 patients with brain tumors neighboring sensorimotor or language cortices and their preoperative fMRIs. Comparing pre- and postoperative neurological performance, there was a significant reduction in the likelihood of postoperative deficits if there was a distance of 10 mm or more between regions of functional activation and the borders of a tumor, compared with the likelihood if the distance was 10 mm or less.

Validation of the fMRI technique has been raised as a central issue regarding its widespread use by clinicians. In what is perhaps one of the most definitive studies, Hirsch et al[28] addressed this by using an integrated approach to map cortical regions associated with tactile, motor, language, and visual functions (see also Ruge et al[29]). Hirsch et al[28] studied 63 control patients and 125 patients with relevant brain lesions: 63 with tumors of the sensorimotor regions, 56 of language areas and 6 of visual cortices. Four different tasks were used, including passive visual viewing of reversing checkerboard, active finger–thumb tapping, silent picture naming, and passive listening to recordings of spoken words. The a priori goal was to use these tasks to localize sensory and motor cortices and language-related activity, which would be expected to be focused in Broca's and Wernicke's areas, as well as the primary and secondary visual areas. For the control patients, there was an overall 100% sensitivity in identifying the language-related cortex in the superior temporal gyrus. Broca's area was identified 93% of the time and the visual cortex 100%. This type of validation of the functional tests and their localization, in relevant control patients, provides a much more compelling argument that the localizations obtained in patients with lesions of cortices typically associated with a particular neurological function are of sufficient quality to aid in surgical planning. Using these 'normative' data, this group was able to ascertain that these tasks were sensitive for functional localization in surgical patients with a lesion in or close to the motor strip: (1) 94% of the time, there was activation in the postcentral gyrus upon tactile stimulation; (2) the finger–thumb task elicited activity in the precentral gyrus in 89% of patients. Signal changes with visual stimulation were evident within the calcarine sulcus and inferior occipital gyrus in all of the control subjects as well as in all of the patients. In patients with lesions in the vicinity of the central sulcus, the composite sensitivity of the test was estimated to be 97%. Comparing the results from the normal controls with those with brain tumors for language mapping, 93% of the normal subjects demonstrated signal change in the inferior frontal gyrus and 100% in the superior temporal gyrus. Seventy-seven percent of the surgical candidates exhibited evidence of frontal brain activation, and 91% of the patients in this group showed signal change in the temporal lobe. These differences from the normal group were attributed to aphasias related to the tumor – an indication of why neurological examination of the patient must always be considered in interpreting the functional mapping of tumor/lesion patients.

These investigators have amassed considerable data comparing the results of fMRI studies with the results obtained using more well-established mapping methods, and have found substantial agreement between fMRI and electrophysiological measures in localization of primary motor and somatosensory cortices. However, fMRI is not able to determine if a region identified is critical and essential to performing a cognitive function or just activated during that task. As a consequence, fMRI alone may have a tendency to overestimate the number or extent of brain areas that are involved with performance of a task, potentially leading to a too-conservative lesion resection. The optimal conditions would appear to be combining an activation study such as fMRI with a lesion/subtractive technique such as cortical stimulation. Roux et al[30] performed exactly this combination in five patients who

had tumors near or in the motor strip. These patients were selected because they had motor weakness and when making a movement with their paretic hand, they activated predominantly or exclusively the ipsilateral hemisphere during fMRI. The functional paradigm used consisted of flexion and extension of the fingers of the paretic hand, as well as the normal hand in a separate experimental run. This task typically activates the precentral gyrus and often the supplementary motor area. Results from both hemispheres were then compared and correlated with cortical brain mapping. For comparison in a subgroup of patients, cortex was directly stimulated using a bipolar Ojemann cortical stimulator (1 mm electrodes separated by 5 mm). In the group where cortical stimulation results and fMRI were correlated, when there was no fMRI activation in primary sensorimotor cortex of the affected hemisphere, cortical stimulation concurred with this fMRI finding. In these patients there was ipsilateral activation which was assumed to represent the residual function of the affected hand. These results showing shifting of functional localization can be seen quickly after the onset of symptoms, can be temporary, and may reflect a compensatory role for ipsilateral motor control in recovery from paresis. Many technical problems were noted, however, such as image distortion related to the echo-planar technique used for data acquisition, paradigm choices, movement artifacts, and venous effects that are seen in fMRI studies (for details on motion artifacts and patient deficits in using and interpreting fMRI results in surgical populations, see Krings et al[31]). Signorelli et al[32] have taken the findings on language localization obtained with fMRI preoperative mapping and similar localization from intraoperative cortical stimulation and have combined these data into a neuronavigational device to determine the spatial co-registration between the two datasets, and to use this as a guide for safe surgical resections (see also Wilkinson et al[33]). We would speculate that further integration of the functional localization findings from multiple investigative techniques will allow for additional refinements of surgical resections, with accompanying reductions in surgical morbidity.

PRESENT LIMITATIONS OF fMRI FOR PRESURGICAL MAPPING

The correlation of fMRI localizations with established brain mapping techniques (e.g. cortical stimulation and electrophysiology measures such as SSEP) has been a major validation of the technique, and there has been a concomitant increase in its use as a surgical planning tool. However, there are certain limitations of the technique that limit its applicability. Some of these limitations are being addressed by fMRI methodologists, but given the increasing popularity of the technique, it is useful to point out some of the current issues (see also Chapter 2).

Lack of statistical quantification of activation and correlation with neuronal function

The recent work of Logothetis and others[34,35] as well as extensive studies of PET blood flow correlations, have suggested that changes in blood flow measured with PET and fMRI predominantly reflect changes in synaptic activity. Whether these changes represent significant neuronal activity (i.e. action potential outputs from the neurons upon which the activated synapses impinge) in populations of neurons is not clear. The correspondence of the spatial extent of the signal changes to the spatial extent of neuronal activation has not been consistently verified, and it may well be regional- or task-dependent. Further, it has not been verified how the amplitude of blood flow changes reflects different neural activity – does higher amplitude represent a larger region of neural activity or a greater degree of neuronal firing? How will analytical techniques deal with assessing the correlation of cerebral blood flow to neuronal firing in the face of individual subjects having a variety of lacunar infarctions, white matter lucencies, cerebrovascular pathology and variability in

cerebral vessel dynamics, and/or chronic medical conditions (e.g. hypertension, diabetes, hyperlipidemia) and medications that affect the brain and its vasculature (e.g. acetylsalicylic acid, non-steroidal anti-inflammatory drugs. and caffeine).[36]

An additional issue is that the present statistical techniques used assume that the differences in blood flow that represent significant neural activity are roughly equivalent for every region of the brain. It is unlikely that, for every brain region, any significant increase in neuronal activation is reflected in the same degree of blood flow change. Among the factors that need to be taken into account are the amount of regional neuronal activity at baseline, the maximal amount of change in neuronal activity that a region can exhibit, the typical duration of region-specific neuronal response, and perhaps regional variations in the mechanisms by which neuronal activity and changes in blood flow are coupled. Therefore, the best statistical method in analyzing fMRI in neurosurgical patients has not been found. Most, if not all, of these issues will need to be addressed using non-fMRI techniques (electrophysiological, neurochemical/pharmacological, and blood flow/oxygenation measures and comparing findings to fMRI).

Reproducibility

A major concern in using fMRI data to guide surgical decisions rests on the reproducibility of the findings, particularly across multiple MRI platforms. Vlieger et al[37] used 12 healthy volunteers on two different 1.5 T MRI scanners from two manufacturers to test the sizes of regions of activation on a visual stimulus task. Three issues were noted: (1) the two systems had different signal intensity changes between baseline and activated conditions; (2) a partial volume effect might occur between sessions and/or MR instruments; (3) *t*-tests may not be optimal in terms of reproducibility. An overall effect appeared to be that same-session reproducibility values were independent of the MRI system, and that the system did not affect intersession reproducibility concerning the number of activated voxels, but did affect the apparent localization of the voxels. Reproducibility of fMRI may appear to depend on the type of system used to get the results, and so possibly the place and type of MRI scanner should be considered if they differ from those typically used prior to surgical planning.

Brain changes with age, lesions, or medication

Other issues to consider in interpreting fMRI findings in presurgical and other evaluations are the changes that age induces on fMRI findings, as well as any possible effects that a given tumor or medication may also have on the brain and/or the vasoreactivity of its vascular supply. While specifics have not been reported for several of these latter issues in fMRI, it is clear that these are general principles that should be considered in interpreting any blood flow study involving brain regions. For example, the effects of lesions were seen when Fujiwara et al[38] compared near-infrared spectroscopy (NIRS) and blood oxygen level-dependent (BOLD) fMRI measures of cerebral blood flow and function in 12 patients with tumors. NIRS showed clear evidence of normal localization of sensorimotor cortices on the non-lesion side, which correlated with fMRI results. However, on the lesion side, NIRS identified sensorimotor cortices that were not identified using fMRI, or greatly reduced in extent/degree of signal change in 7 of the patients. Intraoperative brain mapping with direct cortical stimulation validated the NIRS mapping, suggesting that fMRI had resulted in false-negative localizations in these tumor patients. A likely reason for this lack of localization from fMRI here is the atypical cerebral blood flow regulation associated with tumor and peritumoral vascularity. Thus, notwithstanding the more promising results noted above regarding the utility of fMRI in the setting of tumor surgery, it is clear that the technique must be applied, and

the results interpreted, cautiously, taking into account what has been known for many years about the effects of tumors on the tissues and blood vessels in their vicinity.

