# Brain Imaging in Affective Disorders

edited by

Jair C. Soares

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# Series Introduction

In 1609, Galileo Galilei received rumors of a new Dutch curiosity called a spyglass, which could make faraway objects appear closer. He calculated the proper shape and placement of glass and ground and polished the lenses himself. In autumn Galileo focused his instrument on the face of the Moon. The following spring he discovered "four planets never seen from the beginning of the world right up to our day," in orbit around the planet Jupiter. By March, a copy of the book in which he published his findings was on its way to King James in Venice.* Our image of the world we live in, and our place in it, has never been the same.

In the late 1600s, Antony van Leeuwenhoek, after learning to use lenses in examining cloth as a draper's assistant, assembled a configuration of lenses he had ground, turned them on the hitherto invisible world of bacteria, protozoa, and red cells, and made a detailed observation of capillary circulation. Word quickly spread to London, where he was elected a Fellow of The Royal Society. Through Pasteur, Koch, and many others, we now have an understanding of the interplay of organisms that helps us to understand how they, and we, work. We

*For a delightful exposition on this and Galileo's life and relationship to his family and surrounding political world, see Dava Sobel's *Galileo's Daughter* (Walker & Co., 1999).

also now know how to intervene in helpful ways, such as the use of vaccines in the conquest of smallpox and penicillin in the treatment of pneumococcal pneumonia.

Advances in the technologies of science broaden and deepen our understanding of our biologies and pathologies. They also often provide useful weapons in the battle against disease and disability. For those of us who are interested in what goes on inside our bony crania, the brain and its accompanying mind have remained inside a previously unpenetrable "black box." The last two decades of advances in neuroimaging have provided an expanding capacity to explore the anatomic, chemical, and functional aspects of the brain. New techniques have been applied to both normal patients and patients with a variety of neuropsychiatric problems.

Dr. Soares has brought together a stellar group of investigators to help us understand the latest findings in patients with affective and/or anxiety disorders. All clinicians need to master this material—it is the future of our field.

*William A. Frosch*

# Foreword

Affective disorders represent a major cause of disability worldwide. By the year 2020, it is estimated that unipolar affective disorders will be the second leading cause of death worldwide. Therefore, improving our understanding of the cause of affective disorders, enhancing diagnostic methodology, and developing ways of selecting and monitoring treatment are central priorities in medical practice. At the present time we stand on the verge of seeing the implementation of brain imaging techniques to study both the structure and function of the brain in psychiatry and neurology. This book brings together both the range of the most promising imaging methods, as well as the most current information in terms of structural, functional, and neurotransmitter abnormalities in affective disorders. The development of new treatments for affective disorders, which involve rapid transcranial magnetic stimulation to alter brain function in a favorable manner as well as classical pharmacological approaches, can be studied using brain imaging techniques. At the same time, these techniques can play a crucial role in treatment development. This book provides clinicians and researchers with a rich source of information on what brain imaging techniques are available and what they have yielded. Structural studies using magnetic resonance imaging and functional studies using functional magnetic resonance spectroscopy, single photon emission tomography, and positron emission tomography imaging techniques have begun to yield important insights into the circuitry and neurotrans-

mitter dysfunctions in the brain of patients with affective disorders. Early information on differences in brain function between bipolar and unipolar affective disorders lends a biological basis to the clinical differences. The application of these imaging techniques to study key neurotransmitter systems, such as the dopaminergic, serotonergic, and GABAergic systems, are the subject of individual chapters. Spectroscopy has proven to be a valuable tool, not just in the study of the GABAergic system, but also in the study of energy pathways and a variety of lipid membrane indices. Two chapters have been devoted to the applications of brain imaging for the monitoring of treatment responses, as well as the development of new treatments.

This book is an extremely valuable volume for the reader and an important reference for the clinician who wants to know the state of the art, as well as the researcher.

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# Preface

Over the past two decades, the methods for in vivo brain imaging investigations have advanced substantially. Newer and more sophisticated tools for anatomical, chemical, and functional in vivo studies of the human brain have become available and have increasingly been applied to the study of brain mechanisms involved in major neuropsychiatric disorders.

Affective disorders are a major group of psychiatric illnesses that are very common in clinical practice and pose a considerable burden to patients, their families, and society in general. Despite the enormous importance of these major health problems, their causation remains largely unknown. There has been substantial interest in attempting to elucidate the brain mechanisms involved in these disorders. In recent years, some of the newly developed brain imaging methodologies have been applied to investigations on the brain mechanisms involved in these disorders and the mechanisms of action of available treatments. As the causation of these major psychiatric disorders remains largely unknown, there is considerable hope that this newer generation of studies will substantially contribute to major advances linked to developments in the fields of genetics, pharmacology, and neurosciences.

The applications of brain imaging methods to study affective disorders have initially involved anatomical computed tomography (CT) and magnetic resonance imaging (MRI) studies. Subsequently, single photon emission tomog-

raphy (SPECT) and positron emission tomography (PET) began to examine possible abnormalities in brain blood flow and metabolism. More recent investigations with functional magnetic resonance imaging (fMRI) have contributed to higher-resolution studies of brain networks possibly involved in the pathophysiology of these disorders. Developments in chemical imaging with SPECT and PET radiotracer studies as well as magnetic resonance spectroscopy have allowed unprecedented in vivo neurochemical investigations of the human brain. The emerging findings from available studies suggest anatomical, functional, and chemical abnormalities in cortical and subcortical brain regions and in related neuroanatomic circuits possibly involved in mood regulation. This important new area of investigation in neuropsychiatry has been growing rapidly over the past few years.

The application of newly available methods from brain imaging to the study of affective disorders holds substantial promise to elucidate the brain mechanisms implicated in these illnesses. The latest advances in this important new area of research have not yet been reviewed in a comprehensive book providing complete and easily accessible information on the latest developments. This new volume includes chapters from leading authorities in the field and fills an important gap in the neuropsychiatric literature. It will be an invaluable resource for practitioners in the fields of psychiatry, neurology, primary care medicine, and related mental health professions, as well as researchers, graduate and postgraduate trainees, and students. The book is a source of the latest information on new developments in brain imaging applied to the study of brain mechanisms involved in causation of affective disorders and the mechanisms of action of available treatments.

*Jair C. Soares*

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# Brain Imaging in Affective Disorders

# 1

# Brain Imaging Methods in Neuropsychiatry

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## 1 INTRODUCTION

Emotions are major mental processes that are an important part of our lives and have both cognitive and bodily components in humans as well as other species. Sorrow or happiness are ubiquitous in our normal daily experiences, but when pathologically altered, emotions may lead to severe and life-threatening mental illnesses. Primary mood disorders are among the most prevalent psychiatric disorders and are usually accompanied by persistent disturbances in cognition, motivation, sleep, energy, and appetite. Moreover, mood disorders secondary to neurological or clinical pathologies are remarkably frequent, with symptoms that resemble the primary mood disorders. Despite the enormous importance of these disorders, the neuropathological substrates underlying their clinical presentation are not yet understood.

Until the first half of the twentieth century, most data on the neural correlates of disturbances in human behavior were based on postmortem examinations, with obvious limitations. Some of the very first attempts to map in vivo brain activity were performed in the 1950s by stimulating the exposed cortex during brain surgery [1]. It was only in the past two decades that a technological "boom" has resulted in the availability of tools powerful enough to evaluate the living brain in a less limited fashion. These new tools, which are collectively referred to as neuroimaging techniques, are capable of providing valuable structural, chemical, and functional information about the brains of living human subjects and have given researchers unparalleled opportunities to investigate the neural correlates of major mood disorders. It is expected that the knowledge gained from neuroimaging studies will not only help us understand the mechanisms involved and conceptualize these disorders but also elucidate the therapeutic actions of drugs currently used to treat these illnesses [2]. However, in order to successfully apply these various methodologies for clinical research studies that will help us elucidate the pathophysiology of these disorders, it is crucial to understand the kind of physiological information that each neuroimaging technique can provide, as well as the limitations and drawbacks of each. We do not intend to present an exhaustive review of every neuroimaging technique currently in use but rather to provide a broad overview of the imaging methods that are most relevant to the investigation of the neural basis of behavior, with its characteristic spatial and temporal resolution and methodological limitations. In this chapter, we classified the various techniques into three groups—structural, chemical, and functional neuroimaging—encompassing methodologies that are already well established as well as novel ones that are also of potential utility for in vivo brain imaging studies.

## 2 STRUCTURAL NEUROIMAGING

The first neuroimaging studies on psychiatric disorders were done in the 1950s utilizing pneumoencephalography, a technique that allowed the visualization of the ventricular system. Pneumoencephalography consisted of an x-ray after air injection into the encephalon through a lumbar puncture. This very invasive methodology was largely abandoned after the advent of computed tomography (CT). With CT, researchers were able to identify anatomical abnormalities such as ventricular enlargement and cortical atrophy in severe psychiatric pathologies [3]. However, CT presents some important limitations in spatial resolution, mostly due to its limited contrast between gray and white matter and also to its poor visualization of the structures in

the posterior fossa. Furthermore, the fact that it involves exposure to radioactivity is another factor that limits its potential for longitudinal studies that would involve repeated assessments.

The appearance of magnetic resonance imaging (MRI) has set new standards for spatial resolution. Modern high-resolution MRI scanners can generate three-dimensional images with superb anatomical detail, and the technology is flexible enough to allow the acquisition of a vast range of information—e.g., specific contrasts to better display certain tissue characteristics, concentration of some metabolites (magnetic resonance spectroscopy, or MRS), and vascular response to neuronal activation (functional or fMRI). Nuclear magnetic resonance (NMR) technology is based on the magnetic properties of the atomic nucleus. Briefly, NMR can detect atoms that have an odd number of either protons or neutrons and thus possess a net magnetic charge on their nuclei ("spin"), behaving like small bar magnets. For instance, atoms such as $^{1}H$, $^{31}P$, $^{23}Na$, $^{7}Li$, and $^{19}F$ have this property. When the brain is immersed in a strong magnetic field, the nuclei of these atoms loose the random orientation of their magnetic moments and tend to align, reaching an equilibrium state. In a MR scanner, the usual range of this external magnetic field is around 0.5 to 3 tesla (or approximately 10,000 to 60,000 times the earth's magnetic field). Subsequently, the brain is submitted to a short-duration radiofrequency pulse that excites the atoms and induces a transient phase coherence among the nuclei, whose resonance can be detected by a receiver coil. MRI detects the resonance of $^{1}H$ atoms on water, and the abundance of this element on the human body allows the production of highly precise and detailed anatomical images. Of course this is a very simplistic explanation of the physics involved in the NMR phenomenon; the reader interested on more details can find excellent reviews elsewhere [4,5].

Several parameters in the acquisition of MR images can be changed in order to provide better contrast to specific tissues or lesions; for instance, there is fluid-attenuated inversion recovery (FLAIR) MRI, which can differentiate abnormal from healthy parenchyma [6]; and diffusion tensor imaging (DTI), used to map white matter tracts [7]. However, most structural neuroimaging studies in affective disorders utilize T1-weighted images, which provide excellent anatomical definition. Computer algorithms can segment the image into gray matter, white matter, and cerebrospinal fluid (CSF) with great precision. However, fully automated methods are not yet accurate enough to trace anatomical structures without human intervention. Most morphometric studies of psychiatric populations currently utilize an approach known as "region of interest" (ROI), in which a particular anatomical structure—say, the amygdala or caudate—is manually traced directly

on the image, and the resultant volume for this structure is estimated from the number of slices that intersected it. Usually, standardized protocols are employed, defining the boundaries of the brain structure that is traced in a blind fashion (i.e., the researcher is not aware of the identity or diagnosis of the subject being evaluated). Obviously, ROI-based morphometry presents some limitations, as there is a certain degree of arbitrariness in establishing the limits of anatomical structures that do not have clear boundaries. Nonetheless, this method has generated extremely important information on structural brain abnormalities in mood disorders.

Alternative approaches to ROI have been developed in an attempt to minimize the shortcomings of this method. The main goal of these new methodologies is to establish an automated way to identify structural brain abnormalities, replacing the manual tracing of anatomical structures by fully automated or semiautomated algorithms capable to point statistically significant differences among patients and controls. Through specific mathematical procedures, statistical parametric maps of the whole encephalon can be generated to identify which areas display abnormal concentrations of white or gray matter (voxel-based morphometry), or to compare the relative position (deformation-based morphometry) or local shape (tensor-based morphometry) of anatomical structures among different groups [8]. These novel approaches might solve some of the problems related to morphometric measurements. Nonetheless, relevant caveats of structural neuroimaging studies should still be taken into consideration. First, the data provided by MRI studies may reveal that specific areas in the brain that present abnormal shape or volume, but it will hardly unveil the pathophysiological processes underlying these abnormalities. Data from postmortem analyses and magnetic resonance spectroscopy, or MRS (see below), and functional neuroimaging studies will have to be combined with structural anatomical findings in order to provide a better glimpse into the pathophysiology of mood disorders. Second, brain regions or structures that are dysfunctional at the neuronal level but where there may not be any detectable abnormalities on size or gray matter concentration would be considered "healthy" by purely morphometric approaches. Last, there is substantial overlap between the morphometric measurements found on mood disorder patients and healthy controls, even for the anatomical structures on which patients and controls as a group are significantly different. Even with the major advances achieved in the last decade, structural neuroimaging studies have not produced any finding that is specific enough to be utilized as a biological marker of mood disorder. Nonetheless, the preliminary results from structural neuroimaging studies have been providing a critical and ever-expanding framework to develop and test biological models that could contribute to the understanding of the pathophysiology of mood disorders.

## 3 CHEMICAL NEUROIMAGING

Our limited understanding of the pathophysiology of mood disorders is largely at the cellular level. More recently, studies have attempted to unravel the molecular underpinnings of these brain illnesses. Antidepressants and mood stabilizers seem to exert their therapeutic actions, at least initially, through effects either on the chemical communications between neurons or on intracellular signaling. Hypotheses about imbalances in specific neurotransmitters systems in mood disorders were based on those actions. However, until the advent of chemical neuroimaging techniques, these hypotheses could only be tested using postmortem brain tissue or peripheral blood cells. In this section, we discussed the technical aspects of the techniques that can provide neurochemical information about the in vivo human brain: MRS, positron emission tomography (PET), and single-photon emission computed tomography (SPECT).

MRS is a technique that utilizes principles of NMR to obtain measurements of brain chemistry instead of anatomical images. It is based on the observable fact that the nuclei of the elements visible to NMR (e.g., $^{1}H$, $^{31}P$, $^{23}Na$, $^{7}Li$, and $^{19}F$) generate distinct resonance frequencies depending on which molecule they are part of. This phenomenon takes place due to the influences of nearby electrons and nuclei over the magnetic field of the atomic element under study, which generates a characteristic resonance for each molecule. This distinguishing resonance frequency is positioned in a scale referred as "chemical shift," expressed in parts per million (ppm) [9]. For instance, the atom of $^{1}H$ is present in several distinct molecules in the brain. Since $^{1}H$ has a distinct chemical shift in each molecule, it is possible to measure the levels of these molecules through MRS. Figure 1 shows the most common metabolites detected with $^{1}H$ MRS. Considering that different sets of biologically relevant molecules can be identified with MRS (several molecules where $^{1}H$, $^{31}P$, $^{23}Na$, $^{13}C$, $^{7}Li$, and $^{19}F$ are present, for instance), a vast range of chemical and metabolic information can be obtained. First, information on cell membrane integrity and high-energy phosphate metabolism can be acquired with $^{31}P$ MRS studies, which enable measurement of pH, inorganic P, adenosine diphosphate (ADP) and triphosphate (ATP), phosphocreatine (PCr), phosphomonoesters and phosphodiesters. Second, aspects of neurotransmission (glutamate and choline), energy metabolism (PCr, creatine, lactate, and acetate), second-messenger systems (myo-inositol), membrane metabolism (phosphocholine and phosphoethanolamine), nucleotide turnover (adenine, guanine, uridine, and cytosine), and neuronal viability (N-acetyl aspartate) can be assessed by $^{1}H$ MRS. $^{13}C$ MRS has been used to investigate glucose metabolism and its relationship with the glutamate/GABA cycle. Even elements that are not present in biologically rele-

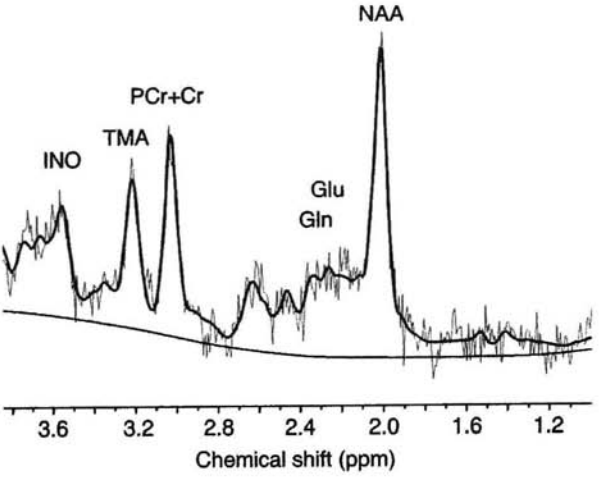


**FIGURE 1** Illustration of a $^{1}$H-MRS spectrum acquired from the dorsolateral prefrontal cortex of a human subject. Metabolites: creatine + phosphocreatine (Cr+PCr), glutamine (GLN), glutamate (GLU), myo-inositol (INS), N-acetyl-aspartate (NAA), and trimethylamines (TMA, which mainly includes phosphorylcholine and glycerophospocholine). The level of each metabolite can be derived from the area under the peak.

vant concentrations in the brain may be useful. For instance, $^{7}$Li MRS can provide interesting information on brain lithium concentration and distribution, whereas $^{19}$F MRS has been utilized to examine the brain concentration of fluorinated compounds, such as fluoxetine and fluphenazine [10,11].

MRS still suffers from some important technical limitations. It is important to note that the concentration of most metabolites under study in the brain is extremely modest. Thus, the signal obtained is quite weak; consequently, MRS must routinely sacrifice spatial resolution to obtain chemical information. The usual MRS study utilizes a volume-of-interest methodology, where the spectrum is obtained from a single voxel ranging from 1 to 8 mL, placed in a specific anatomical region. Moreover, the acquisition times of MRS spectra are usually long; therefore temporal resolution is poor as well. Also, there are several relevant metabolites that are simply not identifiable by MRS due to intrinsic molecular magnetic dynamics. Nevertheless, MRS provides a unique chemical profile of the brain in a noninvasive fashion, and it is expected that more potent magnets and further technical advances will help to improve this important neuroimaging tool further.

The utilization of MRS technology for brain studies of psychiatric disorders is somewhat new. PET, on the other hand, was the first technique

to allow noninvasive functional and metabolic brain studies in human subjects and has been used in research since the early 1970s [12]. PET allows quantification and examination of the spatial distribution of a vast range of molecules in the brain on the basis of specific properties of the decay of radioactive elements. Basically, a molecule of biological relevance is marked with a radioactive nuclide (a PET radiotracer) and injected in the body. The tracer decays rapidly, emitting a positron that collides with an adjacent electron, leading to the annihilation of both particles and to the release of two photons [12,13]. These photons are released in exactly opposite directions, and a very sensitive detector surrounding the brain is able to identify these opposing and coincident photon emissions, ensuring that noncoincident events (such as background radiation) are not recorded by the system [12]. Computer algorithms are then employed to generate three-dimensional maps of the quantity of the radiotracer in a given area of the brain. Most PET radiopharmaceutical agents have very short half-lives (in some cases just a few minutes), and are usually produced in a cyclotron in the same building where the PET scanner is located. The short half-life of a radiotracer has the advantages of allowing repeated measurements at the same scanning session and improving temporal resolution. Nonetheless, it also has limitations related to the cost of preparing the radiotracer and the requirement of quick administration to the patient.

The vast range of radiotracers available for PET studies makes possible the examination of several functional and chemical aspects of the brain. The functional applications (studies of regional blood flow and glucose consumption) are discussed on the next section. Several neurotransmitter systems have been examined with PET radiotracers. Dopaminergic, serotoninergic, opioid, gabaergic, and cholinergic systems can be assessed through a variety of radiotracers that provide information on specific neurophysiological processes [14,15]. For instance, currently available PET radiotracers bind selectively to specific receptor subtypes (e.g., D1, D2, and 5-HT2) or reuptake sites or are analogs of precursor molecules of neurotransmitters (e.g., 6-$^{18}$F-Fluoro-L-dopa) [16]. Furthermore, the in vivo biodistribution and brain kinetics of specific drugs can be evaluated using PET (e.g., $^{11}$C-nicotine and $^{11}$C-flumazenil) [16,17]. With this approach, it is very important to note that radiotracers for distinct aspects of neurotransmission, such as presynaptic reuptake systems and postsynaptic receptors, will present distinct kinetic behaviors due to inherent physiological differences. Also, other factors such as blood flow, intrinsic affinity of the receptor, and peripheral radiotracer clearance will influence the final quantification of the molecule under study. Therefore the analysis of PET radiotracer data is not limited to the raw quantification of the radiotracer in the brain but, in fact, involves mathematical models that take into account variables such as the plasma concen-

tration of the radiotracer, its biodistribution, and the fractions of tracer that are specifically bound to the target receptor or are not bound to receptors in the brain. The most commonly utilized neuroreceptor quantification models are the compartmental models, where physiological "spaces" are modeled as distinct compartments (e.g., the plasma compartment, the intracerebral free tracer compartment, and the specifically bound tracer compartment), and the transfer rates of the radiotracer among the different compartments are estimated mathematically. Comprehensive reviews of models and methods for radiotracer quantification can be found elsewhere [18,19].

PET has indeed revolutionized research in neuroscience, and it is one of the most powerful tools for mapping a vast range of physiological aspects of brain function. Nonetheless, PET also has some important limitations. First, it utilizes ionizing radiation, which obviously limits the number of times that a single person can be evaluated. Also, PET is a very expensive technology. It is estimated that about $5 million is necessary to set up a PET center, not including the costs associated with the maintenance of the extremely specialized multidisciplinary staff required to operate such a facility [12]. Alternatively, a SPECT facility costs only a fraction of the costs of a PET center, and can also be utilized as a powerful research tool for several of the same purposes [20]. SPECT also utilizes molecules marked with a radiotracer. However, in contrast with PET, decaying SPECT radiotracers result in unstable nuclei that emit only single gamma-photons instead of two photons [13]. The SPECT detector covers 360 degrees around the subject's head in order to capture these photons, and registration and processing of this information allow estimation of the location and quantity of the radionuclide in the brain. Since PET and SPECT devices are based on distinct radioactive decay properties, the types of radiotracers utilized by the two methodologies are also distinct. In general, SPECT radiotracers have longer half-lives. The spatial and temporal resolutions of SPECT are generally poorer than those of PET [21]. Like PET, SPECT can also provide functional, chemical, and pharmacological information depending on the radiotracer being utilized. Mathematical models are also necessary for the analysis of SPECT radiotracer data [18,19,21]. SPECT clearly has inferior spatial resolution, but the widespread availability, low cost, and fairly simple instrumentation have guaranteed a wide range of research applications for SPECT technology in neuropsychiatry.

## 4 FUNCTIONAL NEUROIMAGING

Functional neuroimaging techniques have permitted the examination of the neural substrates of cognition and emotion in human subjects by providing the basic tools to explore the spatial and temporal dynamics of regional

neural activation underlying mental functions [22]. Before the advent of neuroimaging technology, the relationship between specific brain areas and cognition could be examined only by studying the neuropsychological deficits in patients with brain lesions. However, this "naturalistic" approach has obvious limitations in the study of brain function, whereas neuroimaging techniques can provide experimental designs sophisticated enough to assess isolated cognitive processes [1,22]. Functional neuroimaging can be divided into two major groups on the basis of physiological rationale underlying the method: (1) techniques that directly evaluate the electrical and magnetic components of neural activation and (2) methodologies that assess the indirect components of neural activity, such as hemodynamic response and energy consumption.

The synchronous synaptic firing of groups of neurons generates electrical currents that are strong enough to be detected on the skull surface. These tiny electrical currents can be detected noninvasively by placing electrodes on the scalp; the more electrodes, the better the spatial resolution obtained. The electrical activity in the brain can be assessed through two distinct procedures: the spontaneous resting-state activity is assessed though electroencephalography (EEG), whereas event-related potentials (ERPs) evaluate electrical events that are time-related to specific motor, sensory, or cognitive tasks [23,24]. The complexity of the spontaneous neuronal activity while a subject is either awake or at rest limits the potential usefulness of EEG to test specific neuropsychological hypotheses. In this sense, ERPs and stimulus-evoked potentials are better suited for evaluating the integrity and temporal dynamics of sensory and cognitive processing systems [23]. Of major interest for the study of neuropsychiatric disorders are the "endogenous" ERPs—i.e., electrical potentials that are not directly related to any sensory or motor stimuli. ERPs have been utilized to assess the temporal and spatial sequencing of neuronal activity in a variety of cognitive functions [25,26]. However, neither EEGs nor ERPs are considered "imaging" methods in the same way that PET or functional magnetic resonance imaging (fMRI) scans are. Although the temporal resolution of EEG and ERP is superb, the spatial resolution obtained is still very poor. The localization of anatomical electrical activation is difficult partly because the surrounding brain tissue, the skull, and the scalp distort the electrical signal. Magnetoencephalography (MEG), on the other hand, is able to generate maps of neural activation with better spatial resolution by detecting the feeble magnetic fields that accompany the electrical synaptic firing, since magnetic fields are not affected by the surrounding tissues and fluids [27]. However, MEG technology requires a much more complex infrastructure than EEG or ERPs, and the anatomical resolution is still far below that of PET and fMRI techniques. As a rule, EEG and MEG face serious technical limitations in

attempting to record magnetic or electric activity below the cortical surface, a shortcoming not present with PET, SPECT, or fMRI methodologies.

Brain functional investigations using PET, SPECT, and fMRI are based on surrogate markers of neuronal activity; among these markers, the hemodynamic response to neuronal activation is undoubtedly the most important. In brief, the firing of a group of neural cells leads to a short-lived increase in the energy demands of these cells. It is believed that an increase in the concentration of specific cell metabolites triggers a local increase in blood flow to supply the metabolic demands of those cells, leading to the localized blood vessel response [28]. Therefore, the spatial correlation between neural activation and increased regional blood flow is relatively precise; however, the temporal correlation between these two events is not immediate. Neuronal activation occurs in a matter of milliseconds, whereas the hemodynamic response is somewhat "sluggish" and requires a few seconds to surge and then subside. Nonetheless, the relationship between neuronal activation and regional increases in blood flow is very robust, and both PET and fMRI technologies explore this phenomenon in order to obtain noninvasive functional imaging of the human brain.

PET studies were the first to quantify changes in regional cerebral blood flow (rCBF) related to sensory and cognitive tasks. Although several radiotracers are available to measure rCBF, the most widely utilized is $H_2{}^{15}O$ owing to its short half-life (around 2 min), allowing repeated measures in a single scan session [12]. SPECT radiotracers, on the other hand, can be used only in steady-state assessment of rCBF owing to their typically long half-lives [21]. The fast, task-related increases in rCBF observed with PET have generated a booming interest in neuroimaging in neuropsychiatry, and a wide variety of technical issues had to be solved in order to amplify and refine the capacity of PET to locate functional activation related to specific mental aspects. Cognitive subtraction, an idea derived from the cognitive neurosciences, underlies the basic design of most functional studies. In brief, this strategy consists of dissecting a simple cognitive function into its most basic units by creating two different tasks that differ only in the very point under study and then subtracting the pattern of neural response during the task of interest from the control task. For instance, in a recent report, Goel and Dolan [29] attempted to isolate a component of humor by having their research subjects perform two specific tasks. On the first, a question is heard and the answer is a joke. On the second, the same question is heard, but the punch line is an affectively neutral sentence. By subtracting the areas activated on the task of interest (joke) from the control test (neutral), the authors identified anatomical regions involved only with the appreciation of humor, disregarding the neural activation involved in auditory perception and semantic understanding. This study was performed with fMRI, not PET; but

similar cognitive paradigms can be utilized with both functional imaging techniques.

As stated above, PET opened up the field of functional neuroimaging, but it is fMRI that has become the most practical and widely available functional brain imaging tool. The advantages of fMRI over PET for brain activation studies are enormous: fMRI is safer and considerably cheaper than PET, produces images with better anatomical resolution, and utilizes a technology that is widely available in most research and medical centers. Moreover, fMRI does not involve radiation, and therefore repeated measurements can be performed. The signal observed with fMRI is based on the fact that the hemodynamic response to neuronal activity usually exceeds the local oxygen needs, leading to an oversupply of oxygenated hemoglobin. Therefore brain areas with stronger neural activity present increased rCBF and thus a higher rate of oxygenated/deoxygenated hemoglobin when compared to surrounding areas. Since the molecule of hemoglobin presents distinct magnetic properties depending on whether it is in its oxygenated or deoxygenated state, it is possible to single out these two molecules and thus identify changes in regional brain activation. This is the most commonly utilized fMRI technique to study brain activation; it is termed BOLD (blood oxygen level–dependent) [30]. fMRI has been extensively utilized to examine the neural correlates of both normal and pathological emotional states and is playing a pivotal role in the functional mapping of emotion in the brain. Sophisticated experimental designs have made possible the evaluation of refined aspects of normal emotional experiences and are currently tackling questions such as how emotion affects other cognitive processes and the influence of personality traits on the reactivity to emotional stimuli [31,32].

Optical imaging is another technique that measures changes in rCBF as indirect markers of neuronal activation. Experiments on exposed living brain cortex in animals have shown that neuronal firing leads to fast changes in the optical properties of the brain region under activation [33]. Noninvasive methodologies, such as near-infrared spectroscopy (NIRS), employ light of long wavelength that is typically able to cross further than visible light into the skull and brain parenchyma. NIRS is capable of measuring cerebral oxygenation changes within a time resolution similar to BOLD fMRI and rCBF PET signals [34–36]. Although the anatomical resolution of optical imaging methods is still far below the resolution provided by fMRI, the low cost and possibility to utilize NIRS at bedside represent potentially important strengths of optical techniques.

Even though the hemodynamic response is the most studied and utilized surrogate marker of neural activity, there are other indirect physiological signs of neuronal activation that can also be measured. The growing demand for energy in the firing neurons leads to quantifiable localized in-

creases in glucose consumption. Early studies with PET utilizing labeled glucose ($^{18}$F-2-fluoro-2deoxy-D-glucose, or FDG) were performed to map neural activation [37], and it was shown that increased glucose utilization is usually bound to increases in rCBF—i.e., metabolic and hemodynamic responses to neural activity occur concurrently. However, the long half-life of FDG (about 2 h) severely limited its use, specifically by preventing quick and repeated measures in the context of cognitive tasks. Because of that, the assessment of rCBF response to neural activity has been a more useful strategy for functional imaging studies. Nevertheless, even the rCBF changes observed by fMRI or PET still have a somewhat poor temporal resolution. As stated above, EEG or MEG are the methods capable of tracking the time course of neural events on a millisecond scale. In order to combine the optimal temporal resolution of EEG and MEG with the superb anatomical details provided with fMRI, new strategies have been under study. Functional modalities such as brain electrical activity mapping (BEAM) and high-density electrical mapping, with up to 256 electrodes, have increased the number of receiver channels and improved their algorithms with the aim of obtaining improved localization of the source of electrical activity and extracting richer spatial information. Techniques such as magnetic source imaging (MSI) utilize a more "hybrid" approach by transforming the coordinates obtained from the magnetic source in order to locate them into high-quality MR images [27,38]. It is expected that, in the next few years, these techniques will be fully validated and will be incorporated into the ever-growing armamentarium of functional neuroimaging methodologies.

## 5 DISCUSSION

The human emotions are currently a topic of major interest for research in cognitive neuroscience [39]. In recent years, we have had unprecedented developments in the field of neuroimaging, with the availability of new tools to examine the brain mechanisms underlying emotional states and other aspects of cognition. Neuroimaging provides a fantastic window into the living human brain and provides a wealth of new information. Detailed three-dimensional anatomical maps, real-time task-related neuronal activation, and noninvasive glimpses into the dynamics of neuroreceptor occupancy are only some examples of the variety of information that neuroimaging techniques can provide. Nonetheless, all this potentially available information will not be useful if it is not accompanied by a solid theoretical framework and specific models of pathophysiology that can be tested. The preliminary evidence gathered from neuroimaging studies has helped to redefine major aspects of the cognitive and psychological theories of emotion. Nonetheless, the most critical questions on the neural basis of emotion and

pathophysiology of mood disorders can be addressed only within a theoretical framework that attempts to integrate neurobiology, environment, and psychological functioning.

A dual approach can be observed in the scientific literature in studies that attempt to utilize neuroimaging for studies of brain function. These two approaches, although seemingly discordant, are not necessarily conflicting. The first could be viewed as reductionist; it is based on the fact that there is substantial evidence showing functional segregation of several brain functions—i.e., activation of localized small regions in the brain are responsible for discrete cognitive or emotional processes. In this framework, strategies such as cognitive subtraction—i.e., the dissection of a certain cognitive or emotional task up to its basic core—are indeed appropriate to identify the exact anatomical brain region whose activation is responsible for the surge of this cognitive or emotional process in the mind. A reductionist approach to the study of the neural basis of emotion is extremely relevant and, in reality, unavoidable given the extreme complexity of the task. However, the brain is a structure with massive interconnections, and it is hard to find a single anatomical area that is not connected by a few synapses with practically all the rest of the brain. The second or connectionist view implies that, although modular processing of cognitive functions can exist, these modules are likely working in an integrated fashion in complex mental activities such as emotion and thinking [40]. Although the design of such connectionist functional studies is very challenging, they will represent crucial steps on the understanding of multifaceted brain activities such as emotion. Moreover, another major challenge concerns the precise definition of the concepts being tested with neuroimaging tools. *Emotion*, for instance, refers to a wide range of phenomena, from specific physiological body responses (e.g., racing heart, sweating) to an integrative conscious experience that can be felt either as pleasant or repulsive, joyous or gloomy. The delimitation of the boundaries of the object under study is a very complex task; it becomes even more challenging and thought-provoking in the study of mental illnesses. Mood disorders, like most psychiatric disorders, are defined by a group of nonspecific signs and symptoms such as depressed mood and lack of energy, for instance [2]. They are broadly defined as syndromes, without a clear pathophysiological process that would define them unambiguously [2]. Accordingly, it is likely that the current psychiatric diagnostic entities as defined in most widely accepted classifications actually include heterogeneous groups with different etiopathologies under the same diagnostic category.

Therefore investigators have been utilizing complementary strategies with the aim of obtaining a better understanding of the pathophysiology of mood disorders. For instance, (1) comparing groups of patients with or with-

out specific clinical characteristics such as presence of psychotic symptoms or positive family history of mood disorders; (2) examining what brain regions are involved in the secondary mood symptoms linked to diseases such as Parkinson's or stroke; (3) assessing the chemical, functional, and even structural changes that result from the use of medications such as antidepressants or mood stabilizers; and (4) obtaining a more complete knowledge of the brain circuits involved in the normal regulation of mood in order to determine whether these circuits would function abnormally in mood disorder patients [41]. These strategies have been utilized in several studies focusing on mood disorders, and preliminary functional, structural, and neurochemical abnormalities have been reported, as reviewed in the other chapters of this book.

In conclusion, the unprecedented technological advances of the last decade have provided powerful tools with which to study the living human brain; it is likely that in the near future these techniques will continue to develop further at an even faster pace. Preliminary findings from neuroimaging studies have begun to identify abnormalities in several aspects of brain functioning in mood disorder patients; these could be key for defining the pathophysiology of these illnesses. It is expected that a more complete understanding of healthy and pathological mood regulation will emerge from research in this area and that such advances will be critical to unraveling the mechanisms involved in mood disorders. Such advances are also likely to contribute to further therapeutic developments in this field by elucidating putative mechanisms of pathology and treatment and guiding future drug development.

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# 2

# Investigation of Mood Disorders by Transcranial Magnetic Stimulation

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## 1 INTRODUCTION

Since its introduction in 1985 by Barker and colleagues [1], transcranial magnetic stimulation (TMS) has become increasingly popular as a neuroscience tool because of its unique ability to noninvasively stimulate the brain and to transiently alter neural activity in targeted regions of the brain. It has been used to probe motor cortex excitability, to map motor and cognitive functions, to study anatomical and functional connectivity, and to modulate brain function with a potential therapeutic aim [2–4]. With regards to mood disorders, the major focus of TMS research to date has been on its clinical utility in treating major depression [5–9]. In this chapter, we introduce various TMS techniques and review the literature on applications that may enhance our understanding of mood disorders.