CONCLUSIONS AND FUTURE DIRECTIONS

As fMRI becomes ever more widespread as a component of presurgical evaluation, increased understanding of its implications has been evolving rapidly, as have technical attributes of this class of techniques. It seems clear that optimal use of fMRI in the clinical setting, as well as in research, will require better understanding of the linkages between neuronal activity and the associated hemodynamic responses, as well as the influences on these linkages of brain region and specific pathophysiological process. Irrespective of any developments, optimal presurgical evaluations have typically involved activation techniques (which demonstrate both those areas essential and also those perhaps more peripherally involved in performing a task) and subtraction techniques (which create temporary lesions that reveal brain regions essential to performing a task). Lesion/subtraction techniques (e.g. cortical stimulation, the Wada test, etc.) are typically invasive, while activation studies (e.g. fMRI, SSEP, etc.) are non-invasive; thus careful consideration should be given to balancing the two based on the clinical scenario.[31] A combination of techniques such as fMRI, MEG, and cortical stimulation as described by McDonald et al,[39] with additions or subtractions as indicated, can provide comprehensive brain function mapping even in the case of problematic lesions neighboring areas of critical brain function. Parmar et al[40] combined fMRI and diffusion tensor imaging with MR tractography to aid in planning surgical resection of tumors neighboring the motor strip with good results. Again, we would predict that multiple combinations of investigative techniques will be explored over the next several years to determine the optimal pairings of studies to improve outcomes and reduce morbidities for a variety of lesion types (tumor types, degrees of malignancy, etc.) in multiple brain locations.

Changes in the way in which the images themselves are acquired will also likely impact on the applicability of fMRI for brain mapping. One recent example from Yoo et al[41] suggests that the optimal spatial resolution for individual patient mapping could be 2 mm × 2 mm × 2 mm, a resolution that is typically finer than most acquired at present. Schulder et al[42] have shown that low-field intraoperative functional MRI may be useful in functional localization, increasing the portability of the technique. Other developments that could yield quantitative measures of blood flow change without using radiation (e.g. NIRS, alluded to above) are being actively sought and could provide for more precise quantitative measures of functional localization.

In addition, consideration must be given to specification of postsurgical outcome measures, in order to make valid comparisons between the predictive value of different testing techniques. At present, it is clear that fMRI offers a safe, relatively reproducible, non-invasive measure of brain–behavior mapping that has proven thus far to correlate to some degree with more established, invasive, temporary lesion-like procedures. With ongoing efforts to provide clearer quantification for fMRI in general, compensatory approaches for abnormal brain states (e.g. aging, medications, lesions, etc.), and development of more sophisticated behavioral/cognitive paradigms, it would appear that fMRI mapping will continue to improve in quality and likely expand in application to a wider array of neurological and psychiatric conditions.

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Schizophrenia

11

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INTRODUCTION

Schizophrenia is a common and devastating mental illness that affects approximately 1% of the population worldwide. Neuroimaging findings now form part of the bedrock of clinical investigation into this disorder. Following on the heels of structural imaging findings of increased ventricular spaces and reduced brain volumes, decreased dorsolateral prefrontal cortex (DLPFC) activity or hypofrontality helped to establish schizophrenia as biological in origin, to encourage a dialogue between basic and clinical scientists regarding neurochemistry, neuronal pathology, and molecular biology within DLPFC, and to foster a keener interest in cognitive dysfunction and its potential pharmacological remediation. However, as the methodology has matured, the essential questions regarding brain dysfunction in schizophrenia have changed as well. Some questions have been altered as a result of new neuroimaging findings. For example, decreased DLPFC activity is not the sole signature of dysfunction in schizophrenia. Some questions have been changed in scope. Instead of an exclusive focus on isolated regions of dysfunction, experiments and analyses are increasingly aimed at networks and interactions within them. Finally, some questions have been changed in kind as the result of rapid advances in other research disciplines. Elucidating the relationship between genetic variation and regional brain activation is a challenge that did not exist in the pregenomic era. This chapter will address recent findings relevant to each of these issues, since new answers may ultimately drive the field in unexpected directions as further improvements in diagnosis and treatment are still desperately needed.

OVERVIEW OF SCHIZOPHRENIA

To put a wide range of neuroimaging research into some context, it is helpful to consider some basic observations about the illness. Schizophrenia has a prevalence of 0.5–1.0%. It is defined by acute psychosis that, once resolved, persists over a lifetime as residual psychotic signs and symptoms and marked social and occupational dysfunction for most patients.[1] While much has been written about the illness within the past several decades, many of the essential details regarding its clinical aspects remain fairly unchanged. In the acute and chronic phases, the hallmark psychotic signs and symptoms include delusions, hallucinations, disorganized speech and thought, disorganized or catatonic behavior, and negative symptoms including flattened affect, alogia, and avolition.

Although not explicitly delineated within the diagnostic criteria for schizophrenia, cognitive impairment has increasingly been appreciated as an additional clinical dimension with important ramifications for long-term outcome. Cross-sectional and longitudinal studies have suggested that cognitive deficits (e.g. executive function and attention) do not deteriorate significantly following adequate treatment,[2,3] although there may be populations with chronic or severe illness that experience further cognitive deterioration.[4]

Regardless of the chronic nature of the illness, particularly disabling aspects such as cognitive or social impairment, the long-term course of the illness is variable and ongoing deterioration is not inevitable (e.g. 20% of patients remit in later life, while only 20% continue to decline).[5] Nonetheless, with a typical onset between the late teens and early thirties, schizophrenia remains an often insurmountable impediment to adult developmental goals such as academic and career achievement, social and financial independence, and interpersonal relationships. Although recovery to a level approaching normality for some patients with schizophrenia has been described for more than a century, an ongoing therapeutic optimism has accrued with continuing introduction of newer medications.

The standard of care remains treatment with antipsychotic medication. The introduction of atypical antipsychotics, particularly clozapine, has offered superior efficacy with fewer extrapyramidal side-effects in comparison with typical antipsychotics such as haloperidol. However, at least two recent large meta-analyses have suggested a more conservative appraisal of the newer atypicals, finding either no superiority when controlling for optimal dosing of high- and low-potency typical agents[6] or small gains without significant extrapyramidal side-effect benefits relative to low-potency typical antipsychotics such as chlorpromazine.[7] Given the variable course of the illness together with the risk of serious long-term side-effects such as tardive dyskinesia, many clinicians seek early intervention with the lowest effective dose of antipsychotics on a continuous basis. Given the lack of sensitive measures for predicting likelihood or severity of relapse, evaluation for gradual discontinuation for some patients remains an option, but one that must be based on the individual patient.[8] Perhaps the most encouraging trend is the ongoing commitment of pharmaceutical companies to the development of more refined antipsychotic medications and, more recently, the exploration of adjunct therapies such as cognitive enhancers.

Differing interpretations regarding the etiological and clinical events proceeding, surrounding, and following what for most patients is a mental illness of early adulthood have led to two main opposing theoretical concepts regarding schizophrenia. There is general consensus that critical lesion(s) predate illness onset, perhaps as early as the second trimester of pregnancy. Harrison[9] summarizes some key observations behind this assumption, such as the presence of ventricular enlargement and reduced cortical volume present at illness onset, cytoarchitectural abnormalities such as disarray of hippocampal neurons and abnormal distribution of neurons in prefrontal white matter, obstetric complications as the most frequently reported environmental risk factors, the presence of subtle motor, behavioral, and intellectual impairments in children who later develop schizophrenia, increased minor physical anomalies, and the observation that neonatal lesions of the hippocampal region in animals produce delayed effects on behavior and neurochemistry arising only after adolescence. The point of debate remains whether or not the onset of psychosis and manifest illness leads to continued changes within the brain. Simply put, the neurodevelopmental hypothesis argues that a lesion early in life leads to a vulnerable brain out of which schizophrenia emerges during the critical stage of late adolescence and early adulthood, perhaps due to associated hormonal changes, significant life stressors, and critical brain developmental changes such as prefrontal cortical maturation.[10] Lack of progression of structural brain findings, the absence of gliosis or other neurodegenerative features at autopsy, and the stability of certain core cognitive deficits argue for a relatively static encephalopathy. The schizophrenic brain would not be immune to continued accrual of pathology given the chronic effects of continued mental illness, social impoverishment, chronic medication treatment, and associated complications such as smoking and alcohol/drug use, but the principal damage would have been done very early in the course of illness.[11]

In contradistinction, the concept of schizophrenia as an illness of chronic deterioration has a long history dating back to its initial clinical descriptions by Kraeplin.[12] The neurodegenerative hypothesis of schizophrenia argues that disease-specific pathology continues to accrue over time. As noted above, symptoms vary over time, with some patients experiencing an unremitting course, negative symptoms often appear to crystallize over time, and longitudinal studies of chronic patients have documented progression in cognitive impairments and structural imaging abnormalities.[4,13] While this latter viewpoint has recently fallen from favor, neither is a true hypothesis in a testable sense. Eventually, some eventual synthesis including both static and progressive processes will be needed.[14] At the time of writing, for practical purposes, the preponderance of evidence for a neurodevelopmental lesion currently directs much research effort towards the antecedent and initial events in schizophrenic psychosis.

Perhaps the single most anticipated development along these lines is the potential identification of susceptibility genes that might clarify the initial conditions in at-risk individuals, reveal mechanisms leading to acute symptomatology, and offer novel treatment options for improving outcome. Schizophrenia (MIM 181500; http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?db=OMIM) has a prominent genetic basis. The concordance rate for monozygotic twins is approximately 50%, as opposed to a concordance rate of approximately 15% for dizygotic twins and a lifetime risk of approximately 10% for first-degree relatives.[15] Although it is highly heritable (with a rate as high as 80%), multiple genetic components appear to underlie schizophrenia.[16] While consensus criteria such as the DSM represent ongoing improvements in diagnostic clarity for schizophrenia, it remains a syndrome that could represent the common endpoint of a number of etiologies or could share genetic susceptibilities with other schizophrenia spectrum disorders or psychiatric illnesses with a psychotic component.

Diagnostic and theoretical uncertainties aside, the largest problem facing psychiatric genetics is one shared with all studies of genetic disorders of complex heritability. Namely, specific genes are likely to exert small individual effects and may significantly increase risk only via additive, epistatic, or otherwise-complex interactions with other genes of equally small effect size. The practical implication is that much larger sample sizes are needed to detect and replicate linkage and/or association findings than are often reported. Further unknown parameters complicating the search for schizophrenia susceptibility genes include environmental factors, penetrance, locus heterogeneity, and pleiotropy. Linkage studies have been difficult to replicate and allelic association studies are hampered by a limited understanding of pathogenesis with which to evaluate potential candidate genes or establish prior probabilities when multiple alleles are tested. Nonetheless, some strong findings are emerging. Linkage to chromosomes 1q21–22, 6p24–22, and 13q32–34 has been established at genome-wide significance levels and strong evidence has been reported for 1q42, 5q21–33, 6q21–25, 8p21–22, 10p11–15 and 22q11–12.[17] Replicated association studies have identified several genes, including *dysbindin* (*DTNBP1*),[18] *G72*,[19] *COMT*,[20] and *neuregulin1* (*NRG1*).[21] However, statistical associations are often weak and remain unconvincing on their own. Some investigators are now taking an alternative approach – compiling convergent data about the effect of variations in the gene on biological characteristics of the illness that are in turn plausibly related to the biology of the gene can greatly strengthen such statistical results.[22,23] These biological characteristics or intermediate phenotypes quantify some physiological aspect of a given illness, analogous to the quantification of blood lipid levels in coronary artery disease, which is an aspect of the illness but additionally carries a simpler physiological basis and thus a less complex relationship to susceptibility genes.[24] As detailed below, abnormal functional brain

activation during an imaging study that is characteristic of the illness would be associated with allelic variations that are in turn associated with the illness.

The purpose of this chapter is to present recent functional neuroimaging findings in the context of this basic overview, with an eye towards trends that may ultimately lead to significant changes in the field. Individual sections will deal with the following issues raised above: symptomatology (in this instance, cognitive impairment), antipsychotic treatment, and finally the identification of susceptibility genes. Since a comprehensive review of all such studies is impractical, it is hoped the reader will be alerted to general trends and specific sources for further reading. Since functional magnetic resonance imaging (fMRI) is enjoying particular prominence at this time, this review will be limited largely to these studies. Papers have been selected using Medline with a variety of search terms covering the period since the wide introduction of fMRI in schizophrenia research in the late 1990s.

GENERAL FUNCTIONAL NEUROIMAGING ISSUES IN SCHIZOPHRENIA

Like the structural imaging studies that have been frequently reviewed elsewhere, functional neuroimaging studies of schizophrenic patients have revealed abnormalities that are more a matter of degree than of kind. Computed tomography (CT) and structural MRI (sMRI) together have reported repeatedly enlarged lateral and third ventricles, reduced cortical gray matter, and volume changes in the DLPFC, medial temporal lobe (hippocampus, parahippocampus, and amygdala), superior temporal gyrus, and thalamus.[25–27] However, even when mean effect sizes are significant, overlap in the distribution of patients and comparison subjects is high. Davidson and Heinrichs[27] found mean effect sizes of –0.39 and –0.41, respectively, for right and left frontal volumes as measured by sMRI, but approximately 73% overlap between patients and controls across studies encompassing roughly 1000 subjects in each diagnostic category. Effect sizes were higher in right and left hippocampus (–0.58 and –0.55, respectively) and right and left superior temporal gyri (–0.40 and –0.55, respectively), but overlap was also significant (62–73%). Of course, etiological heterogeneity may play a role, for example by obscuring some hitherto unrecognized subgroups with differing patterns of abnormalities that become obscured when grouped by today's diagnostic classification. Nonetheless, as dramatic as the clinical picture appears, the structural imaging findings for most patients are subtle and for some patients not apparent relative to the healthy population.

In a wider context, the observation of subtle changes that exist along a continuum with healthy brain function resonates with observations of subtle pathology at the cellular level. For example, increased neuronal density as a result of reduced neuropil in the DLPFC is of the order of 21%.[28] Structural imaging has yet to identify pathognomic findings, and instead points towards multiple areas with significant volume reductions of a moderate effect size. Technological or methodological improvements (such as increased resolution or multivariate analyses capable of identifying patterns or networks of volumetric abnormalities) may eventually alter this conclusion. Given this history, it should not be surprising that functional neuroimaging has similarly failed to generate pathognomic findings. Rather, functional neuroimaging remains a vital tool for localizing dysfunction and testing hypotheses in vivo.

For decades, the discussion of functional neuroimaging findings in schizophrenia has largely concerned questions regarding reductions in regional measures of cerebral blood flow and metabolism. Ingvar and Franzen[29] first described the phenomenon of relatively reduced frontal regional cerebral blood flow (rCBF) in the schizophrenic brain at rest. In subsequent studies, it became increasingly clear that while results during the resting condition were less consistent, cognitive challenge

paradigms consistently demonstrated reduced frontal rCBF in patients.[30] For example, a series of xenon-133 (^{133}Xe) inhalation experiments contrasting schizophrenic patients and healthy comparison subjects during the Wisconsin Card Sorting Task (WCST) showed reduced DLPFC rCBF in patients, as opposed to no differences in rCBF during simple control conditions such as number matching or continuous performance tests.[31,32] This result has been replicated using fMRI.[33]

Reduced frontal activity during cognitive challenge or hypofrontality would be replicated in numerous subsequent studies (although not universally), but would not be more diagnostically specific than sMRI. Returning to the meta-analysis of Davidson and Heinrichs,[27] frontal hypofrontality during cognitive activation has a large effect size (d = –0.81), but there remains a 53% overlap with healthy individuals. In regions outside of the frontal cortex, effect sizes drop significantly and overlap with the healthy population increases (d = 0.43 with 73% overlap for temporal lobe and d = –0.07 to –0.13 with 92% overlap for left and right hippocampus). Such meta-analyses are not yet available for fMRI in schizophrenia, so effect sizes may be larger, particularly with the spread of high-field magnets and sophisticated event-related designs. Nonetheless, while it remains difficult to accumulate large samples, the current sample sizes in the teens and twenties often reported may be significantly underpowered to identify the full breadth of brain dysfunction elicited by a given cognitive imaging paradigm. On a more positive note, the fact that quantitative measures of brain function overlap between healthy individuals and patients is not a limitation for the intermediate-phenotype approach. It is likely that many of the multiple common alleles of small effect will associate with intermediate brain phenotypes regardless of diagnostic status. Since the illness is only expressed given a particular combination of these genes, one would expect a continuum of brain function, with some healthy subjects carrying a subset of these genes overlapping with patients.

Two other quandaries that will likely continue to carry over from past imaging experiments are the issue of patient performance on cognitive challenges and the impact of antipsychotic medication. From the earliest reports of functional activation differences between patients and controls during cognitive activation, critics have argued that findings such as hypofrontality could simply reflect artifacts of impaired performance or decreased motivation and engagement on the part of schizophrenia patients rather than representing fundamental disease processes.[34] This criticism has been addressed in two ways. First, experiments have been designed so that they included a component that patients performed as well as controls. These control tasks demonstrated adequate engagement, and comparable activation between diagnostic groups during these tasks supported the contention that abnormal activation during the impaired task of interest was disease-related.[31,35] On a more practical level, because methodologies such as blood oxygen level-dependent (BOLD) fMRI are vulnerable to artifacts such as greater head movement during acquisition by patients, we have proposed utilizing such measures (e.g. activation in the motor cortex during a control task) as a component of data quality assurance.[36]

Still, given that the task of interest is generally more complex and demanding than the control task, adequate engagement during a control task and comparable activation in certain control regions does not entirely negate this criticism. A further conceptual problem arose when it became clear that certain functional abnormalities are quantitatively and qualitatively similar between poor-performing patients and healthy subjects past their capacity on the same cognitive activation task. This problem can be illustrated by examining the DLPFC response to increasing working memory (WM) load. While patients with schizophrenia have well-documented WM impairments, WM capacity is a limited cognitive resource for everyone.[37,38] We found a significant decrease in DLPFC fMRI activation as healthy subjects were pushed beyond

their WM capacity during the *N*-back WM task.[39] At higher WM load, healthy subjects experienced impaired performance and concomitant hypofrontality relative to lower WM load. Thus, hypofrontality in schizophrenia coupled with poorer patient performance is not distinct from the normal brain response to task failure. This interpretation was further supported by Fletcher et al,[40] who in a parametric word list length memorization task demonstrated that decreases in frontal activation measured via PET only occurred when performance fell for schizophrenic patients with longer list length. An obvious statistical solution for parsing out aspects of abnormal activation not related to performance impairment is to covary activation with performance predicated on the assumption that reduced activation is beyond the extent expected merely by poor performance. As noted above, even if indices of prefrontal function in patients and healthy populations were entirely driven by performance, their utility as a potential quantitative trait for genetic analyses would not suffer.