## 2 BASIC PRINCIPLES

TMS utilizes the principle of electromagnetic induction, which was first discovered by Michael Faraday in 1831. It involves the discharge of a large current (peak current: approximately 5000 amps) from a capacitor through a copper-wire coil. A rapid time-varying magnetic field is induced (rise time, approximately 0.05 msec; field strength: approximately 2 T) at the level of the coil. When the coil is held to the head of a subject, the magnetic field pulse penetrates the scalp and skull and induces a small current parallel to the plane of the coil in the adjacent brain. When the induced current is sufficient (several milliamperes per square centimeter), depolarization of neuronal membranes occurs and hence action potentials are generated. When the coil is held tangentially to the scalp, the induced current flows parallel to the surface of the brain surface, thereby preferentially activating interneuronal elements that are oriented horizontally to the surface of the brain [10]. In the case of the hand area within the primary motor cortex, TMS is thought to predominantly activate the pyramidal cells transynaptically through excitatory interneuronal elements [10–13]. This hypothesis was supported by several studies in humans [10,12,13] and monkeys [11] that showed that the difference in latency between electromyographic (EMG) responses or corticospinal volleys evoked by electrical and magnetic stimulation was due to synaptic transmission time in cortical circuits. This became known as the direct (D) and indirect (I) wave hypothesis, based on the pattern of waveforms recorded at the level of the spinal cord. The D wave represents the first volley of the multiple descending volleys in the spinal cord evoked by transcranial stimulation and is believed to be evoked by direct excitation of pyramidal tract neurons. I waves are the subsequent volleys which appear to be generated by indirect excitation of the pyramidal tract neurons via cortical interneurons. Transsynaptic activation of pyramidal cells seems to be the most likely mechanism provided that the stimulation intensity is low and the induced current is in a direction anterior and perpendicular to the central sulcus [14–19].

The spatial resolution of TMS is thought to be approximately 0.5–1.0 cm within the hand area of the motor cortex [20]. There is a good correlation between the location of the cortical representation of finger movements measured with TMS and with neuroimaging techniques such as positron emission tomography and functional magnetic resonance imaging [21,22]. The depth of direct stimulation achieved with TMS is thought to reach approximately 1–2 cm, sufficient to achieve direct neuronal depolarization only within superficial cortex [20]. This limitation is critical for interpreting studies of neuropsychiatric disorders in which subcortical regions may play a role. Transsynaptic effects of TMS to remote areas of the brain, however,

have been inferred from TMS-induced hormone release (23), and have recently been shown by simultaneous neuroimaging techniques (see Sec. 3, Techniques). Its excellent temporal resolution (a magnetic pulse duration is approximately 0.3–1.0 ms) and wide range of unique applications make TMS a valuable tool that is complementary with other neuroimaging techniques.

## 3 TECHNIQUES

### 3.1 TMS

#### 3.1.1 Single-, Paired-, and Dual-Pulse TMS

TMS may be delivered every few seconds at random intervals (single-pulse TMS), two pulses at short intervals (typically within millseconds) through one coil to the same brain region (paired-pulse (PP) TMS), or two pulses at short intervals to different brain regions (dual-pulse TMS).

Nonrepetitive TMS (non-rTMS) can be used to affect a certain brain region locally and/or through remote effects with precise temporal accuracy. When applied to the primary motor area and combined with EMG recordings, TMS can be used to measure corticospinal excitability [2]. When applied to a specific brain region and combined with appropriate behavioral measures, TMS can be used to modulate a specific cognitive function [4]. Transcranial magnetic stimulation has been combined with other neurophysiological tools such as EMG, electroencephalography (EEG), positron emission tomography (PET), or functional magnetic resonance imaging (fMRI). Alternatively, TMS can be applied to multiple brain regions. Using these techniques, the effects of TMS at remote locations can provide information about effective connectivity between different cortical and/or subcortical structures [4,24–26]. By repeating these measurements, one can study changes over time to examine plastic changes in brain organization in the natural course of a disorder, in recovery, or as a function of learning and therapeutic interventions (for example, see Refs. 3,27,28).

The various motor excitability measures include the following (Fig. 1) (see Ref. 29 for details):

*Motor evoked potential (MEP)*

*Definition*: a twitch induced by magnetic stimuli in a muscle of interest with or without voluntary contraction of the muscle. One can measure the latency to the onset of the MEP as well as the size (peak-to-peak amplitude or the area under the curve of a rectified MEP).

*Mechanism*: reflects predominantly glutamatergic corticospinal excitability. GABAergic drugs are known to suppress I waves.

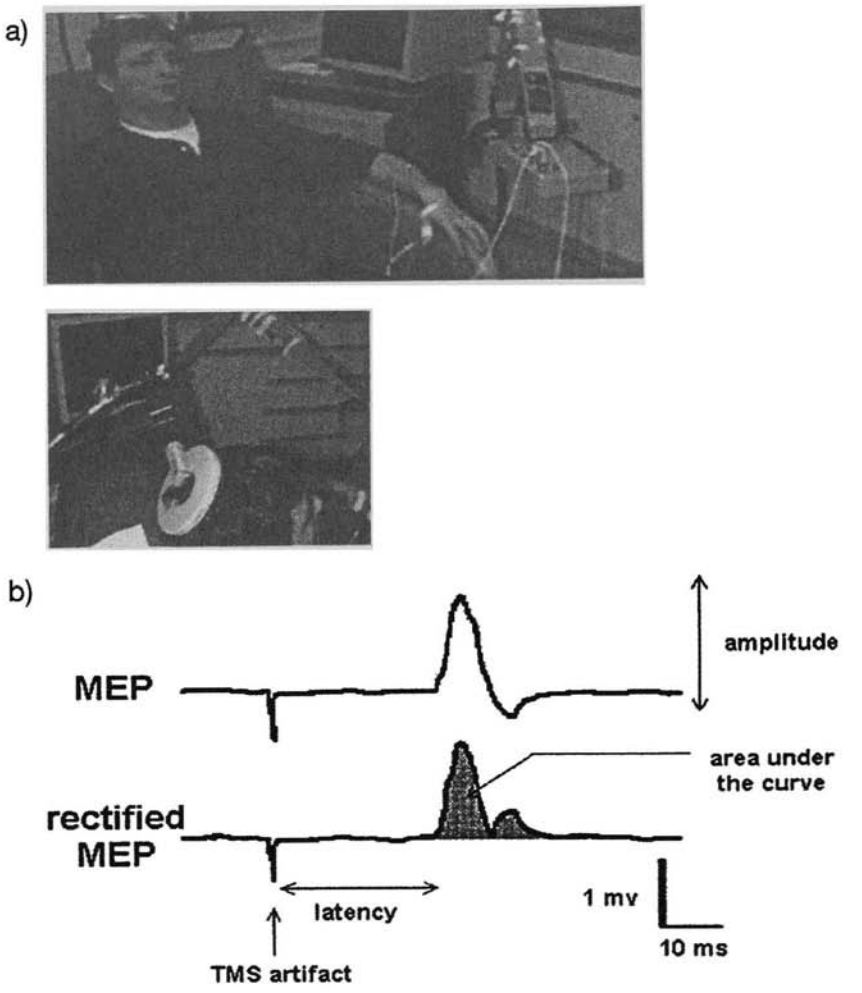



**FIGURE 1** Motor excitability measures: (a) Electromyographic (EMG) recording of an intrinsic hand muscle by magnetic stimulation with a round coil, (b) MEP: motor evoked potential, (c) SP: silent period, (d) PP: paired pulse. A subthreshold conditioning stimulus (CS) produces no MEP. A suprathreshold test stimulus (TS) produces a MEP. An MEP induced by short interval PP (e.g., 1 msec) is smaller than the TS-induced MEP (ICI: intracortical inhibition). An MEP induced by long interval PP (e.g., 10 msec) is larger than the TS-induced MEP (ICF: intracortical facilitation). (From Ref. 48. Reprinted with permission Psychopharmacology. Copyright © Springer.)

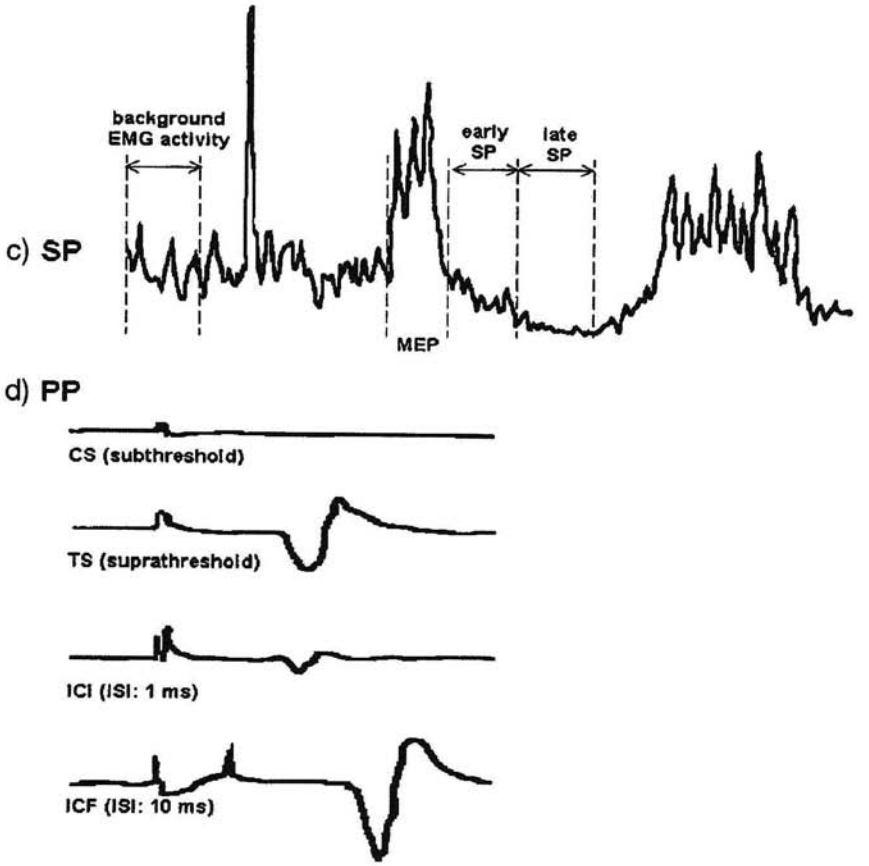



FIGURE 1 Continued

*Motor threshold (MT)*

*Definition*: the minimum intensity of stimulation required to induce a twitch (MEP) of at least 50 $\mu$V in peak to peak amplitude in a muscle of interest in at least 5 out of 10 trials.

*Mechanism*: reflects predominantly the ion channel conductivity and neuronal membrane-related excitability of stimulated neurons.

*Input-output curve, or MEP recruitment curve*

*Definition*: a curve generated by plotting the relationship between MEP size and TMS intensity.

*Mechanism*: reflects corticospinal excitability. The gradient of the generated curve is sensitive to postsynaptic neuronal excitability and benzodiazepines are known to change the gradient.

*Silent period (SP)*

*Definition*: duration of EMG silence after an MEP is elicited in a target muscle under voluntarily contraction.

*Mechanism*: reflects GABAergic or dopaminergic inhibition or the accessibility of the motor cortex by voluntary drive. The early phase of the SP includes spinal motor neuron segmental excitability (most likely Renshaw inhibition and motoneuron afterhyperpolarization), whereas the later part of the SP is purely suprasegmental (possibly cortical).

*Paired-pulse (PP) or intracortical inhibition (ICI) and intracortical facilitation (ICF)*

*Definition*: the influence of one TMS pulse on the MEP evoked by a second magnetic pulse delivered at the same location.

*Mechanism*: PP with a subthreshold conditioning stimulus (CS) and suprathreshold second test stimulus (TS) of very short intervals [interstimulus interval (ISI) of 1.1–4.5 msec] reflects the excitability of neuronal structures responsible for the generation of I waves; PP with subthreshold CS and suprathreshold TS, reflects GABA-, dopamin- and glutamatergic ICI (ISI of 1–5 msec) or ICF (ISI of 7–20 msec); and finally PP, with two suprathreshold stimuli of long intervals reflects intracortical and corticospinal excitability (ISI of 10–40 msec: facilitation, ISI of 50–250 msec: inhibition).

Some of these techniques have been applied in patients with mood disorders to study the relationship of motor excitability to known motor dysfunctions, hemispheric lateralization of affect, global cerebral abnormalities, or abnormalities of neurotransmitter systems (see Sec. 4.1, Probe of Motor Excitability).

### 3.1.2 Repetitive TMS (rTMS)

rTMS can be divided into slow (low-frequency) or fast (high-frequency TMS) rTMS depending on the frequency of stimulation ($\leq$ or >1 Hz). This distinction has been made on the grounds of safety considerations, as fast rTMS carries a greater risk for provoking a seizure [30]. There are also theories about differing effects on cortical excitability of fast and slow rTMS; however, controversy surrounds this distinction and there seems to be a large variability among individuals [31,32].

rTMS can be used to measure local and remote effects as in single-pulse TMS but with possibly less spatial resolution (due to spreading of cortical excitability) and less temporal resolution (due to the delivery of

multiple pulses over a period of time) than single-pulse TMS. For many applications, however, the exact timing of stimulation to a given brain region does not necessarily have to be known. Moreover, rTMS has a distinct advantage over single-pulse TMS in the greater duration of its effects, which could be relevant in a clinical setting [3,33].

Because of these advantages, rTMS has been used in a variety of ways. For example, one can map different brain functions by causing a transient disruption of a given brain region and compare behavioral measures before and after rTMS (see Ref. 34 for review). Although the majority of studies showed disruption, some have reported facilitation of certain cognitive functions either from local disruption and disinhibition to connected regions, from local facilitation or simply from intersensory facilitation [35–41]. One recent and major advance in the TMS literature has been the mapping of local and remote effects of rTMS in combination with neuroimaging techniques such as PET [42–44], single-photon emission computed tomography (SPECT) [45,] and fMRI [46,47].

### 3.1.3 TMS Parameters

The results of TMS research must be interpreted cautiously. Not only may there be variability in the effects of TMS related to the population being studied, but there are also many TMS parameters. These parameter include waveform of the magnetic field (biphasic or monophasic), strength of the maximum magnetic field the stimulating device can induce (approximately 1–2 T), coil type (typically figure-of-eight or round with various diameters), stimulation intensity (percentage of maximum output, often expressed in percentage of the subject's MT), interval (ISI: between single pulses; rTMS frequency: typically ranging from 1–20 Hz; intertrain interval: time between trains of rTMS; intersession interval: time between sessions, usually days to weeks), and site of stimulation.

## 3.2 Combining Brain Mapping Techniques

TMS can be combined with various brain imaging techniques. Such approaches have become increasingly popular in the field of cognitive and affective neuroscience [4,44,46]. Structural or functional images of the brain can be obtained prior to the TMS session and used to target the stimulation to a particular focal brain region. Alternatively, one can combine brain imaging concurrently with TMS to study the time at which activity in a particular cortical region contributes to a given task and to map the functional connectivity among brain regions. Finally, imaging the brain after the application of TMS can be used to study the acute and long-term effects of TMS. These approaches are described in detail in the following subsections.

### 3.2.1 Localization of Site of Stimulation

The use of a frameless stereotactic system to target stimulation sites requires the prior acquisition of high-resolution T1-weighted images [43,44]. One can also use functional imaging maps overlaid onto the MR images to target the TMS to functionally salient regions. Subsequently, the MR image is coregistered to the individual's scalp surface using anatomical landmarks such as the bridge of the nose and the tragus of ear and by localizing these landmarks with a digitizing pen using a radiofrequency (RF)-based or optical tracking system. Real-time monitoring of the coil position relative to the head position is achieved by using the optical tracking system (Fig. 2). This system uses a camera to track the infrared light emitting diodes (LEDs) attached to the coil and head or LEDs attached close to the camera, which then reflect on the reflectors on the coil and head. This method allows us to position the coil relative to the head prior to the experiment, monitor coil and head shifts in real-time during the experiment, and mark the sites of stimulation on the cortical surface of the individual's brain in the MRI im-

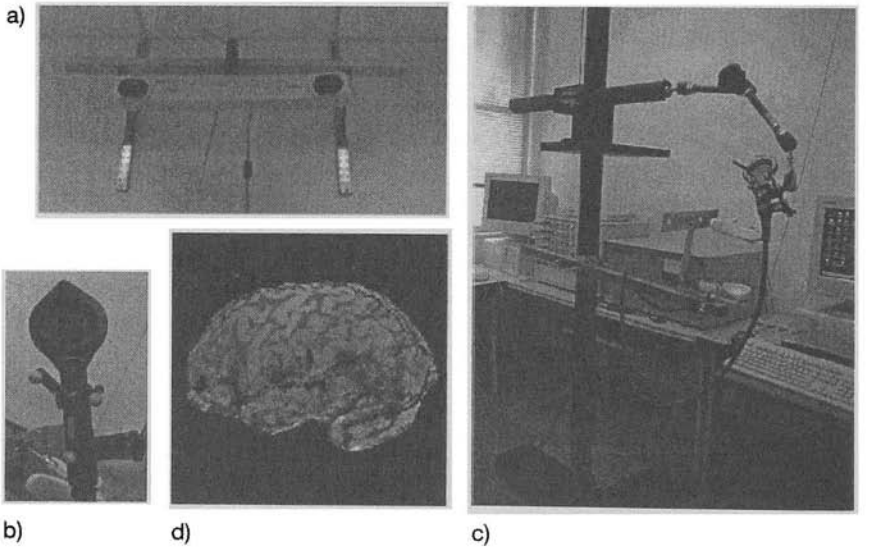



**FIGURE 2** Frameless stereotactic system (Rogue Instruments): (a) Around the two cameras (Polaris) are two rings of emitters, (b) The LEDs reflect on the reflectors attached to the coil and the subject's head, (c) The subject's head rests on a head-coil stand (Bogen) and is coregistered onto their MR image, (d) Target (site of stimulation) can be identified according to their anatomy or functional data.

age. These effects can then be compared with functional data to investigate the difference between the site of disruptive or facilitatory effects of a given behavior induced by TMS and brain activity induced during the same task.

### 3.2.2 Imaging During TMS

Perfusion SPECT (Fig. 3) and fluorodeoxyglucose (FDG) PET were two of the first imaging techniques to be combined with TMS. These techniques allow for tracer injection and magnetic stimulation away from the scanner and hence avoid the more problematic technical issues involved in combining TMS with other imaging techniques (see below and Ref. 49).

Techniques with better temporal resolution, such as EEG (Fig. 4), O-15 PET, and fMRI (Fig. 5), have been conducted concurrently with TMS but entail certain technical modifications. To avoid the saturation of EEG amplifiers by the TMS-induced electrical current, some have used a sample-and-hold circuit that pins the amplifier output to a constant level during the pulse [24]. Using this method, the amplifier recovers in just 100 $\mu$sec after the termination of the magnetic pulse [24], whereas conventional EEG amplifiers remain saturated for 6–10 sec. Others have used conductive plastic electrodes with short leads connected to low-power amplifiers and a special amplifier/analog multiplexor allowing the amplifiers to recover within 15–20 msec [50]. Potential adverse effects such as eddy currents resulting in overheating of the electrodes can be avoided by using low-conductive material and introducing a slit in the electrode [51].

During perfusion PET imaging, the magnetic fields of TMS can theoretically affect the photomultipliers and the related electronic circuits in the gantry of the PET scanner, resulting in the distortion of the crystal identification matrix [43]. Placing mu metal between the coil and the PET scanner avoids this problem but results in an attenuation of the gamma rays arriving at the photomultipliers and a resulting decrease in the number of detected coincidence counts. Others have arranged the TMS coil so that the field maximum is parallel to the axis of the scanner [42]. The other technical issue that requires attention is the possibility of the coil moving during scanning. This can result in an incorrect application of the attenuation correction when calculating the distribution of counts measured in emission scans [52]. To avoid this, one can either place the coil parallel to the scanner axis and outside the field of view or else track the coil and head position throughout the PET scan using an optical tracking system, as described above.

fMRI possesses both the spatial and temporal resolution required to document the action of TMS on a pulse-by-pulse basis. A variety of technical issues however, make the coupling of fMRI with TMS challenging. Formerly, it was thought to be impossible to introduce the TMS coil into the

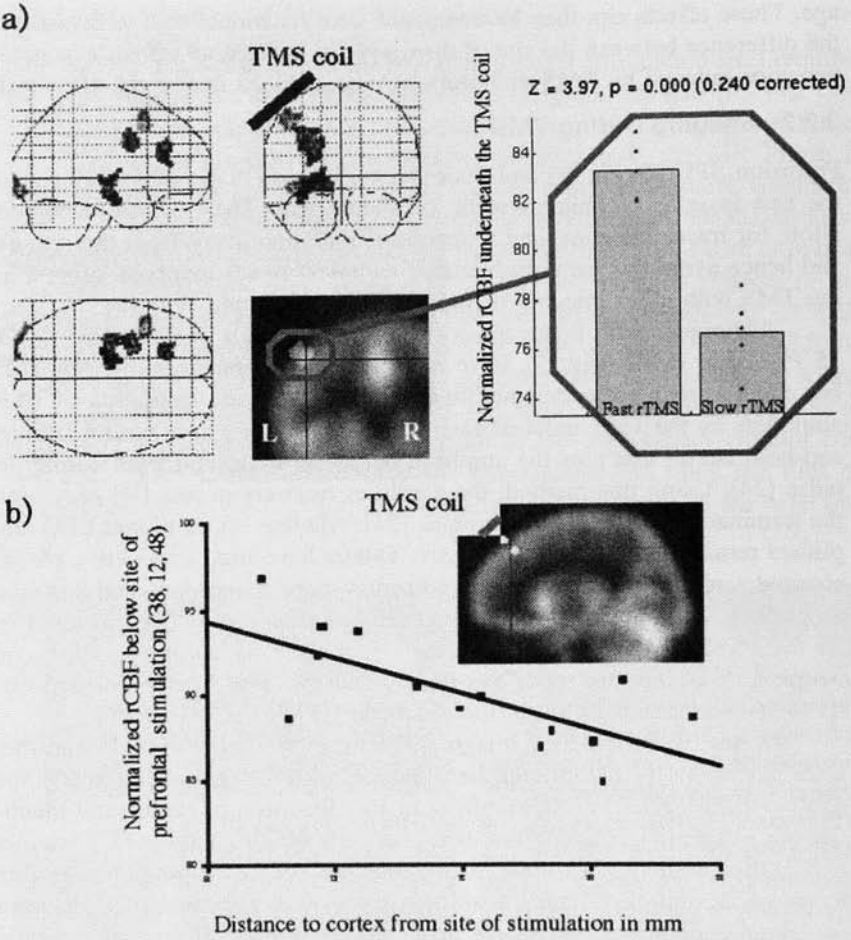



**FIGURE 3** (a) Specific changes related to different frequencies: superimposed increases in left prefrontal and decreases in left mid-cingulate and left hippocampus in rCBF during fast left prefrontal TMS compared with slow rTMS. Note the site underneath the coil (42,14,48). (b) Normalized rCBF (SPECT) below left dorsolateral prefrontal cortex stimulation site in nine depressed subjects. Negative correlation with distance of scalp (TMS coil) to outer cortex. (From Ref. 138. Reprinted with permission from the *Journal of Neuropsychiatry and Clinical Neurosciences* 2001(13):459–470. Copyright © 2001 American Psychiatric Association.)

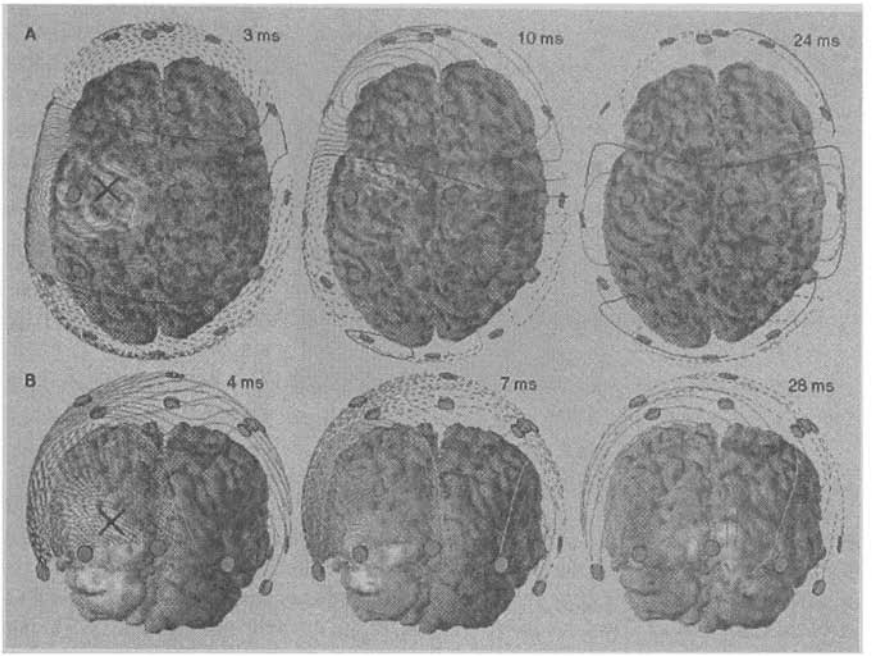



**FIGURE 4** Activation maps based on TMS-evoked averaged EEG responses, subject JA. Minimum-norm estimates of the cortical activity are shown as color maps drawn on three-dimensional magnetic resonance images of the cortical surface of the same subject. The magnetic resonance images (MRIs) were acquired with a Siemens Vision 1.5-T system (Siemens, Germany) using a set of 1-mm-thick sagittal MPRAGE images (TR 9.7 msec, TE 4 msec, TI 20 msec, flip angle 10 degrees). In order to register the EEG data with the 3D MRI images, electrode and coil locations with respect to head landmarks were determined with a 3D digitizer pen (Polhemus, USA). Superimposed, the EEG is displayed as contour maps, with red lines indicating positive potential. The TMS coil position is indicated with a cross. L and R indicate the left and right hemispheres, respectively. (A) The response to left motor cortex stimulation. At latencies of 3 and 10 msec, the ipsilateral hemisphere shows prominent activation; at 24 msec, the contralateral activity dominates (between 10 and 24 msec, the two hemispheres showed simultaneous strong activation). The EEG contour spacing is 1 mV. (B) The response to visual-cortex TMS at 4, 7, and 28 msec poststimulus; the contour spacing is 2 mV. (From Ref. 24. Copyright © 2000 Lippincott Williams & Wilkins.)

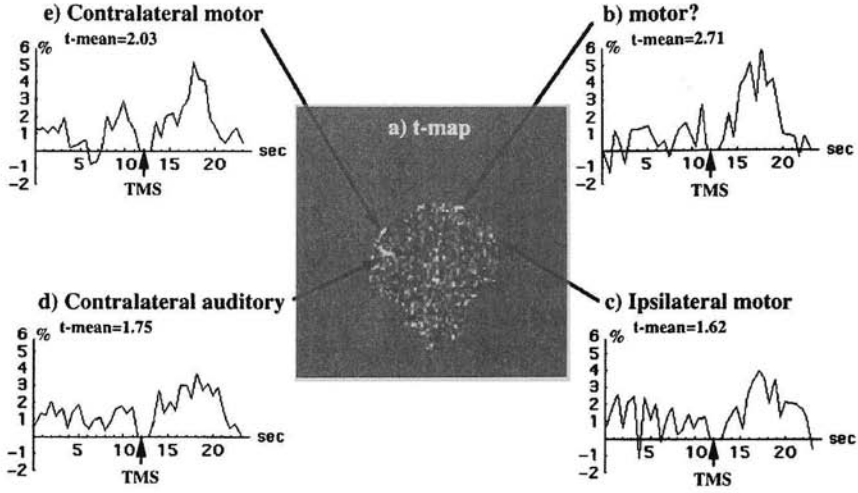



FIGURE 5 (a) A *t*-map indicating clusters of pixels identified with the BOLD response to single-pulse TMS in the medial ipsilateral motor, ipsilateral motor under the TMS coil, contralateral auditory and contralateral motor areas. The cycle-averaged time curves associated with the clusters are as follows: (b) medial ipsilateral motor, (c) ipsilateral motor under the TMS coil, (d) contralateral auditory, and (e) contralateral motor. (From Ref. 26. Reprinted with permission from Wiley-Liss, Inc., a subsidiary of John Wiley & Sons, Inc. Copyright © 2000 John Wiley & Sons, Inc.)

MRI suite due to interference effects and electromagnetic field (EMF) noise. It is possible however, to construct TMS coils from nonferromagentic materials, shield the scanner from EMF noise with a RF shielded panel, and interleave TMS stimulations with fMRI acquisitions so that they do not occur simultaneously [46]. An external computer is used to count the RF synchronization pulses generated by the scanner in its free running steady-state mode, and triggers the magnetic stimulator at appropriate times. Correspondence between TMS-induced blood-oxygen level dependency (BOLD) changes and BOLD changes induced by voluntary movement of a digit has been demonstrated (Fig. 6) [26]. TMS-induced changes in BOLD signal are intensity-dependent [53]. Other design advances include MRI phase mapping of induced magnetic fields [54]. In the near future, it may be possible to map induced electric current applying this technique.

These measures of brain activity in combination with TMS promise to further expand the application of TMS in the study of the pathophysiology

of neuropsychiatric disorders. Such approaches allow one to investigate the relationship between focal cortical activity and behavior, to study the timing at which activity in a particular cortical region contributes to a given task, and to map the functional connectivity between brain regions (for reviews, see Refs. 4 and 55).

### 3.2.3 Imaging of Long-Lasting TMS Effects

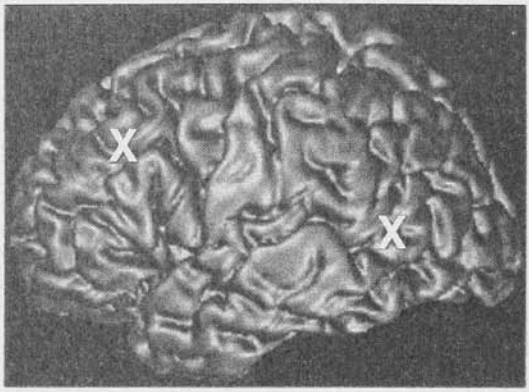
Functional data may be obtained before and after the application of rTMS with the goal of studying the relative change in brain activity due to rTMS treatment [49]. Such studies have been attempted using most functional brain imaging techniques but are limited to rTMS effects that last for a relatively long period of time. The longest effect observed so far has been an increase in cerebral blood flow 1 week after termination of a 10-rTMS sessions [56].

## 4 APPLICATIONS

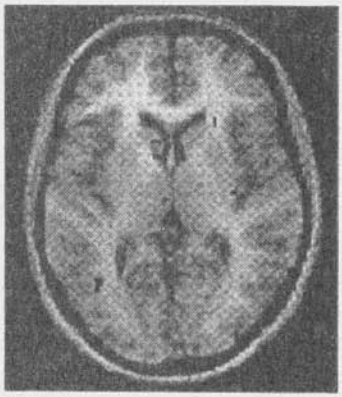
### 4.1 Measurements of Motor Excitability

A number of studies have investigated motor excitability in patient populations using different TMS techniques. The very first attempt to study the neurophysiological properties with TMS in depression and schizophrenia has been conducted by Grisaru et al. [57] and Abarbanel et al. [58]. They studied central motor conduction time (difference in MEP latency between cortical and cervical stimulation) and MEP size. They found no significant difference in central motor conduction time between patients and normal controls. The MEPs induced by cortical stimulation but not cervical stimulation was significantly larger and MT was significantly lower in patients with schizophrenia compared to patients with depression and normal controls. There was no interhemispheric laterality in these measures. While all patients were on chronic medication and the effect of medication on these measures are known to be large, these pioneering studies opened the field to use TMS as a neurophysiolgical tool in the investigation of neuropsychiatric disorders.

Some have addressed the shared symptoms between chronic fatigue syndrome and depression, such as cognitive disturbance, depression, and anxiety. Samii et al. [59] studied postexercise MEP facilitation and suppression in 12 patients with chronic fatigue syndrome, 10 with unipolar or bipolar depression, and 18 healthy controls. Postexercise facilitation/suppression refers to enhanced/decreased MEP responses by preactivation of muscles due to exercise. All subjects were medication-free. Normal control subjects show an initial facilitation of motor excitability after physical exercise followed by a longer period of depressed motor excitability. The authors found that postexercise facilitation but not suppression was signifi-




a)



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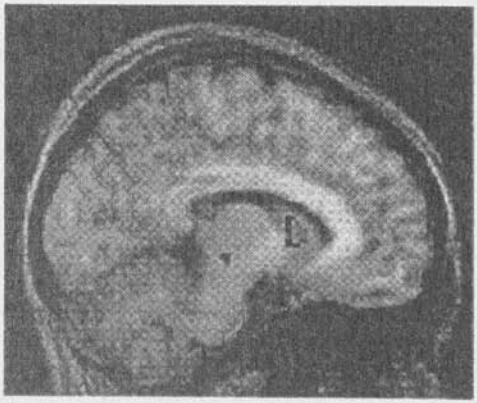


c)

cantly reduced in patients with chronic fatigue syndrome and depression compared to controls. The characteristics of the reduced postexercise facilitation differed across the patient groups, however, in that patients with chronic fatigue syndrome had reduced size of facilitation, whereas the degree of facilitation in the depressed patients was similar to that of controls but decayed more quickly. This observation may relate to some of the symptoms in depression, such as fatigue and motor retardation. However, another study reported somewhat conflicting findings to the notion of a relative dopamine deficit in depressed patients with clinical retardation. In 16 patients with major depressive disorder (MDD; unipolar and bipolar), most of them on medication, Steele et al. [60] found a longer duration of the silent period compared with normal controls (consistent with increased dopamine function). Future studies using a variety of excitability measures in the same group of subjects are necessary to clarify these issues.

Other studies have examined postexercise facilitation and suppression in depressed patients who were on medication. Ten patients with MDD (unipolar and bipolar) were compared with ten healthy controls [61]. Initial MEP facilitation was observed in both groups. In patients, however, this facilitation returned to baseline significantly faster than in controls. In a follow-up study, the authors included patients who had recovered from depression [62]. They compared 10 depressed patients, 10 patients (5 of whom crossed over from the depressed group) who had recovered with medication within the last 6 months, and 10 healthy controls. All the patients were on medication. The currently depressed patients showed reduced mean postexercise facilitation compared to the other two groups, whereas the recovered patients and controls had no significant difference in facilitation. They found no significant difference in a clinical measure of psychomotor performance between the depressed group and the recovered group. Since the TMS measures showed differences between the depressed group and the recovered group and the clinical measures did not, the authors suggest that TMS measurement

**FIGURE 6** (a) Location (*X markers*) of the two stimulation sites, the left mid-dorsolateral prefrontal cortex and the left occipital cortex, on the MRI of one subject in stereotaxic space. (b) Transverse ($Z = 6$) and (c) sagittal ($X = 8$) sections of the statistical parametric map of the change in [$^{11}$C]raclopride BP overlaid on the average MRI of all subjects in stereotaxic space. The peak in the left caudate nucleus shows the location at which [$^{11}$C]raclopride BP changed significantly after rTMS of the left mid-dorsolateral prefrontal cortex. (From Ref. 134. Copyright © Society for Neuroscience.)

may be a sensitive neurophysiological marker of subclinical psychomotor impairment. In addition, although MEP measures have been shown to be sensitive to the effects of pharmacological interventions, these studies suggest that the abnormalities in postexercise facilitation observed in depressed patients exist independent of the fact that they are on medication.

A recent study by Triggs et al. [63] investigated the effects of a therapeutic intervention on motor excitability in depressed patients. Ten depressed patients who underwent high-frequency (20 Hz) rTMS treatment to the left prefrontal area for 2 weeks showed a significant decrease in MT of the ipsilateral hemisphere (i.e., an increase in cortical excitability). These decreases were observed after each rTMS session compared to the presession baseline and also on the second week of rTMS treatment compared to the first. The authors suggested, based on these results, that rTMS to the prefrontal area may alter brain activity at sites remote from the stimulation, which is consistent with functional imaging data [64,65] and spectral EEG analysis [66].

We recently studied whether cortical excitability was asymmetric in medication-free patients with treatment-refractory MDD compared to healthy controls [67]. Prior to this study, we found that in normals, the PP curves of the left and right hemispheres were not significantly different and were stable across two separate days of testing [68]. In addition, we found that ICI but not ICF showed a good correlation across days within the individual indicating the stability of the measurement. In MDD patients using the PP technique, we found that the left primary motor cortex compared to the right showed significantly lower intracortical excitability at an ISI of 6 msec, which is presumed to be affected by both inhibitory and facilitatory interneuronal circuits [67]. There was no significant asymmetry in healthy controls. In another study, we examined intracortical excitability before and after high-frequency (10 Hz) rTMS to the left dorsolateral prefrontal cortex (DLPFC) [69]. Unlike previous studies of the effects of rTMS, our study was designed to assess the correlation between PP hemispheric asymmetry and responsivity to the rTMS therapy. The degree of asymmetry in the patients' pretreatment baseline excitability (i.e., left motor cortex lower than right motor cortex) was predictive of treatment outcome. In addition, we found "normalization" of excitability in treatment responders (i.e., similar PP curves for both hemispheres), whereas nonresponders showed even greater "asymmetry" compared to pretreatment baseline. Although the primary motor cortex is not a region that is considered to be primary in the pathophysiology of depression, these findings provide evidence suggesting that there may be some degree of left hemispheric hypoactivity in depressed patients, which tends to disappear with successful treatment.