A second approach to this problem is to remove patient performance differences entirely, either by choosing tasks that patients perform as well as controls or by matching patient and control populations for performance measures. During an auditory recognition task comparing a group of performance-matched patients and controls, Holcomb et al[41] still identified a reduced prefrontal response in patients with schizophrenia. In a slight twist to this concept, Goldberg et al[42] compared patients with schizophrenia with performance-matched patients with Huntington's disease using the WCST, and found that schizophrenic patients were relatively hypofrontal. However, this approach is not without its own pitfalls. One obvious criticism is that the construction of a matched set of patients and controls might mean that either group is non-representative – patients who are minimally impaired by the illness or controls who are relatively impaired on the task. A second criticism is that the selection of a task that is readily performed by patients may not tap into cognitive processes or invoke activation within regions primarily affected by the illness. Finally, experimental designs involving similar performance have not definitively clarified relative brain activation differences in schizophrenia. Curtis et al reported attenuated frontal activation during a word generation task,[43] but no such difference when patients performed a semantic decision task.[44] They suggested that differences in prefrontal demand could have explained equal prefrontal activation in the latter case, but without demonstrable measures of such task characteristics these differences are difficult to quantify and even more difficult to interpret when there are no demonstrable group differences in behavioral measures such as accuracy or reaction time. As scanning time per task decreases with improvements in technology and experimental design, we and others have advocated comparing patients and controls either on one task given at multiple levels of demand (including those wherein patients perform well) or a range of tasks targeted at specific cognitive functions or particular brain regions. In the manner of Fletcher et al,[40] two parametric studies using the *N*-back task have demonstrated normal prefrontal blood flow at lower load followed by reduced prefrontal blood flow as performance drops below that of healthy controls.[45,46] The verbal tasks studied by the Curtis group would be an example of multiple tasks directed at a cardinal region (prefrontal cortex) that suggest task-, and presumably process-, specific dysfunction in schizophrenia.

The issue of medication effects in schizophrenia imaging research has been approached as in the latter case with performance – removing their effect by studying medication-naive or medication-free patients. An early PET regional metabolism study by Volkow et al[47] suggested that acute administration of a single dose of antipsychotic did not alter metabolism in previously unmedicated schizophrenic patients, although only four patients were studied. Since they also failed to document hypofrontality, Volkow et al[47] raised

the question that this finding might be the result of chronic medication treatment. However, in the years that followed, it became clear both that the majority of studies comparing never-treated patients or those briefly taken off medications still found regional abnormalities such as hypofrontality and that antipsychotic medications likely increased measures of regional blood flow, thus questioning the supposition of hypofrontality as an epiphenomenon of medication treatment.[30] Typical of these studies, Andreasen et al[48] compared 13 antipsychotic-naive schizophrenic patients with 23 medicated patients and 15 healthy volunteers using the Tower of London task. Compared with healthy subjects, both groups showed reduced regional blood flow. More recent experiments regarding antipsychotic treatment using fMRI will be discussed below, but the overall contention that abnormal findings do not arise solely from medication treatment is supported.

fMRI AND COGNITION IN SCHIZOPHRENIA

In reviewing the findings in schizophrenia, most studies use various cognitive challenges to elicit region- and network-specific activation patterns in patients as compared with healthy individuals. Many, if not all, studies of higher cognitive functions have produced abnormal findings. Prior to their discussion, it is important to address two potential confounds. The first is a general concern regarding the integrity of the BOLD fMRI response in patients with schizophrenia. While it is generally believed that the illness does not affect cerebral vasculature, some very early fMRI studies suggested that the BOLD response might vary between populations,[49,50] thus potentially complicating the interpretation of between-group differences. However, follow-up studies that carefully controlled for other sources of between-group differences (e.g. subject movement) have failed to confirm these early findings, and instead suggest that the BOLD response to simple sensory and motor demands remains intact in schizophrenia.[51]

The second general concern is that these tasks, designed to elicit focal abnormalities, are actually reflections of global dysfunction. After all, if some of the genetic and molecular abnormalities at the heart of the illness affect very basic cellular processes such as neural transmission or synaptic architecture, as many have proposed,[52] it is not unreasonable to posit that such effects would produce activation differences from the most basic to the most complex imaging task, thus limiting the conclusions that could be drawn about higher cognitive dysfunction. Several recent fMRI studies raise the question of this kind of elemental, widespread dysfunction with simple tasks designed to probe the response to sensory input. Braus et al[53] examined simple sensory processing in medication-naive subjects. Subjects were asked to passively experience flashing checkerboards and drumbeats. While primary visual cortex activation was comparable between patients and controls, Braus et al[53] found abnormally reduced activation in the auditory portion of the superior temporal gyrus, as well as in the dorsal visual pathway from parietal to frontal lobes. Wible et al[54] used an auditory sensory mismatch paradigm wherein subjects were required to identify deviant tones occurring in a string of standard tones. While both groups activated auditory processing regions in the superior temporal gyrus, schizophrenic patients showed a diminished response. Both findings suggest elementary neuronal dysfunction that would likely be present throughout sensory and association cortices and suggestive of a global defect. Using a traditional auditory oddball task, Kiehl and Liddle[55] identified a network including the dorsolateral frontal cortex, thalamus, superior temporal gyri, parietal cortex, and cingulate gyrus. Once again, patients produced less activation in the primary sensory region of the superior temporal gyrus, together with frontal, parietal, and cingulate association cortices.

These data illustrate how the failure of a basic sensory adaptation response might lead to apparent abnormalities in higher cortical

regions. The potential significance of processing abnormalities at entry-level stages of cognitive processing may also help explain some of the symptomatology of schizophrenia. For example, sensory hallucinations could arise as a by-product of extraneous or inappropriate neuronal activity during basic sensory processing that the individual then misinterprets as real sensory input. Several fMRI studies of hallucinating patients have found either a diminution of primary auditory cortex response to external stimuli during hallucinations[56] or a signature of auditory cortex response during self-reported hallucinations occurring in the scanner.[57–59] Surguladze et al[60] examined schizophrenic patients while performing a silent lip-reading and perception of meaningless lip movements, and found that patients under activated temporal cortex during lip reading but recruited additional frontal, insular, and striatal regions during the perception of meaningless lip movements. In sum, while there is a tremendous amount of data supporting abnormal higher cortical function, we should not dismiss the importance of more elementary dysfunction that might represent a separable phenomenon in the schizophrenic brain.

At a stage higher in the complexity of cognitive function, several studies have now found abnormalities in processing information for skills acquisition and automatization of tasks. In one of the earliest studies to examine neural adaptation in schizophrenia, Mattay et al[61] found that patients were unable to generate an appropriately focal motor response in comparison with controls when given an increasingly complex finger opposition task. In contrast to reduced and more focused brain activation in controls following 1 week of motor skills training, Kodama et al[62] found that schizophrenic patients continued to show increased activation. Similarly, Kumari et al[63] found that schizophrenic patients failed to activate a network inclusive of thalamus, striatum, precuneus, cingulate gyrus and premotor cortex during a rule-based procedural learning task. In a particularly novel study, Manoach et al[64] examined sleep-dependent procedural learning in schizophrenic patients. Using a motor task that control subjects perform better following a night of sleep, they failed to find this improvement in patients following the same sleep interval. However, these findings are difficult to reconcile with the clinical picture in schizophrenia, wherein impairments in motivation and utilization of already-acquired social and cognitive skills are much more apparent than acquisition of new skills. Prior to onset in late adolescence and early adulthood, there is also not evidence for gross impairments in acquisition or new learning. On the other hand, perhaps this kind of training deficit would be more apparent if it were studied more carefully in patients, although several past studies of procedural learning have not found significant deficits in patients. For example, Weickert et al[65] studied procedural learning using a probabilistic weather prediction task and suggested that abnormal cortical input into an otherwise-functioning motor learning system was responsible for the observation of an identical learning rate between patients and controls, coupled with an overall performance offset in patients. In this sense, perhaps skill acquisition tasks are tangentially tapping into larger impairments in information processing.

A related issue is that of task automatization. Normally, as tasks become familiar and overlearned, healthy subjects reduce the amount of fMRI activation as if the brain were focusing resources on only those necessary to perform the rote task at hand. In a series of studies using a verbal Sternberg Item Recognition Task by the Ramsey group, subjects are presented with different lists of five letters followed after a delay by probe letters testing recall. One list is practiced repeatedly prior to and during scanning, thus becoming the automatically processed data while the other lists are novel. Contrasting the practiced with the novel stimuli, healthy subjects reduce the extent of activation within DLPFC after practice.[66] In contrast, schizophrenic patients fail to automatize within DLPFC.[67]

However, to understand some of the most debilitating symptoms of schizophrenia, such as delusions and loss of motivation, it is necessary to look beyond basic processing at more complex cognitive functions. A likely candidate brain region for understanding complex cognitive dysfunction is the DLPFC – both because of its central role in higher cognition and the similarities between symptoms such as lack of motivation and impaired abstract thinking associated with DLPFC lesions. The most replicated cognitive finding is dysfunction attributable to DLPFC. While numerous reports have documented DLPFC abnormalities in schizophrenia, there is continuing controversy regarding the particular flavor that prefrontal dysfunction takes – specifically increased versus decreased DLPFC activity. The findings by Barch et al[68] are typical of the so-called hypofrontality findings. They examined 14 first-episode untreated schizophrenic patients compared with 12 controls during the AX-CPT, which measures context processing and in which subjects are required to inhibit their responses following certain cues but not others. During the context processing part of the task, patients showed reduced activation in DLPFC but not in inferior and posterior prefrontal cortex. Lack of motivation or impairment in executive processes could thus be conceived of as occurring in the setting of reduced capacity to activate needed neuronal subsystems in DLPFC. With a larger sample of 38 patients and 48 controls performing both working memory and long-term memory tasks, Barch et al[69] found reduced DLPFC activation in both tasks (Figure 11.1). Similar to Barch et al, Perlstein et al[45] compared 17 schizophrenic patients with 16 controls during the *N*-back WM task. In this task, subjects are required to recall a stimulus seen *N* previously (typically, *N* = 2) in an ongoing string of stimuli. Perlstein et al[49] found reduced activation in right DLPFC associated with reduced WM performance. Furthermore, increased impairment was correlated with symptoms of cognitive disorganization. Perlstein et al[70] reported similar reduced DLPFC activation using both the *N*-back task and the AX-CPT. Using the 'gold standard' of DLPFC function, the WCST, Riehemann et al[32] found reduced right DLPFC activation, in accordance with a large positron emission tomography (PET) literature with similar findings. DLPFC dysfunction has also been found in tasks not requiring complex processing. For example, Rubia et al[71] examined six patients and seven controls during the 'go/no-go' inhibition task, and found that patients showed reduced DLPFC activation. Volz et al[72] also found reduced DLPFC function in patients during a time estimation task.

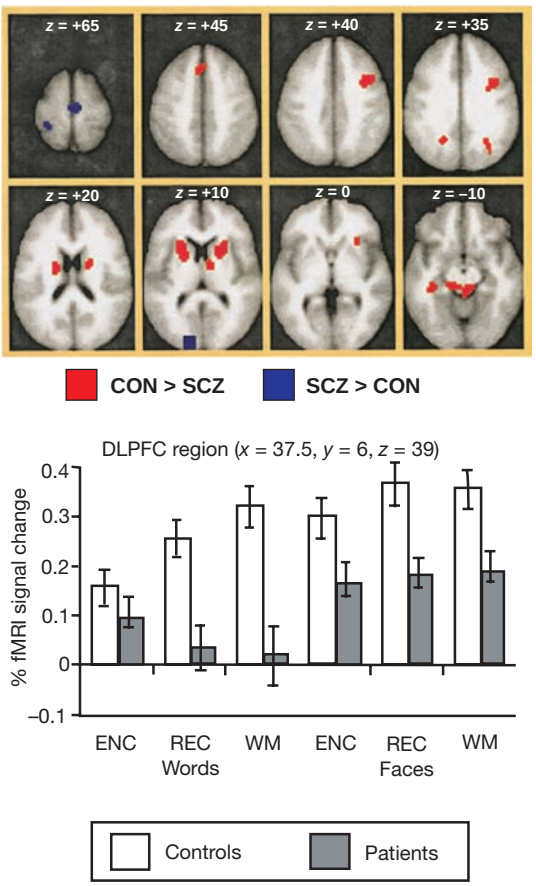

Figure 11.1 Common dysfunction of DLPFC during short- and long-term memory tasks. Using both working memory and encoding/retrieval tasks, Barch et al[69] demonstrated that a common area of DLPFC exhibited reduced activation during all tasks, suggesting a generalized prefrontal deficit. Adapted from Barch et al.[69]

However, a number of fMRI studies in schizophrenia have failed to find hypofrontality. Honey et al[72] used a verbal *N*-back task in 20 patients and 20 matched controls and found no difference in DLPFC activation. There was, however, a loss of the normal relationship between reaction time and parietal activation. More striking, Callicott et al[74] found greater activation of DLPFC during the *N*-back WM test that was also correlated with the extent of neuronal pathology as assessed by proton magnetic resonance spectroscopy (MRS) (Figure 11.2). Similarly, Manoach et al[75] found increased DLPFC activation at both test and retest in schizophrenic patients performing the Sternberg Item Recognition Paradigm. When remembering faces, Quintana et al[76] found that patients overactivated DLPFC, ventral prefrontal cortex (Brodmann area 44), and premotor cortex when compared with controls. Finally, Ramsey et al[77] found increased DLPFC activation during a WCST-like task in medication-naive subjects.

The relationship of increased DLPFC activation to symptoms in schizophrenia is not straightforward. These data suggest that patients are inefficient in the recruitment of neuronal resources or, alternatively, activate additional DLPFC neurons inappropriately. The fact that increased DLPFC activation has been directly correlated with the extent of neuronal abnormalities in DLPFC[74] suggests that even though the interpretation is not straightforward, hyperfrontality shows a direct relationship with the neuropathology underlying the illness. In addition, hyperfrontality is immune from the most common confound plaguing the hypofrontality literature – the observation that reduced DLPFC activation only occurs in the setting of reduced performance, thus raising the supposition that these findings track poor performance in general and not schizophrenia in particular. However, the fact that hypofrontality during PET scanning has also been linked to *N*-acetylaspartate (NAA) (a measure of neuronal integrity) mitigates this concern to some extent.[78].

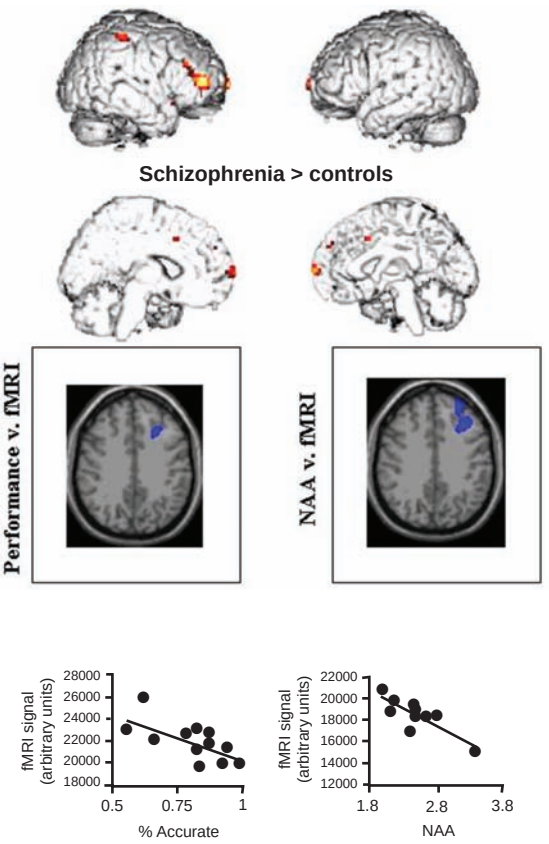

Figure 11.2 Reduced prefrontal neuronal integrity predicts abnormal prefrontal fMRI response. During the *N*-back WM task, patients with schizophrenia who perform nearly normally produce an exaggerated prefrontal fMRI response compared with controls. This is illustrated in the top four images, which show the areas where patients showed a greater fMRI response during the *N*-back task as compared with controls. The bottom two images and graphs depict the relationship between fMRI signal and performance and neuronal integrity as indexed by *N*-acetylaspartate (NAA) measured by MRS. The boxed images above the graphs indicated the prefrontal cortex (PFC) regions in which these correlations were most significant in patients with schizophrenia. On the left, those patients with the lowest accuracy were those who produced the greatest overactivation of dorsal PFC. It should be pointed out that even though patients with higher accuracy had less PFC activation than lower-performing patients, this level of activation was still abnormally high compared with controls. On the right, those patients with the lowest NAA concentrations (and, by inference, the greatest PFC pathology) showed the greatest fMRI signal in dorsal PFC. Adapted from Callicott et al.[74]

FUNCTIONAL NEUROMAGING AND GENETICS

Although only a decade old, fMRI has dramatically impacted the study of mental illness. While a complete review of recent developments in the imaging of mental illness is beyond the scope of this chapter, a review of recent progress in the study of schizophrenia is worthwhile in that work in schizophrenia often provides a template upon which researchers base their approach to other mental illnesses. Within the past few years, the sequencing of the human genome has raised expectations that the identification of susceptibility genes for the major psychiatric disorders such as schizophrenia should be near at hand. Perhaps the most promising development in schizophrenia neuroimaging has been the expansion of functional brain imaging into the characterization of intermediate phenotypes for psychiatric genetics studies. The intermediate phenotype attempts to quantify some physiological aspect of a given illness (analogous to the quantification of blood glucose in diabetes) that impacts on overall susceptibility to the illness but carries a simpler physiological basis and, hopefully, genetic architecture. Since the heritability of mental illnesses such as schizophrenia is complex, this approach is particularly attractive given the frustratingly slow progress of linkage studies that have used the clinical phenotype as a starting point. Next, a summary of recent findings from the functional neuroimaging literature in schizophrenia as a means of identifying candidate phenotypes will be presented. Finally, recent attempts to define specific genetic abnormalities associated with functional intermediate phenotypes will be discussed. Although issues such as susceptibility to movement artifact and controversy over study design remain to be overcome, functional neuroimaging, largely via its non-invasive nature and ease in accumulating large numbers of subjects, is poised to make revolutionary contributions towards uncovering the etiology of major mental illnesses such as schizophrenia.