Interhemispheric asymmetry and "normalization" with treatment in motor pathways may fit with theories regarding the role of functional brain asymmetry in the regulation of mood and antidepressant effects [70,71]. Segregated basal ganglia (BG) projections innervate the DLPFC, the anterior cingulate region, and the lateral temporal lobe. This observation is consistent with a theory of depression positing that abnormalities in basal ganglia-thalamocortical circuitry may underlie its abnormalities in motor excitability. The high rates of mood disorder occurring in the context of neurologically based motor disorders such as Parkinson's disease, supranuclear palsy, Huntington's disease, Meige's syndrome, and Wilson's disease provide further evidence linking common dysfunctions of the motor and mood systems.

## 4.2 Effects on Mood Regulation

### 4.2.1 Healthy Subjects

Two groups have reported that TMS applied over the DLPFC in normal subjects has a modulatory effect on mood [23,72,73]. In these studies, a single session of high-frequency (10 Hz) rTMS to the left DLPFC at high intensities (110% of MT) induced transient sadness while rTMS to the right DLPFC resulted in elevation of mood. The effects were small, were not apparent to the researchers nor to the subjects, and were detected only by visual analog ratings of mood.

More recent studies with larger sample sizes, however, have thus far failed to find any effects of rTMS on mood, using either high- or low-frequency rTMS [74–79]. These crossover studies included either low- [77,79] or high- [78] frequency rTMS to the left and right prefrontal cortex or high-frequency rTMS to the left prefrontal cortex vs. a sham condition [76].

While these studies did not observe rTMS effects on mood, they did report some interesting findings that may shed light on our understanding of the potential antidepressant effects of rTMS in mood disorders. Reports of increased rapid-eye-movement (REM) latency [74] and increased level of thyroid stimulating hormone (TSH) [23,80] resulting from rTMS are consistent with other studies on the neurophysiological correlates of improvement from depression. In contrast, one study showed a decrease in both TSH and cortisol level with high-frequency rTMS [81].

Others have found other behavioral effects related to mood while rTMS itself did not produce any effect on mood itself. One group studied lateralized changes of facial expressions while watching short humorous movies (e.g., *Mr. Bean*) [78]. In their study, the frequency of laughing reactions increased significantly after left prefrontal rTMS. Another group

found that high-frequency rTMS over the medial-frontal cortex impaired processing of angry but not happy facial expressions of emotion [82].

Interestingly, there is a study reporting that transient hypomanic symptoms have been found in 3 out of 50 subjects following high-frequency rTMS over the left hemisphere [75]. More recently, Schutter et al. [83] reported significant increases in the contralateral EEG theta activity, together with a reduction in anxiety, after low frequency rTMS to the right prefrontal cortex. In summary, the role of prefrontal rTMS in modulating mood in healthy subjects has yet to be determined.

### 4.2.2 Patients with Mood Disorder

In the last several years, there are accumulating suggestions that rTMS may have antidepressant effects, but the clinical utility of rTMS is far from established [33,84]. Initial clinical trials on depression were performed with a small number of pulses of very low frequency TMS (0.017–0.5 Hz) over the vertex with nonfocal round coils [85–87]. More recent studies focused on the left or right prefrontal regions based on certain observations from the literature on depression: (1) DLPFC is involved in the network of brain regions important for mood regulation, having dense connections with the limbic system [88]; (2) prefrontal cortex is important in the efficacy of electroconvulsive therapy (ECT) [89]; (3) hypofrontality is a common feature of depression, especially in the left hemisphere (for a review, see Refs. 90 and 91; for discussion, see Ref. 92); and (4) there is hemispheric lateralization in the control of emotion (right hemisphere: negative emotions and withdrawal behavior, left hemisphere: positive emotions and approaching behavior) [70,71] (for discussion, see Ref. 93).

Most open studies of prefrontal rTMS have reported a significant antidepressant effect [94–101]. Interpretation of these results is complicated by the possibility of placebo response and the nature of this device-based intervention, which involves substantial direct contact with the investigators [102], although the treatment-resistant patients who are often selected as the patient population do tend to have lower placebo response rates [33].

Recently conducted blinded controlled trials tend to support the antidepressant effects of rTMS delivered at low-frequency (1 Hz) to the right DLPFC [8] or at high-frequency (5–20 Hz) to the left DLPFC [5,7,103–105], but some studies have failed to find a difference between TMS and sham [9]. Even in studies that find a statistically significant difference between active TMS and sham, the effect size is often small and of limited clinical value [104]. It may be that the typical 2 weeks of daily stimulation is inadequate to achieve maximal clinical response with TMS. In support of that point, two studies which lengthened the duration of TMS to 4 weeks reported more robust antidepressant response [99,106,107].

Technical challenges in the conduct of controlled clinical trials with rTMS include: achieving true double-blind conditions for both subjects and investigators, developing adequate sham stimulation conditions, positioning and orienting the coil appropriately, and determining the appropriate stimulation intensity. Blinding the investigators that apply rTMS is difficult but could theoretically be achieved by having an unblinded assistant attach either a sham coil that looks and sounds identical to the active coil or an active coil prior to the rTMS session. In all published work to date, the investigator was not blinded, but most controlled trials blind the raters.

Sham conditions typically consist of tilting the coil off the head, an approach whose validity has recently been examined [108,109]. The newly available sham coils, which mimic the sound and scalp sensation without tilting the coil nor inducing current in the brain, may be promising but also require validation [110]. In most studies, localization of the stimulation site is done by measuring 5 cm rostrally to the optimal site to induce MEPs in an intrinsic hand muscle, regardless of individual head size and anatomical variability. With this technique, the site of stimulation can sometimes be located in the premotor cortex rather than in the middle frontal gyrus of the prefrontal cortex [111], and there is considerable variability across subjects in the stimulated site [112,113]. Indeed, there is evidence that the distance from the coil to the middle frontal gyrus correlates with the clinical efficacy of rTMS as a treatment for depression [7]. The concurrent use of the frameless stereotactic system to navigate the coil position relative to the individual's MRI in real time may be one solution to this problem [43,114]. Some researchers have suggested its use in positioning the coil in therapeutic trials of depression [115].

Coil orientation, which determines the direction of induced current, is rarely reported in clinical trials. However, the direction of induced current has long been recognized to be an important factor in stimulating the motor cortex, and a recent study has shown that current direction also influences performance on cognitive tasks when applied over the prefrontal cortex [116]. Hence, it might not be surprising to find a preferred orientation for coil orientation in modulating mood.

With regard to stimulation intensity, most studies so far have set the intensity relative to individual motor threshold. There is no a priori reason to predict that motor threshold should correlate with "prefrontal threshold," but motor threshold has been used as a "stand in" in the absence of a readily obtainable behavioral or physiological measure of prefrontal threshold. One study comparing motor threshold and phosphene threshold showed no correlation [117]. Since motor threshold correlates with distance from the coil to primary motor area [112], one approach has been to obtain a structural

MRI, measure the distance from the coil to the target cortex, and then mathematically correct for that distance [118].

There have been suggestions that low- and high-frequency rTMS depress or excite the motor cortex, respectively [30,119]. Recent studies suggest that these frequency-dependent effects may not be easily generalized to all individuals and a high variability across subjects can be found by measurements of MEP size [31,32]. It is also the case that patients with depression represent a heterogeneous group in terms of their functional brain activity [90,91] and their hemispheric lateralization in the control of mood [70,71]. Thus, predicting the effects of a given frequency of TMS to a given brain area may depend upon the baseline patterns of brain activity, which will vary across individuals and could represent a source of variability in the therapeutic efficacy of rTMS. When these factors are considered alongside the variability in patient population tested, age, concurrent medication, distance from coil to the target site, stimulation intensity, and site of stimulation, it becomes clear that larger trials will be needed to definitively demonstrate the therapeutic efficacy of TMS.

## 4.3 Probe of Functional Connectivity

Until recently, our knowledge of functional neuronal connectivity has relied primarily on data from nonhuman primates or on correlational analyses using a variety of functional neuroimaging techniques in humans. These techniques are indirect, involving either extrapolation across species or the performance of a behavioral task, which may have a confounding influence on activity in the regions under study. A more direct way to study neuronal connectivity, without the necessity of having the subjects engage in a behavioral task, is to measure peripheral responses to centrally applied TMS or acquire functional brain images while applying TMS to a given brain region.

### 4.3.1 Healthy Subjects

Initial studies in normal subjects have been conducted by stimulating brain regions in which either the functional connectivity patterns have been well established in monkeys or humans, or can be compared with functional data. Functional connectivity has been studied with TMS in the following cortical regions: frontal-eye field (PET) [43], primary visual area (Fig. 4) (EEG) [24], primary motor cortex (PET) [25,42,120], (EEG) [24,121], (fMRI) (Fig. 5) [26], somatosensory cortex (EEG) [122], mid-DLPFC (PET) [123], and prefrontal cortex (SPECT) [45]. Dual-pulse TMS or rTMS to multiple locations have been used to study the cerebellothalamocortical pathway (TMS)

[124–126], transcallosal connections (EEG) [24], (TMS) [127–129], and premotor-primary motor cortex interactions (TMS) [130–132]. TMS in combination with functional neuroimaging techniques has also shown dose-dependant reductions (PET) [133], frequency-dependent increases (PET) [120] and intensity-dependent increases in activity (fMRI) [53], and positive correlations with the amount of ICI and ICF (PET) [25] with rCBF in the sensorimotor area. One study has recently shown remote dopamine release in the caudate nucleus by prefrontal rTMS (Fig. 6) (PET) [134]. The effect of ethanol on brain activity has also been studied using TMS and simultaneous EEG (EEG) [135]. Several of these studies may be of direct relevance to research on mood disorders, including the investigations on the functional connectivity of the prefrontal areas [45,123] and the remote effects of dopamine release (Fig. 6) [25]. Studies of functional connectivity in patient populations are described in more detail in the following section.

### 4.3.2 Patients with Mood Disorder

In patients with mood disorders, the main focus of research using TMS combined with other imaging techniques has been the study of alterations in brain activity after rTMS treatment. Kimbrell et al. [136] examined cerebral glucose metabolism and found that a better antidepressant response to 20-Hz rTMS to the left DLPFC was associated with the degree of baseline hypometabolism, whereas antidepressant response to 1-Hz rTMS to the left DLPFC tended to be associated with baseline hypermetabolism. Another study examined cerebral blood flow before and after rTMS treatment [64]. They found a negative correlation between the severity of depression and blood flow in the bilateral medial temporal lobes, left prefrontal cortex, and caudate. Treatment responders showed increased inferior frontal lobe activity compared to nonresponders and this became more significant after treatment. Speer et al. [137] studied the effects of rTMS frequency on brain activity and found that 2 weeks of daily 20-Hz rTMS over the left prefrontal cortex induced persistent increases in rCBF in bilateral frontal, limbic, and paralimbic regions implicated in depression, whereas 1-Hz rTMS produced decreases in more circumscribed regions, including the left amygdala. These data demonstrate frequency-dependent, opposite effects of high- and low-frequency rTMS on local and distant regional brain activity. Nahas et al. [138] reported that repeated daily TMS over the prefrontal cortex in medication-free depressed adults appears to change both local and remote blood flow in a manner that may also depend on the frequency of stimulation and coil to outer cortex distance (Fig. 3). Taken together, these studies suggest that antidepressant response varies as a function of stimulation frequency and depends on pretreatment cerebral metabolism. These data may partly explain initial studies of the inverse effect on the regulation of mood in

normals compared to patients with depression. Most studies combining TMS and neuroimaging techniques in patients with mood disorders found local and remote effects mostly confirming the established patterns of connectivity and brain regions involved in mood regulation in other literature on depression [56,64,65,136–139].

## 5 SAFETY

There is thus far no evidence that TMS leads to structural alterations [140] or clinically apparent lasting impairment in cognitive functions [141,142] even after long-term treatment in humans. Animal studies have failed to demonstrate structural alterations or adverse behavioral changes (for a detailed review, see Ref. 143). Nevertheless, more safety data on the long-term effects of chronic exposure to long courses of TMS would be useful in determining the long-term side effect profile. The major known risk of rTMS is seizure. Seizures have occurred with rTMS when stimulation parameters were sufficiently high, the intertrain interval was sufficiently short, or the subjects had risks factors for seizure (such as structural brain lesion, epilepsy, family history of epilepsy, etc.). Of note, no inadvertent seizures have been reported in appropriately screened individuals since the safety guidelines were established [30] except for cases when a seizure was induced deliberately using rTMS under anaesthesia for the treatment of depression (termed magnetic seizure therapy, or MST) [144,145]. Other less serious side effects include headache, neck pain, scalp pain, and hearing loss (which is mitigated by the use of earplugs). The safety of TMS in pregnant subjects is not known. There is a report of a normal birth following TMS exposure in a pregnant woman [146], but in the absence of systematic safety data, it is generally advised to screen for pregnancy.

## 6 CONCLUSION

We have reviewed the use of TMS as an investigative tool to probe the underlying pathophysiology of mood disorders. Measurements of motor excitability, studies of the role of the prefrontal cortex and other connected regions in the regulation of mood, and studies of cognitive function in normal subjects and patients are examples of some of the applications. Further studies in basic animal research to understand the mechanism of action of TMS, patient studies with improved study designs and larger systematic investigations, and technical improvements will all help to expand research in this field and increase its clinical relevance.

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# 3

# Structural Brain Investigations in Affective Disorders

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## 1 INTRODUCTION

The last decade has witnessed an explosion in advanced neuroimaging technology. Higher-resolution images allow for a greater ability to visualize the brain, and investigators have utilized these advances to better understand the pathophysiology behind neurological and psychiatric disorders. Research in affective disorders has particularly benefited from these advances and will continue to benefit as imaging technology is further refined and the clinical implications of neuroimaging findings are elaborated.

Computed tomography (CT) scans were used for earlier research, but magnetic resonance imaging (MRI) provides several advantages over CT. These higher-resolution images allow for more accurate measurement of structural volumes, which is facilitated by the MRI's ability to distinguish gray and white matter. Additionally, the MRI can discern smaller abnormalities not visible on CT. This chapter reviews recent MRI findings and emphasizes their clinical importance.

## 2 STRUCTURAL IMAGING IN DEPRESSION

### 2.1 Introduction

Structural imaging research in depression has typically focused on two types of studies: research on structural volumes and research on the presence, severity, or volume of high-intensity lesions (hyperintensities) reflecting pathology. Unlike neuroimaging research in many other psychiatric disorders, neuroimaging research in depression has typically focused on the elderly. In some ways this limits the applicability of some of this research, as geriatric depression is often clinically different from depression in younger individuals. However, it also provides a chance to examine brain pathology where it is most common: even healthy elderly exhibit more atrophy and hyperintensities than do younger individuals. Elders are thus a natural population to test hypotheses of which regions are most involved in the pathophysiology of depression.

Beyond distinguishing result by age, we must also consider the presence of psychosis. Psychotic depression has a different clinical course than nonpsychotic depression and demands more aggressive treatment. Some authors have suggested that it may represent less a subtype of depression than a distinct syndrome. To underscore this approach, we present data on psychotic depression separately. Unfortunately, there are less imaging studies in this disorder than in nonpsychotic depression, so results are limited.

### 2.2 Volumetric Measures in Depression

#### 2.2.1 Global Brain Abnormalities and Normal Aging

Many techniques have been used to estimate cerebral atrophy. Indirect measures, such as ventricular volume, the ventricle/brain ratio (VBR), and cerebrospinal fluid (CSF) volumes have been used as indicators of atrophy. Direct brain volume measurements may provide the most accurate measurement of atrophy, but these studies do not all distinguish between different regions, nor do they all distinguish between gray and white matter. To further complicate matters, various investigators have used different techniques to measure brain regions, a fact that may explain some conflicting results. Clinically, these studies also have limited utility, as there are no well-established age- and gender-specific normal values [1]. In general, whole-brain volume data are less informative than data on specific regions that distinguish between gray and white matter.

Studies do clearly demonstrate that the brain's volume decreases with normal aging [2–4]. This is seen in cortical regions but also in subcortical structures such as the caudate, putamen, and thalamus [5,6]. There is also a

suggestion that in normal aging, the frontal lobe may atrophy at a faster rate than the temporal lobe [7].

There are also gender-related differences. Most studies have concluded that men exhibit more atrophy with normal aging than do women [2,3,7,8]. There may be a difference as to where the volume loss occurs, as various studies identify atrophy occurring preferentially in the frontal lobe [7], the parieto-occipital region [2] or as loss of total white matter volume [3]. Although the effect of gender on normal aging of specific structures requires more investigation, these data emphasize the need for age- and gender-matching when performing controlled neuroimaging studies. Unfortunately, most of these studies are cross-sectional; true longitudinal studies are limited. More longitudinal studies are clearly needed to better describe normal aging with respect to each gender.

*Total Brain Volume.* The majority of studies examining whole-brain volumes between elderly depressed subjects and controls showed no significant difference between the two groups. Most studies show no difference between elderly subjects with late-onset depression and controls [9–13], nor was there a difference between subjects with late- and early-onset depression [9]. In contrast, one study has found a decreased total brain volume in those with late-onset depression compared with controls [14]. Gender-specific studies of depressed women have also demonstrated no difference in total brain volume as compared with age-matched controls [15,16]. Neither depression severity [10] nor age of depressive symptom onset, after controlling for the subjects' current age [4], has been associated with total brain volume.

*CSF Volume Measurements.* Despite fairly consistent findings of no differences in total brain volume, another persistent finding in depressed elders is increased ventricle size. Subjects with late-onset depression have increased whole-brain CSF fluid volumes, larger VBRs [11,14,17], and larger lateral and third ventricles than controls [11,14,17,18]. These findings have been interpreted as "atrophy" in depressed subjects, specifically central white matter atrophy; this conclusion conflicts with the results of studies examining total brain volume. The precise neurobiological implication of larger CSF volumes in the presence of normal brain volumes is thus unclear [19].

### 2.2.2 Regional Brain Measurements

*Frontal Lobe.* The frontal lobe has long been implicated in the regulation of both emotion and executive functioning [20]; therefore this region has been highly studied in affective disorders. Multiple studies have demonstrated a smaller frontal lobe volume in depressed elders compared with controls [6,21,22]. Smaller frontal lobes have also been observed in subjects

with familial depression [23]. Only one study found no significant difference in frontal lobe volume between late-onset depression and controls [14], but they defined late onset as after age 50, while other studies use an older age. Laterality may play a role, as part of this reduced volume may be a result of decreased asymmetry in the frontal lobes of depressed subjects. Kumar et al. demonstrated a significant right- greater than left-volume asymmetry in the frontal lobe of controls and subjects with minor depression. This asymmetry decreased (by diminishing right-sided volume) with increasing severity of depression. The group with major depressive disorder did not exhibit a significant difference in volumes of the two lobes [24].

Because the frontal lobe comprises almost one-third of the brain, efforts have been made to examine specific regions, particularly the prefrontal cortex (PFC). Late-onset depressed subjects have a smaller PFC volume than controls [10]. Even after controlling for age and gender, there was a linear decrease in PFC volume with increasing severity of depression. Subjects who met criteria for major depressive disorder had the smallest PFC, nondepressed controls the largest, and subjects with minor depression had intermediate volumes that were still significantly smaller than those of controls [10,11]. The odds ratio for major depressive disorder increased with decreasing PFC volume [24]. To clarify the matter even further, specific regions of the PFC have also been examined. A decreased volume of gray matter in the subgenual PFC has been observed in subjects with familial depression; this finding correlated with decreased blood flow PET scan [25]. Depressed subjects also exhibit a decreased orbitofrontal cortex volume when compared with controls [26]. This finding correlates with postmortem studies that have demonstrated atrophy in the orbitofrontal and dorsolateral regions of the PFC [27].

The frontal lobe may also play a role in psychotic depression. In comparing elderly nonpsychotic depressed subjects with psychotic depressed subjects, the strongest predictor of the presence of psychosis was diencephalic atrophy, left frontotemporal atrophy, and enlargement of the lateral ventricles [23]. Another study demonstrated that the absolute volume of the PFC was smaller in the psychotic group, but it found no difference in volumes of the temporal lobe or lateral ventricles [28].

*Temporal Lobe.* The temporal lobe exhibits no statistically significant reduction in volume when subjects with late-onset depression are compared with controls [11,14]. There are reports of small, statistically insignificant differences in temporal lobe volumes when elders with both major and minor depression are compared with controls [10,29]; however, when the small effect size is coupled with the negative studies, the relevance of this observation must be questioned [19]. Furthermore, temporal lobe volume was not

associated with age of depression onset once controlled for current age [4]. Although the total volume of the temporal lobe may not be associated with late-onset depression, there may be regional atrophy that contributes to the depression pathophysiology of depression. A comparison of elderly subjects with late-onset depression to those with early-onset depression showed that the late-onset group had more left medial temporal atrophy [30]. Another study, combining subjects with late-onset depression and others with late-onset bipolar depression demonstrated greater left sylvian fissure size and greater bilateral temporal sulcal enlargement in subjects with mood disorders when compared with control subjects [31].

*Hippocampus and Amygdala.* In depression research, the hippocampus has been primarily studied in two populations—women and the elderly. The studies in women intentionally excluded men to eliminate brain differences related to gender [16]. This research has demonstrated smaller hippocampi bilaterally in women with recurrent major depressive disorder [15,16] and smaller bilateral volumes of the amygdala core nuclei [15]. These changes were not associated with either current age or age of depression onset but rather with lifetime duration of depression [15,16]. A separate study in a cohort of men and women found a significant 19% decrease in left hippocampal volume and a similar but statistically insignificant trend in the right hippocampus; this lack of significance on the right may have been due to the small sample size. This study did not find any correlation with hippocampal volume and duration of depression [32].

Several investigators have hypothesized that the association between loss of hippocampal volume and duration of depression may be explained by episodes of hypercortisolemia during depressive episodes [16,33,34]. This hypothesis is supported by animal studies that found the hippocampus to be sensitive to the neurotoxic effect of elevated cortisol levels [35–37] and by the demonstration of deficits in hippocampus-mediated memory function in depressed patients with associated hypercortisolemia [38]. One study in depressed subjects and controls found a significant negative correlation between hippocampal volume and both age of depression onset and number of hospitalizations; reduced hippocampal volumes also correlated with specific changes in cortisol concentration [39].

Studies in the elderly have been less conclusive; however, it is important to consider that these studies included both male and female subjects. Several studies have failed to demonstrate a significant difference in the amygdala/hippocampal complex volume between subjects with late-onset depression and controls [14,21,39,40] or between subjects with late-onset compared with those with early-onset depression [40]. One study did find that depressed elders had significantly smaller right hippocampal volumes

than controls, with a trend towards smaller left volumes [41]—a finding similar to that of the study of Bremner et al. in a younger population [32]. These apparently contradictory data are difficult to interpret due to the small size of the amygdala/hippocampal complex and the different techniques used to measure it; many studies measured the amygdala and hippocampus together, which could be a partial explanation of this discrepancy. Additionally, earlier studies estimated its size [14,21,39], while more recent studies used presumably more accurate measurement techniques with good reliability [41].

If reduced hippocampal volume is confirmed in other depressed, elderly populations, does this mean glucocorticoid toxicity is also responsible? Possibly, but it is not the only conceivable etiology. Late-onset depression can precede the onset of Alzheimer's dementia [42–44], which is itself associated with hippocampal degeneration [45,46]. In this case, hippocampal atrophy may be associated with a neurodegenerative process. Further research is needed to clarify the etiology of hippocampal atrophy in individuals with late-life depression.

*Subcortical Gray Matter Structures.* Like the frontal lobe, the basal ganglia have been extensively studied in depression. This research was initially driven by early observations about the increased frequency of depression seen in diseases that affect the basal ganglia, like Parkinson's disease. Smaller caudate nuclei are consistently found in subjects with late-onset depression when compared with control [5,6,9,22] or early-onset subjects [9], although the volume differences between early- and late-onset groups may be specific to the left caudate [30]. The putamen is also smaller in subjects with late-onset depression than in controls, and younger age at the first depressive episode correlated with smaller putaminal volumes [5,6]. Although intriguing, these results are not consistent across all populations. One study of depressed women with a mean age of 53 years demonstrated no significant difference in caudate volumes from controls [47]. Likewise, there is no difference in thalamic volumes between controls and subjects with either late- or early-onset depression [5,9].

## 2.3 Cerebral Hyperintensities in Depression

### 2.3.1 General Associations

Hyperintensities, or high-intensity lesions, appear as bright areas in the brain parenchyma on T2-weighted MR images and have strongly been associated with late-onset depression. They are traditionally classified into three major groups based on their location: periventricular hyperintensities (PVH), deep white matter hyperintensities (DWMH), and subcortical gray matter hyper-

intensities (SCH) (Fig. 1). Large, irregular hyperintense lesions greater than 5 mm are often considered to represent actual infarcts.

In reviewing research in this area, it is important to understand the methodology used for measuring hyperintensities. Many early studies used qualitative scales to estimate hyperintensity severity [48], broadly classifying them into these three regional groups. More recent quantitative studies that examined hyperintensity volume may provide a more accurate representation of their contribution to neuropsychiatric disease.

Hyperintensities are strongly associated with increased age [4,49,50] and are seen in normal aging [48,51]. Because of this research, most studies of hyperintensities have focused on older populations [52]. One large study of community-dwelling elders demonstrated that the majority of subjects had mild DWMH but more frequently PVH; increasing age was the most important factor explaining the presence of hyperintensities [53]. Studies have associated hyperintensities in specific regions with increased age, such as gray and white matter hyperintensities [54], hyperintensities of the basal ganglia [55], and PVH [17]. At least one recent study has not found a relationship between SCH or DWMH and increased age [17].

In addition to age, the other strong association is with medical comorbidity. Hyperintensities appear in Alzheimer's dementia [17,56] and multiple sclerosis [57], but most research has focused on their relationship with cardiovascular disease and cerebrovascular risk factors. Increased hyperintensity severity correlates strongly with cerebrovascular risk factors [48, 50,53], including hypertension [48–50], diabetes [48], history of smoking [50], low cerebral blood flow velocity [48,58], carotid artery disease [48], and prior episodes of cerebral ischemia [49,50,55]. However, hyperintensities can occur in many subjects without obvious risk factors. A recent study using diffusion tensor imaging, a MRI variation exquisitely sensitive to ischemic disease, concluded that hyperintensities had diffusion characteristics similar to those of ischemic lesions, thus supporting a cerebrovascular or ischemic etiology [59].

Because of the correlation between depression and hyperintensities as well as that between hyperintensities and cerebrovascular risk factors, there have been efforts to correlate depression with cerebrovascular risk factors. This hypothesis is complicated when more than just cerebrovascular risk factors are examined; one study found that subjects with late-onset depression had an increased volume of hyperintensity compared with controls, but the difference was not significant after adjusting for overall medical burden [29]. One group initially found no association between cerebrovascular risk factors, severity of depression, or age at depression onset [60], but a later study with more subjects found a significant association between baseline cerebrovascular risk factors and depression at 1 year [61]. Like Kumar et

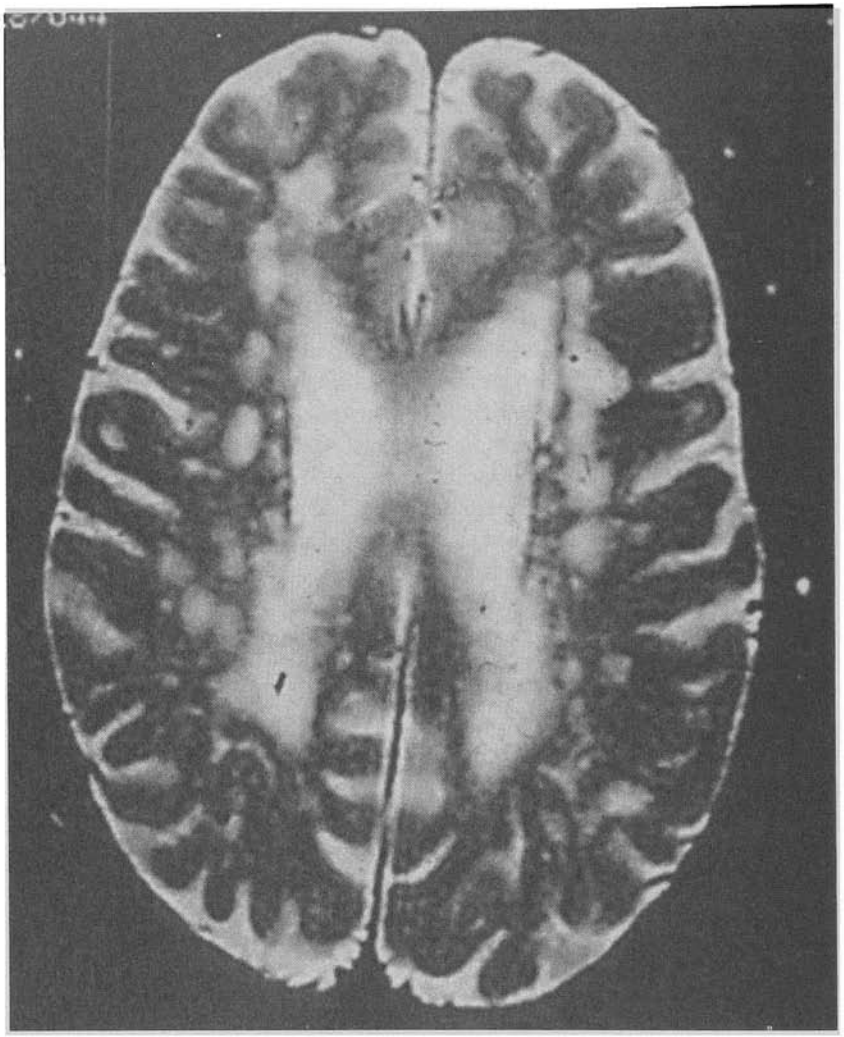

**FIGURE 1** An axial slice with a brain exhibiting severe confluent deep white matter (DWMH) and periventricular hyperintensities (PVHs). PVHs tend to hug the ventricular border, while DWMH is further from the ventricles in the white matter. At this level, subcortical hyperintensities (SCHs) cannot be viewed because subcortical gray matter structures are not visible. (From the Neuropsychiatric Research Imaging Laboratory, Duke University Medical Center, Durham, NC.)

al. [29], they found that this difference was no longer significant after controlling for overall medical burden [61]. Another study found that subjects with late-onset psychotic depression had more cerebrovascular risk factors than nonpsychotic depressed elders [62], but other groups have not found this association [60]. More work is clearly needed to define the relationship between depression, hyperintensities, and cerebrovascular disease, possibly including prospective studies to determine whether the treatment or minimization of cerebrovascular risk factors could decrease the risk of hyperintensity formation or depression.

### 2.3.2 Hyperintensity Location

The majority of studies have noted a significantly greater number of hyperintensities in late-onset depressed subjects compared with age-matched controls [17,18,63–65]. One study in a younger female population did not confirm this finding and reported no significant difference in the total number or volume of hyperintensities between 24 physically healthy women with recurrent major depression (only 5 of whom had late-onset depression), screened to exclude cerebrovascular risk factors, and age-matched controls. Using a regression analysis, this group did discover that age and depression status were significant predictors of total lesion number, indicating that lesions increased with age and were more numerous in depressed individuals [66].

Evidence is strongest for a contributory effect of SCH, particularly as to hyperintensities of the basal ganglia. These are more common in subjects with late-onset depression than in controls [18,65,67–69], although one large study of community-dwelling elderly concluded that lesions of the nonbasal ganglia were more strongly associated with depression than those of the basal ganglia [55]. The putamen may be particularly important, as one study has found that left putaminal hyperintensities predicted assignment into the depressive or control group [70].

PVHs have also been extensively studied, but these results are more mixed. There is a higher frequency of PVHs in depressed elders compared with controls [21] and in subjects with late-onset as opposed to early-onset depression [71]. Other studies, however, have not shown a correlation between PVHs and depression [18,68,72].

Studies examining the relationship between DWMH and depression are more promising. Subjects with late-onset depression have more significant DWMH disease than do controls [18,29] or early-onset depressed subjects [9,71,73,74]. Research has also demonstrated that increased severity of DWMH is associated with increased risk of depression [29,72]. Again, medical comorbidity clearly plays a role; when some of these data were reexamined, the depressed elders had more medical comorbidity than did the controls. The differences in hyperintensities between subjects with early-

late-onset depression became insignificant once they were controlled for cerebrovascular disease and medical burden [9,29,65]. Despite this strong evidence, one large study of over 3600 community-dwelling elders found that white matter hyperintensities were overall not associated with depression [68]. Age of depression onset also did not correlate with whole-brain lesion volume after controlling for current age and intracranial volume [4].

This suggests that hyperintensity location, as much as hyperintensity severity, may be particularly important. One study found that left frontal hyperintensities predicted assignment into the depressed group [70]. This is supported by a study that found the odds ratio of acquiring major depressive disorder significantly increased with a combination of increased hyperintensity volume and decreased frontal lobe volume [29] and meta-analysis that found a strong association between depression and frontal lobe hyperintensities [75]. Another study specifically examined hyperintensities in the prefrontal cortex and found increased lesion density in the medial orbital PFC and a region of the left internal capsule correlated with depression severity [69]. This may be a crucial area for future investigation, as the orbital PFC is implicated in the role of emotional processing and decision making [20].

Studies in those with psychotic depression are more limited. Such patients have more vascular risk factors than nonpsychotic depressed subjects, and one study found a trend toward more DWMH in the psychotic group [62]. Another study found increased hyperintensities in the pontine reticular formation but not elsewhere [23].

## 2.4 Clinical Significance of Neuroimaging Findings in Depression

These findings are intriguing but serve for no more than to satisfy our sense of curiosity unless they contribute to a fund of knowledge that will ultimately guide us toward better care of depressed individuals. And although these findings cannot currently be applied to individual patients, they do correlate with treatment and outcome variables.

Increased severity of SCH and DWMH is associated with poor treatment response to both pharmacotherapy and electroconvulsive therapy (ECT) [54,76,77]. One author, having previously coined the term *silent cerebral infarction* (SCI) in referring to hyperintensities [78], retrospectively found that individuals with more severe SCI had more and significantly longer hospitalizations for depression [79] than those with moderate SCI [80]. More severe SCI is also associated with an increased occurrence of adverse central nervous system reactions to antidepressants [80]. This research has been replicated elsewhere, demonstrating that hyperintensities are

associated with a higher risk of delirium from both antidepressant drug therapy [81] and ECT [82]. Moreover, caudate hyperintensities are associated with an increased risk of antipsychotic-induced parkinsonism [83]. Lesion severity in younger depressed subjects is not significantly correlated with outcome, as it is in elderly depressed subjects [84].

But even beyond treatment outcomes, neuroradiological abnormalities in depressed patients may have grave consequences. Several investigators have explored how hyperintensities or atrophy affects neuropsychological function. Most research associates increased hyperintensity severity, particularly PVH and DWMH, with impaired psychomotor speed [54,76], deficits in executive functioning [54,71,76], and impairment in verbal and nonverbal memory [71,85]. Although one large study of community-dwelling elders found impaired cognitive function to be correlated with severity of white matter hyperintensities [50], damage to specific regions is probably the more important factor. Caudate lesions are associated with impairment on tasks requiring planning and sequencing [86].

Beyond these more general findings, further evidence exists for involvement of the prefrontal cortex. Subjects with psychotic depression exhibit more frontal atrophy and impairment in frontal lobe function and mental processing speed than did nonpsychotic depressed subjects [23]. Decreased PFC volume correlates with impairment on the Wisconsin Card Sort [28], while reduced regional cerebral blood flow in the left medial PFC by PET is associated with depression and cognitive impairment [87]. These impairments may progress; the severity of SCH seen 6 to 24 months previously is associated with greater functional impairment and cognitive decline at follow-up [88]. Increased severity of gray matter hyperintensities is also associated with the subsequent development of frank dementia [89]. There is some suggestion that with antidepressant treatment, cognitive function may improve marginally (although still remaining mildly impaired) [90], but further research is needed to confirm this finding and associate improvement with neuroanatomical findings. This finding is counterbalanced by research indicating that prefrontal dysfunction, specifically psychomotor retardation and abnormal initiation/perseveration scores on the Mattis Dementia Rating Scale (MDRS) [91], is associated with poor or delayed response to antidepressant therapy [92] and increased rates of relapse and recurrence of geriatric depression [93].

The combination of depression and neuropsychological impairment also leads to increased disability, which itself may be worsened by lesion severity. Increased severity of hyperintensity is associated with greater impairment in the activities of daily living (ADLs) [94]. A large study of over 3300 elderly subjects found that ADL and IADL (instrumental ADL) impairment was associated with basal ganglial hyperintensities, but the risk of

impairment further increased if hyperintensities were present both inside and outside the basal ganglia. This study also found that difficulty in one or more IADLs was strongly associated with depression severity, indicating a complex relationship between impairment, mood, and neuroradiological abnormalities [55]. This relationship is further complicated by findings associating prefrontal dysfunction, such as deficits in psychomotor retardation and the initiation/perseveration scale of the MDRS, with greater impairment in IADLs [95].

### 2.5 Vascular Depression

Because of these findings, various authors have proposed that vascular disease may result in a distinct subtype of depression. Initially termed *arteriosclerotic depression* [96], this described a syndrome of vascular changes associated with depressive symptoms, including apathy, psychomotor retardation, cognitive impairment, functional disability, and lack of a family history of mood disorders [54,96,97]. Later, to be more consistent with the current concept of vascular dementia, the term was changed to *vascular depression* [97,98]. Authors have used varying definitions of this syndrome: Krishnan et al. defined it by MRI findings [97] while Alexopoulos et al. used a broader definition that included depressed patients with any vascular disease [99]. Regardless, this term implies both a biological basis for a subtype of major depressive disorder and defines a specific clinical syndrome. Criteria for this subtype, utilizing both MRI findings and clinical symptoms, have been proposed (see Table 1) [1].

### 2.6 Conclusion

Both volumetric studies and hyperintensity measurements correlate with depression. The frontal lobe, particularly the PFC, and the basal ganglia are most associated not only with depression but also with neuropsychological deficits and functional impairment. It is very likely that hyperintensities and atrophy in these regions represent two separate pathways to a common clinical syndrome.

## 3 STRUCTURAL IMAGING IN BIPOLAR DISORDER

### 3.1 Introduction

Historically there has been less structural neuroimaging research on bipolar disorder than on depression. Also, in contrast to the research in depression, most neuroimaging studies in bipolar disorder have focused on younger populations, with several recruiting first-episode manic subjects.

**TABLE 1** Proposed Criteria for Vascular Depression Subtype

Specify vascular subtype (can be applied to the current or most recent major depressive episode in major depressive disorder or bipolar disorder) if A and either B1, B2, or B3:

A. A major depressive episode occurring in the context of clinical and/or neuroimaging evidence of cerebrovascular disease or neuropsychological impairment.
B1. Clinical manifestations may include history of stroke or transient ischemic attacks, or focal neurologic signs or symptoms (e.g., exaggeration of deep tendon reflexes, extensor plantar response, pseudobulbar palsy, gait disturbance, extremity weakness).
B2. Neuroimaging findings may include white or gray matter hyperintensities (lesion >5 mm in diameter and irregular in shape), confluent white matter lesions, or cortical or subcortical infarcts.
B3. Cognitive impairment manifested by disturbance of executive function (e.g., planning, organizing, sequencing, abstracting), memory, or speed of processing of information.

The diagnosis is supported by the following features:

1. Depression onset after 50 years of age or change in course of depression after the onset of vascular disease in patients with onset before 50 years of age.
2. Marked loss of interest or pleasure.
3. Psychomotor retardation.
4. Lack of family history of mood disorders.
5. Marked disability in instrumental or self-maintenance of activities of daily living.

*Source*: Ref. 1.

Upon examining this research, one finds several confounders. Substance abuse is more common in this group than the general population, and bipolar patients more frequently have smoking histories; both may affect neuroimaging results. At a minimum, histories of tobacco use qualify as a cerebrovascular risk factor. Beyond this, there is also the potential confounder of treatment, as chronic lithium use has been associated with an increased volume of certain cortical regions, including the hippocampus [100,101].

## 3.2 Volumetric Studies in Bipolar Disorder

Most research has not shown any sign of global cerebral atrophy in subjects with bipolar disorder [102]. Studies examining ventricular enlargement are more mixed, with some studies not finding increased VBRs in bipolar pa-

tients [103–106] and some finding significant differences in ventricular size from controls [107–112]. One CT study found no progression in ventricular size over several years [113]. Similarly, no difference is seen in cerebral, cortical, or sulcal volume between bipolar subjects and controls [106,110,114,115]. There is an early suggestion that specific cerebellar regions may be atrophic in bipolar patients with multiple past affective episodes, but it is difficult to distinguish disease process from treatment effect [116].

Bipolar subjects generally exhibit no frontal or parietal lobe volume abnormalities, even when specific regions such as the PFC is measured [1,117]. This information alone cannot rule out the contribution of the PFC in bipolar disorder; a small study found an increased metabolic rate in the PFC of manic bipolar subjects [25], while another small study did find a significantly smaller PFC in bipolar subjects compared with controls [102]. There may be differences in the temporal lobes [1], although most research has shown no difference in temporal lobe volume when compared with controls [112,118]. Late-onset bipolar subjects may differ from early-onset subjects, as increased volume of the left sylvian fissure and bilateral temporal sulcal enlargement has been observed in late-onset subjects are compared with controls [31].

The hippocampus may also be involved. Some studies have found a decreased size of the hippocampus when compared with controls [117,118], particularly the right hippocampus [118]. There is a suggestion of increased volumes of amygdala in bipolar subjects [117,119], but there was no correlation between structural volumes and duration or severity of illness [117]. Others have not found differences in amygdala volumes [118] or smaller left amygdala volumes [120].

Data regarding subcortical structural volumes are also mixed. Some studies have reported enlarged thalami and basal ganglia [117]. One report demonstrated larger caudate volumes exclusively in male bipolar patients compared with controls [114]. Other studies have not found an increased volume of the caudate [118], putamen [114,118], or globus pallidus [114].

### 3.3 Cerebral Hyperintensities in Bipolar Disorder

There are significantly fewer studies examining the presence and severity of hyperintensities in bipolar disorder than in depression. Most research shows that hyperintensities are increased in bipolar patients compared with controls, that they are more common in bipolar patients at all ages [121], and that hyperintensities are stable over time [104,108,114,122–124]. Similar trends are also noted in treatment-naïve bipolar patients [109], but there are also studies reporting no significant increase in hyperintensity prevalence in

this population [104]. This last study did not find increased frequency of hyperintensities in bipolar subjects but did find that the risk of bipolar disorder was significantly greater in those with focal signal hyperintensities. One case series, with the majority of patients developing bipolar disorder after age 40, found a predominance of right hemispheric lesions [125].

In the studies that reported an increased severity of hyperintensity in bipolar patients, the most commonly reported region was the deep white matter of the frontal and parietal lobes [73,114,122,124]. In younger bipolar subjects, there is an increased frequency of PVH [104,123,124]. Unlike hyperintensities seen in older patients, these hyperintensities are not located in watershed zones but rather in the deep white matter of the frontal and frontoparietal regions of both hemispheres [115]. Further, these changes seen in young bipolar patients have not been related to any vascular risk factors. Rather, in contrast to late-life depression, there may be a familial component [115]. One study reviewed the MRIs of a family with a strong history of bipolar disorder and reported that the majority of family members had MRI hyperintensity findings, including all those individuals with bipolar disorder [126].

Despite the strong association between hyperintensities and aging, there is a dearth of research into hyperintensities found in elderly bipolar subjects. Such patients do have increased subcortical white matter lesions when compared with controls [124]. Also, one controlled study of subjects with an onset of mania after age 50 reported a high prevalence of DWMH and subcortical ischemic changes [105]. Similar findings were reported in studies of SCI, which found SCI to be more common in late-onset than in early-onset mania. A mixed type of SCI, consisting of basal ganglia and deep white matter infarcts, was found to be more common in bipolar than in unipolar depressives [127].

### 3.4 Clinical Significance of Neuroimaging Findings in Bipolar Disorder

The clinical correlations of neuroimaging abnormalities occurring with bipolar disorder have not been as extensively studied as those in depression. The presence of hyperintensities is related to the presence of psychosis, the likelihood of rehospitalization in 2 years [124], and the total number of psychiatric hospitalizations [122]. One study classified bipolar subjects in terms of poor outcome or good outcome and found that poor-outcome subjects had a greater number and more severe subcortical hyperintensities than did good-outcome or control subjects [128].

As in depression, hyperintensities in bipolar subjects may correlate with neuropsychological impairment—in this case, with deficits on tests of

fluency or recall [122], although some research has been unable to correlate white matter lesions in bipolar subjects with cognitive deficits [129]. Other research has associated larger hippocampal volumes in bipolar subjects with greater cognitive dysfunction [130]. This area of research desperately needs further study. Several studies demonstrate that neurocognitive deficits observed in young bipolar subjects do not fully reverse with remission of mood symptoms [18,131] and that elderly bipolar patients with cognitive deficits may experience progression of their cognitive impairment [132,133]. These findings have not been correlated with neuroimaging or with treatment options.

## 3.5 Conclusion

Given the limited research, it is more difficult to reach firm conclusions about neuroanatomical substrates of bipolar disorder. As in depression, hyperintensities are more common, but unlike the case in depression, they are more common at earlier ages. There may be a familial component to hy-

**TABLE 2** Proposed Criteria for Vascular Mania Subtype

Specify vascular subtype (can be applied to the current or most recent manic episode in bipolar disorder) if A and either B1, B2, or B3:

A. Mania occurring in the context of clinical and/or neuroimaging evidence of cerebrovascular disease or neuropsychological impairment.
B1. Clinical manifestations may include history of stroke or transient ischemic attacks, or focal neurologic signs or symptoms (e.g., exaggeration of deep tendon reflexes, extensor plantar response, pseudobulbar palsy, gait disturbance, extremity weakness).
B2. Neuroimaging findings may include white or gray matter hyperintensities (lesion >5 mm in diameter and irregular in shape), confluent white matter lesions, or cortical or subcortical infarcts.
B3. Cognitive impairment manifested by disturbance of executive function (e.g., planning, organizing, sequencing, abstracting), memory, or speed of processing of information.

The diagnosis is supported by the following features:

1. Mania onset after 50 years of age or change in the course of mood disorder after the onset of vascular disease in patients with onset before 50 years of age.
2. Lack of family history of mood disorders
3. Marked disability in instrumental or self-maintenance activities of daily living.

*Source*: Ref. 1.

perintensities in bipolar subjects, and they also appear related to worse treatment outcomes, although data for this conclusion are sparse. Volumetric studies are mixed, and the findings are complicated by recent discoveries of the potential neurotrophic effects of mood stabilizers.

Although the clinical correlates of neuroimaging findings have been better studied in depression, there is evidence that cerebrovascular disease may contribute to bipolar disorder. To promote future research and further define this syndrome, criteria for vascular mania have been proposed (see Table 2) [1].

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# 4

# Brain Anatomic Circuits and the Pathophysiology of Affective Disorders

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## 1 INTRODUCTION

Affective processes are diverse, and vary in duration, frequency, quality, and intensity. Subtyping affects by temporal domains—with emotions the briefest, moods intermediate, and temperaments the most sustained—offers an approach to better understand these complex processes, which differ in other ways in addition to duration (Table 1). Thus, emotions are brief (lasting seconds to minutes) experiences that are often intense, reactive to acute precipitants, accompanied by acute robust autonomic arousal (increased heart rate and blood pressure), and lead to actions. In contrast, moods are of longer duration (lasting hours to days), somewhat less intense, range from reactive to spontaneous, may be accompanied by more subtle (hypothalamic-pituitary-adrenal axis dysregulation) arousal, and tend to result in cognitions. Temperaments are the most sustained (lasting years to decades), generally the least intense, and largely constitutional, but they can occasionally be modified by persistent experiential factors. They generally lack autonomic features and yield integrative styles of interacting with the environment.

**TABLE 1** Temporal Domains of Affects

| | Emotions | Moods | Temperaments |
|---|---|---|---|
| Duration | Seconds to minutes | Hours to days<br>Weeks to months[a] | Years to decades |
| Relative intensity | High | Intermediate | Low |
| Precipitants | Acute | Variable/absent | Genetic/chronic |
| Autonomic arousal | Acute, robust | Variable/subtle | Absent/subtle |
| Products | Actions | Cognitions | Cognitive-affective interactions |
| Possible neural substrates | Anterior limbic/ brainstem | Anterior cortical/ anterior limbic | Anterior cortical/ anterior limbic/ brainstem |

[a]In mood disorders.

These temporal domains of affective experiences are related to one another, with different temperaments yielding predispositions to varying moods, which in turn yield tendencies to diverse emotions. Influence also occurs in the opposite direction, with intense emotional experiences in rapid succession yielding particular moods, and repeated or chronic moods on occasion resulting in temperamental shifts.

Below we describe how considering affective processes with respect to these temporal domains and integrating recent brain imaging findings may aid in exploring differential neurobiological substrates of such processes, yielding insights into relationships between brain anatomic circuits and the physiology of affective experience both in health and in mood disorders.

Emerging evidence, supported by recent functional brain imaging observations, suggests that emotions may be mediated by phylogenetically older anterior paralimbic structures. Such structures have access to motor circuits and could thereby provide primitive, perceptually triggered, action-oriented affective processing. Moods may be related to more recently evolved overlying prefrontal neocortical elements and could thus provide more refined, complexly (perceptually, mnemonically, and cognitively) trig-

gered, cognition-oriented affective processing. Integrative aspects of emotion and mood processing may be related to activity in prefrontal and anterior paralimbic basal ganglia–thalamocortical circuits. To date, there has been less exploration of the neuroanatomical substrates of temperament, but some studies have explored proposed brainstem-subcortical-cortical network models, which reflect integrative aspects of temperament. In this chapter we review how functional brain imaging research has been increasingly useful in testing hypotheses regarding the neuroanatomical substrates of affects across different temporal domains.

## 2 NEUROANATOMICAL SUBSTRATES OF AFFECTIVE PROCESSES

### 2.1 Temperament

Theories of temperament have existed since antiquity and reflect some of the earliest attempts to understand affective processing. In ancient Greece, humors or bodily fluids (blood, phlegm, black bile, yellow bile) were thought related to combinations of qualities (wet, dry, hot, cold) associated with elements (water, earth, fire, and air). Thus, blood was hot and wet, black bile cold and dry, phlegm cold and wet, and yellow bile hot and dry. Galen (ca. 170) suggested that excesses of individual humors were related to temperaments. Thus, sanguine (happy) temperament was related to excessive hot wet blood, melancholic (sad) to excessive cold dry black bile, phlegmatic (calm) to excessive cold wet phlegm, and choleric (irritable) to excessive hot dry yellow bile. This was thus a two-(sanguine/melancholic and phlegmatic/choleric) dimensional model of temperament. In early times only limited distinction was made between temperamental types and mood disorders. Humoral theory was integrated to a limited extent with anatomical theory. Thus, humors were thought to exert their effects from within the cerebral ventricular system, which was thought crucial to sensory, affective, and cognitive processing. The humoral and ventricular theories persisted for centuries, into medieval times (Figure 1), and only declined with advances in neuroanatomy and neurophysiology, which began in the Renaissance. Such advances yielded emerging theories of the neural substrates of affective processes which focused more on mood and emotion (as described below) than on temperament.

Theories of temperament and personality continued to evolve over time, and ultimately attempts were made to relate such theories to neuroanatomical substrates. Eysenck integrated clinical observations with earlier theories to initially develop two major dimensions of personality, namely introversion/extraversion and neuroticism/stability [1]. These axes were di-

agonal to the above classical formulation, so that sanguine temperament was viewed as extraverted and stable, melancholic introverted and neurotic, phlegmatic introverted and stable, and choleric extraverted and neurotic. Introverts tend to be reclusive, less socially active, quiet, reserved, and introspective, preferring books to people, while extraverts are gregarious, socially active, cheerful, excitable, impulsive, and assertive.

Eysenck proposed that introverts have more active, and extraverts less active cortical activity/arousal as regulated by ascending reticulocortical activating system (ARAS) pathways [2,3]. In contrast, he suggested that neuroticism or emotionality was related to high levels of "visceral brain" (limbic—i.e., amygdala, hippocampus, cingulate, septum, and hypothalamus) activity. Eysenck later expanded his model with a third (psychoticism/normalcy) dimension, which ranged from clinically psychotic through antisocial through normal behavior.

Gray focused on behavioral inhibition and suggested that introverts had more active and extraverts less active reticulo-septal-hippocampal-orbitofrontal-cortical pathways mediating behavioral inhibition [4,5]. He later proposed a two-dimensional model with axes diagonal to those of Eysenck's schema [6]. Thus, an anxiety (inhibition, avoidance) dimension ran from high anxiety (high neuroticism, high introversion, low psychoticism) to low anxiety (low neuroticism, low introversion, high psychoticism) and an orthogonal impulsivity (approach) dimension ran from high impulsivity (high neuroticism, low introversion, high psychoticism) to low impulsivity (low neuroticism, high introversion, low psychoticism).

Gray proposed that the anxiety (behavioral inhibition) system consisted of the aforementioned reticulo-septal-hippocampal-orbitofrontal network and the impulsivity (approach) system consisted of dopaminergic reward circuitry running from brainstem (ventral tegmental area) to limbic and neocortical regions. He postulated that cortical arousal through the ARAS was related to the sum of behavioral inhibition and approach system activity and

**FIGURE 1** Medieval doctrine of cells. For centuries, three intracerebral cells (the ventricles) were considered the sites of affective and cognitive processing. The anterior first cell (lateral ventricles) was believed to be the substrate of *sensus communis* (sensory and common sense functions) and *imaginativa* (imagination). Within the middle second cell (third ventricle), processes underlying *fantasia* (imagery) and *aestimativa* (judgment) were believed to occur. *Memorativa* (memory) and *memborum motiva* (motion) were considered mediated by processes in the posterior third cell (fourth ventricle). (From Ref. 202.)

that introversion/extraversion was related to the balance of activities in these two circuits.

Later, Cloninger devised a model in which three main dimensions of personality are functions of basal tone in distributed brain biochemical networks [7]. Thus, novelty seeking, harm avoidance, and reward dependence are putatively related to dopamine, norepinephrine, and serotonin, respectively.

## 2.2 Emotion and Mood

Emotions have evaluative, experiential, and expressive components, which are intimately related to one another. One can scarcely evaluate a powerful affective stimulus without eliciting some feelings, which in turn tend to result in some affective expression.

Darwin focused on emotional expression, which he viewed as an evolutionary vestige and thus considered relationships between such expression and social behaviors, with only brief consideration of neural substrates, confined to vagal-mediated bidirectional communication between the brain and viscera [8,9]. James emphasized relationships between emotions and somatic perception [10] and thus contended that there need not be any special brain centers for emotions [11]. The James-Lange theory was influential into the early part of the twentieth century [12], when it declined, challenged by Cannon's animal studies, which suggested that affective responses were more rapid than visceral responses and persisted after the brain was disconnected from the viscera [13,14].

In contrast, Jackson had a cerebrocentric regional view and suggested that the right hemisphere was dominant for emotion. He extended Darwin's theories concerning evolution and hypothesized that failure of higher (more phylogenetically recent) structures to control lower (more primitive) structures could lead to psychiatric disorders [15]. This view, in a metaphorical form, was reflected in Freud's theory that psychiatric disorders were due to the loss of the ability of higher functions (the ego) to manage internal conflicts between learned values (the superego) and primitive drives (the id) [16]. Psychoanalytic models remained influential for much of the twentieth century, but they gradually declined as psychopharmacology provided important new treatment options for psychiatric disorders and advances in neuroscience methodology provided opportunities to directly test specific hypotheses regarding the neural substrates of affective experiences.

Deep midline cerebral structures have been suggested as mediators of affective experiences since the nineteenth century [17]. Broca defined the *great limbic lobe* as a midline cortical ring seen in mammals [18] and proposed relationships between these structures and olfaction and assessment

of the affective significance of olfactory stimuli (Figure 2). Brown and Schäfer found that bilateral temporal lobectomy in monkeys yielded remarkable tameness, decreased fear, and visual agnosia [19]. Fifty years later, Klüver and Bucy reported that bilateral temporal lobectomy in monkeys caused the syndrome named after them, which included visual agnosia, dietary changes, coprophagia, excessive oral and other exploration, hypersexuality, and loss of emotional reactivity [20]. Orbitofrontal and temporal pole lesions can cause some features of this syndrome. Although rare, the full syndrome can occur in humans after extensive bilateral temporal lobe damage [21]. Even more focal bilateral amygdalar damage can produce an inability to recognize fearful facial expressions [22].

Papez suggested corticothalamic mediation of emotion [23]. MacLean used the term *limbic system* to describe limbic cortex and related structures

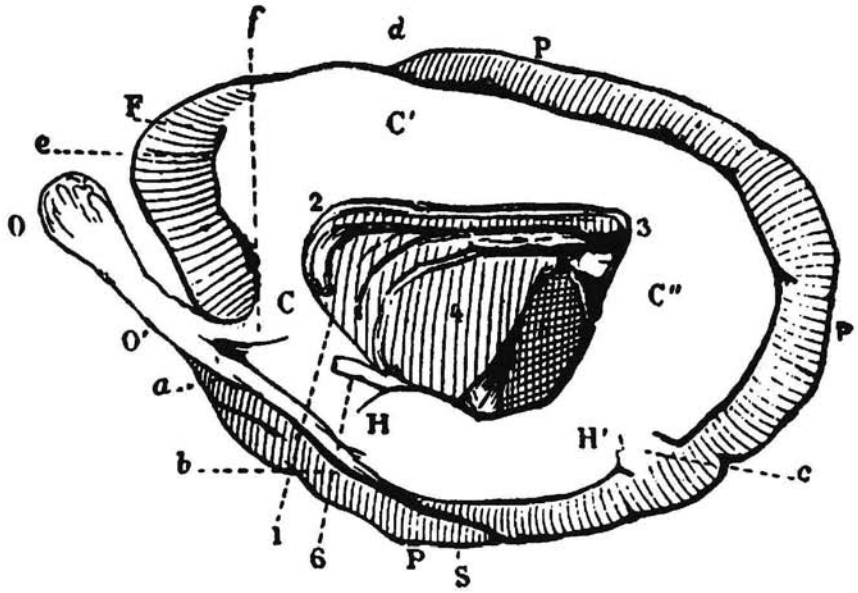



**FIGURE 2** The great limbic lobe. Broca defined the "great limbic lobe" as a midline cortical ring seen in mammals and proposed relationships between these structures and olfaction as well as assessment of affective significance of olfactory stimuli. In the 1890s the limbic lobe was referred to as the rhinencephalon, reflecting Broca's emphasis on olfactory functions. This figure depicts a midsagittal view of the deep structures of an otter's brain, with anterior regions on the left. C, C′, C″ = limbic lobe, O = olfactory bulb. (From Ref. 18.)

[24]. He was intrigued by phylogenetic aspects of neuroanatomy and proposed a triune organization of the brain with primitive (brainstem) structures evident in reptiles, underlying more recent (limbic) regions seen in early mammals, which in turn were underlying the most recent (neocortical) regions seen in later mammals (Figure 3) [25]. Alexander and colleagues described a series of basal ganglia–thalamocortical circuits [26], including limbic and lateral orbitofrontal circuits implicated in affective processes (Figure 4) and dorsolateral prefrontal circuits, which may contribute to integration of such processes with higher cognitive functions. Dysfunction in these prefrontal and anterior paralimbic basal ganglia–thalamocortical circuits may yield impaired thalamic gating or modulation of sensory or affective information, which in turn could allow such data to disrupt cognitive

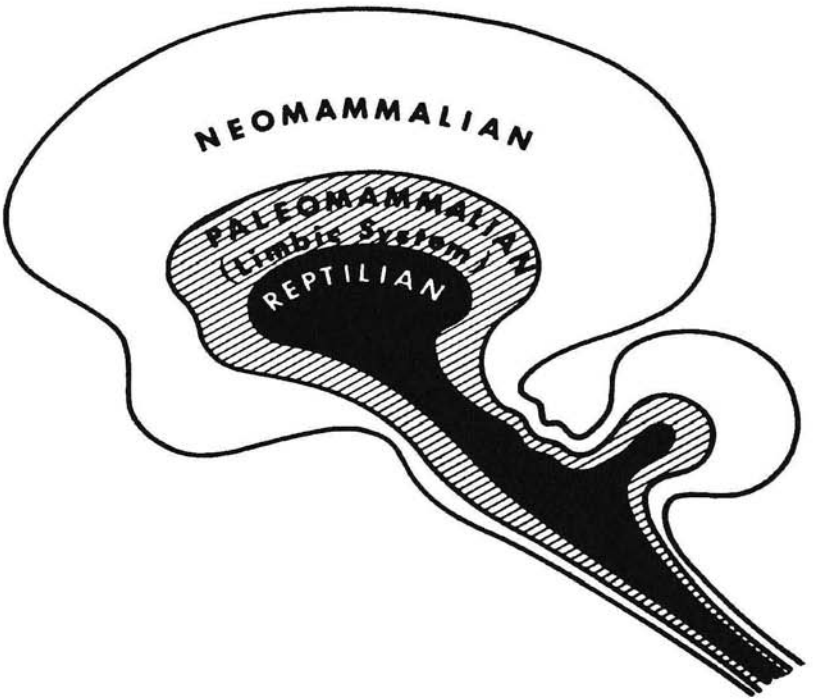



**FIGURE 3** The triune brain. MacLean proposed a triune organization of the brain, with primitive (brainstem) structures evident in reptiles; underlying more recent (limbic) regions seen in early mammals; which, in turn, were underlying the most recent (neocortical) regions seen in later mammals. (From Ref. 25.)

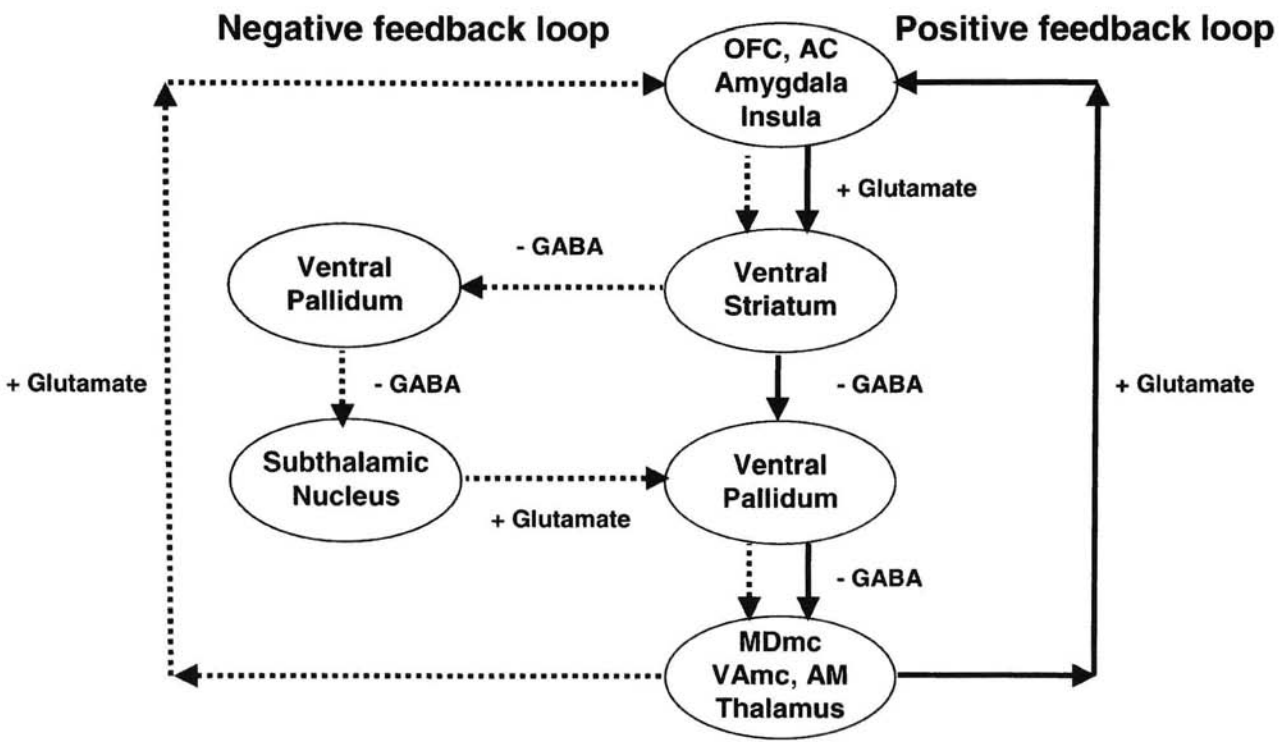



**FIGURE 4** Limbic basal ganglia–thalamocortical circuits. Solid lines indicate positive feedback loop, and dashed lines indicate negative feedback loop. − GABA indicates inhibitory (GABAergic) connections. + Glutamate indicates excitatory (glutamatergic) connections. AC = anterior cingulate; OFC = orbitofrontal cortex; MDmc = medial dorsal nucleus of thalamus pars magnocellularis; VAmc = ventral anterior nucleus of thalamus pars magnocellularis. AM = anterior medial nucleus of thalamus. (Adapted from Ref. 26.)

and motor processes and thus contribute to the clinical profiles of mood disorders.

The valence model of affects assigns major roles in positive affect (approach behavior) and negative affect (withdrawal behavior) to the left and right frontotemporal regions, respectively [27]. Electrophysiological studies suggested that state changes in emotion were related to shifts in anterior activation asymmetry, which were superimposed upon stable baseline (temperamental) differences. However, more recent functional brain imaging studies have produced inconsistent findings with respect to valence [28].

Clinical observations have related damage to components of prefrontal and anterior paralimbic basal ganglia–thalamocortical circuits to affective changes. The high prevalence of mood disorders in patients with stroke, Huntington's disease, Parkinson's disease, traumatic brain injury, epilepsy, multiple sclerosis, and brain tumors has yielded hypotheses regarding the neuroanatomy of mood disorders due to such conditions. Thus, the risk of depression has been proposed to be greater after anterior compared to posterior strokes and left compared to right strokes, while the risk of mania has been hypothesized greater after right compared to left strokes [29–31]. However, not all clinical studies support this lateralization hypothesis [32,33], and a recent metaanalysis failed to find support for the notion that the risk of depression after stroke is related to lesion location [34]. Basal ganglia strokes may be associated with secondary depression [35]. The profound damage to the basal ganglia noted in Huntington's and Parkinson's diseases and the high prevalence of mood symptoms in these disorders also provides support of a role for dysfunction of the basal ganglia in secondary mood disorders [36–39]. With traumatic brain injury, left dorsolateral prefrontal and/or left lesions of the basal ganglia may increase the risk of depression [40], while right temporal basal polar lesions may increase the risk of mania [41]. The risk of depression in patients with epilepsy may be greater with left than with right temporal lobe lesions [42]. Temporal [43] and left frontal lobe [44] lesions may also increase the risk of depression secondary to multiple sclerosis, although a recent study failed to replicate these findings [45]. Finally, frontal lobe brain tumors may be associated with depression [46,47].

Hence, increasingly sophisticated models of the neural substrates of affects have evolved, incrementally implicating anterior paralimbic, prefrontal, and brainstem-subcortical-cortical networks as contributing importantly to emotions, moods, and temperaments, respectively. Below, we review brain imaging studies in healthy volunteers and mood disorder patients, which in many cases implicate the putative neuroanatomical substrates mentioned above. We emphasize recent studies. Readers with particular interest in earlier studies may wish to refer to prior review articles [48–53].

## 3 BRAIN IMAGING STUDIES OF TEMPERAMENTS

There are relatively few brain imaging studies of temperament. We focus on studies that have used the models of Eysenck and Cloninger. Space does not permit review of the related emerging literature describing cerebral function in personality traits such as impulsivity [54], aggression [55], violence [56], and detachment [57,58]; or disorders such as schizotypal [59–64], borderline [55,65–67], and antisocial [68–71] personality disorders.

Emerging data suggest relationships between brainstem-subcortical-cortical networks and temperament. Eysenck's hypotheses [3] linking introversion with higher global cortical activity and neuroticism with higher limbic activity have been supported [72], partially supported [73], and not supported [74] by imaging studies. However, other possible relationships have emerged, such as introversion being associated with higher anterior and extroversion with higher posterior cerebral activity [75].

In contrast, preliminary imaging evidence may more consistently support Cloninger's biochemically oriented tridimensional model of temperament. Thus, three studies using different radiotracers detected relationships between novelty seeking and activity in the left caudate [76–78], an area rich in dopaminergic innervation, consistent with the notion that novelty seeking is related to dopaminergic function.

## 4 BRAIN IMAGING STUDIES OF MOODS AND EMOTIONS

Broadly considered, brain imaging studies of moods and emotions can be divided into those concerned with exploring neuroanatomical substrates independent of specific biochemistry and those aiming to explore specific biochemistry in different neuroanatomical regions. The former outnumber the latter and have consistently implicated components of prefrontal and anterior paralimbic basal ganglia–thalamocortical circuits as important contributors to affective processing. The latter were initially limited by the expense and availability of specific biochemical radiotracers, but they have recently been aided by developments in spectroscopy.

### 4.1 Neuroanatomically Oriented Brain Imaging Studies

Various techniques have allowed assessment of the neuroanatomy of affective processing. Initial structural brain imaging studies were followed by functional brain imaging studies, which have explored diverse aspects of affective processing such as the evaluation of facial emotion and emotion and mood induction in healthy volunteers. Clinical studies have included assessments of subjects with primary (bipolar disorder and major depressive disorder) and secondary (due to substances or general medical conditions)

mood disorders. Below, we review examples of how such studies have implicated prefrontal and anterior paralimbic basal ganglia–thalamocortical circuits in affective processing.

### 4.1.1 Structural Brain Imaging Studies

Computed tomography (CT) and magnetic resonance imaging (MRI) studies have displayed cerebral structural differences between groups of patients with depressive and bipolar disorders and groups of healthy controls. However, there is overlap between some mood disorder patients and healthy controls; thus such studies cannot currently be used to diagnose depressive and bipolar mood disorders. In addition, early (CT) structural studies were limited by variable findings, lack of regional specificity, and inconsistent clinical correlations. Thus, early studies tended to detect only regionally nonspecific changes (such as ventricular enlargement and sulcal atrophy in mood disorder patients compared to healthy controls). Potentially confounding influences that could contribute variability of findings include methodology, age, nutritional status, comorbid alcohol abuse, somatic therapies, and heterogeneity of mood disorders.

With the above considerations in mind, the major initial structural findings in bipolar disorder patients compared to healthy controls included increased lateral and third ventricular size; increased subcortical hyperintensities (in younger and older patients); and cerebellar atrophy. Overlapping but nonidentical findings—namely increased lateral and third ventricular size, increased subcortical hyperintensities (in older patients), and cerebellar and frontal atrophy—were reported in unipolar disorder patients.

MRI has yielded a substantial methodological advance with increased spatial resolution (allowing volumetric assessments of smaller structures) as well as gray-white resolution (allowing segmentation) and is beginning to yield more regionally specific findings implicating alterations in prefrontal and anterior paralimbic basal ganglia–thalamocortical circuits in mood disorders.

Thus, prefrontal volumes appear decreased in mood disorder patients compared to healthy controls [79–81]. Recent evidence suggests that gray matter volume is decreased in the prefrontal cortex ventral to the genu of the corpus callosum in both familial bipolar and familial unipolar mood disorders [82], consistent with decreased cerebral blood flow and metabolism [82] and histopathological changes [83] observed in that region.

Decreased hippocampal volumes in patients with depression have been reported [84–86] and have been related to total duration of depression and age of onset. One study failed to find this difference but noted that in men, left hippocampal volume correlated with severity of depression, and that in women, fluoxetine responders compared to nonresponders had larger right

hippocampal volumes [87]. In a twin study, affected compared to well monozygotic twins with bipolar disorder had a smaller right hippocampus and less hippocampal asymmetry [88]. However, other studies failed to find differences in hippocampal volume in bipolar disorder patients [80,89].

Amygdala [86] and amygdala core [90] volumes have been decreased in patients with depression, while amygdala volumes in patients with bipolar disorder have been reported to be increased [80,89]. In bipolar disorder patients, caudate volumes may be increased [80,88], but other studies either found that this was restricted to men [91] or failed to find this difference [92].

Thus, with technological refinements, structural studies are offering emerging evidence of alterations in prefrontal and anterior paralimbic basal ganglia–thalamocortical circuits in mood disorders.

### 4.1.2 Functional Brain Imaging Studies

Functional brain imaging studies have consistently yielded insights into the neural substrates of affective processes. Neuroanatomically oriented functional brain imaging methods include positron emission tomography (PET) with fluorine-18-deoxyglucose ($^{18}$FDG), which can determine the cerebral metabolic rate for glucose (CMRglu), and with oxygen-15 water ($H_2{}^{15}O$), which can assess cerebral blood flow (CBF). Single photon emission computed tomography (SPECT) with technetium-99m-hexamethylpropyleneamineoxime ($^{99m}$Tc-HMPAO) or technetium-99m-exametazime ($^{99m}$Tc-EMZ) can determine cerebral CBF. Functional MRI (fMRI) studies also yield data considered related to cerebral activity. Thus, these methods assess cerebral activity independent of specific neurotransmitters, which may be used to investigate complex multistructure and/or multineurotransmitter networks such as prefrontal and anterior paralimbic basal ganglia–thalamocortical circuits. These techniques allow assessment of regional cerebral changes related to affective processing. A substantial literature has emerged supporting the roles of prefrontal and anterior paralimbic basal ganglia–thalamocortical circuits and specific anterior paralimbic and prefrontal regions in such processes (for a review, see Ref. 28).

### 4.1.3 Evaluation of Facial Emotion in Healthy Volunteers

Limbic structures appear crucial in the evaluation of the affective salience of stimuli. Thus, patients with bilateral lesions of the amygdala have difficulty in assessing facial emotion expression [22]. Functional brain imaging studies have consistently indicated that evaluation of the emotional content of facial expressions involves the amygdala. Hence, activation of the amygdala was present in nine [93–101] studies and absent in only one [102] study of the evaluation of emotion in facial visual stimuli. The amygdala

finding appeared consistently despite being performed at multiple centers and despite implicit-explicit, conscious-subconscious, and aggregated-segregated differences in emotion paradigm across studies. Activation of the amygdala was most consistently related to fear processing. There was modest evidence of left-sided laterality, but this was not consistently related to affective valence.