The search for brain imaging phenotypes has been underway since seminal studies in structural brain imaging during the late 1970s and early 1980s. Early computed tomography (CT) studies showed that lateral ventriculomegaly was a replicable and robust group finding. Johnstone et al[79] examined 17 elderly institutionalized patients with schizophrenia and matched controls. Patients as a group had larger ventricles and, at the level of the individual patient, ventriculomegaly predicted the extent of cognitive impairment. This study suggested the phenotype was definable in a meaningful fashion at the individual level; therefore, it only remained to be determined if the lateral ventriculomegaly phenotype was heritable within families afflicted by schizophrenia. Taken together, three seminal studies showed just this. Weinberger et al[80] compared the distribution of lateral ventriculomegaly in seven healthy sibships with nine sibships in which at least one member had schizophrenia. Ventricle-to-brain ratio (VBR) was examined as a putative heritable phenotype in two ways: (1) quantitatively via intraclass correlation of VBR within sibships; (2) qualitatively via scatterplots that compared VBR of any given individual with established mean VBR in controls. Both analyses suggested that VBR was heritable. Reveley et al[81] addressed the same questions in monozygotic (MZ) and dizygotic (DZ) twins. Using VBR, heritability was calculated between 11 pairs of healthy MZ twins, 8 pairs of healthy DZ twins, and 7 pairs of MZ twins discordant for schizophrenia. VBR was highly heritable in healthy MZ twins ($h^2 = 0.98$) and roughly twice that of healthy DZ twins ($h^2 = 0.45$). VBR was also highly heritable in schizophrenic DZ twins ($h^2 = 0.87$). However, echoing an apparent genetic loading effect in which a strong family history of psychosis (either manifest by frank schizophrenia or simply by family history) predicted greater concordance for the phenotype within sibships as found by Weinberger et al,[80] the two schizophrenic DZ sibships in the Reveley et al[81] study with a strong family history of psychosis showed the least within-pair variance. Finally, DeLisi

et al[82] demonstrated a significant familial component to lateral ventricular enlargement in 11 sibships (including non-psychotic siblings of schizophrenic patients or so-called unaffected siblings) that was not entirely explained by non-genetic or environmental factors such as early head injury or obstetrical complications.

In principle, a phenotype related to genetic risk should be found in ill individuals and in some at-risk individuals who do not manifest illness. Thus, the search for phenotypes at the level of brain imaging begins with patients who manifest schizophrenia. While functional brain imaging techniques have been applied to the study of mental illnesses, particularly schizophrenia, for almost 30 years, they have failed to generate pathognomonic findings. For instance, as already discussed, the most replicated functional brain imaging finding in patients with schizophrenia remains hypofrontality. While functional imaging findings have been unable to fully disentangle the pathophysiology of schizophrenia, several studies suggest greater success in determining the genetic causation of schizophrenia. First, it will be important to demonstrate that functional abnormalities associated with schizophrenia represent heritable phenomena. Callicott et al[83] examined the fMRI response to the *N*-back WM task in two cohorts of healthy controls and healthy siblings of patients with schizophrenia. Since siblings share on average 50% of genes, it is likely that schizophrenia susceptibility genes (and the adverse physiological effects of these genes) will be overtransmitted to siblings relative to the general population. In both cohorts, siblings and controls performed with the same accuracy and reaction time during the task. However, in both cohorts, siblings of patients with schizophrenia showed increased DLPFC activation (inefficiency) relative to controls. These data suggest that hyperfrontality may be heritable.

Three papers have directly linked fMRI abnormalities to gene function. Egan et al[20] examined a well-known functional polymorphism in the gene encoding for the enzyme catechol-*O*-methyl transferase (COMT). A valine (Val)-for-methionine (Met) substitution results in a fourfold difference in the enzymatic breakdown of dopamine, leading to lower dopamine levels from a Val *COMT* allele. In addition to being overtransmitted to patients with schizophrenia, Val *COMT* conferred DLPFC overactivation in healthy subjects similar to that seen in patients with schizophrenia and their healthy siblings. Although the following studies do not relate directly to schizophrenia, they are illustrative of the power of functional imaging to document gene effects. Hariri et al[84] examined the response of the amygdala to fearful stimuli and found that the short allele of the gene encoding for the serotonin transporter (5-HTT) was associated with increased amygdala activation. The short *5-HTT* allele had previously been linked to pathological anxiety and neuroticism, thus suggesting that an inappropriately exaggerated amygdala response may explain these earlier findings. Egan et al[85] examined a functional polymorphism in the gene encoding for brain-derived neurotrophic factor (BDNF) consisting of a Val-for-Met substitution. In addition to reduced secretion of BDNF and impaired memory function, Met *BDNF* was associated with inappropriate activation of the hippocampus during the *N*-back WM task in the two cohorts of healthy subjects. Finally, allelic variations in the *GRM3*[86] and *DISC1*[87] genes have been linked to increased risk for schizophrenia and abnormal fMRI responses of the dorsal prefrontal cortex and hippocampal formation, respectively. In addition, we have repeatedly demonstrated (for reasons that remain unclear), the increased power of fMRI to detect the effect of such allelic variation in healthy volunteers.[87]

CONCLUSIONS

Advances in functional brain imaging coupled with the sequencing of the human genome are promising developments for schizophrenia research. Armed with as little as a broad knowledge of the brain imaging

literature, a standard MRI scanner, and collaborators from a number of other disciplines (notably psychology, radiology, and genetics), interested investigators from around the world are poised to critically apply this approach. Preliminary results suggest that fMRI quantification of brain function is a powerful tool in determining in vivo effects of gene variation. While much of the pathophysiology of schizophrenia remains to be unraveled by brain imaging, we are likely to unravel some of the genetic (and in turn physiological) mysteries that have characterized this disorder

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Traumatic brain injury

12

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INTRODUCTION

New technologies, as well as advances in existing ones, have changed how both healthy and injured brains are evaluated in research and clinical settings. In combination with the traditional neuromedical examination and psychometric testing, functional neuroimaging is providing a means through which additional information about brain structure, function, and recovery may be obtained. Enthusiasm for functional neuroimaging advances can be readily appreciated, yet it must be balanced by the need for empirical evidence and a healthy level of caution. Increasingly, clinicians are encountering advanced imaging techniques (e.g. single photon emission computed tomography (SPECT), positron emission tomography (PET), and functional magnetic resonance imaging (fMRI)) in persons with traumatic brain injury (TBI). Clinical application of most of these techniques still remains investigational, however, within the context of TBI.[1] This chapter provides an overview of several functional neuroimaging procedures and their applications in the context of TBI. It also addresses many limitations of these procedures, with implications for exercising caution if they are utilized in clinical evaluation.

OVERVIEW OF TRAUMATIC BRAIN INJURY

The TBI population presents both challenges and advantages in comparison with other clinical populations. For example, although a disproportionate percentage of individuals who sustain TBI have pre-injury histories of learning disabilities and substance abuse, most individuals with TBI are younger, and, in contrast to many other neurological conditions (e.g. multiple sclerosis and Alzheimer's dementia), TBI in and of itself does not have a progressive or degenerative natural history.

In the USA, the incidence of brain injury has been estimated from 100 to 392 per 100 000,[2] with the most often cited estimate being 200 per 100 000 of the population. These findings are compared with newly analyzed information for three previous large-scale studies: the International Data Bank involving the UK, the Netherlands, and the USA; the North American Traumatic Coma Data Bank; and data from four centers in the UK. The comparisons showed substantial similarities in the incidence of TBI, but also differences in practice that may reflect variations in policy for admission to hospital units.[3]

Penetration of the skull case by objects or fragments is one form of brain injury, but a more common source of TBI derives from the mechanical forces to which the brain might be subjected during a fall, assault, or motor vehicle accident in the absence of skull penetration. Sufficient inertial loading (i.e. the speed at which the head – and therefore the brain – moves, also referred to as 'acceleration') combined with a sudden stop (e.g. head impact or abrupt change in the direction of the head's movement, also referred to as 'deceleration'), may cause the brain to come into abrupt contact with one or more internal surfaces of the skull. Because the posterior areas within the skull are relatively smooth, primary contusions in posterior brain regions are unusual in deceleration events (although direct trauma to the posterior regions of the head may result in localized contusions). More frequently,

however, the anterior portions of the brain (the frontal lobes and anterior temporal lobes) become contused against the bony prominence of the skull (e.g. the sphenoid wing and temporal fossa). This may result in localized contusions of the cerebral cortex and immediate underlying white matter. In addition, the brain may move within the skull, which may result in twisting of ascending and descending axonal pathways. Furthermore, commissural fibers (e.g. the corpus callosum) and other fiber tracts (e.g. the fornices) may also become stretched or torn as the result of differential deceleration of the brain within the skull case. This widespread disruption of axonal tracts is typically referred to as diffuse axonal injury (DAI), and is thought to underlie many of the chronic neurocognitive and neurobehavioral consequences of TBI.[4]

Milder sequelae of head trauma such as postconcussive symptoms have been of growing interest, as well as controversy. The increased attention paid to mild head trauma has been fueled, at least in part, by increased research, increased numbers of outpatient brain injury rehabilitation programs, and increased personal injury litigation in some areas. From a prospective and empirical viewpoint, the literature suggests that the natural history of uncomplicated mild head injury is that of complete or nearly complete recovery. In a meta-analytic review, Binder[5] demonstrated that little of the neurobehavioral symptoms reported following mild head impact could be directly attributed to brain damage. Yet, there appear to be a minority of individuals who continue to report neurocognitive and other symptoms for many months or years following mild head trauma.