Anterior cingulate and related structures also appeared to contribute to evaluation of the emotional content of facial expressions. Thus, anterior cingulate–medial frontal gyrus–basal forebrain activation was noted in 7 [93,95–99,101] but absent in 3 [94,100,102] studies of emotion evaluation of facial visual stimuli, with little evidence of valence or laterality effects. Anterior cingulate activation is seen in a variety of tasks, and emerging evidence supports the notion that this structure may have a ventral division that contributes to affective processing and a dorsal division related to cognitive processing (Figure 5).

Thus, functional brain imaging studies of emotion evaluation suggest a framework of how the brain perceives and processes emotional stimuli. The amygdala appears crucial in processing emotional stimuli, especially fear. Also, the anterior cingulate–medial frontal gyrus–basal forebrain were implicated in the evaluation of facial emotion. For both the amygdala and anterior cingulate, laterality effects were modest. In spite of the considerable variability in paradigms, these studies provide substantial support for involvement of these regions in the evaluation of facial emotion.

### 4.1.4 Emotion and Mood Induction in Healthy Volunteers

Limbic structures appear important not only in the evaluation of emotion but also in emotional experience. Physiological and pharmacological methods have been utilized to induce emotion. The former offer naturalistic approximations of spontaneous emotional reactions, which are useful in assessing the underlying neuroanatomy. The latter allow not only neuroanatomical but also biochemical probing of the neurobiological substrates of emotions. These methods, combined with functional brain imaging, have implicated anterior paralimbic structures as contributing importantly to emotional experiences.

Physiological methods of emotion induction employ cognitive, perceptual, and other somatic stimuli to yield affective responses. Cognitive methods include recalling or imagining emotionally salient events, attempting to solve demanding or even insoluble problems, and punishment or reward or the anticipation thereof. Perceptual stimuli include visual, auditory, olfactory, gustatory, and somatosensory challenges intended to evoke specific emotions. For example, viewing emotionally charged still pictures, films, or facial expressions or experiencing music, odors, tastes, or somatosensory stim-

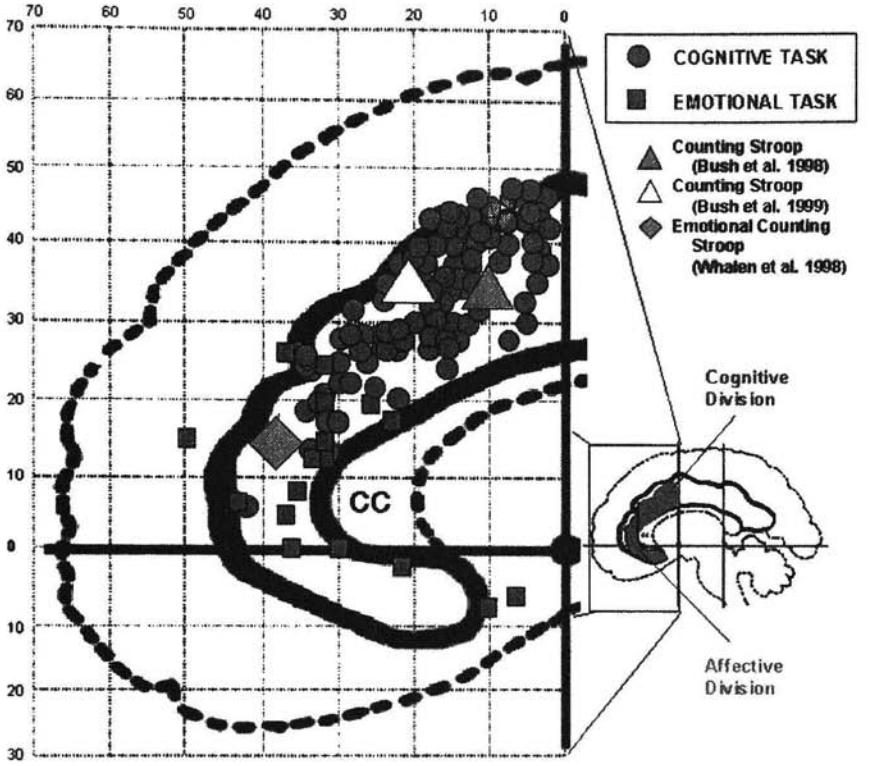



**FIGURE 5** Affective and cognitive divisions of the anterior cingulate. Midsagittal view of anterior cingulate depicting locations of activations reported in studies of cognitive (circles) and emotional (squares) tasks. Findings of brain imaging studies are consistent with a ventral-rostral affective division and dorsal cognitive division. CC = corpus callosum. (Adapted from Ref. 200.)

ulation (mild electrical shocks, exercise, and hyperventilation) can induce emotional reactions.

Brain imaging studies of physiological induction of emotion have had regional specificity, consistently implicating anterior paralimbic structures and nearby cortical regions. However, the direction of change of activity in these structures has been variable, perhaps due to variation in the age and gender of subjects, methods and durations of inductions, the particular emotions induced, scanning methodology, and data analysis methods. In addition, heterogeneity of cerebral organization across individuals may yield subgroups that utilize different brain areas to induce affects, by employing

different induction strategies or perhaps even when utilizing similar strategies. The small sample sizes used in many studies may provide inadequate power to explore such heterogeneity or to detect changes, particularly in smaller structures.

Multiple studies have used still pictures from the International Affective Picture System [103] or similar stimuli to externally elicit negative and positive affective responses. Negative and high-arousal positive images from this instrument yield increases and decreases, respectively, in magnitude of eye-blink responses to an acoustic startle probe, offering objective evidence of the presence of physiological responses associated with negative and positive emotions [104,105]. Activation of the amygdala (most commonly bilateral) was present in 7 of 10 negative but only 1 of 8 positive affect induction studies. Habituation effects could explain some negative findings. Activation of the anterior cingulate–medial frontal gyrus was seen in 5 of 10 negative and 3 of 8 positive affect induction studies. Taken together, these data suggest a role for the amygdala in affect processing. Affective valence appeared more related to the presence (with negative affect) or absence (with positive affect) rather than the laterality of amygdala activation. Valence appears to have less influence on anterior cingulate activation.

Studies of sadness and happiness induction have had variable findings. Restricting attention to studies using recall (some of which also used looking at faces), amygdala activations were seen in 6 of 13 sadness but in only 2 of 11 happiness studies. Anterior cingulate–medial frontal gyrus activations were seen in 7 of 13 sadness but in only 4 of 11 happiness studies. There was a tendency for left-sided amygdala activation preponderance in sadness induction (4 left, 1 bilateral, 1 right) and left-sided amygdala changes (1 left increases, 1 left decreases) in happiness induction. Thus, affective valence appeared more related to the presence (negative affect, i.e., sadness) or absence (positive affect, i.e., happiness), rather than the laterality of activation. Gender may be an important factor in sadness induction, with three studies [106–108] finding more widespread activation in women than in men.

Pharmacological methods of affect induction are diverse and complex. Different substances have varying dosage ranges, routes of administration, pharmacokinetics (rates of absorption, distribution, and excretion), and pharmacodynamics (effects at receptors). Dosage is important because some drugs yield biphasic responses, with certain effects at lower doses and different (even opposite) effects at higher doses. Route of administration matters, since very rapid (for example intravenous) administration can provide high brain concentrations too quickly for cerebral homeostatic mechanisms to intervene. Duration of administration is a crucial factor. Some agents (such as benzodiazepines, alcohol, and drugs of abuse) have rapid-onset (within minutes) effects, which attenuate with ongoing exposure (tolerance)

and may yield opposite effects with rapid discontinuation after chronic exposure (withdrawal).

The local anesthetic procaine (Novocain) activates limbic structures in animals. In humans, acute intravenous procaine yields brief, compelling emotional and psychosensory experiences with considerable interindividual variability, ranging from intensely positive (euphoria) to intensely negative (fear, panic) and hence can model both positive and negative emotions. In healthy volunteers, affective changes were accompanied by increased global and to a greater extent anterior paralimbic CBF [109]. Subjects with intense procaine-induced fear compared to those with euphoria had greater increases in left amygdalar CBF. Amygdalar CBF changes tended to correlate positively with fear and negatively with euphoria intensity. Thus, procaine increased anterior paralimbic CBF, and different clinical responses appeared to be associated with different patterns of CBF changes. These findings were subsequently independently replicated [110].

Induction of transient sadness or dysphoria by recalling sad events [107] or by acute intravenous procaine [109] yields overlapping anterior paralimbic CBF patterns (Figure 6). In contrast, more sustained (30-min) self-induced sadness (which perhaps is a more temporally appropriate model of depressed mood) yields CMRglu decreases in similar paralimbic regions [111]. These observations are consistent with the hypothesis that, in vulnerable individuals, repeated, prolonged, or intense cerebral activations associated with negative affective experiences can deplete neurochemical substrates, diminishing cerebral metabolism and yielding clinical depression. Similarly, putative hypermetabolism in mania could eventually yield substrate depletion and thus subsequent decreased metabolism and postmania depression.

### 4.1.5 Bipolar Depression and Major Depressive Disorder

PET and SPECT studies have demonstrated CMRglu and CBF abnormalities in bipolar depression and major depressive disorder. The most consistent regional finding in depressed bipolar disorder patients in "rest" (resting state or continuous performance task) studies has been decreased prefrontal CMRglu [112–119] and CBF, using $H_2{}^{15}O$ PET [120] or $^{99m}$Tc-HMPAO SPECT [121].

In a recent study, depressed patients with bipolar disorder compared to controls had decreased absolute prefrontal and anterior paralimbic cortical metabolism and increased normalized anterior paralimbic subcortical metabolism [122] (Figure 7). Moreover, the degree of depression correlated negatively with absolute prefrontal and paralimbic cortical metabolism and positively with normalized anterior paralimbic subcortical metabolism.

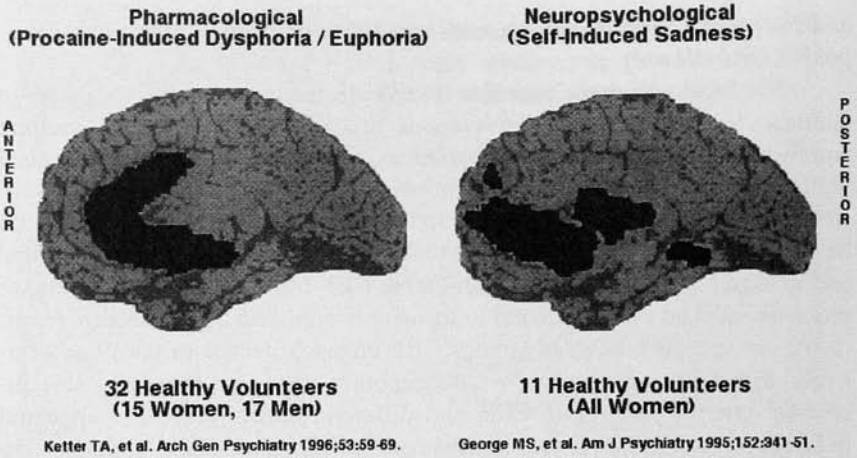
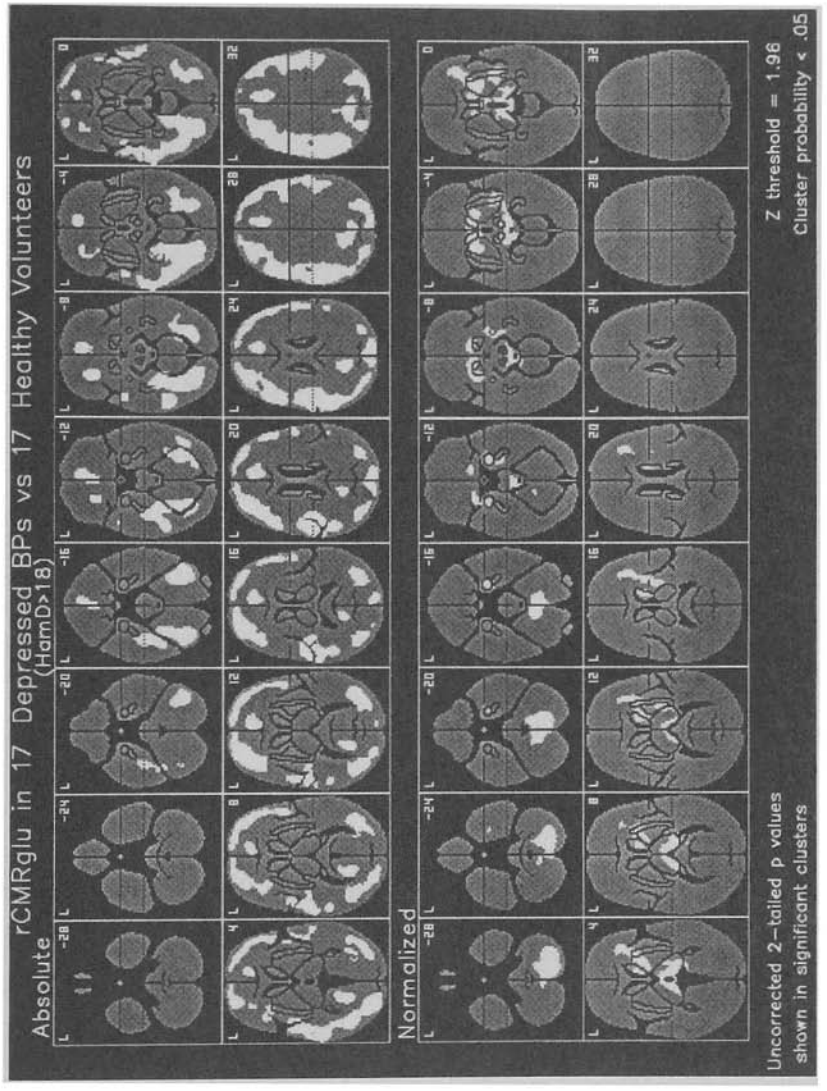



**FIGURE 6** Overlapping anterior paralimbic activation with neuropsychologically and pharmacologically induced acute affective changes in healthy volunteers. Images are statistical parametric maps (SPMs) of cerebral blood flow activation rendered on the mesial aspect of the right hemisphere. Right: Regions activated during transient self-induced sadness in 11 healthy women (From Ref. 107.) Left: Regions activated during acute intravenous procaine-induced affective symptoms in 32 healthy volunteers. (From Ref. 109.) Note the overlap of anterior paralimbic activation patterns with these two different methods of inducing affective changes. (From Ref. 120.)

These depressed bipolar patients had absolute decreases in prefrontal and anterior paralimbic cortical activity, consistent with reports of decreased activity in such regions not only in bipolar depression [82,112–121,123,124] but also in many studies of unipolar depression [82,115,125–144] and secondary depression [145–152]. This convergence suggests the possibility of

**FIGURE 7** Regional cerebral metabolism in depressed bipolar disorder patients compared with healthy controls. Z-maps of decreases in absolute (top) and increases in normalized (bottom) cerebral metabolism in 17 depressed patients with bipolar disorder compared to 17 healthy controls. Numbers in upper right corners indicate distances from the intercommissural plane. L = left. Absolute prefrontal and anterior paralimbic cortical metabolic decreases and normalized anterior paralimbic subcortical metabolic increases evident in these images may be a state marker for depression in bipolar disorders. (From Ref. 122.)



a common pathway to depressive symptoms to some extent independent of illness etiology (primary versus secondary) and subtype (unipolar versus bipolar).

Depressed bipolar disorder patients compared to healthy controls also had increased normalized metabolism in subcortical paralimbic structures including ventral striatum, thalamus, and right amygdala, consistent with a limbic-cortical dysregulation model of depression, wherein dorsal neocortical hypofunction could lead to ventral paralimbic overactivity or vice versa [153] (Figure 8). Relative activation of bilateral medioposterior thalamus was also seen, consistent with altered thalamic relay and gating function with respect to communication between subcortical and cortical regions.

Heterogeneity appears in studies of mood disorder patients and may be in part related to differences in affective symptoms. In a recent study, depression ratings correlated directly with bilateral medial frontal, right anterior cingulate, and right dorsolateral prefrontal globally normalized metabolism [154]. In contrast, anxiety ratings correlated directly with right parahippocampal and left anterior cingulate and inversely with cerebellum, left fusiform, left superior temporal, left angular gyrus, and left insula globally normalized metabolism.

Successful treatment with psychotherapy [155], antidepressants [155–158], mood stabilizers [159], and sleep deprivation [160] may attenuate baseline abnormalities. Moreover, improvements in specific symptoms may be related to normalization of activity in specific components of prefrontal and anterior paralimbic basal ganglia–thalamocortical circuits [161].

In "activation" studies, depressed patients have manifested altered prefrontal and anterior paralimbic responses compared to healthy controls during facial emotion recognition [162], Stroop color-word interference [163], planning and guessing with and without feedback [164], word generation [165], and transient sadness self-induction [165a] tasks, and following acute pharmacological activation with intravenous procaine [166], oral amphetamine [167], and oral dl-fenfluramine [168]. Although rest and continuous performance task studies indicate similar frontal deficits in schizophrenia and mood disorders, during the Wisconsin Card Sort frontal activation was blunted in schizophrenia but preserved in depression [169].

### 4.1.6 Secondary (Due to Substances or General Medical Conditions) Depression

If components of prefrontal and anterior paralimbic basal ganglia–thalamocortical circuits mediate affect processing, then damage to such structures ought to yield affective processing disturbances independent of the nature of the pathological process. Indeed, anterior cerebral hypoactivity occurs in depression secondary to diverse neurological and medical disorders such as

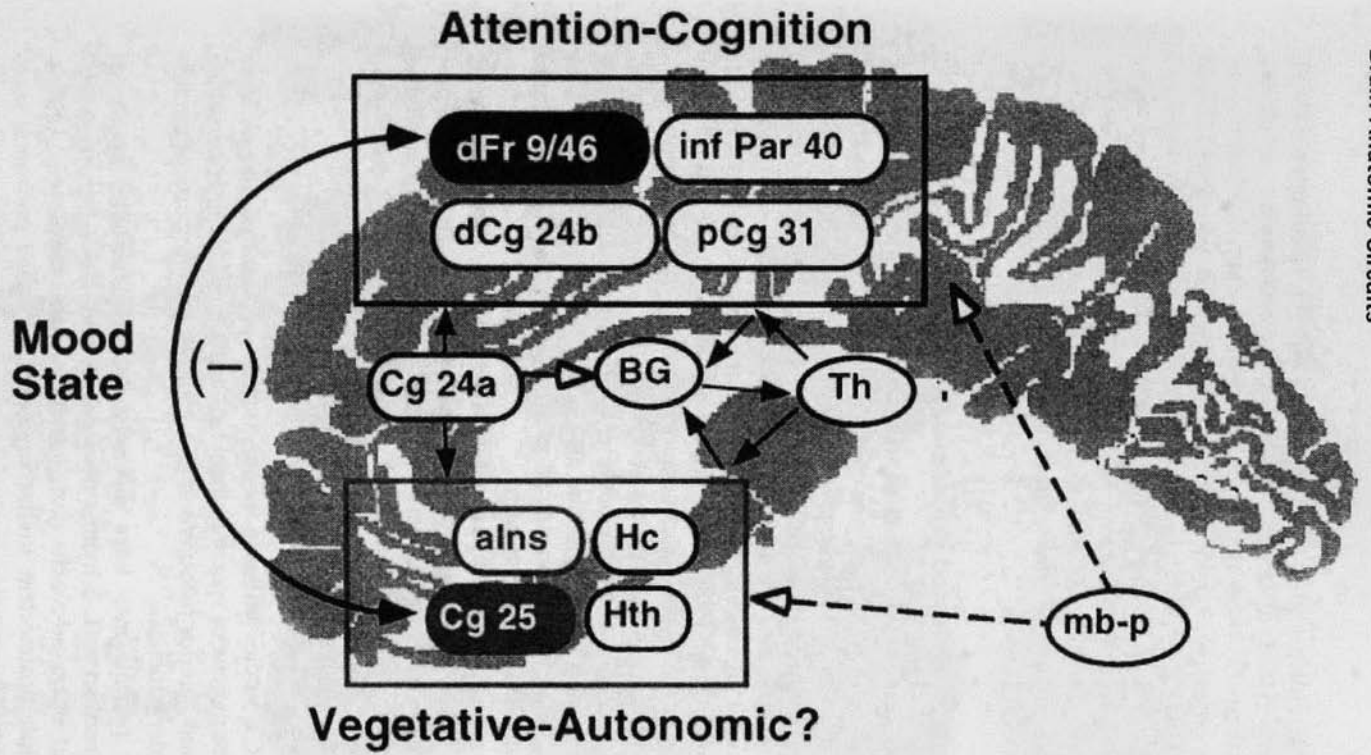



**FIGURE 8** Corticolimbic-dysregulation model of depression. Dorsal neocortical hypofunction (dark gray rectangle) could lead to ventral paralimbic overactivity (light gray rectangle), or vice versa. Curved arrows and filled regions emphasize the inverse relationships between right dorsal prefrontal cortex (dFr 9/46, dark gray) and subgenual cingulate (Cg 25, light gray). Short black arrows indicate subcortical pathways. Numbers are Brodmann area designations. dFr = dorsolateral prefrontal; inf Par = inferior parietal; dCg = dorsal anterior cingulate; pCg = posterior cingulate; Cg25 = subgenual cingulate; aIns = anterior insula; Cg 24a = rostral anterior cingulate; BG = basal ganglia; Th = thalamus; Hc = hippocampus; Hth = hypothalamus; mb-p = midbrain-pons. (From Ref. 153.)

stroke [146,170]; epilepsy [149]; Parkinson's [145,151], Huntington's [148], and Alzheimer's [171] diseases; acquired immunodeficiency syndrome [150]; and postherpetic encephalitis [152] as well as other psychiatric conditions such as obsessive compulsive disorder [115], bulimia [129,172], and cocaine abuse [147]. The degree of anterior hypoactivity has often correlated with the severity of depression [115,145,147,170,172]. As noted above, these findings are convergent with those in primary (major depressive and bipolar) mood disorders and suggest that anterior cerebral hypoactivity may represent a common substrate of depressive symptoms independent of illness etiology (Figure 9).

## 4.2 Biochemically Oriented Brain Imaging Studies

Monamines have long been considered important biochemical substrates of affective processes. This notion was initially suggested by the actions of psychotropic drugs such as antidepressants (on serotonin and norepinephrine) and antipsychotics (on dopamine and later on serotonin). To the extent that such neurochemicals are implicated in affective processes indirectly through therapeutic agents and biochemical challenge studies and more directly through PET and SPECT radioligand and magnetic resonance spectroscopy (MRS) assessments, we can explore the neuroanatomical substrates of affective processing. The major sources of monoaminergic innervation for serotonin (raphe nuclei), norepinephrine (locus ceruleus), and dopamine (substantia nigra and ventral tegmental area) are found in the brainstem and have connections with components of prefrontal and anterior paralimbic basal ganglia–thalamocortical circuits.

Recent advances in MRS have allowed noninvasive determination of diverse cerebral chemicals, some of which may be related to affective processing. Below, we consider evidence from brain imaging studies exploring the roles of specific neurochemicals in prefrontal and anterior paralimbic basal ganglia–thalamocortical circuits in affective processing.

### 4.2.1 PET and SPECT Radiotracer Studies

PET and SPECT studies utilizing biochemically specific radiotracers have permitted investigations of specific neurochemical alterations in components of prefrontal and anterior paralimbic basal ganglia–thalamocortical circuits in mood disorder patients.

Unipolar patients may have diffusely decreased cerebral uptake of monoamine precursors (L-5-hydroxytryptophan and L-3,4-dihydroxyphenylalanine) and increased mesial prefrontal L-5-hydroxytryptophan utilization [173]. While postmortem studies suggested increased prefrontal serotonin $5HT_2$ receptors in suicide victims, in unipolar depression some [174–

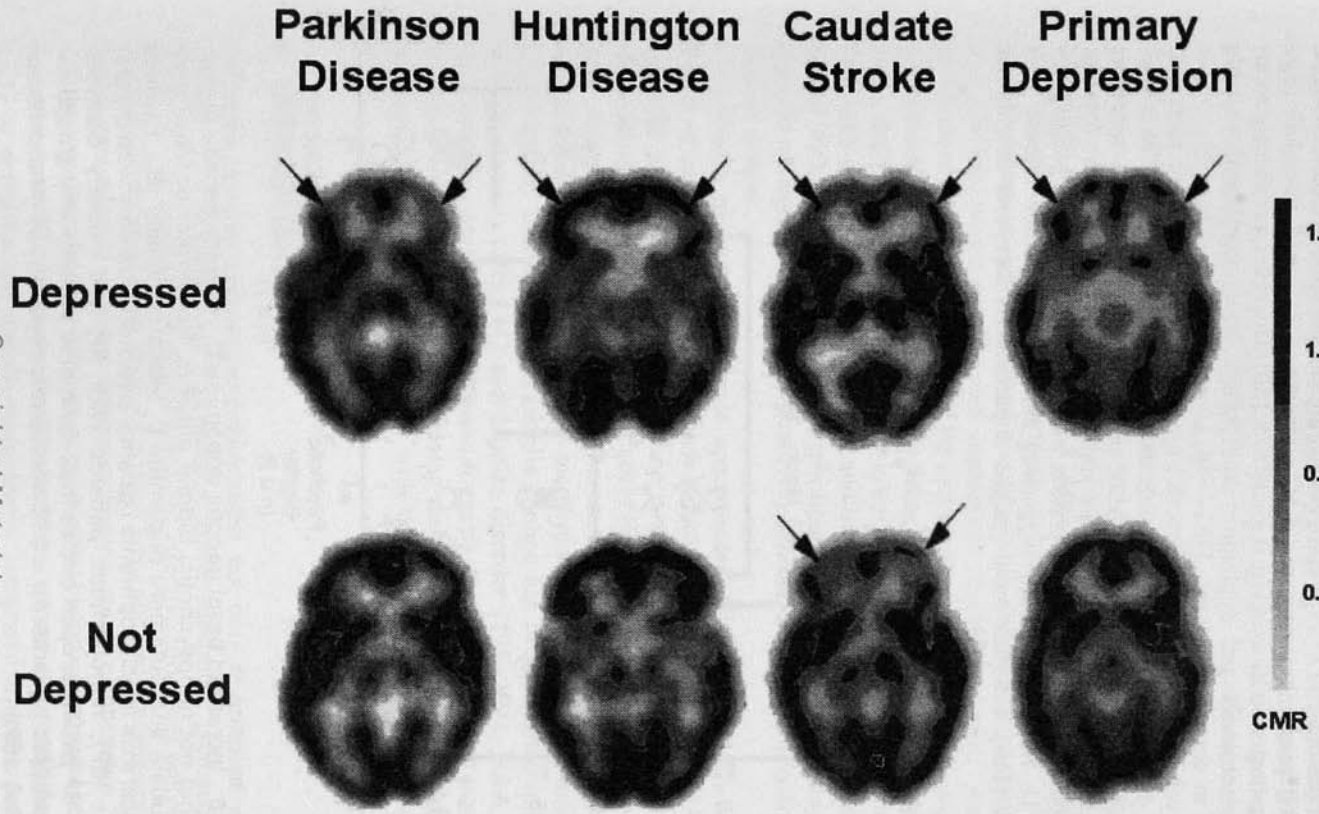



FIGURE 9 Hypofrontality in secondary and primary depression. Patients with depression secondary to neurological conditions as well as with primary depression (top row) have decreased prefrontal cerebral activity (arrows) compared to patients with similar neurological conditions without depression or healthy controls (bottom row). (From Ref. 201.)

176] but not other [177,178] clinical imaging studies have detected changes. Decreased paralimbic serotonin 5-$HT_{1A}$ receptors in mood disorders have been demonstrated in imaging studies [179,180]. However, paralimbic monoamine (serotonin and dopamine) transporters have manifested variable changes in depressed patients [181–184].

Psychotic (but not nonpsychotic) bipolar patients may have increased caudate dopamine $D_2$ receptors, with these increases correlating with psychosis ratings (Figure 10) [185]. Although baseline dopamine $D_2$ receptors in depressed bipolar II patients were similar to controls, responders (but not nonresponders) after sleep deprivation had decreases in basal ganglia dopamine $D_2$ receptor binding, suggesting enhanced dopamine release with response [186]. Baseline basal ganglia dopamine $D_2$ receptors in unipolar

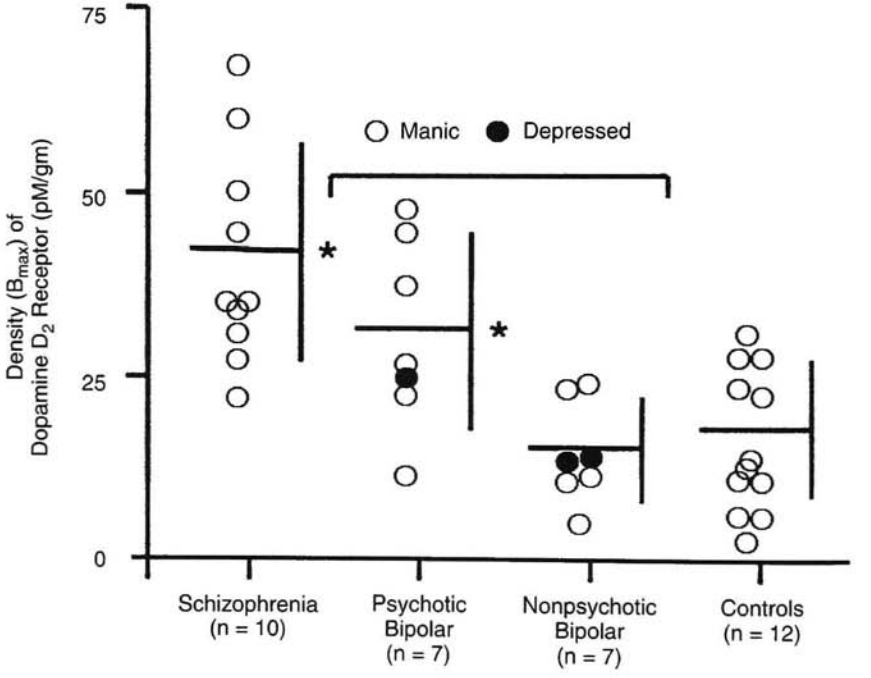



**FIGURE 10** Increased basal ganglia dopamine $D_2$ receptor density in psychotic (but not nonpsychotic) bipolar patients. Scatterplot of basal ganglia (caudate and putamen) dopamine $D_2$ receptor density ($B_{max}$) values on vertical axis in schizophrenia patients, psychotic patients with bipolar disorder (BP), nonpsychotic patients with BP, and healthy controls. Among BP patients, open circles indicate manic patients and closed circles depressed patients. $*p < 0.05$ versus nonpsychotic BP and controls. (From Ref. 185.)

depression have been increased [187], decreased [188], or unchanged [189–191]. However, even among the latter negative studies, dopamine $D_2$ receptors were altered in patient subgroups, that is, increased in patients with psychomotor retardation [189] and decreased in patients who later responded to serotonin reuptake inhibitor therapy [190].

### 4.2.2 Magnetic Resonance Spectroscopy Studies

Clinical MRS studies in mood disorder patients have detected metabolite alterations in prefrontal and anterior paralimbic basal ganglia–thalamocortical circuits. Phosphorus-31 magnetic resonance spectroscopy ($^{31}$P-MRS) permits determination of cerebral phospholipids, including phosphomonoesters (PMEs), which may be cell membrane "building blocks," and phosphodiesters (PDEs), which could be cell membrane "breakdown products." In metaanalyses of eight studies involving 139 bipolar and 189 control subjects, euthymic bipolar patients had lower prefrontal PMEs (but not PDEs) than both depressed bipolar patients and healthy controls [192]. This is consistent with altered membrane phospholipid metabolism, which may reflect changes in signal transduction putatively related to the pathophysiology of bipolar illness.

Proton magnetic resonance spectroscopy ($^{1}$H-MRS) allows determination of cerebral metabolites, which include N-acetyl aspartate (NAA) and cytosolic choline compounds. Choline is an acetylcholine precursor and is involved in second-messenger cascades. However, in $^{1}$H-MRS, the choline peak represents total cellular choline stores, the dominant component of which is believed to be from cell membranes (phospholipids) rather than acetylcholine. Increased basal ganglia choline has been reported in patients with depression [193,194] and bipolar disorder [195–197]. NAA reflects neuronal integrity. Recent evidence suggests that bilateral dorsolateral prefrontal NAA in patients with bipolar disorder is decreased compared to healthy controls [198], consistent with decreased gray matter this region [199].

## 5 CONCLUSION

Emotions, moods, and temperaments differ not only in temporal domains but also in phenomenology and putative neural substrates. Increasingly sophisticated models of the neurobiology of affective processes are evolving. Recently, functional brain imaging studies have allowed investigators to test hypotheses relating affective processes to their putative substrates. Temperaments may be related to activity in brainstem-subcortical-cortical networks. Anterior paralimbic and prefrontal structures appear to contribute importantly to emotions and moods, respectively. Integrated affective processing

may be related to activity in prefrontal and anterior paralimbic basal ganglia–thalamocortical circuits. Advances in imaging technology and paradigm design promise to help further advance our knowledge of the neural substrates of affective processes in health and in mood disorders.

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# 5

# Functional Magnetic Resonance Imaging Investigations in Mood Disorders

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## 1 INTRODUCTION

Pathological disturbances of mood may follow a unipolar course in which only depression occurs or a bipolar course in which normal mood alternates with both depression and mania [1]. Both unipolar and bipolar disorders can be heritable illnesses associated with neurochemical, neuroendocrine, and autonomic abnormalities. The neurobiological basis for these abnormalities has not been established. Although most agree that pathological states like depression and mania are brain-based, relatively little is known about the precise regions that are important in inducing and regulating normal mood and whether these are also involved in producing affective illness. An understanding of the pathophysiology of mood disorders may aid in the development of more effective treatments and means of diagnosis.

### 1.1 Background Work Using Positron Emission Tomography (PET) and Healthy Adults

Better understanding of emotional experience in normal persons may aid in understanding abnormalities in affective disorders. Since depressive symptoms reflect distortions of emotional states that can be expressed by non-

depressed subjects, the nature of blood flow or metabolic changes related to the depressed state can be explored by imaging hemodynamic changes in healthy subjects during emotion recognition tasks or experimentally induced states of sadness and anxiety. George et al. [2] conducted a PET study in nine healthy women, who were instructed to perform a matching task with facial emotions, facial identity, and spatial position. Whereas processing of facial identity and spatial positions was associated with activation of bilateral parieto-occipital and midtemporal regions, the recognition of facial emotions activated limbic structures, the right anterior cingulate, and the bilateral inferior frontal gyri. In another study, George et al. [3] probed normal limbic function not by examining emotion recognition but rather by having subjects experience different mood states. Eleven healthy women were instructed to try to induce in themselves separate happy, sad, and neutral states by recalling affect-appropriate life events while looking at pictures of affect-appropriate faces. Sadness was found to be associated with activation in bilateral limbic and paralimbic regions as well as areas in the brainstem, thalamus, caudate, and putamen. Happiness was associated with decreased regional cerebral blood flow in the right prefrontal and bilateral temporoparietal areas. They noted that transient sadness and happiness affected different brain regions in divergent directions and was not merely an opposite activity in identical brain regions. George et al. [4] also examined 10 healthy men and 10 healthy women during resting, happy, sad, and neutral states using PET. Although men and women reported comparable induction of the mood states, women exhibited more widespread limbic activation during other mood states, including happiness.

*Studies of normal mood states are important, as they demonstrate that anterior paralimbic structures are broadly involved in emotional processing and normal mood regulation.* Different emotions appear to demonstrate subtle variations in activation patterns. Hence, models of pathophysiology in patients with mood disorders can be considered against the setting of normal emotions and their mediating anatomy. Functional imaging studies that directly compare regional brain activation in depressed subjects versus healthy controls have found no differences [5], selective deficits [2], or areas of increased activity [6], largely depending on the task employed during the scan.

As discussed in more detail in Chap. 4, the phenomenology of major depression probably mirrors the relative involvement of various functional neuroanatomical systems. Presumably a relatively simplistic mapping of symptoms onto brain regions would be as follows:

The cognitive deficits reflect hypofunction within lateral prefrontal cortex

Affective manifestations result from disordered paralimbic activity

Anhedonia results from hypofunction within the ventral striatum
Slowed motor manifestations arise from the interface of motor systems with the dorsal striatum or thalamus
Amygdalar hyperactivity or hypersensitivity may underlie a tendency toward comorbid anxiety and misperception of danger signals
The hypothalamus probably mediates disturbances in sleep, appetite, and neuroendocrine regulation [7]

For a more complete discussion of this disordered functional neuroanatomy, see Chap. 4.

Before we review the studies done to date using functional magnetic resonance imaging (fMRI) to understand mood disorders, several general principles should be kept in mind. First, any imaging study of someone with depression will likely reflect brain changes associated with both the *trait of developing a mood disorder*, the *current state of depression*, brain changes that have occurred *over time as a function of living with depression*, and brain changes associated *with attempted treatments*. Teasing out which of these factors are contributing to a brain image can be quite challenging. Moreover, it is likely that regional brain changes associated with state changes in mood disorders do not necessarily occur at the same time as symptom expression. For example, for people recovering from a depressive episode, brain changes visible with functional imaging may precede the emergence of improved clinical symptoms. Thus, static intermittent images of depressed patients need to be integrated into their dynamic course of illness.

Further, *mood disorders often occur* together with other neuropsychiatric and general medical illnesses. These are difficult confounds in functional imaging studies. Additionally, patients are commonly on medications for their depression, or they have received medications or procedures such as electroconvulsive therapy (ECT) that may fundamentally alter regional functional brain activity. Finally, regional brain activity likely changes over the life of someone who struggles with recurrent depression. Thus, the integration of imaging with the life course of the illness is an important caveat as well.

## 2 fMRI AS A NEUROSCIENCE TOOL

Recently, it has become possible to modify a conventional MRI scanner to study brain function as well as brain structure. This new field is collectively called functional magnetic resonance imaging (fMRI). Currently there are four types of fMRI that can provide functional information:

1. *Blood-oxygenation level–dependent (BOLD)-fMRI*, which measures regional differences in oxygenated blood over time
2. *Perfusion fMRI*, which measures regional cerebral blood flow
3. *Diffusion-weighted fMRI*, which measures random movement of water molecules
4. *MRI spectroscopy*, which can measure certain cerebral metabolites

## 2.1 BOLD-fMRI

BOLD-fMRI is currently the most common fMRI technique. Ogawa et al. [8] and Turner et al. [9], working independently, had shown in laboratory animals that similar changes of MRI image contrast extending around the blood vessels could be obtained simply by changing the oxygenation state of the blood. This observation arose from the fact that deoxyhemoglobin is more paramagnetic than oxyhemoglobin, which itself has almost exactly the same magnetic susceptibility as tissue. Thus, *deoxyhemoglobin can be seen as nature's own contrast agent.* Brain activity changes, which create an imbalance between oxygen uptake and blood flow, will thus inevitably cause a change of MRI signal around the cortical vessels if MRI sequences that are sensitive to magnetic field inhomogeneity are used. Then, Kwong et al. [10] and Ogawa et al. [11] succeeded in showing that the change in deoxyhemoglobin in the human visual cortex while the subject viewed a bright light was sufficient to cause measurable changes in gradient-echo MRI images of a slice passing through the calcarine fissure. This technique was called blood-oxygenation level–dependent (BOLD) contrast. Thus the way was opened to functional mapping studies of the human brain without use of a contrast agent or a radiation dose and with the high spatial resolution of MRI. It is significant that a rise in signal can be observed during visual stimulus, indicating a relative decrease in the concentration of paramagnetic deoxyhemoglobin. *Block-design BOLD-fMRI* paradigms generally have several periods of rest alternating with several periods of activation. Images obtained over the first 3 to 6 sec of each period are generally discarded because of the delay in hemodynamic response. Alternating paradigms are used in case the signal intensity generated by the MRI scanner drifts with time. The extreme sensitivity of BOLD-fMRI to movement limits tasks to those without large head movement. Another limitation is that echo-planar acquisition, needed for rapid imaging of BOLD images, is susceptible to artifacts produced by air in sinuses. This confound makes it more difficult to observe important emotional regions at the base of the brain, such as the orbitofrontal and mediotemporal cortices. Sometimes observed areas of activation are located in large draining veins rather than directly at a capillary bed near the site of neuronal activation [12], although several imaging sequences can minimize this venous contribution.

## 2.2 Perfusion fMRI

Two fMRI methods have been developed for measuring cerebral blood flow. The first method, which is called *intravenous bolus tracking*, relies on the intravenous injection of a magnetic compound, such as a gadolunium containing contrast agent, and measuring its T2*-weighted signal as it perfuses the brain over a short period of time [13,14]. Areas perfused with the magnetic compound show less signal intensity as the compound creates a magnetic inhomogeneity that decreases the T2* signal. The magnetic compound may be injected once during the control and once during the activation task, and relative differences in blood flow between the two states may be determined to develop a difference perfusion image. Alternatively, one can measure changes in blood flow over time after a single injection to generate a perfusion map [14]. Although gadolinium-based contrasts are not radioactive, the number of boluses that can be given to an individual is limited by the potential for kidney toxicity. This technique generates only a map of relative cerebral blood flow, not absolute flow. Some call this technique the *dynamic susceptibility contrast (DSC MRI) method* [13]. DSC MRI takes advantage of the parametric properties of standard MRI contrast agents as magnetic tracers. Susceptibility effects result from the fact that paramagnetic substances disturb the homogeneity of uniform magnetic fields. These local field inhomogeneities cause a loss of coherence of signal from nearby protons and thus a reduction in measured MR signal [15]. Although slightly more invasive than intrinsic contrast fMRI techniques (e.g., BOLD fMRI), DSC MRI provides more robust signal intensity changes as well as unique hemodynamic information [16]. However, it has limitations, such as requirement of at least two acquisitions, one at baseline and another during activation, and therefore two or more doses of contrast agent [15].

The second method, which is called *arterial spin-labeling*, is a T1*-weighted noninvasive technique where intrinsic hydrogen atoms in arterial water outside of the slice of interest are effectively magnetically "tagged" and then imaged as they enter the slice of interest [17]. Since arterial spin-labeling is noninvasive and does not involve an intravenous bolus injection, it can be repeatedly performed in individual subjects. Absolute regional flow, which cannot be obtained with single photon emission computed tomography (SPECT) or BOLD-fMRI and requires an arterial line with PET, can be measured with arterial spin-labeling. As absolute information is obtained, cerebral blood flow can be measured serially over separate imaging sessions, as by measuring blood flow in bipolar subjects as they course through different disease states [18]. The arterial spin-labeling technique currently has some limitations: its signal-to-noise ratio as well as its poor spatial resolution have limited its utility. Since it takes several minutes to acquire information

on a single slice of interest, it is necessary to pinpoint a specific region of the brain to be examined. It would also be a tedious process to obtain enough images on this slice in a single session to make a statistical statement on a given subject. Therefore this technique does not appear to be useful within individuals unless scanner acquisition time is shortened.

## 2.3 Diffusion-Weighted fMRI

Diffusion-weighted imaging is very sensitive to slow flow and thus to random movement of $^{1}H$ in water molecules [19]. Water flows more easily within myelin sheaths than across them. Thus, diffusion fMRI can show the directional patterns of white matter fiber tracts. Further, regulation of water across nerve cell membranes is one of the first processes to be interrupted when a cell is damaged. Therefore *diffusion imaging is quite sensitive to brain trauma* and shows abnormalities almost immediately. The amount of water diffusion for a given region can be calculated and is known as the apparent diffusion coefficient (ADC). Areas with low ADC values appear brighter. While the usefulness of diffusion-weighted imaging in mood disorders has not been established, it holds great promise for the treatment of neurological disorders, as in changing the clinical management of acute ischemic stroke by potentially refining the criteria for patients most likely to benefit from thrombolytic therapy [20].

## 2.4 MRI Spectroscopy

MRI spectroscopy (MRS) offers the capability of using MRI to study tissue biochemistry noninvasively. In the conventional and previously mentioned fMRI techniques, the hydrogen atom in water is the main one that is flipped (resonated). In MRS, either $^{1}H$ atoms or other atoms such as isotopes $^{31}P$, $^{23}Na$, $^{39}K$, $^{19}F$, or $^{7}Li$ are flipped [21,22]. MRS as a neuroscience tool is discussed in Chap. 6.

While certain fMRI procedures can be performed on standard clinical scanners, the neuroscience field has greatly benefited from technological advances in MR physics. Of particular importance has been the development of extremely rapid imaging techniques that utilize novel pulse sequences as well as improved hardware configurations [15]. Pulse sequence development, particularly fast gradient echo imaging technique [23], as implemented on standard clinical scanners has facilitated image acquisition on the order of a few seconds as compared to a few minutes with conventional sequences. However, the introduction of *echo-planar imaging (EPI)* has had the most profound effect on the development of fMRI. One of the reasons for the slow emergence of EPI as an MRI imaging method of widespread availability is that it places stringent demands on the performance of the MRI

scanner hardware, in particular the gradient subsystem. EPI allows functional imaging experiments to be performed with improved spatial resolution to PET while introducing a temporal dimension to activation experiments. Echo-planar imaging (EPI) imposes other potential limitations. Spatial resolution is often more limited and less flexible than in the use of conventional gradients, although there is an improved signal-to-noise ratio [24]. EPI's enhanced sensitivity to susceptibility effects can also lead to susceptibility artifacts, which are particularly prominent in brain regions adjacent to air sinuses, such as inferior frontal and temporal regions, often areas of considerable interest [25]. Another limitation is related to safety and subject comfort, particularly with ultrarapid imaging techniques. Because it relies on extremely rapid changes in magnetic field gradients over time, large and fast forms of EPI scanning can potentially cause excitation of long neurons running through the arms or rib cage. Cardiac stimulation is another theoretical risk [24]. Finally, the gradient changes are extremely loud, which can be uncomfortable for some subjects. But, none of these safety and comfort considerations has proven to be significant [15].

Recently fMRI acquisition schemes have enabled the development of *event-related fMRI* (as opposed to the more conventional block designs described above), where the local cerebral hemodynamic response to single events can be studied. Such events can comprise a planned protocol, where oddball or go/no-go paradigms are now feasible, and the differential time courses relating to the different events can be observed in relevant cortical areas. In addition, the noninvasive nature of MRI makes it ideal for study of unpredictable events, in which the subject has only to signal that such an event has occurred.

## 2.5 Application of fMRI

In a typical fMRI paradigm, a subject lies on the bed of an MRI scanner while viewing a screen illuminated by a liquid crystal display (LCD) video projector and listens to auditory output via headphones, or performs some other form of cognitive task, during which a sequence of images is obtained. When EPI is used, generally 3–10 images per second are acquired for a period of 5–10 min. The subject's head is kept still using foam pads or one of a number of exclusive methods for head immobilization. Ideally, multislice images are obtained, giving upward of 50 consecutive images of the entire brain during the experimental run. With a repeat time of 3 sec for any particular slice, effects on the image caused by cardiac and respiratory pulsations are relatively small compared with functionally related changes and are mostly confined to large vessels and cerebrospinal fluid (CSF). However, head movement of even as little as 0.5 mm can cause an apparent change of signal in a given voxel of as much as 40% [26].

## 2.6 The Interpretation of Imaging Signal

In applying modern functional imaging methods to understand brain function, we assume that the imaging signal measures neuronal activity. In fact, the signal is not a direct measure of neuronal activity. It derives from changes in blood flow, glucose consumption, and glucose oxidation, which are physiological measures of brain energy consumption [27]. Functional imaging experiments are generally set up to measure differences in the signal observed in the brain image between two behavioral tasks. In the control task, the subject is usually at rest in the absence of the stimulation being evaluated. Images collected during rest are subtracted from those collected during performance of a task (Fig. 1). Difference images, the usual presentation of results, are plots of regions in which changes in the signal are statistically significant. This presentation does not mean that other imaging signals are nonexistent; it merely means that they do not appear on the image because their magnitude does not change significantly between the task and control images. The prevailing interpretation in functional imaging is that change in the signal measures the neuronal activity associated with the mental processes involved in the task [27].

Functional imaging experiments have shown that at stimulation from rest, brain energy consumption and accompanying neurotransmitter flux increase by several percent over resting values. In stimulated anesthetized animals, the regional energy is once again higher than resting values. Psychiatrically oriented neuroscientists have recognized the central role of this unstimulated state. Andreasen et al. [28] proposed that "we refer to this particular state (lying with eyes closed and thinking about whatever comes to mind) with a simple descriptor; random episodic silent thinking (REST).

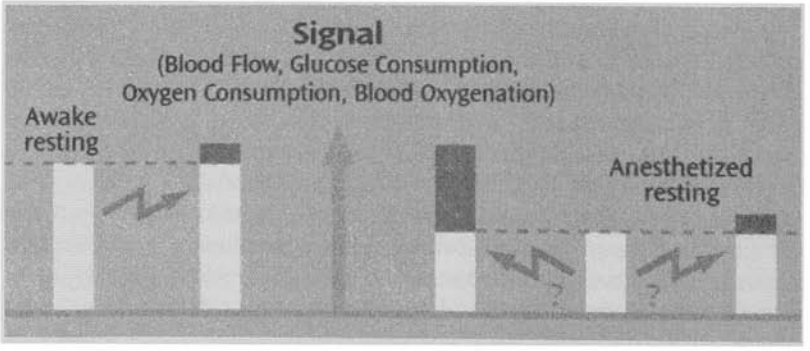


**FIGURE 1** Change in energy consumption during stimulation of anesthetized animal. (From Ref. 27.)

The acronym is intentionally ironic, indicating that the 'resting brain' is both active and interesting" [27] (Fig. 1).

The changes occurring in blood flow and glucose utilization exceed changes in oxygen consumption. The degree to which oxygen consumption actually changes remains to be determined. PET imaging measures the changes in blood flow, whereas fMRI measures a BOLD signal or contrast that arises when changes in blood flow exceed changes in tissue oxygen consumption [29] (Fig. 2).

Thus, fMRI research holds great promise for elucidating the pathophysiology of mood disorders, since neurochemical and neuroendocrine data indicate that mood disorders are associated with disruptions of brain function. With the exception of late-onset major depressive disorder (MDD), structural imaging and postmortem studies have shown that the corresponding brain morphology is relatively well preserved (see Chap. 3). fMRI with blood-oxygenation level–dependent (BOLD) contrast offers us a noninvasive, repeatable method for imaging brain activity with high temporal and spatial resolution. The new generation of functional studies, using various activation paradigms, may uncover abnormalities in specific neuroanatomical circuits not seen under resting conditions as well as help to clarify the function of individual brain structures in various cognitive tasks.

## 2.7 Problems Specific to fMRI

With these general concerns in mind, what are the specific advantages and disadvantages of using fMRI to study mood disorders?

Some relative advantages of fMRI over other brain imaging techniques are its noninvasiveness and good spatial and temporal resolution. fMRI is thus well suited for studies using a within-subject design over time. fMRI studies can image the brain every 2–3 sec without requiring radioactive

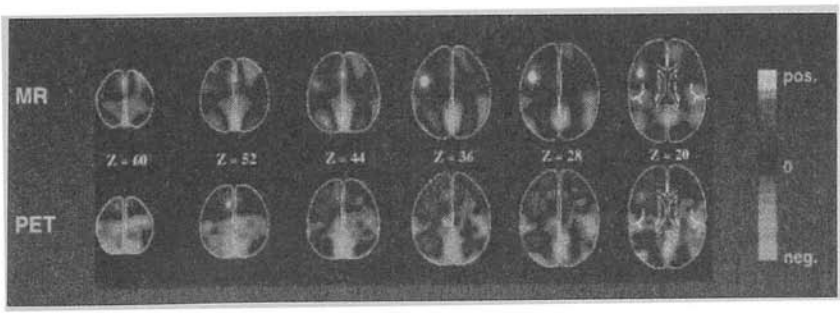


FIGURE 2 fMRI (upper) of the BOLD signal and PET (lower) images of blood flow change. (From Ref. 29.)

tracers. Thus, fMRI allows safe repeated testing within individual subjects. Finally, in contrast to PET, MRI scanners are widely available, often requiring only minor modifications of existing clinical MRI scanners.

There are, however, certain disadvantages of using fMRI. It is movement-sensitive and is not suited for agitated (manic) patients. Further, because fMRI measures only relative changes in blood flow, one must have alternating behaviors repeated over time. The brain activity is thus linked to performance on the tasks. There is thus a large confound of differences in attention and performance when using fMRI with cognitive activation paradigms.

## 3 FUNCTIONAL MAGNETIC RESONANCE IMAGING: APPLICATIONS IN DEPRESSION RESEARCH

Major depressive disorder is one of the most common psychiatric disorders and among the most costly of all diseases. The lifetime prevalence rate for unipolar depression is 4.4% [30]. With proper diagnosis and treatment, up to 60–80% of patients with depression will respond to currently available therapies.

Virtually all forms of psychopathology involve some dysregulation of emotion, and for many forms of psychopathology, affective dysfunction is a central defining characteristic of the disorder. Over the past several years, rapid developments have been made in characterizing the neural substrates and circuitry of emotion and disorders of emotion, leading the emergence of affective neuroscience as a scientific specialty (Table 1).

Schneider et al. [31] performed a BOLD-fMRI study with block design to reveal left amygdala activation during emotion. The subjects were 12 right-handed healthy volunteers (7 men, 5 women; mean age = 29.7, SD = 4.3). The stimuli consisted of photographs of different actors manifesting happy or sad facial expressions of varying intensity. During happy induction, a face with a happy expression was shown, and during sad induction, a face with a sad expression was shown. As a control, a single neutral slide was used. Schneider et al. demonstrated differential lateralized BOLD changes in the amygdala in response to experimentally induced happiness and sadness. The left cingulum was also more activated during mood induction. These findings were consistent with those of Drevets et al. [32], who reported an increase in tissue activity in the left amygdala in a PET study with $H2^{15}O$, using a resting condition in depressed patients. Whereas, George et al. [3] found activated limbic and paralimbic regions during sadness and noted that happiness was associated with temporal parietal reductions, Pardo et al. [33] reported different rCBF increases in inferior and orbitofrontal regions. Likewise, Ketter et al. [34] described a left amygdala activation in

normal subjects in a PET study with $H2^{15}O$ during procaine-induced fear, and Morris et al. [35] described a left amygdala activation with PET in healthy subjects during presentation of fearful faces. Limitations of this initial Schneider are; the conservative method for image analysis that relied on a predefined MRI based and standard-sized region of interest (ROI) approach. A partial volume effect may have contributed to the high variability seen, because single ROIs contained to some extent minimal white matter except amygdala. Because of the limited number of regions, it was not possible to examine the possibility of ipsilateral cortical suppression by differential lateralized activation of amygdala. It should be noted that global changes in cerebral perfusion due to happy and sad mood induction could not be addressed with their regional approach.

Kalin et al. [36] performed a BOLD-fMRI study with block design and echo-planar imaging technique using positive and negative emotional stimuli in two depressed patients and two healthy control right-handed subjects between 18 and 70 years of age. Each depressed subject was given venlafaxine in an open-label design and underwent three scans: before treatment, 2 weeks after venlafaxine treatment, and 8 weeks after venlafaxine treatment. The investigators used photographs depicting positive, negative, and neutral scenes as the emotion elicitors. The negative and positive pictures were matched for their ability to elicit the same intensity of emotional response. For both depressed and control subjects, the negative pictures induced a greater volume of activation than did the positive pictures in the baseline and 2-week scan. In both groups at both time points, the negative stimuli induced bilateral activation in regions of the prefrontal cortex (Brodmann's areas 10 and 46) and in parietal and occipital regions (Brodmann's areas 19 and 37). Exposure to negative pictures resulted in greater activation at baseline compared with the 2-week scan in both the depressed and control subjects. Responses to positive pictures differed between the depressed and control subjects. Little activation of prefrontal regions was observed in either group. From the baseline to the 2-week scan, the control subjects showed an overall reduction in global activation, whereas the depressed patients displayed an increase in overall brain activity. This activation was located in the middle occipital sulcus (part of Brodmann's area 19). A focus of activation was also present in the cerebellum. The negative pictures induced bilateral activation of the amygdala in the baseline scans of the control subjects. In the depressed patients at baseline, exposure to the negative pictures resulted in a small focus of activation in the left amygdala. This area of activation was not present in the 2-week scan. Amygdala activation was not observed in response to the positive pictures in either depressed or control subjects. Interestingly, the depressed patients demonstrated an increased response to presentation of the positive stimuli in the right occipital region

**TABLE 1** Summary of fMRI Studies in Mood Disorders

| Study | Subjects | Mood activation task | fMRI technique |
|---|---|---|---|
| Schneider et al. (1997) [31] | 12 right-handed healthy volunteers (7 men, 5 women; mean age = 29.7, SD = 4.3). | The photographs of happy, sad facial expressions; a single neutral slide as for cognitive task. | BOLD-fMRI, T2*-weighted FLASH sequence. |
| Kalin et al. (1997) [36] | 2 right-handed depressed and 2 right-handed healthy control subjects. | The photographs depicting positive, negative, and neutral scenes (International Affective Pictures System). | BOLD-fMRI, T1-weighted spin echo and T2*-weighted gradient echo echo-planar imaging (EPI) sequence. |

| Findings | Limitations | Comments |
|---|---|---|
| Increase in signal intensity during sad and happy mood induction in left amygdala, activation in left cingulum during mood induction. | The neuroimaging technique used does not provide absolute flow quantification. The conservative method for image analysis that relies on a predefined MRI-based and standard sized region of interest (ROI) approach. A partial volume effect may have contributed to the high variability seen because single ROIs contained to some extent minimal white matter, except amygdala. | Because of the limited number of regions, it was not possible to examine the possibility of ipsilateral cortical suppression by differential lateralized activation of amygdala. Global changes in cerebral perfusion could not be addressed with their regional approach. |
| Exposure to the negative pictures resulted in greater brain activation at baseline in both depressed and control subjects. The negative stimuli induced bilateral activation in the prefrontal cortex (Brodmann's areas 10 and 46) and in parietal and occipital regions (Brodmann's areas 19 and 37), positive pictures induced little activation of prefrontal regions in both groups, a focus of activation is present in the middle occipital sulcus (part of Brodmann's area 19) and in the cerebellum in control subjects. The negative pictures induced bilateral activation of the amygdala in the baseline scans of the control subjects. Depressed patients at baseline, showed a small focus of activation in the left amygdala. | The data presented are preliminary with an exceptionally small sample size, no definitive conclusions can be drawn. | The negative pictures elicited greater brain activity than did the positive pictures. This might have suggested that the negative pictures had a greater physiological impact compared with the positive pictures. The reduced brain activity in the 2-week scan observed in response to the positive stimuli could be due to habituation to the second presentation of the stimuli. |

**TABLE 1** Continued

| Study | Subjects | Mood activation task | fMRI technique |
|---|---|---|---|
| Beauregard et al. (1998) [37] | 7 right-handed patients with unipolar depression (4 women, 3 men; mean age = 42, age range = 27–53 years) and 7 right-handed nondepressed controls (4 women and 3 men; mean age = 45, age range = 31–58 years). | Passive viewing of an emotionally laden film clip inducing a transient state of sadness contrasted with passive viewing of an emotionally neutral film. | BOLD-fMRI, T1-weighted gradient echo pulse sequence and T2*-weighted gradient echo echo-planar imaging (EPI) sequence. |

| Findings | Limitations | Comments |
|---|---|---|
| Transient sadness produced significant activation in the right, midline and left prefrontal gyri (BA 6, 9, 10), right inferior (BA 47) and superior (BA 9) prefrontal gyri, the right fusiform gyrus (BA 37), and the left middle occipital gyrus (BA 19, 39), bilateral middle prefrontal gyrus (BA 9,10), bilateral cingulate gyrus (BA 24, 32), bilateral superior temporal gyrus (BA 37, 42), bilateral caudate, the right fornix, and left cerebellum in depressed subjects.<br>Healthy subjects revealed significant activation in the right midline and left medial prefrontal gyri (BA 9, 10), the right inferior (BA 47) and superior (BA 8, 10) prefrontal gyri, the right middle temporal gyri (BA 37), the left fusiform gyrus (BA 37), the left cuneus (BA 19), the left precuneus (BA 7), the left superior parietal lobule (BA 7), the right middle occipital gyrus (BA 19), the right caudate and the left cerebellum. | Relatively small sample size, subjective ratings of emotional experience, no adequate control of medication effects (2 of depressed patients were on fluoxetine and sertraline), difficulty of distinguishing brain regions activated by the method used to produce a modification in the emotional state from areas activated by experiencing the actual target emotion. | This study suggested that the left medial prefrontal cortex and the right anterior cingulate gyrus might be part of the neural circuit implicated in the pathophysiology of major depression. |

**TABLE 1** Continued

| Study | Subjects | Mood activation task | fMRI technique |
|---|---|---|---|
| Baird et al. (1999) [45] | 12 healthy adolescents, 5 males (3 right-handed), and 7 females (6 right-handed); mean age = 13.9, age range = 12–17 years. | Fearful facial affect recognition paradigm (Ekman and Friesen) contrasted with nonsense stimuli matched for size and intensity, and during baseline and off periods visual fixation on a white point in the middle of the screen. | BOLD-fMRI, T1-weighted gradient echo pulse sequence and T2*-weighted gradient echo echo-planar imaging (EPI) sequence. |
| Teasdale et al. (1999) [47] | 6 healthy right-handed (3 male, and 3 female; mean age = 29.8, age range = 25–36 years). | Cognitive route in generation of emotions, experimental and control conditions included identical pictures and captions and differed only in the relationship between them, experiment 1 and 2 involved comparison of negative and positive images with reference images, conditions differed in the relationship between captions and images, in experiment 3 only meshing pairs of pictures and captions were used in a comparison of images evoking positive and negative feelings. | BOLD-fMRI, T2*-weighted gradient echo echo-planar imaging (EPI). |

| Findings | Limitations | Comments |
|---|---|---|
| The amgdala was shown to exhibit a significantly stronger response during presentation of the facial expression stimuli than during the point-fixation condition. Significantly greater activation was found in the amygdala in response to recognition of fear faces compared to nonsense stimuli. | Lack of randomization of stimulus presentation, examination of only fearful affect, not neutral, happy, or sad faces, small sample size, skewed distribution of age with more older adolescents, inability to have morphometric measures including relative volume of gray and white matter. | These results demonstrated the limbic system activation in adolescents suggesting its involvement in affect recognition prior to adulthood. This study extended our understanding of amygdala function and suggested that one role of the amygdala during development may have been to recognize facial expression and, through experience, learn to assign a label to facial expression. |
| Significant activation in the medial and right middle frontal gyri, right anterior cingulate gyrus, and right thalamus with presentation of negative-picture caption pairs. Positive caption pairs was associated with activation of the left and right insula, right inferior frontal gyrus, splenium, and left precuneus. Coherent positive picture-caption pairs was associated with significant areas of activation within the right and left medial frontal gyri, right precentral gyrus, right anterior cingulate, and left caudate. No evidence of amygdala activation. | Small sample size. | The amygdala, hypocampal formation, and hypothalamus may have been involved in emotional response to stimuli that are emotive at a directly perceptual level, they may be less relevant to cognitively elicited emotions. This study implicated that the medial prefrontal cortex in processing the affect related schematic mental models that, according to the interacting cognitive subsystem account, encoded the affective meanings, which generate emotion by the cognitive route. |

**TABLE 1** Continued

| Study | Subjects | Mood activation task | fMRI technique |
|---|---|---|---|
| Kumari et al. (2001) [50] | 6 female patients suffering from major and treatment-resistant depression and 6 healthy female subjects. | Cognitive generation of emotions, alternating blocks of pairs with pictures and captions eliciting negative feelings and the same materials irrelevantly paired to elicit less emotion (experiment 1), alternating blocks of pairs with pictures and captions eliciting positive feelings and the same materials irrelevantly paired to elicit less emotion (experiment 2), and alternating blocks of pairs with pictures and captions eliciting positive and negative feelings (experiment 3). | BOLD-fMRI, T2*-weighted gradient echo echo-planar imaging (EPI). |
| Mitterschiffthaler et al. (2001) [51] | 7 anhedonic females with a diagnosis of unipolar depression and 7 hedonic females, nonpsychiatric controls. | Cognitive generation of emotions, pleasant versus hedonically neutral visual images. | BOLD-fMRI, T2*-weighted gradient echo echo-planar imaging (EPI). |

| Findings | Limitations | Comments |
|---|---|---|
| Healthy subjects showed significant activation in the medial frontal lobe, thalamus and cingulate gyrus in experiment 1, in the dorsolateral prefrontal cortex in experiment 2, and in the medial frontal lobe, anterior cingulate, and dorsolateral prefrontal cortex in experiment 3. Patients showed decreased activation in the medial frontal lobe and cingulate gyrus and increased activation in parahippocampal and temporal lobe regions during all three experiments. | Small sample size. | This study showed that the areas within the medial and prefrontal cortex are involved in affect generation. Reduced cerebral response in these areas may underlie a treatment-resistant form of depression. |
| In controls, activation during processing of pleasant stimuli was observed in left and right posterior cingulate gyrus, right precuneus, and right medial frontal lobe. In patients, processing of pleasant stimuli led to activation of left insula, left middle temporal gyrus, left inferior posterior temporal lobe, left angular gyrus, left and right retrosplenial cortex, and right posterior cingulate. Activation of temporal lobe structures, retrosplenial cortex, and cingulate during processing of emotional stimuli in depressed patients. | Small sample size. | This study pointed to the differences in neural processing of emotional stimuli between depressed patients with anhedonia and healthy controls. Activation of temporal lobe structures, retrosplenial cortex, and cingulate during processing of emotional stimuli in depressed patients may point to the involvement of these structures in the pathophysiology of depression and anhedonia. |

**TABLE 1** Continued

| Study | Subjects | Mood activation task | fMRI technique |
|---|---|---|---|
| Loeber et al. (1999) [64] | 10 subjects with schizophrenia (8 men and 2 women; mean age = 30 years, SD = 4), 10 subjects with bipolar disorder (8 men and 2 women; mean age = 28 years, SD = 7), and 10 psychiatrically healthy control subjects (8 men and 2 women; mean age = 30 years, SD = 4). | Not used. | Dynamic susceptibility contrast MRI (DSC MRI). |
| Yurgelun-Todd et al. (2000) [68] | 14 right-handed patients with bipolar affective disorder (7 men and 5 women) and 10 right-handed nonpsychiatric adult control subjects (5 men and 5 women). | Happy and fearful affect recognition task. | BOLD-fMRI, T1-weighted gradient echo pulse sequence and T2*-weighted gradient echo echo-planar imaging (EPI) sequence. |

| Findings | Limitations | Comments |
|---|---|---|
| Mean cerebellar blood volume was higher in schizophrenic subjects and lower in bipolar subjects than in controls. The overall between-group difference was significant for the right tonsil, cerebellar blood volume measures was significant for both tonsils. Bipolar patients had the lowest and schizophrenic patients had the highest cerebellar blood volume. | Relatively small sample size, inadequate control of medication effects (4 bipolar patients were on lithium, average doses of antipsychotics were different between bipolar and schizophrenic patients), morphometric analyses derived from data based on the structural images matched to the functional images provided a less accurate estimate of cerebellar volume than a three-dimensional reconstruction. | There appeared to be a substrate for the cerebellum to modulate affect based upon the connections between the cerebellum and the hypothalamus, paralimbic and limbic regions, and this study supported the role of cerebellum in cognitive and affective processes, thus cerebellar insult may have been an etiologically plausible source of risk for both schizophrenia and bipolar disorder. |
| The reduced activation in the right prefrontal area and increased activation in the left amygdalar region in patients with bipolar affective disorder suggested changes in fronto-limbic circuitry underlying fearful affect recognition. In female patients with bipolar affective disorder, notable decreases in activation were present in the right dorsolateral prefrontal cortex and increases in the left amygdala. | Relatively small sample size, use of only a limited range of facial affect (fearful and happy), inadequate control of medication effects (13 bipolar patients were on mood stabilizing medications, 2 patients were taking antipsychotics), lack of morphometric measures such as measurement of relative volume of gray and white matter, ROI approach increased the statistical power of the study, but also constrained the analyes of brain regions examined. | For patients with bipolar affective disorder, poor performance on a task requiring the discrimination of facial affect was associated with a reduction of attentional capacity during early visual processing. This study is suggestive of a differential pattern of signal intensity change in female patients with bipolar affective disorder compared to healthy control subjects. The reduction in cortical activation in the right prefrontal region with an increase in left amygdalar activation suggests a disruption of higher-order processes within the frontolimbic system in bipolar affective disorder. |

at the 2-week scan, and this was significantly associated with a clinically significant treatment response to venlafaxine. One possible explanation for the investigators' inability to detect more robust negative stimuli–induced amygdala activity in the depressed patients could be that, in fMRI studies, activation is determined by the difference in activity detected between the negative and neutral stimuli. If, in the depressed patients, amygdala activity in response to the neutral stimuli is already high, the likelihood of observing further increases might be reduced. Since these data were preliminary, with an exceptionally small sample size, no definitive conclusions can be drawn.

Beauregard et al. [37] performed a BOLD-fMRI study with block design and echo-planar imaging technique, examining the brain activation associated with passive viewing of an emotionally laden film clip aimed at inducing a transient state of sadness contrasted with that associated with passive viewing of an emotionally neutral film clip. The subjects were 7 right-handed patients suffering from unipolar depression (4 women and 3 men; mean age = 42, age range = 27–53 years) and 7 right-handed nondepressed healthy controls (4 women and 3 men; mean age = 45, age range = 31–58 years). They found that transient sadness produced significant activation in the medial and inferior prefrontal cortices, the middle temporal cortex, the cerebellum, and the caudate in both depressed and healthy subjects. They also revealed that passive viewing of the emotionally laden film clip produced a significantly higher activation in the left medial prefrontal cortex and in the right anterior cingulate gyrus in depressed patients than in healthy subjects. With respect to the depressed patients, when the emotionally laden film clip aimed at inducing transient sadness was contrasted with the emotionally neutral film clip, significant blood-oxygenation level–dependent (BOLD) signal increases were seen in the right, midline and left prefrontal gyri, the right inferior and superior prefrontal gyri, the right fusiform gyrus, and the left middle occipital gyrus. This contrast also produced significant signal increase bilaterally in the middle prefrontal gyrus, the cingulate gyrus, the superior temporal gyrus, the caudate, the right fornix, and the left cerebellum (see Fig. 3). Normal control subjects when passive viewing of the emotionally laden film clip contrasted with viewing of the emotionally neutral film clip, revealed significant activation in the right, midline and left medial prefrontal gyri, the right inferior and superior prefrontal gyri, the right middle temporal gyri, the left fusiform gyrus, the left cuneus, the left precuneus, the left superior parietal lobule, the right middle occipital gyrus, the right caudate and the left cerebellum (see Fig. 3). Such a view was supported by the fact that cerebellar lesions could produce a blunting of affect [38] and that medial prefrontal lesion could lead to emotional disturbances [39]. The medial prefrontal cortex is the site of convergence for limbic inputs with highly processed information and it has been postulated

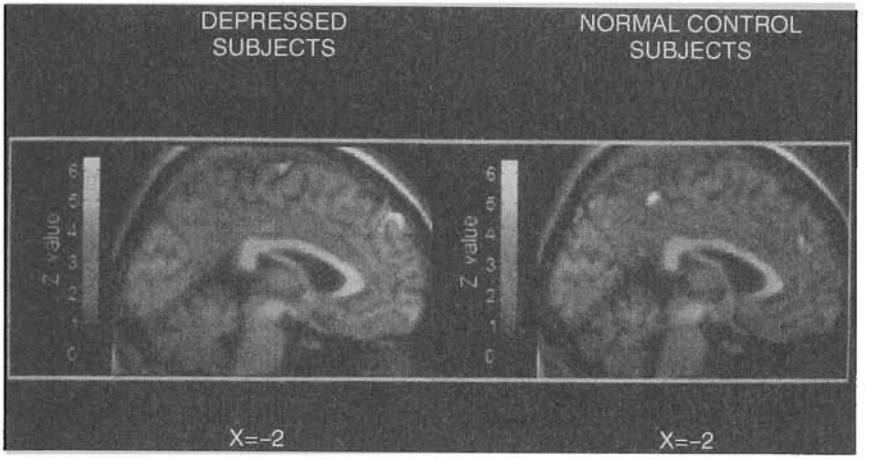


**FIGURE 3** Sagittal statistical maps showing activated voxels in depressed patients and normal control subjects. The merged MRI scans were coregistered with their BOLD activation. This activation is displayed as a Z-statistical map coded according to the color bars. For the sagittal section through the left hemisphere, the frontal lobe of the image is to the right. Note particularly the greater spatial extent of the BOLD signal in the left medial prefrontal cortical region in depressed patients compared to the normals as well as absence of cingulate activation in the normal subjects. (From Ref. 37.)

that this area participates in the integration of cognition and emotion [40], functions that are disrupted in major depression. Clinically it has been found that patients with infarction of the left frontal lobe have an increased frequency of depression [41] and that medial prefrontal cortical lesions can disturb socioemotional behavior [39]. The cingulate cortex has also been implicated in the mediation of cognition and emotion given that, anatomically, it is a component of an interconnected network between neocortical and limbic associative cortices [42]. In humans, functional imaging studies have demonstrated that the anterior cingulate is associated with attentional [43] and emotional [34] processes. Both medial prefrontal and anterior cingulate cortices have been postulated to participate in the conscious experience of emotion, the regulation of emotional expression [44], and to be involved in a neural circuit underlying the pathophysiology of unipolar depression [32]. The emotional challenge produced a significantly more robust activation in the medial prefrontal and cingulate cortices in depressed patients compared to nondepressed subjects may indicate that in presence of abnormal frontal activity, limbic structures might be relatively disconnected

from normal prefrontal modulatory influences, resulting in impaired affective modulation. The limitations of this study are relatively small sample size, subjective ratings of emotional experience, inadequate control of medication effects (two of the depressed patients were on fluoxetine and sertraline), and difficulty of distinguishing brain regions activated by the method used to produce a modification in the emotional state from areas activated by experiencing the actual target emotion. It should also be noted that, demonstrating a correlation between regional brain activity and a transient change in subjective emotional experience does not necessarily involve a casual relationship.