METHODOLOGICAL CONSIDERATIONS IN FUNCTIONAL NEUROIMAGING STUDIES OF TBI

Participant selection and comorbid considerations

The presence of a brain injury does not negate or override issues of premorbid educational achievement, language, pre-existing psychopathology, or learning style (including the presence of a formal learning disability). Furthermore, many of these premorbid or comorbid factors may have significant impact on functional neuroimaging findings. For example, the results of both resting and activated functional imaging studies of persons with depression are different from those obtained from individuals without depression.[6] Issues of differential diagnosis and pre-injury considerations are extensive and beyond the scope of this chapter; the reader is referred to other reviews of the topic.[7]

As with many neurological populations, treatment-related factors might pose safety concerns for some types of functional imaging. For example, before undergoing fMRI, individuals with TBI must be carefully screened for implanted medical devices (e.g. infusion pumps for antispasticity medications) or other potential safety risk factors (e.g. embedded shrapnel) that are not uncommon among individuals sustaining brain trauma.

Anatomical/morphometric considerations

By definition, individuals with TBI have acquired some form of change to the brain. Although much of this might be at a microscopic level (in the case of diffuse axonal injury), many individuals with more severe initial injuries will sustain significantly large focal contusions, particularly in regions of the brain that are of interest to cognitive neuroscientists (e.g. prefrontal cortex). In addition, many individuals with severe TBI will undergo removal of brain tissue as part of decompressive procedures or other neurosurgical interventions. This is not unique to TBI, of course, as issues such as brain atrophy in dementia or focal lesions from stroke may cause technical problems for image reconstruction. Historically, this has been addressed through manipulations such as lesion masking,[8] an approach by which lesions are assigned zero-values in each image slice of a series. Recent

advances in software are allowing researchers to address problems encountered when attempting to normalize brains that do not meet a priori software expectations for morphological 'normality'.[9] At present, however, the most obvious and sound methodological approach is to take morphological integrity into account during participant recruitment and selection, which of course might place constraints on sample size or time to complete an investigation.

Cognitive domains of relevance after TBI

Given the differing etiologies and diffuse nature of brain dysfunction following a given TBI, it is difficult to predict the specific neuropsychological sequelae for a given individual. In general, the following types of cognitive impairments are often observed following TBI:[10] deficits in arousal, attention, and capacity for new learning; problems in initiating, maintaining, organizing, or engaging in goal-directed behavior; compromised self-monitoring and decreased awareness of deficits; impaired language and communication; and behavioral manifestations such as agitation, aggression, disinhibition, and depression. The nature, severity and chronicity of these deficits are highly variable between individuals and dependent on the interaction between a variety of factors, including the nature of the brain dysfunction, time since injury, pre-injury neuropsychological and psychological status, family support, and receptivity of physical, psychological, and social environments.

It is notable that several of the domains of cognitive processing that have been widely studied using fMRI are also domains that may be disproportionately impaired after TBI. Among these are working memory, episodic memory, and executive control. The vast majority of imaging studies within these cognitive domains have been in healthy individuals, with only a small number of studies having been published in the TBI literature.

REVIEW OF FUNCTIONAL NEUROIMAGING STUDIES OF TBI

Acute resting studies in TBI

Animal models of TBI have demonstrated a well-defined three-part pattern of change in cerebral metabolic rate of glucose (CMR_{glu}).[11] The initial response is that of brief hyperglycolysis. The second period is characterized by hypometabolism, which typically lasts several hours and is associated with persistent neurological deficits throughout the time that hypometabolism is present. In the third phase, the rate of recovery of neurological and neurobehavioral function closely parallels metabolic improvement. A generally similar triphasic metabolic pattern has been described following TBI in humans.[12–14] Using [^{18}F]fluorodeoxyglucose (FDG)-PET, it has been demonstrated that hyperglycolysis occurs both regionally and globally after severe head injury in humans.[15] Acute metabolic changes often begin to resolve within the first month following injury, regardless of injury severity, but the correlation between the extent of change in disability and the changes in brain metabolism are minimal.[15] Acute oxygen-15 (^{15}O)-PET studies of human TBI have demonstrated significant changes in regional, but not necessarily global, hemodynamics, such as lower contusional and pericontusional blood flow and flow-to-volume ratios.[16] Such changes are seen acutely and occur more in gray matter relative to white matter.[17]

Magnetic resonance spectroscopy (MRS) is a technology that has also been used to characterize early biochemical changes in human TBI,[18] but remains investigational in the differential diagnosis of head trauma.[1] *N*-acetylaspartate (NAA) is one of the more commonly studied neurochemicals that can be examined with MRS.[19] NAA occurs exclusively in the central nervous system and is second only to glutamate in terms of cerebral representation. NAA is generally accepted as a marker of axonal repair, thus its relationship to brain injury has received a significant amount of investigation. Animal studies have

demonstrated TBI-related reductions in NAA reductions at 1 hour after injury.[20] MRS studies of NAA in human TBI have demonstrated that NAA suppression can continue for several months after the initial injury.[21]

Another MRS marker is Cho, which represents choline, phosphocholine, and glycerophosphocholine levels. Cho levels increase in response to tissue inflammation.[21] A decline in NAA accompanied by an increase in Cho is considered as a fairly reliable index of brain injury recovery.

Glutamate (Glu) is an additional MRS-derived marker that has been implicated as an index of TBI severity and may have implications for recovery. Hyperglycolysis results when Glu and other excitatory biochemical compounds are released, and levels of Glu may remain elevated for several days after injury. This may lead to neuronal overexcitation without corresponding oxygen metabolism, and ultimately may result in neuronal death. Glu has been studied in animals,[22] but its utility in human MRS remains investigational.

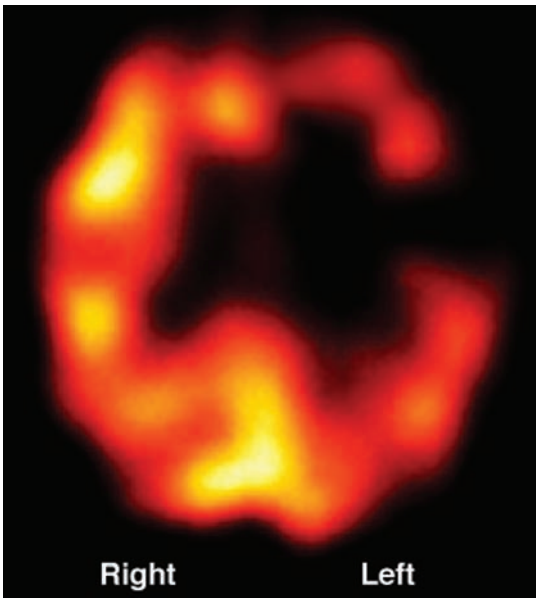

Figure 12.1 Resting xenon-133 (^{133}Xe)-SPECT image demonstrating chronic left anterior temporal hypoperfusion 1 year post severe TBI.

Chronic resting studies in TBI

Resting brain SPECT studies of individuals acquired months (or sometimes years) after moderate and severe brain trauma have demonstrated decreased cerebral blood flow, primarily within prefrontal cortex and anterior temporal lobes[23,24] (for an example, see Figure 12.1). In most of these studies, decreased blood flow and metabolism were generally beyond what might be expected based solely on findings from structural computed tomography (CT) and MRI scans. The presence of decreased resting blood flow and/or decreased metabolism is not, however, in and of itself evidence of non-functional brain tissue.[25]

Numerous investigations have demonstrated that SPECT is superior to CT and structural MRI in the detection of the presence and extent of trauma-related lesions. SPECT has been applied to mild brain injury and has demonstrated regionally decreased blood flow in the presence of normal acute CT scans, but there is much variability across individuals (i.e. no pathognomonic profile emerges). Positive SPECT findings have also sometimes been demonstrated in cases of below-average neuropsychological test scores in cases of mild brain trauma, but it should be noted that SPECT findings in and of themselves are usually not very predictive of neuropsychological test performance.[26]

In spite of advances in technology and data analysis, the utility of SPECT in characterizing specific injury states or predicting outcome remains controversial. SPECT has shown particular utility when correlating neuropsychological parameters with the effects of brain injury,[27,28] but caution must be exercised given that SPECT findings are routinely positive in a variety of medical and neurological disorders,[29–33] as well as in substance use and emotional disorders.[34–43] Some investigators have noted that when used in a prospective design, a negative SPECT scan is a good predictor of a favorable outcome after brain

injury, and that SPECT overall correlates well with the severity of the initial trauma.[44] Still, there are relatively few well-controlled prospective studies of SPECT (and, for that matter, PET or fMRI) that are of clinical applicability in differential diagnosis, prognosis, and intervention.[45,46] The use of normative data[47] rather than subjective impressions of SPECT images will greatly facilitate the development of such clinical utility.