Baird et al. [45] performed a BOLD-fMRI study with block-design and echo-planar imaging technique, using a facial affect recognition task in 12 healthy adolescents, 5 males (3 right-handed), and 7 females (6 right-handed); mean age = 13.9, age range = 12–17 years. Fearful facial affect recognition paradigm [46] contrasted with nonsense stimuli matched for size and intensity, and during baseline and off periods visual fixation on a white point in the middle of the screen. The amygdala was shown to exhibit a significantly stronger response during presentation of the facial expression stimuli than during the point-fixation condition; the nonsense visual stimulus condition did not activate the amygdala. Significantly greater activation was found in the amygdala in response to recognition of fear faces compared to nonsense stimuli. No differences between conditions were observed in the control region of interest in the superior parietal lobe. The results demonstrated the limbic system activation in adolescents suggesting its involvement in affect recognition prior to adulthood. This study extended our understanding of amygdala function and suggested that one role of the amygdala during development may have been to recognize facial expression and, through experience, learn to assign a label to facial expression. The limitations of this study were; lack of randomization of stimulus presentation, examination of only fearful affect not neutral, happy or sad faces, small sample size, skewed distribution of age with more older adolescents, and inability to have morphometric measures including relative volume of gray and white matter.

Teasdale et al. [47] performed a BOLD-fMRI study with block-design and echo-planar imaging technique, using a cognitive route in generation of emotions in 6 healthy right-handed (3 male, and 3 female; mean age = 29.8, age range = 25–36 years) subjects. Experimental and control conditions included identical pictures and captions and differed only in the relationship between them, experiment 1 and 2 involved comparison of negative and positive images with reference images, conditions differed in the relationship between captions and images, in experiment 3 only meshing pairs of pictures and captions were used in a comparison of images evoking positive and

negative feelings. They found significant activation in medial and right middle frontal gyri, right anterior cingulate gyrus, and right thalamus with presentation of negative-picture caption pairs (Fig. 4). Presentation of positive caption pairs was associated with activation in the left and right insula, right inferior frontal gyrus, splenium, and left precuneus (Fig. 4). Presentation of coherent positive picture-caption pairs was associated with significant areas of activation within the right and left medial frontal gyri, right precentral gyrus, right anterior cingulate, and left caudate (see Fig. 4). They found no evidence of amygdala activation and interpreted this, as although the amygdala, hippocampal formation, and hypothalamus may have been involved in emotional response to stimuli that were emotive at a directly perceptual level, they may have been less relevant to cognitively elicited emotions. Damage to areas of the medial prefrontal cortex has marked emotional consequences consistent with involvement of these areas in the affect-related processing. Patients with lesions of the medial orbitofrontal cortex show disrupted social and emotional behavior and impairments in real-life decision making in spite of otherwise preserved intellectual abilities [48]. Such deficits are consistent with this brain region playing a central role in assessing the affective significance of events and outcomes. It is possible that areas of the medial prefrontal cortex are involved in accessing both affective and nonaffective schematic mental models of personal and social relevance. Despite the limitation of small sample size, this study implicated that the medial prefrontal cortex in processing the affect related schematic mental models that, according to the interacting cognitive subsystem account [49], encoded the affective meanings, which generate emotion by the cognitive route.

Kumari et al. [50] investigated the functional brain activation associated with the cognitive generation of affect in patients with depression as compared to nondepressed comparison subjects, performing a BOLD-fMRI study with block-design and echoplanar imaging technique. Six female patients suffering from major and treatment resistant depression and six healthy female subjects underwent a BOLD-fMRI while viewing: (1) alternating blocks of pairs with pictures and captions eliciting negative feelings and the same materials irrelevantly paired to elicit less emotion (reference pairs; experiment 1), (2) alternating blocks of pairs with pictures and captions eliciting positive feelings and the same materials irrelevantly paired to elicit less emotion (experiment 2), and (3) alternating blocks of pairs with pictures and captions eliciting positive and negative feelings (experiment 3). The order of experiments was counterbalanced across subjects for both patient and control groups. Healthy subjects showed significant activation in the medial frontal lobe, thalamus and cingulate gyrus in experiment 1, in the dorsolateral prefrontal cortex in experiment 2, and in the medial frontal lobe, anterior cingulate, and dorsolateral prefrontal cortex in experiment 3. Pa-

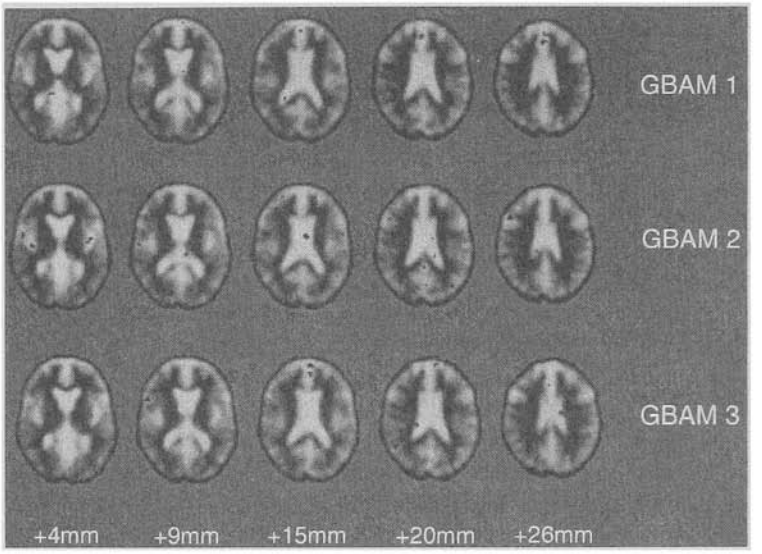


**FIGURE 4** Median generic brain activation maps (GBAM) for each of the three experiments in an fMRI study of the cognitive generation of affect. All identified activation sites with a total fundamental power quotient greater than 3 and size (number of voxels) greater than 2 are listed. For all sites shown, randomization $p < 0.0005$, $N = 6$. Numbers in parentheses in the following descriptions of experiment results indicate Talairach and Tournoux coordinates ($x$, $y$, $z$). The right side of the figure corresponds to the left side of the brain. *GBAM1, experiment 1*: coherent negative picture and caption pairs versus reference pairs. Activations within the right anterior cingulate gyrus [3, 31, 28; 6, 39, 20; 3, 3, 42 (not shown)], medial frontal gyrus (0, 39, 26), right thalamus (0, −14, 4;9, −33, 4), and right middle frontal gyrus (32, 36, 26) were associated with presentation of negative pairs; no activations meeting criteria were associated with presentation of reference pairs. *GBAM2, experiment 2*: coherent positive picture and caption pairs versus reference pairs. Activations within the right inferior frontal gyrus (49, 17, 26), right insula (40, −17, 4), left insula (−38, −6, 4), posterior cingulate (−3, −28, 9), and left precuneus [−12, −60, 42 (not shown)] were associated with presentation of positive pairs and within the left thalamus (−6, −6, 15) were associated with presentation of reference pairs. *GBAM3, experiment 3*: coherent positive picture and caption pairs versus coherent negative pairs. Activations within the left caudate (−17, −11, 26), medial frontal gyrus (0, 53, 15;−3, 50, 20), right medial frontal gyrus [3, 0, 53 (not shown)], right precentral gyrus (55, 8, 9), and right anterior cingulate [0, 42, 15; 3, 3, 42 (not shown)] were associated with presentation of positive pairs; no activations reaching criterion levels were associated with presentation of negative pairs. (From Ref. 47.)

tients showed decreased activation, in comparison to healthy subjects, in the medial frontal lobe and cingulate gyrus and increased activation in parahippocampal and temporal lobe regions during all three experiments. Despite the limitation of small sample size, this study implicated that the areas within the medial and prefrontal cortex were involved in affect generation involving schematic mental models of personal and social relevance. Reduced cerebral response in these areas may underlie a treatment-resistant form of depression.

Mitterschiffthaler et al. [51] investigated neural processing associated with pleasant versus hedonically neutral visual images in depressed patients with anhedonia and healthy controls, performing a BOLD-fMRI study with block-design and echo-planar imaging technique. Whole-brain scans were obtained from 7 anhedonic females with a diagnosis of unipolar depression and 7 hedonic females who were nonpsychiatric controls. In controls, activation during processing of pleasant stimuli was observed in left and right posterior cingulate gyrus, right precuneus, and right medial frontal lobe. In patients, processing of pleasant stimuli led to activation of left insula, left middle temporal gyrus, left inferior posterior temporal lobe, left angular gyrus, left and right retrosplenial cortex, and right posterior cingulate. Despite the limitation of small sample size, this study pointed to differences in neural processing of emotional stimuli between depressed patients with anhedonia and healthy controls. Activation of temporal lobe structures, retrosplenial cortex, and cingulate during processing of emotional stimuli in depressed patients was consistent with recent studies [37,52,53] and may have pointed to the involvement of these structures in the pathophysiology of depression and anhedonia.

Our group at Medical University of South Carolina (MUSC) has recently pioneered the ability to perform transcranial magnetic stimulation (TMS) within the fMRI scanner [54,55,56]. This technique allows one to noninvasively stimulate a brain region and simultaneously image regional brain activity. We have performed a series of studies using this technique to elucidate brain connectivity [57]. Prefrontal TMS has been shown to change mood in healthy adults [58] as well as to reverse depression symptoms when applied daily for several weeks (Ref. 59; for review see Ref. 60). We have recently begun to image the brain activity in depressed adults while they are receiving TMS. Fig. 5 shows an example of this important new line of work. The ability to perform TMS within the scanner may allow us to make more causal rather than correlational statements about the relationship between mood dysregulation and regional brain activity. Fig. 5 shows recent work from MUSC, where we are using this method to determine potential differences in brain circuitry in depression, as well as to elucidate the antidepressant mechanisms of action of TMS.

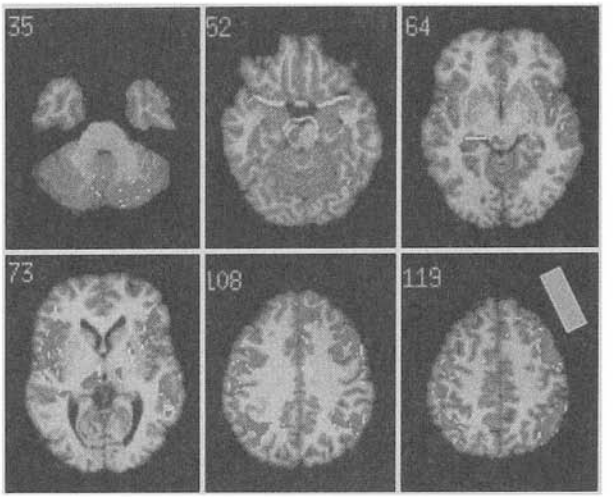


**FIGURE 5** Performance of a system for interleaving transcranial magnetic stimulation (TMS) with steady-state magnetic resonance imaging in depressed patients. The ability to perform TMS within the scanner may allow one to make more causal rather than correlational statements about the relationship between mood dysregulation and regional brain activity. (From Ref. 59.)

Vagus nerve stimulation (VNS) is a new technology that serves as an effective anticonvulsant and has recently shown promise as an antidepressant [61,62]. We have recently solved the technical problems associated with performing fMRI in depressed subjects implanted with a vagus nerve stimulator [63]. In nine depressed patients implanted with VNS generators, we found that VNS caused increased activation in the hypothalamus, bilateral orbitofrontal and medial prefrontal cortex, insula, and amygdala. *Ongoing work combining VNS with fMRI will hopefully aid in showing how VNS is able to treat depression as well as in revealing further information about the pathogenesis of depression.*

## 4 FUNCTIONAL MAGNETIC RESONANCE IMAGING fMRI: APPLICATIONS IN BIPOLAR DISORDER RESEARCH

Given its versatility and safety, it is perhaps surprising that there are few studies utilizing fMRI in the study of bipolar disorder. In fact, our search ended with only two studies. The reason for this may be the complexity of defining emotional states and the difficulty of specifying the behavioral unit

to be studied in bipolar disorder. Another limitation may be our relative inability to monitor subjects' performance during the activation paradigms. Generally, while assuming that all subjects are in fact completing the task to the best of their ability inside the scanner, no absolute measure of compliance during the scanning sequence can be administered. This lack of monitoring does not allow us to conclude that changes in activation are specifically associated with changes in performance, as one cannot rule out the effects of effort.

Loeber et al. [64] performed a dynamic susceptibility contrast MRI (DSC MRI), a technique that uses MRI technology coupled with a contrast agent and provides a more accurate measurement of regional blood volume than is possible with PET [15]. They included 10 subjects with schizophrenia (8 men and 2 women; mean age = 30 years, SD = 4), 10 subjects with bipolar disorder (8 men and 2 women; mean age = 28 years, SD = 7), and 10 psychiatrically healthy control subjects (8 men and 2 women; mean age = 30 years, SD = 4). Mean cerebellar blood volume was higher in schizophrenic subjects and lower in bipolar subjects than in controls. Although these differences did not reach statistical significance, the blood volume measurements of individual cerebellar regions consistently showed this same trend across diagnostic groups for all nine subdivisions. The overall between-group difference was significant for the right tonsil ($F = 3.57$; df = 2,21; $p < 0.05$). Statistical analysis comparing only schizophrenic and bipolar subjects' cerebellar blood volume measures was significant for both tonsils (right: $F = 12.80$; df = 1; $p = 0.003$; left: $F = 5.06$; df = 1,15; $p < 0.05$). Bipolar patients had the lowest and schizophrenic patients the highest cerebellar blood volume. This difference was most significant in the tonsillar region. The between-group differences are greatest for the right side of the cerebellum (CBL). There appeared to be a substrate for the cerebellum to modulate affect based upon the connections between the cerebellum and the hypothalamus and the paralimbic and limbic regions, including the monoaminergic-producing brainstem nuclei [65]. Additionally, many imaging studies have shown CBL activation, particularly of the vermis, during tests of emotional modulation, such as induced sadness [66,67]. This study supported the role of the cerebellum in both cognitive and affective processes and thus demonstrated that a cerebellar insult may have been an etiologically plausible source of risk for both schizophrenia and bipolar disorder. Relatively small sample size and inadequate control of medication effects (four bipolar patients were on lithium, average doses of antipsychotics were different between bipolar and schizophrenic patients) were the main limitations of this study. Additionally, morphometric analyses derived from data based on the structural images matched to the functional images provided a less accurate estimate of cerebellar volume than a three-dimensional reconstruction.

Yurgelun-Todd et al. [68] performed a BOLD-fMRI study with block-design and echo-planar imaging technique, examining signal activation in the prefrontal cortex and the amygdala in 14 right-handed patients with bipolar affective disorder (7 men and 5 women) and 10 right-handed non-psychiatric adult control subjects (5 men and 5 women) by using a happy and fearful affect recognition task. Subjects were instructed to view the stimuli and to silently identify the facial expression presented. The reduced activation in the right prefrontal area and increased activation in the left amygdalar region in patients with bipolar affective disorder suggested changes in frontolimbic circuitry underlying fearful affect recognition, which was in agreement with previous reports which have hypothesized disruptions of the frontal network in bipolar affective disorders [69,70]. Results were particularly striking in female patients with bipolar affective disorder, where notable decreases in activation were present in the right dorsolateral prefrontal cortex and increases in the left amygdala were evident during the process of affect recognition (Figs. 6 and 7). At this time, we do not have a measure of the relative importance of any single brain region or any individual cognitive function for the accurate completion of affective labeling tasks. The complexity of the demands inherent in the affective labeling task has been highlighted in a recent study that examined the relationship between affective processing and neuropsychological function. Authors reported that for patients with bipolar affective disorder, poor performance on a task requiring the discrimination of facial affect was associated with a reduction of attentional capacity during early visual processing [71]. Yurgelun-Todd et al. [68] demonstrated a differential pattern of signal intensity change in female patients with bipolar affective disorder compared to healthy control subjects during a task requiring the discrimination of facial affect. Their findings were consistent with previous neuroimaging studies that have implicated the dorsolateral prefrontal region in affective processing [67,72]. The reduction in cortical activation in the right prefrontal region appeared coincident with an increase in left amygdalar activation, suggesting a disruption of higher-order processes within the frontolimbic system in bipolar affective disorder. The limitations of this study were relatively small sample size, use of only a limited range of facial affect (fearful and happy), inadequate control of medication effects (13 bipolar patients were on mood-stabilizing medications, 2 patients were taking antipsychotics), relative inability to monitor subjects' performance during the activation paradigms, and lack of morphometric measures such as measurement of relative volume of gray and white. Temporal resolution of their data acquisition and the use of a block design restricted the detection of signal responses that may have occurred early in processing. Additionally, an ROI approach increased the

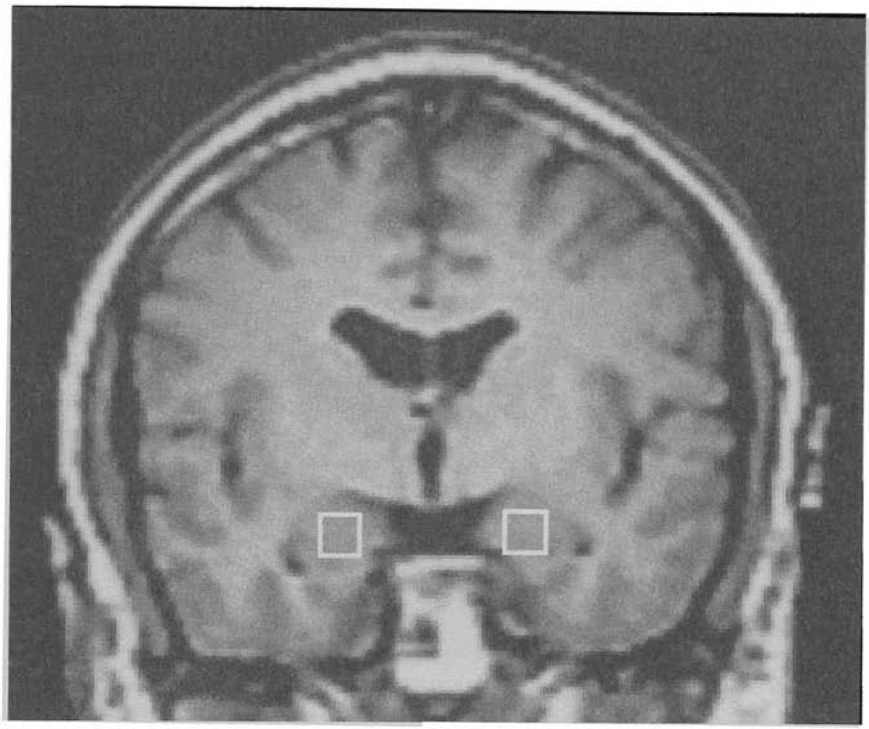

**FIGURE 6** Coronal slice of bipolar patient showing relative changes in signal intensity in the amygdala during the viewing of fearful facial affect. (From Ref. 68.)

statistical power of the study by allowing the testing of a specific hypothesis; however, it constrained the analyses of brain regions examined.

Several years ago we performed a longitudinal imaging study using the perfusion fMRI technique in rapid-cycling bipolar patients. Given that the perfusion technique measured absolute blood flow and involved no radiation, we wondered if serial scans in patients with rapid-cycling bipolar affective disorder (BPAD) would show different brain regions changing over time as a patient's state changed. We performed a manpower-intensive study in 6 BPAD subjects scanned numerous times over several months. Nonill controls were scanned as well on the same days. Unfortunately the signal to noise ratio of the scanning technique did not allow us to make statements about specific regions. The absolute blood flow measures did change over time and were softly associated with depression or mania [18]. Figure 8

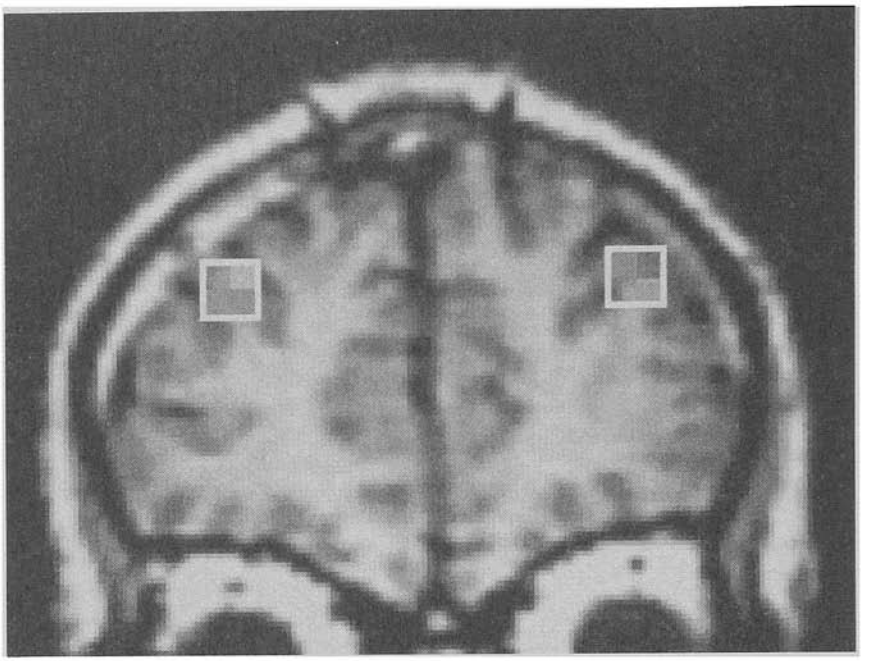

**FIGURE 7** Coronal slice of bipolar patient showing relative changes in signal intensity in dorsolateral prefrontal cortex during the viewing of fearful facial affect. (From Ref. 68.)

shows an example of work from this project. As the technique of perfusion MRI improves, serial studies like this may be very enlightening.

## 5 FUTURE DIRECTIONS FOR fMRI STUDIES IN MOOD DISORDERS

The rapid progress made by using the functional neuroimaging methods has encouraged widespread optimism about our ability to understand the brain basis of mood disorders. However, the relationship between the signal and the neurobiological processes related to function is not completely understood, since the functional imaging signal is not a direct measure of neuronal processes related to information transfer, such as action potentials and neurotransmitter release. Rather, the intensity of the imaging signal is related to neurophysiological parameters of energy consumption and blood flow. The integration of fMRI studies with other neuroimaging and neurostimulation

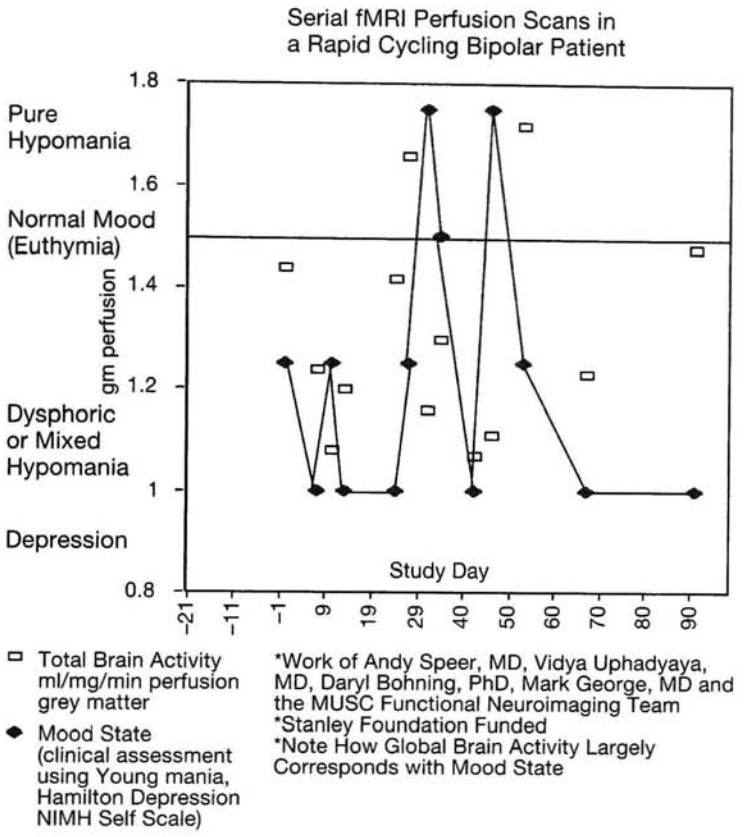


**FIGURE 8** Serial fMRI perfusion scans in a rapidly cycling bipolar patient. (From Ref. 18.)

(TMS, VNS) methods will provide an opportunity to advanced neuroscientific understanding of mood disorders.

The major limitation of these fMRI studies is the inclusion of small sample size, which does not allow for analysis of clinical subtypes or for an adequate control of drug effects. Another limitation is that mood disorders appear to represent diseases of heterogeneous origin and manifestation. For this reason it is wise to look not only at mean differences between subject groups but also at variances and to study outliers on a measure. Outliers may represent a subgroup of individuals who are more homogeneous in etiology or pathophysiology. Larger subject samples will also aid in such analyses. Data analysis methods that allow intraindividual statistical com-

parisons will help address the important confound of diagnostic heterogeneity. Future studies that control for these effects may further clarify these differences between mood-disordered patients and healthy controls.

Given the rapid progress in MRI over the past decade, the next decade should be even more interesting with respect to using MRI to understand mood disorders. The current techniques (BOLD fMRI, perfusion, diffusion, and spectroscopy) will only improve. Further, combining TMS with the brain stimulation methods offers much promise for understanding the pathological circuitry involved in depression. And there will likely be new developments with MRI that are not foreseen. The near future is bright.

However, for centuries, the only view that psychiatrists had of mood-disordered patients was their sad faces or irritable behaviors. One could easily observe the external manifestations of mood disorders as well as the problems this disease caused in people's lives. However, psychiatrists were speculating and imagining what was happening inside the brain. Advanced functional imaging techniques identifying the neuroanatomical changes associated with these disorders may ultimately be correlated with symptom expression, aid in targeting new and more focal treatment interventions, and help to destigmatize these illnesses by showing that these disorders are truly diseases of the brain.

Finally we repeat the credo of neuroscientists expressed by Francis Crick, "The scientific belief is that minds—the behavior of our brains—can be explained by the interactions of nerve cells (and other cells) and the molecules associated with them." It is our ultimate hope that the neuroimaging studies of mood disorders can serve this goal.

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# 6

# Magnetic Resonance Spectroscopy Investigations and the Pathophysiology of Affective Disorders

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## 1 INTRODUCTION

Despite intensive research in bipolar disorder, its biochemical basis is not yet totally elucidated, mainly due to methodological difficulties. Because of complex mode of inheritance and heterogeneity of the disorder, results in linkage studies are not yet conclusive. Neurochemical analysis of postmortem brain tissue is difficult to interpret because of effects of medication, and it cannot reveal changes associated with manic or depressive states. Peripheral samples may not reflect the event in the brain.

Considering these limitations, the in vivo neurochemical assay may be one of the most powerful tools to study the biochemical basis of bipolar disorder. Among such tools, magnetic resonance spectroscopy (MRS) can detect various important metabolites in the brain without any application of radioisotopes and has the potential to measure several kinds of biochemical parameters, metabolite concentration, relaxation time, enzyme activity, and intracellular pH.

Since the initial MRS studies in mood disorders were reviewed in 1998 [1], great progress was made especially in the proton MRS studies. Although

initial MRS studies were relatively simple in methodologies, recent MRS studies have been performed in order to clarify specific hypotheses using more sophisticated strategies. In this review, recent progress in $^{1}H$ and $^{31}P$ MRS in mood disorders is summarized. Most of important papers published before 1998, unless they are clinical MRS studies in mood disorder, could not be cited in this article due to limitation of space. Please refer to the previous review for those articles [1].

## 2 BASIC PRINCIPLES OF MRS

In spite of its complexity, it is important to understand the basic principles of MRS for interpretation of the results, especially in assessing conflicting results between different studies. Basic principles of MRS are summarized in our previous review [1]. Only a brief summary of the methodology is given below.

Nuclei having odd numbers of protons or atomic number, such as $^{1}H$ or $^{31}P$, have magnetic properties. Under a strong magnetic field, typically 1.5 tesla or more, the nuclear spin resonates and absorbs energy by application of a particular radiofrequency (RF) pulse (Larmor frequency). Larmor frequency changes largely with the type of nuclei on the order of megahertz and slightly with the type of chemical bonding with other nuclei on the order of hertz. This slight difference of resonance frequency depending on the molecular structure, referred to as *chemical shift*, enables discrimination of the same nuclei in different molecules. During the return of nuclei to the previous state, they emit electromagnetic waves referred to as *free induction decay* (FID). The process in which the nuclei return to the initial state is referred to as *relaxation*, and two different components of relaxation, T1 and T2, are observed. When the second pulse is applied after a certain interval (echo time), the other signal, echo, is observed. The signal from each metabolite changes differentially with the echo time, because the T2 relaxation process depends on the molecular structure and molecular environment. The concentration of nuclei is theoretically related to the intensity of FIDs or echoes observed. Generally, FIDs or echoes are averaged with a specific interval of repetition time (TR), because the MRS signal is too small to be detected by single acquisition. When TR is not large enough, and this is usually the case in clinical studies, signal intensity decreases depending on its T1 relaxation time.

To localize MRS signals to a particular region of the brain, many kinds of signal localization methods are used: a simple surface coil method, depth-resolved surface coil spectroscopy (DRESS), phase encoding or one-dimensional chemical shift imaging (1D-CSI) and image-selected in vivo spectroscopy (ISIS) for $^{31}P$-MRS, and stimulated-echo acquisition mode

(STEAM) and point-resolved spectroscopy (PRESS) for $^{1}$H-MRS. Magnetic resonance spectroscopic imaging (MRSI), using the same principle as MRI, can be used for both $^{31}$P and $^{1}$H MRS. Different kinds of artifacts can arise depending on the type of localization method used. Data processing of FIDs or echoes is also a source of artifacts and poor reproducibility; therefore this process should be performed blindly to the diagnosis of the subjects.

## 3 WHAT CAN BE MEASURED?

### 3.1 $^{31}$P-MRS

In the $^{31}$P-MR spectra of the brain, seven major peaks can be resolved; phosphomonoester (PME), inorganic phosphate (Pi), phosphodiester (PDE), phosphocreatine (PCr), and three phosphate residues from adenosine triphosphate ($\gamma$, $\alpha$, and $\beta$-ATP) (Fig. 1).

#### 3.1.1 Phosphomonoester (PME)

The phosphomonoester (PME) peak originates from many metabolites. Major components were phosphocholine (PC), phosphoethanolamine (PE), and various sugar phosphates. Of those, PC and PE are precursors of membrane phospholipids. Inositol-1-phosphate (I-1-P) is also predicted to contribute to this peak when it is accumulated on the order of millimoles due to inhibition of inositol monophosphatase by lithium treatment. When the proton-decou-

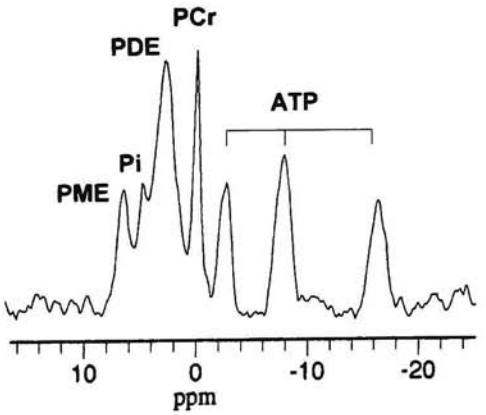


**FIGURE 1** Phosphorus-31 magnetic resonance spectra in the left frontal lobe detected by one-dimensional chemical shift imaging (phase encoding). PME: phosphomonoester, Pi: inorganic phosphate, PDE: phosphodiester, PCr: phosphocreatine, ATP: adenosine triphosphate.

pling technique is applied, PC and PE can be differentiated. However, even in the proton-decoupled $^{31}$P-MR spectra after chronic lithium administration, I-1-P could not be discriminated from other PMEs [2].

It is still controversial whether PME peak increases in the human brain after lithium administration. Silverstone et al. [3] reported that lithium treatment alone did not elevate PME in healthy volunteers, but amphetamine challenge after 1 week of lithium treatment increased PME. Keshavan et al. [4] reported no increase of PME peak after 2 weeks of lithium treatment in patients with schizophrenia. In our first study [5], PME was increased in the manic state but not in the euthymic state during lithium treatment in patients with bipolar disorder. However, in our subsequent study, there was no difference between manic patients before and after lithium treatment [6]. These discrepancies may be caused mainly by difference in the duration of lithium treatment, because the PME peak was elevated in the manic patients treated with lithium for about 1 week, but it was not high in patients treated for 2 weeks or more [1].

More recently, Yildiz et al. [2] reported that the PME peak was increased after 1–2 weeks of lithium treatment. The discrepancy between this study and that of Silverstone et al. may be due to improved methodologies in the former study—i.e., use of proton decoupling enabling better spectral resolution and spin-echo sequence eliminating baseline distortion.

In summary, these findings suggest that PME is only slightly increased by lithium alone but increases more markedly after 1 week of lithium treatment and concomitant activation of monoaminergic systems. This is compatible with a hypothesis predicted by the effects of lithium on phosphoinositide (PI) pathway; inhibition of inositol monophosphatase causes accumulation of I-1-P, and this accumulation is further enhanced during stimulation by agonists linked with PI pathway.

### 3.1.2 Phosphodiester (PDE)

Most of the signals in the PDE peak is thought to be arisen from relatively mobile component of membrane phospholipids [7]. Soluble PDEs such as glycerophosphocholine (GPC) and glycerophosphoethanolamine (GPE), degeneration products of membrane phospholipids, have only minor contribution to in vivo PDE peak. A broad component of PDE from membrane phospholipids may be omitted by postspectral processing [7].

### 3.1.3 Inorganic Phosphate

Because the inorganic phosphate (Pi) peak overlaps with the PME and PDE peaks, quantitative analysis is sometimes difficult. This peak contains both $H_2PO_4^-$ and $HPO_4^{2-}$, having different chemical shifts, but produces a single

peak because of fast exchange. Intracellular pH can be calculated from the chemical shift of this peak.

### 3.1.4 Phosphocreatine (PCr)

Phosphocreatine (PCr) is a high-energy phosphate abundant in the brain and muscles. PCr is made from ATP and creatine by creatine kinase [8]. By using saturation transfer $^{31}$P-MRS, creatine kinase reaction can be measured in vivo in human brain [9].

### 3.1.5 Adenosine Triphosphate (ATP)

Adenosine triphosphate (ATP) forms three distinct peaks, $\gamma$, $\alpha$, and $\beta$. ATP is a high-energy phosphate, a substrate of many kinds of biochemical processes in the brain. Because a magnesium ion changes the chemical shifts of the $\alpha$ and $\beta$ phosphates of ATP, intracellular magnesium concentration can be determined by the chemical shifts of these two peaks [10].

## 3.2 $^{1}$H-MRS

The signal of water, exists in the brain at very high concentration, should be suppressed to obtain proton MR signal. At relatively long echo time (TE) (135–270 msec), three prominent signals from N-acetyl-L-aspartate (NAA), creatine/phosphocreatine (Cr), and choline-containing compounds (Cho), are seen, while other metabolites such as myo-inositol, glutamine/glutamate, and gamma aminobutylic acid (GABA) are observed in short TE (less than 30 msec) $^{1}$H-MRS (Fig. 2). Glutamine, glutamate, and GABA make mixed and overlapped peaks, and they are difficult to quantify. Using spectral editing technique or two dimensional MRS, GABA can be quantitatively measured [11,12].

### 3.2.1 N-Acetyl-L-Aspartate (NAA)

NAA is thought to be a neuronal marker because it localizes mainly in neurons rather than glial cells. Decrease of NAA reflects cell death or dysfunction of neurons.

### 3.2.2 Creatine (Cr)

The creatine (Cr) peak contains signals from creatine and phosphocreatine. Creatine is a substrate of creatine kinase. Cr peak is relatively constant and was previously used as an internal standard. This peak increases after creatine administration [13].

### 3.2.3 Choline-Containing Compounds (Cho)

The peak of choline-containing compounds (Cho) includes many metabolites that have a trimethylamine (choline) residue, such as PC, GPC, phosphati-

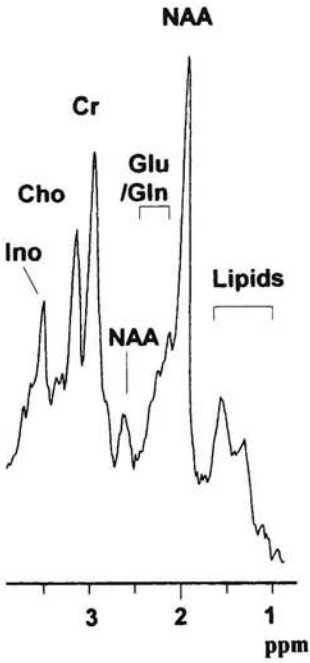


FIGURE 2 Proton magnetic resonance spectra in the left basal ganglia detected by stimulated echo method (STEAM). Echo time period is 20 msec. Ino: myoinositol, Cho: choline-containing compounds, Cr: creatine and phosphocreatine, NAA: N-acetylaspartate, Glu/Gln: glutamate and glutamine.

dylcholine, sphingomyelin, choline, and acetylcholine. This peak increases after choline ingestion.

### 3.2.4 Myoinositol

This peak contains myoinositol (mI), which has two functions: as an osmolite and as a substrate for the phosphoinositide cycle. When inositol monophosphatase is inhibited by lithium and I-1-P accumulates in the brain, mI is decreased. Sodium valproate may also decreases the mI peak, possibly by inhibiting inositol transporter [14]. This peak transiently increases after inositol ingestion [15].