SPECT has been shown to be of use in research studies following brain injury, but there is no particular SPECT profile that is solely clinically pathognomonic for any level of traumatic brain injury.[45,48] The Therapeutics and Technology Subcommittee of the American Academy of Neurology[49] has rated SPECT as an investigational procedure for the study of brain trauma. More recently, the American College of Radiology[1] has rated SPECT as inappropriate (a rating of 2 on a 1–9 scale, with 1 indicating 'least appropriate') in clinically evaluating postconcussion symptoms. In spite of the absence of evidence supporting routine use of SPECT in brain injury, it does appear to be used frequently in clinical and forensic contexts as a means of supporting a diagnosis of brain injury. With increasing evidence and appropriately designed studies, however, and greater specificity of diagnostic criteria (particularly in the context of known or suspected mild head injury), SPECT is likely to be of improved clinical utility in the future.[46,50,51] For example, technetium-99m (^{99m}Tc)-SPECT has been used to examine the therapeutic effects of hyperbaric oxygen on recovery after TBI.[52] SPECT has also been found to be predictive of post-traumatic amnesia acutely after TBI[53] and to be useful in assessing the efficacy of intraventricular shunt placement after TBI.[54]

Several studies have demonstrated the ability of PET to detect brain abnormalities that are not visualized on CT or standard MRI sequences in cases of moderate and severe brain injury.[46] In addition, functional imaging data exist to suggest that there can be regions of physiological dysfunction beyond the boundaries of static lesions (e.g. contusions) seen with structural imaging. This has been demonstrated for many years using both FDG-PET[55] and cobalt-55 (^{55}Co)-PET.[56] Such changes are seen acutely and occur more in gray matter than in white matter.[17] Acute metabolic changes often begin to resolve within the first month following injury, regardless of injury severity, but the correlation between the extent of change in disability and the changes in brain metabolism are minimal.[15]

Although PET would appear intuitively to lend itself well to the many clinical issues that emerge after brain trauma, there are surprisingly few studies that have actually attempted to directly relate functional imaging findings with cognition after TBI. In most of these studies, the findings from neuropsychological and other assessments have been obtained at points in time that were quite disparate from the time at which imaging occurred (for a review, see Ricker and Zafonte[57]). In more carefully designed studies, it has been noted that localized abnormal cerebral metabolic rates in frontal and temporal regions correlate with both subjective complaints and neuropsychological test results obtained during the chronic phase of recovery.[58] In moderate and severe TBI, resting PET studies have demonstrated frontal hypometabolism, with related decreased performance on neuropsychological tests that are mediated by frontal lobe functioning.[59] Through the use of PET, an association between post-TBI anosmia and orbitofrontal hypometabolism has been demonstrated.[60]

ACTIVATION STUDIES IN TBI (^{15}O PET, fMRI)

Activation studies are likely to be far more sensitive to the functional effects of brain injury or disease, as such paradigms introduce in vivo cognitive challenges.[25] The first published PET study[23] to apply a cognitive activation paradigm with individuals that sustained brain injury demonstrated cerebral blood flow changes in the left prefrontal cortex among individuals 3 years after severe

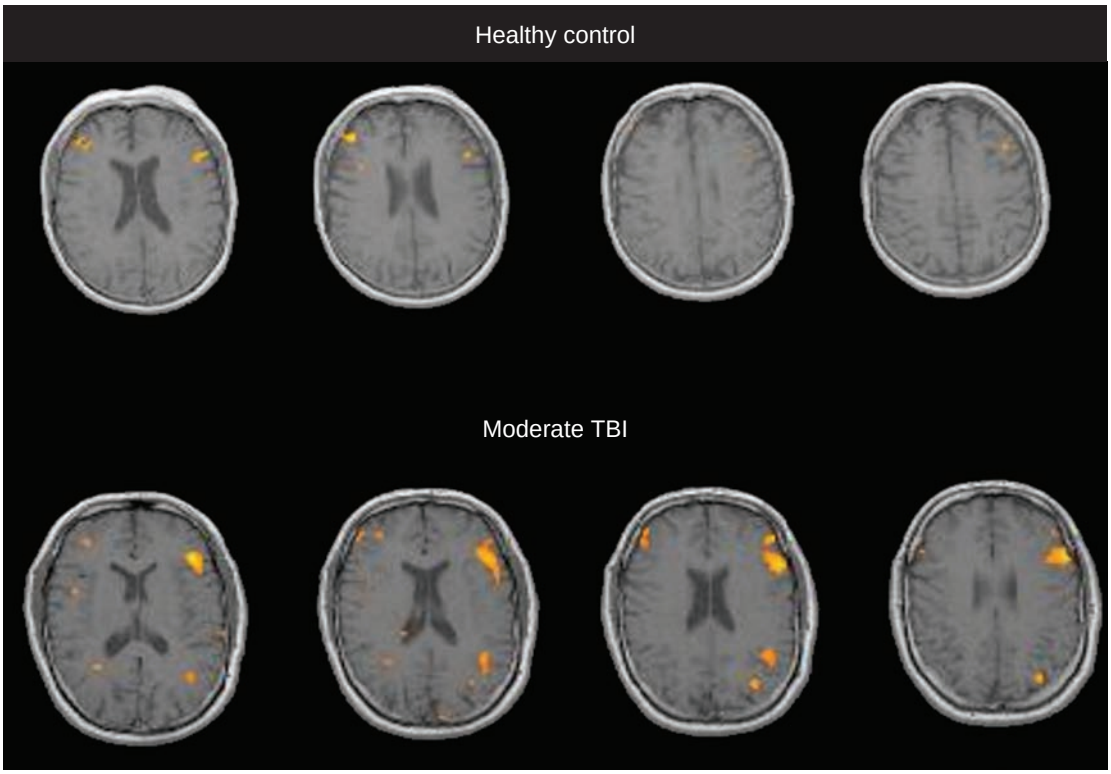

Figure 12.2 Blood oxygen level-dependent (BOLD) fMRI acquired during a modified auditory serial attention task on one healthy individual (top) and one individual approximately 2 years following moderate TBI (bottom). Note the increased activations in the individual with TBI.

TBI during a free recall task when compared with controls. Blood flow increases in TBI patients were also noted, however, in more posterior brain regions during both free and cued recall. In addition, it was demonstrated that during recognition tasks, both the controls and the TBI patients performed at comparable behavioral levels (and within normal limits), yet the TBI patients still demonstrated increased change in regional cerebral blood flow relative to the controls. This suggests that after brain injury, TBI individuals must exert more cognitive effort than controls to attain the same level of overt behavior. In a more recent publication,[61] a different group of investigators also demonstrated comparable findings in a larger sample of individuals with TBI, again using ^{15}O-PET and an episodic verbal memory task.

At the time of writing, there have been very few fMRI studies of TBI patients, although there are several centers with active funding and ongoing protocols that will address this significant dearth in the scientific and clinical literature. In the first fMRI studies of TBI patients,[62,63] investigators examined patients with mild head trauma that had occurred within the previous 30 days. Mild TBI patients demonstrated intact behavioral performance on a verbal working memory task, but they did show increased right-hemisphere lateralized fMRI activation in response to increased working memory load, as compared with healthy controls.

In subsequent fMRI investigations of working memory following moderate and severe TBI, more widespread dispersion of cortical activation was noted during two

different verbal working memory tasks: an adaptation of the Paced Auditory Serial Addition Test[64] and the verbal *N*-back paradigm.[65] In a study of working memory and response inhibition, fMRI was used to demonstrate increased recruitment of cerebral resources following severe diffuse TBI, particularly during response inhibition or when task difficulty was increased.[66] These recent studies again suggest that increased cognitive effort during working memory tasks is reflected by increased brain activation on fMRI (for an example, see Figure 12.2). The nature of this presumed greater expenditure of cerebral resources after TBI is not definitively tied solely to cognitive impairment, however, as increased activations have been demonstrated in an fMRI study of simple motor performance (i.e. finger tapping) among severe TBI patients examined several years after injury.[67] Although fMRI clearly represents a very advanced approach to brain imaging of cognitive correlates compared with SPECT and PET, it has not reached a sufficient threshold of evidence for routine use at any level of injury severity after head trauma.[1,68]

CONCLUSIONS AND FUTURE DIRECTIONS

Over the past decade, there have been exponential advances in functional brain technologies and preliminary investigations in humans with TBI. In spite of these advances, functional neuroimaging techniques remain investigational with regard to routine clinical application to persons who have sustained brain trauma. As with any technology, the transition from 'investigational' to 'routine' application after brain trauma does not occur overnight, nor will it occur exclusively from the publication of case studies or small-sample investigations. This transition will occur after much additional, well-designed, systematic research using large samples of individuals with well-characterized injuries. No-one should misinterpret this as an overly negative assertion, however. It is, in fact, the expectation of the authors that functional neuroimaging technologies will eventually be able to demonstrate sufficient sensitivity and specificity to warrant routine clinical application, particularly among individuals with much potential to be helped by evidence-based rehabilitation interventions.

The development of novel markers (for radioligand studies) and improvements in MR-based technologies will only strengthen imaging research in TBI. Novel agents that label specific neurotransmitter systems or precursors (e.g. 2-β-carbomethoxy-3-β-4-fluorophenyl tropane (CFT), a dopamine transport-specific ligand) are beginning to see application in TBI.[69] More recently, investigators have demonstrated that S100β protein, a serum-based marker of neuronal damage, may actually be measured using MRS. Such biomarkers will not only allow better characterization of TBI pathophysiology but may also be used as a measure of response to pharmacological[70] and other treatments.

Demonstration of true 'brain reorganization' as differentiated from the natural history of the brain's response and recovery from injury remains elusive in human TBI. Nevertheless, existing and yet to be developed functional imaging technologies will likely assist in this important area of functional outcome research. At least one published case study[71] has demonstrated correlations between changes in fMRI activations and improvement in cognitive status following rehabilitation of an individual who sustained a severe TBI. It is anticipated that eventually large-sample studies of individuals with TBI undergoing rehabilitation will yield data supporting the integration of functional imaging and cognitive assessment after brain trauma.

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