Whether this peak decreases during lithium treatment is still controversial, both theoretically and practically. Because I-1-P and mI have similar chemical shifts, decrease of mI may be obscured by increase of I-1-P. The inositol peak decreased after lithium treatment in patients with bipolar dis-

order [15,16], while it did not decrease after lithium treatment in healthy volunteers [17] or patients with bipolar disorder [18].

### 3.2.5 Other Peaks

Lactate peak is not prominent in the normal brain but is detectable after pharmacological or physiological challenge, as by lactate infusion, hyperventilation, or photic stimulation [19]. Since lipid signals from outside the brain can easily contaminate into $^{1}$H-MR spectra even in the deep regions in the brain, lipid suppression technique is used for MRSI studies [20].

Many other substances can be detected by $^{1}$H-MRS in certain conditions; glucose, ethanol, phenylalanine, ketone bodies, and macromolecules [21].

## 4 APPLICATIONS TO AFFECTIVE DISORDERS

### 4.1 $^{31}$P-MRS

#### 4.1.1 Bipolar Disorder

Published studies of $^{31}$P-MRS in mood disorders are summarized in Table 1. All studies of $^{31}$P-MRS in bipolar disorder are reported from only two research groups.

4.1.1.1 *PME/PDE.* As indicated in Sec. 3.1.1, effects of lithium on the PME peak and its interaction with pathophysiology of bipolar disorder may be complex and is still controversial.

In the studies using DRESS, we found a decrease of PME in medicated patients with bipolar disorder in the euthymic state compared with controls [6,22]. PME in the manic [5,6] and depressive [23,24] states was higher than in the euthymic state. Deicken et al. also reported decrease of PME in the frontal lobes in euthymic bipolar patients who were drug-free for 1 week [25]. They also reported increase of PDE in the frontal lobes [25] and decrease of PME in the temporal lobes [26]. In our study, levels of PDE in patients did not differ from those controls. This discrepancy may depend on the postprocessing method. In our subsequent study of a limited number of euthymic patients with bipolar disorder who were drug free more than 1 month, no decrease of PME was found [27]. Therefore a possibility that the decrease of PME is caused by adaptation to lithium treatment and lasts several weeks after termination of lithium treatment cannot be ruled out. State-dependent alteration of PME was confirmed in the other method, 1DCSI, not in the manic state but only in the depressive state [28]. There were no differences in PME and PDE in the basal ganglia in 12 euthymic patients with bipolar disorder using outer volume suppression [29].

**TABLE 1** Phosphorus-31 Magnetic Resonance Spectroscopy in Mood Disorders

| First author | Year | Method/region | Number of subjects D | M | E | C | Major findings |
|---|---|---|---|---|---|---|---|
| Bipolar disorder | | | | | | | |
| Kato [5] | (1991) | DRESS, frontal | — | 9 | 9 | 11 | PME was higher in the manic state than the euthymic state and controls. |
| Kato [23] | (1992) | DRESS, frontal | 10 | — | 10 | 10 | Depressive patients with higher HDRS had lower PCr. |
| Kato [6] | (1993) | DRESS, frontal | — | 17 | 17 | 17 | Euthymic patients had low PME and pHi. |
| Kato [24] | (1994a) | DRESS, frontal | 25 | 10* | 21 | 59 | Depressive patients had low PCr. PCr was low in BPII in all psychiatric states. |
| Kato [22] | (1994b) | DRESS, frontal | — | — | 40 | 60 | PME and pHi were low in BP. PME did not correlate with ventricular enlargement. |
| Deicken [25] | (1995a) | MRSI, frontal | — | — | 12 | 16 | PME was low and PDE was high in both frontal lobes. BP had high PCr in the right. |
| Deicken [26] | (1995b) | MRSI, temporal | — | — | 12 | 14 | PME was low in both temporal lobes. |
| Kato [28] | (1995) | 1D-CSI, frontal | 11 | 12 | 21 | 21 | Left PCr was low in depressives. Right PCr was low in all mental states. |

| | | | | | | | |
|---|---|---|---|---|---|---|---|
| Kato [27] | (1998) | DRESS, frontal | — | — | 7 | 59 | Drug free more than 1 month.<br>pH is lower but PME was not lower than controls.<br>Subcortical hyperintensity was associated with higher PDE and lower pH (n = 14). |
| Murashita [32] | (2000) | DRESS, occipital | — | — | 19 | 25 | Photic stimulation (PS) at 10 Hz for 12 min.<br>No difference in baseline 31P-MRS parameters.<br>PCr after PS was lower in lithium non-responders. |
| Kato [30] | (2001) | DRESS, frontal | Reanalysis | | | | pHi was lower in patients with 5178C compared with 5178A. |
| Kato [31] | (2001) | DRESS, frontal | Reanalysis | | | | pHi was lower in lithium responders. |
| Major depression | | | | | | | |
| Kato [23] | (1992) | DRESS, frontal | 12 | | 12 | 10 | No difference in major depression compared with controls. |
| Felber [38] | (1993) | ISIS, central | 3 | | — | — | No change after ECT. |
| Moore [36] | (1997) | ISIS, basal ganglia | 36 | | — | 17 | $\beta$-ATP was low in depressive patients. |
| Volz [37] | (1998) | ISIS, left and right F | 14 | | — | 8 | PME was increased and ATP was decreased compared with controls. |

*Key*: D, depressed; M, manic; E, euthymic; C, control; *, hypomanic state; BP, bipolar disorder; ATP, adenosine triphosphate; DRESS, depth-resolved surface coil spectroscopy; ECT, electroconvulsive therapy; HRSD, Hamilton Depression Scale; ISIS, image-selected in vivo spectroscopy; MRSI, magnetic resonance spectroscopic imaging; 1DCSI, one-dimensional chemical shift imaging; PME, phosphomonoester; PDE, phosphodiester; PCr, phosphocreatine.

4.1.1.2 *Intracellular pH.* In the studies using DRESS, intracellular pH was lower in the euthymic state than controls [6,22]. Intracellular pH in the manic [6] and depressive [23,24] states did not differ from that in controls and was higher than in the euthymic state. This was confirmed in drug-free euthymic bipolar patients [27]. Deicken et al. reported no difference of pH [25,26]. The authors also could not confirm this finding using 1D-CSI [28]. This discrepancy may be due to lower reliability of pH measurement in MRSI due to use of phase encoding and smaller data points. Decrease of pH was associated with white matter hyperintensity [27], 5178C genotype in the mitochondrial DNA [30], and positive lithium response [31], suggesting that it may be related to the pathophysiology of bipolar disorder. Decrease of pH was also noted in the basal ganglia, and it was also observed in the whole brain [29], which suggest that decrease of pH may reflect altered cellular metabolism in this disorder.

4.1.1.3 *Phosphocreatine.* In the studies using DRESS, PCr was lower in depressive patients with bipolar disorder [23,24]. This was confirmed in the left frontal lobe using 1D-CSI [28]. PCr correlated negatively with the Hamilton Depression Scale. In the right frontal lobe, PCr was decreased in all mental states, causing reversal of the left-to-right ratio of phosphocreatine between depressive and manic states. On the other hand, Deicken et al. [25] reported an increase of PCr in the left frontal lobe in the euthymic state. Although these findings are contradictory, asymmetry of left higher than right in the euthymic state was similar in these two studies.

4.1.1.4 *Functional $^{31}$P-MRS.* The authors also reported functional $^{31}$P-MRS by photic stimulation in bipolar disorder. In lithium nonresponders, PCr was lower after the photic stimulation [32]. This finding is difficult to interpret because of lack of relevant data in other neurological disorders. We performed the same experiment in patients with MELAS (mitochondrial myopathy, encephalopathy, lactic acidosis, and stroke-like episodes), but the finding was not similar to that in lithium-resistant bipolar disorder, where PCr decreased markedly during photic stimulation [33]. However, this outcome was similar to the recently reported finding in patients with chronic progressive external ophthalmoplegia, a mitochondrial disease, without clinical central nervous system involvement [34], who showed decrease of PCr after photic stimulation. Therefore, a decrease of PCr after stimulation may reflect subtle mitochondrial dysfunction in the brain [35]. However, the effects of drugs cannot be ruled out.

### 4.1.2 Major Depression

In major depression, the authors could not find any clear difference of $^{31}$P-MRS findings in major depression [23]. Moore et al. reported that $\beta$-ATP

was decreased in the basal ganglia in the depressive state [36]. Decrease of ATP was also reported in the frontal lobes [37]. PME was increased in the frontal lobes [37], which is in accordance with the finding in bipolar depression [28].

Felber et al. [38] examined effects of electoconvulsive therapy (ECT) on phosphorus metabolism and found no effect of ECT. Murashita et al. also reported preliminary results of $^{31}$P-MRS in the frontal lobes in a patient with major depression before, as well as 5 hr and 55 hr after, ECT [39]. Before ECT, PME was higher and PCr was lower than controls, which tended to be normalized after the ECT. PDE was increased 5 hr after ECT. Murashita et al. also examined the effect of sleep deprivation on $^{31}$P MR spectra in healthy volunteers and found no difference after sleep deprivation [40].

## 4.2 $^{1}$H-MRS

### 4.2.1 Bipolar Disorder

4.2.1.1 *Choline and Creatine.* In early $^{1}$H-MRS studies in a limited number of patients with bipolar disorder, no difference in $^{1}$H-MRS was reported in extrafrontal cerebral cortex (Table 2) [41–44]. On the other hand, the Cho/Cr ratio in the basal ganglia was found to be increased in patients with bipolar disorder in the euthymic [41,45,46] and depressive [46] states except for one study [47]. Alteration of PME and Cho may reflect the change of phosphocholine, which contributes to both of these peaks. However, no difference of PME and PDE in the basal ganglia [29] suggests that difference of the Cho peak in the basal ganglia may reflect change of relaxation times of choline-containing compounds or concentration of free choline. Stoll et al. reported that the Cho peak increased after choline treatment in patients with rapid-cycling bipolar disorder who responded to augmentation therapy by choline [48].

Hamakawa et al. [49] examined medicated patients with bipolar disorder by quantitative $^{1}$H-MRS in the medial frontal lobes and found that creatine peak was significantly decreased in the left frontal lobe. NAA and Cho was not changed. This finding is in accordance with the other finding, decrease of phosphocreatine in the left frontal lobe by $^{31}$P-MRS [28]. Moore et al. [18] reported that Cho/Cr was higher in the right cingulate cortex in medicated bipolar patients and right Cho/Cr positively correlated with the scores of Hamilton Depression Scale. These findings may be due to either increase of choline or decrease of creatine. Deicken et al. [50] reported increase of choline peak in the dorsolateral prefrontal cortex (DLPFC) in medicated patients with bipolar disorder, suggesting increase of choline rather than decrease of creatine. However, these findings were not confirmed by other studies in drug-free patients [51,52]. Lithium did not increase Cho/

**TABLE 2** Proton Magnetic Resonance Spectroscopy in Affective Disorders

| First author | Year | Method/location | Number of subjects D | M | E | C | Major findings |
|---|---|---|---|---|---|---|---|
| Bipolar disorder | | | | | | | |
| Sharma [41] | (1992) | STEAM, basal ganglia occipital | — | — | 5 | 9 | BP had high NAA/Cr, Cho/Cr, Ino/Cr. No difference in the occipital lobe. |
| Stoll [42] | (1992) | STEAM, temporal | — | — | 7 | 6 | No difference between BP and controls. |
| Bruhn [43] | (1993) | STEAM, cortex | — | — | 8 | 80 | No difference in Cho and Ino. Glutamate was higher in BP. |
| Yurgelun-Todd [44] | (1993) | STEAM, temporal | — | — | 12 | 14 | No difference between BP and controls. |
| Lafer [45] | (1994) | STEAM, basal ganglia | — | — | 19 | 14 | BP had higher Cho/Cr. No effect of lithium. |
| Stoll [48] | (1996) | STEAM, basal ganglia | — | — | 5 | — | Responders to choline had high Cho levels. |
| Hamakawa [46] | (1998) | STEAM, left basal ganglia | 11 | — | 16 | 20 | Cho was high in the depressive and euthymic state. |
| Ohara [47] | (1998) | PRESS, basal ganglia | — | — | 10 | 10 | No difference in NAA/Cr, Cho/Cr, and NAA/Cho. |
| Hamakawa [49] | (1999) | STEAM, L and R frontal | — | — | 23 | 20 | Cr the left frontal was lower in BP. |
| Moore GJ [58] | (1999) | STEAM, 4 cortical regions R–F, L–P, central O, L–T | 12 | — | — | 9 | 14-day wash out, and after 1-week and 3–4 week Li treatment.<br>ml decreased in the right frontal both at 1 week and 3–4 week. |
| Moore GJ [52] | (2000) | STEAM, 4 cortical regions R–F, L–P, central O, L–T | 12 | — | — | 9 | 14-day wash out, and after 4-week Li treatment.<br>NAA increased after Li treatment in all 4 regions.<br>Tissue segmentation by MRI; controls were also given lithium.<br>No difference of baseline NAA between BP and controls. |

| | | | | | | | |
|---|---|---|---|---|---|---|---|
| Winsberg [51] | (2000) | PRESS, DLPFC | — | — | 20* | 20 | Drug free for 2 weeks.<br>NAA/Cr was lower in left and right both in BPI and BPII. |
| Castillo [59] | (2000) | PRESS, 4 regions F and BG(T) in L and R | — | 10 | — | 10 | Children (mean 8 years old), drug free for 1 week.<br>"Glutamate" (TE = 135) was higher in BP in all regions.<br>"Lipid" in the frontal lobes was detectable only in patients. |
| Moore CM [18] | (2000) | MRSI, anterior cingulate | 9 | ———— | | 14 | Nine patients were examined at different mental states (mean 3.1 times).<br>HAM-D positively correlated with Cho/Cr in the left.<br>Cho/Cr was higher in BP than controls. |
| Devanzo [16] | (2001) | PRESS, anterior cingulate | — | 11 | — | 11 | Children (mean 11.4 years old) only. Before and after one week Li treatment.<br>Li induced reduction of ml. Reduction of ml more in responder.<br>Baseline ml tended to be higher than controls. |
| Deicken [50] | (2001) | MRSI | — | — | 15 | 15 | Medicated BPI male. Tissue segmentation by MRI.<br>Thalamic NAA and Cr are higher in BP in both sides. NAA L > R. |
| Major depression | | | | | | | |
| Woods [60] | (1990) | STEAM, frontocentral | 7 | | — | — | Large increase of lipid peak after ECT. |
| Felber [38] | (1993) | STEAM, central | 3 | | — | — | No change after ECT. |
| Charles [63] | (1994) | STEAM, basal ganglia | 7 | | 7 | 10 | Cho/Cr was high in depressive patients. |
| Renshaw [64] | (1994) | STEAM, basal ganglia | 25 | | 13 | 15 | Cho/Cr was high in depressive patients. |

**TABLE 2** Continued

| First author | Year | Method/location | Number of subjects D | M | E | C | Major findings |
|---|---|---|---|---|---|---|---|
| Renshaw [65] | (1997) | STEAM, basal ganglia | 41 | | | 22 | Cho/Cr was lower in the depressive patients than controls. High Cho/Cr was more prominent in responders to fluoxetine. Tissue segmentation by MRI. |
| Hamakawa [46] | (1998) | STEAM, left basal ganglia | 19 | | 12 | 20 | Cho/NAA was higher in the depressive state. |
| Frey [68] | (1998) | STEAM, frontal | 22(10)‡ | | — | 22(10) | ml in the right was lower in medicated patients than controls. |
| Sonawalla [66] | (1999) | STEAM, basal ganglia | 15 | | — | — | Before and after 8 week treatment with fluoxetine. Cho/Cr increased in responders and decreased in nonresponders. |
| Sanacora [11] | (1999) | Homonuclear editing midoccipital | 14 | | — | 18 | 52% reduction of GABA in depressive patients. |
| Steingaard [67] | (2000) | "STEAM, orbitofrontal" | 17 | | — | 28 | Cho/Cr and Cho/NAA were higher in depression than controls. |
| Ende [62] | (2000) | MRSI, hippocampus | 17 | | 6 | 24 | Increase of Cho after ECT. No changes in lipids/lactate/NAA. |
| Auer [69] | (2000) | PRESS, anterior cingulate | 19 | | — | 18 | Glutamine/glutamate is decreased in depressive patients. Tissue segmentation by MRI. |

*Key*: D, depressed; M, manic; E, euthymic; C, control; *, hypomanic state; BP, bipolar disorder; Cho, choline-containing compounds; Cr, creatine/phosphocreatine; ECT, electroconvulsive therapy; GABA, gamma aminobutylic acid; HAM-D, Hamilton Depression Scale; Ino, inositol; MRSI, magnetic resonance spectroscopic imaging; NAA, N-acetylaspartate; PRESS, point-resolved spectroscopy; STEAM, stimulated-echo acquisition mode; TE, echo time; DLPFC, dorsolateral prefrontal cortex; F, frontal; T, temporal; P, parietal; O, occipital; BG, basal ganglia; L, left; R, right.
*10 bipolar I and 10 bipolar II.
†4 manic and 12 mixed.
‡Of 22 subjects, age-matched 10 subjects each were used for analysis.

Cr in healthy volunteers [53]. Therefore, alteration of choline and/or creatine peaks in the frontal region may be due to effects of antidepressants.

4.2.1.2 *N-Acetyl-Aspartate (NAA).* In contrast to other studies suggesting no alteration of NAA in medicated patients with bipolar disorder in the extrafrontal cerebral cortex [41–44], basal ganglia [46,47], anterior cingulate cortex [54] or in the medial frontal lobe [49], and in drug-free patients in the frontal lobe [52], decrease of NAA in the dorsolateral prefrontal cortex (DLPFC) was also reported in drug-free [51] or medicated [50] patients with bipolar disorder. Decrease of NAA in the hippoccampal region in drug-free patients [55] and increase of thalamic NAA in medicated patients [56] were also reported in bipolar disorder.

Moore et al. [52] also reported that NAA in the frontal lobe was increased after lithium administration when the data of patients and controls were combined. This effect may be due to increase of gray matter volume after lithium treatment [57]. They hypothesized that these changes may be caused by neuroprotective effect of lithium. However, in a similar study design comparing subjects' states before and after lithium treatment, change of NAA was not reported [16,53].

In summary, whether NAA is altered in patients with bipolar disorder is still controversial. It is not yet conclusively known whether lithium affects NAA.

4.2.1.3 *Myoinositol.* Moore et al. [58] examined the effect of long-term lithium administration after a 2-week drug-free period using $^{1}$H-MRS in 12 patients with bipolar depression. Inositol peak was significantly decreased in the right frontal lobe but not in the temporal, parietal, and occipital cortex. This finding was replicated in the study of bipolar children (mean age 11.4 years old) by Devanzo et al. [16]. They reported that mI was reduced during lithium treatment and that this decrease was correlated with a positive response to lithium.

4.2.1.4 *Other Metabolites.* Castillo et al. [59] reported that "glutamate peak" at the echo time of 135 msec was increased (mean age, 8 years) and the lipid peak became detectable in children with bipolar disorder. However, these findings should be interpreted cautiously because glutamate cannot be detectable at long echo time, and contamination of extracranial lipid can occur even if a deep region of interest is selected.

### 4.2.2 Major Depression

4.2.2.1 *Effects of Electroconvulsive Therapy.* Woods et al. reported increase of lipid signal after ECT in seven patients with major depression [60,61]. However, such changes of lipid were not observed in subsequent

studies [38,62]. Instead, Ended et al. [62] reported that Cho peak was increased in the hippocampus after ECT.

4.2.2.2 *Choline.* Initial studies suggested that the Cho/Cr peak area was higher in drug-free or medicated patients with major depression [46, 63,64] and that it decreased after antidepressant treatment [63]. However, subsequent studies suggested that the Cho/Cr peak ratio was lower before treatment [65] and elevated in responders after flextime treatment, while it was decreased in the basal ganglia of nonresponders [66]. In the orbitofrontal cortex, Cho/Cr peak ratio was higher in the depressive patients than in controls [67]. Only 4 of 17 patients were medicated in that study. Whether Cho/Cr peak ratio is increased or decreased in depression and how antidepressants affect this parameter is still controversial.

### 4.2.3 Other Metabolites

Frey et al. [68] reported that mI peak was decreased in the frontal lobes in medicated patients with major depression. Auer et al. [69] reported that glutamine/glutamate was decreased in the anterior cingulate cortex in depressive patients. Using the homonuclear spectral editing technique, gamma-aminobutyric acid (GABA) was found to be decreased in the occipital cortex [68].

## 5 CONCLUSION

### 5.1 Summary of the Findings

Studies using $^{31}$P and $^{1}$H-MRS in mood disorders are summarized as follows:

1. PME peak is increased by lithium administration, and it may be affected by pharmacological challenge or mental state. This is compatible with the theoretically predicted effects of lithium on phosphoinositide pathway. The effect of lithium on myoinositol peak is still controversial.
2. PME peak may be decreased in the euthymic state and increased in the depressive state in the frontal lobes. This may not be the effect of lithium.
3. Decrease of intracellular pH in the brains of patients with bipolar disorder is reported from only one group but by two methods, and it may reflect the pathophysiology of bipolar disorder.
4. Decrease of PCr in bipolar disorder was reported only from one group but by several different methodologies.
5. ATP in the basal ganglia and frontal lobes may be decreased in major depression.

6. Cho/Cr peak ratio in the basal ganglia and frontal lobes may be increased in the depressive state, but this may be due to antidepressant treatment.
7. Changes of NAA due to either the pathophysiology of bipolar disorder or effects of lithium are still controversial.
8. Other findings are not well replicated yet.

## 5.2 Pathophysiological Significance

MRS was initially used to confirm and extend the previously suggested pathophysiology of mood disorders, and effects of lithium on phosphoinositide pathway were confirmed by $^{31}$P and $^{1}$H-MRS studies. Moreover, unexpected findings from these MRS studies have drawn new hypotheses. We proposed the mitochondrial hypothesis [35] based on the $^{31}$P-MRS findings of bipolar disorder; neuroprotective effect of lithium [56] was proposed by Manji et al., partly based on $^{1}$H-MRS findings. These hypotheses may be related to each other [70]. These MRS findings need to be replicated by further studies and these hypotheses need to be verified using different strategies.

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# 7

# Brain Imaging Studies of Dopamine Function in Mood Disorders

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## 1 INTRODUCTION

Randrup and colleagues first hypothesized that dopamine deficits play an important role in depression [1]. Several observations are consistent with this hypothesis. For instance, reserpine and $\alpha$-methyldopa, two antihypertensive agents that deplete dopamine from synaptic vesicles, have been reported to cause depressive symptoms. As well, Parkinson's disease, which is characterized by degeneration of dopaminergic neurons, is associated with an increased incidence of depressive symptoms [2–4]. Treatment with L-dopa, a precursor of dopamine, has also been reported to be associated with an antidepressant effect in patients with Parkinson's disease; this effect appears to precede the improvement in physical symptoms [5]. Finally, administration of antipsychotic drugs that block dopamine $D_2$ receptors induce

dysphoria, anergia, and anhedonia, symptoms that are commonly present in depression (6).

In mania in contrast to depression, dopamine function is hypothesized to be overactive. The most robust evidence for this hypothesis is derived mainly from the observations of behavioral effects of dopamine agonists and antagonists. For example, euphoria and other behavioral effects induced by amphetamine, a psychostimulant, are very similar to mania [7], and dopamine antagonists block these responses [8–13]. That a dopaminergic mechanism is involved in d-amphetamine–induced arousal and euphoria in humans is indicated by the observation that such effects are abolished by the selective dopamine receptor blocker pimozide [14]. As well, L-dopa, d-amphetamine, piribedil, and bromocriptine, drugs that increase dopamine transmission, have all been reported to precipitate mania in patients with bipolar depression [5,15–19].

Fusaric acid, which inhibits dopamine-$\beta$-hydroxylase and raises dopamine levels, worsens manic symptoms, whereas alpha-methyl-p-tyrosine (AMPT), which blocks tyrosine hydroxylase and decreases dopamine synthesis, is effective in reducing manic symptoms [20,21]. Conventional neuroleptics such as chlorpromazine, haloperidol, trifluperazine, which block dopamine receptors, are all very effective in the treatment of mania [22]. That the efficacy of neuroleptics is related to dopamine receptor blockade is suggested by the similar efficacy of pimozide, a more specific dopamine receptor antagonist, in reducing manic symptoms [23,24]. Further support for the dopamine hyperactivity theory of mania is provided by the observation that the *cis* isomer of clopenthixol, which possesses $D_2$ receptor blocking properties, is effective in treating mania, while the *trans* isomer of clopenthixol, which does not block $D_2$ receptors, has no antimanic properties [25].

Dopamine has also been suggested to be involved in the mechanism of action of antidepressants and mood stabilizers. For instance, preclinical studies have shown that chronic administration of antidepressants and electroconvulsive shock (ECS) enhances mesolimbic dopamine functioning [26]. Similarly, d-amphetamine–induced locomotor activity, a behavior dependent on the integrity of the mesoaccumbens dopamine neurons, is enhanced after chronic administration of antidepressants. In humans, electroconvulsive therapy (ECT) appears to increase dopamine (DA)-receptor responsiveness, as indicated by apomorphine's effect on plasma prolactin [27,28]. Additionally, chronic ECT increases cerebrospinal fluid (CSF) homovanillic acid (HVA) levels, suggesting increased DA turnover. Several of the recently developed antidepressants—including bupropion, amineptine and perhaps venlaxafine —are thought to inhibit presynaptic dopamine reuptake.

With regard to the involvement of dopamine in the mechanisms of action of mood stabilizers, attention has focused primarily on lithium. There is substantial evidence from preclinical studies to suggest that lithium is effective in preventing the development of neuroleptic-induced dopaminergic behavioral manifestations of supersensitivity [29]. Clinically, lithium has also been shown to decrease the amount of dopamine and its metabolites, including DOPAC and HVA in unipolar and bipolar women [30]. The authors hypothesized that this reduction might play a role in blocking, delaying, or reducing the intensity of the switch from depression to mania [30]. Waldmeier [31]—surveying the effects of mood-stabilizing agents such as lithium, carbamazepine, and valproate on neurotransmitter systems implicated in mood disorders—concluded that similarities of the effects of these drugs are most evident with respect to reduced dopaminergic transmission. For example, lithium has been reported in some animal studies to reduce dopamine turnover, block the development of dopamine receptor supersensitivity, and reduce the density of dopamine receptors, as shown by a decrease in $^{3}$H-spiperone binding (see Ref. 31 for review). Similarly, other effective antimanic agents, such as valproic acid and carbamazepine, have also been reported to reduce dopamine turnover and attenuate the increase in dopamine turnover induced by neuroleptics [32,33]. Although more recent theories link the efficacy of mood stabilizers in bipolar disorder to their effects on G proteins and second-messenger signaling systems such as cyclic AMP or inositol pathways [33,34], the dopaminergic hyperactivity hypothesis of mania is not inconsistent with such theories.

In summary, there is considerable indirect evidence—based on behavioral effects of dopamine agonists and antagonists and preclinical effects of mood stabilizers and antidepressants—that dopamine deficiency is associated with depression and dopamine hyperactivity with mania.

## 2 BRAIN IMAGING STUDIES

Brain imaging techniques such as single photon emission computed tomography (SPECT) and positron emission tomography (PET) offer the opportunity to assess dopamine function in vivo in living humans. Although there have been several excellent reviews of dopamine function in mood disorders [26,36–38], most did not include a review of recent SPECT and PET studies. In this chapter, we systemically review and summarize the current state of knowledge of brain imaging studies of dopamine function and the effect of antidepressants and mood stabilizers on dopamine function in patients with mood disorders.

### 2.1 PET and SPECT Ligands for Dopamine Function

Brain imaging techniques can be used to measure both pre- and postsynaptic aspects of the dopaminergic system in humans. Several ligands are available for this purpose, and some commonly used PET and SPECT ligands are listed in Table 1. For instance, [$^{18}$F]-dopa has been used to measure presynaptic dopamine function with PET. [$^{18}$F]-dopa signal in the brain provides a measure of the combined effect of [$^{18}$F]-dopa transport across the blood brain barrier, the decarboxylation of [$^{18}$F]-dopa into $^{18}$F-dopamine by the aromatic L-amino acid decarboxylase (AADC) and the storage and metabolism of [$^{18}$F]-dopamine. The vesicular monoamine transporter can be measured with carbon 11–labeled dihydrotetrabenazine, [$^{11}$C]DTBZ, and dopamine $D_2$ receptors can be measured with [$^{11}$C]raclopride.

## 3 IMAGING STUDIES OF DOPAMINE FUNCTION IN DEPRESSION

Wong and colleagues were the first to attempt to assess dopaminergic function in mood disorders in vivo [39]. They used PET and the radioligand [$^{11}$C]-N-methylspiperone, [$^{11}$C]-NMSP, to assess striatal dopamine $D_2$ receptor binding in a group of patients with bipolar affective disorder, patients

**TABLE 1** PET and SPECT Ligands for Dopaminergic System

| Technique | Ligand | Measure |
|---|---|---|
| PET | [$^{18}$F]-dopa | Presynaptic dopamine function (i.e., activity of AADC and uptake of $^{18}$F-dopamine into vesicles) |
| | [$^{11}$C]DTBZ | Vesicular monoamine transporter 2 (VMAT2) |
| | [$^{11}$C]-Methyl phenidate<br>[$^{11}$C] $\beta$-CIT-FE | Dopamine transporter |
| | [$^{11}$C]raclopride<br>[$^{11}$C]N-methyl-spiperone<br>[$^{18}$F]FESP | $D_2$ receptors |
| | [$^{11}$C]-FLB 457 | Extrastriatal $D_2$ receptors |
| | [$^{11}$C]SCH23390 | $D_1$ receptors |
| SPECT | [$^{123}$I] $\beta$-CIT | Dopamine transporter |
| | [$^{123}$I]IBZM | $D_2$ receptors |
| | [$^{123}$I]epidepride | Extrastriatal $D_2$ receptors |

with schizophrenia, and normal controls. They found no significant difference in striatal [$^{11}$C]-NMSP binding between these three groups. Since then, a number of studies have assessed dopamine function in depression using SPECT or PET.

### 3.1 Dopamine $D_2$ Receptors

Six studies used SPECT with [$^{123}$I]iodobenzamide, or [$^{123}$I]IBZM, to measure dopamine $D_2$ receptors in patients with major depression in comparison with normal controls [40–45]; the results of these studies are summarized in Table 2. Of these, two reported an increase in [$^{123}$I]IBZM binding in depressed patients compared with controls [40–43] but the other four found no difference between the two groups [41,42,44,45].

D'haenen and Bossuyt [40] first reported that depressed patients had significantly higher [$^{123}$I]IBZM binding in the striatum compared with normal subjects. Patients in this study were medication free for at least 7 days, and 4 out of 21 patients had previously received neuroleptics. The authors' interpretation of these results was that the depression was associated with decreased dopamine levels and that increased $D_2$ receptor density noted in patients was an upregulation secondary to low dopamine levels. This finding was partly replicated in the study by Shah and colleagues [43], who reported higher striatal uptake in the right but not in the left striatum in depressed patients compared with controls.

All patients in the first study [41] and half of the patients in the second study [42] assessed by Ebert and colleagues were on antidepressants at the time of scanning. Overall, although no changes in [$^{123}$I]IBZM binding were observed between depressed patients and controls, an increase in binding in the left striatum was noted in four patients with psychomotor retardation compared with those without psychomotor retardation and healthy controls in the second study [42]. Two more recent studies [44,45] also failed to detect any significant increase in $D_2$ binding between depressed patients and controls. In contrast to previous studies that used a single bolus injection of [$^{123}$I]IBZM, Parsey and colleagues [45] employed a constant infusion paradigm to exclude the confounding effects of striatal blood flow and peripheral metabolism on the estimates of $D_2$ receptor density.

In summary, the majority of studies did not find an increase in $D_2$ receptors in patients with major depression.

### 3.2 Dopamine Transporter

Laasonen-Balk and colleagues were the first to report on dopamine transporter density in 15 drug-naïve patients with major depression compared with 15 healthy controls [46]. Using SPECT and [$^{123}$I]$\beta$-CIT, they reported

**TABLE 2** Studies of [$^{123}$I]IBZM $D_2$ Receptor Binding Potential in Major Depression

| Study | Sample size | Drug-free period | Findings |
|---|---|---|---|
| D'Haenen and Bossuyt, 1994 [40] | Depression (N = 21)<br>Controls (N = 11) | ≥1 week | ↓ In striatum |
| Ebert et al., 1994 [41] | Bipolar, 2 with depression (N = 5 + 5)<br>Controls (N = 5) | On amitriptyline for 2 weeks | No change |
| Ebert et al., 1996 [42] | Depression (10 + 10) (N = 20)<br>Controls (N = 10) | 10 on amitriptyline for 2 weeks<br>10 drug free for 6 months | No change<br>↑ Binding in right striatum in those with psychomotor retardation |
| Shah et al., 1997 [43] | Depression (N = 15)<br>2 with bipolar disorder<br>Controls (N = 15) | 8 on antidepressants | ↑ In right striatum<br>No change in left striatum |
| Klimke et al., 1999 [44] | Depression (N = 15)<br>Controls (N = 17) | ≥1 week | No change |
| Parsey et al., 2000 [45] | Depression (N = 9)<br>Controls (N = 10) | ≥2 weeks | No change |

a significant increase in [$^{123}$I]$\beta$-CIT binding on both the left and right basal ganglia in depressed patients. They suggested that the increase in the dopamine transporter may be a primary abnormality in depression, which, by increasing dopamine reuptake into the presynaptic neuron, is expected to lead to lower synaptic dopamine levels. In a replication study, these authors confirmed the increase in the dopamine transporter in 20 patients with major depression compared with 18 healthy controls [47]. Dopamine transporter density was not different in 10 depressed patients with cluster C personality disorder compared with the other 10 depressed patients without any comorbid personality disorder.

Two other studies measured the dopamine transporter using SPECT and [$^{123}$I]$\beta$-CIT but neither had a normal control group [46,47]. Dahlstrom and colleagues [49] found no difference in dopamine transporter density between 31 children and adolescents with major depression and 10 children and adolescents with a history of adjustment disorder but no active depressive or anxiety symptoms at the time of scanning. Laine and colleagues [48] measured transporter density in 28 patients with alcohol dependence during the acute alcohol withdrawal state and following 4 weeks of abstinence. Dopamine transporter density was lower during the withdrawal phase compared with when patients were sober. Patients had significant depressive symptoms as measured by the Montgomery-Asberg depression rating scale (MADRS) (21.8 $\pm$ 12.9) during alcohol withdrawal, and the MADRS scores decreased significantly (8.6 $\pm$ 12.6) following 4 weeks of sobriety. There was a significant correlation between depressive symptoms and changes in dopamine transporter density.

To summarize, both studies that employed a normal control group reported an increase in dopamine transporter density in depression.

### 3.3 Presynaptic Dopamine Function

Agren and Reibring were the first to report a decreased uptake of [$^{11}$C]L-dopa in 6 patients with major depression in comparison to 8 healthy volunteers [50]. In a recent study, Martinot and colleagues found decreased [$^{18}$F]-dopa uptake in the left caudate in 6 patients with major depression with affective flattening and psychomotor retardation compared with 6 patients with major depression with impulsivity and anxiety and 10 normal controls [51]. A relationship between depressive symptoms and decreased [$^{18}$F]-dopa uptake was also observed in first episode schizophrenic patients with prominent depressive symptoms [52].

It is currently believed that amphetamine-induced dopamine release provides a measure of presynaptic dopamine function. An indirect estimate of the magnitude of amphetamine induced dopamine release can be obtained

by measuring the $D_2$ receptor binding potential with [$^{11}$C]raclopride and PET or [$^{123}$I]IBZM and SPECT before and after amphetamine administration [53,54]. The changes in $D_2$ receptor binding potential are considered to provide an index of the magnitude of dopamine release as animal studies have shown a correlation between the increase in extracellular dopamine levels as determined by microdialysis studies and changes in $D_2$ receptor binding potential [55].

Using this strategy, Parsey and colleagues [45] were unable to find any difference in amphetamine-induced decreases in [$^{123}$ I]IBZM binding between 9 depressed patients and 10 matched healthy controls. Although amphetamine led to transient improvement in depressive symptoms in patients, there was no correlation between the improvement in symptoms and changes in [$^{123}$ I]IBZM binding. Because amphetamine is a powerful stimulus for dopamine release, any deficiency in dopamine release in depression could have been overcome by the amphetamine. Hence, this study does not rule out the possibility that depression is associated with decreased dopamine release from presynaptic neurons.

In summary, there is some evidence for a decreased presynaptic dopamine function in depression, particularly in those with psychomotor retardation.

### 3.4 Effects of Antidepressant Treatments on Dopamine Function in Depressed Patients

Five studies assessed the effects of treatment on $D_2$ receptors in patients with a major depression. Ebert and colleagues examined the effects of sleep deprivation on IBZM binding in 10 bipolar II depressed patients who were on amitriptyline for 2 weeks [41]. Of the 10, half were considered to respond to sleep deprivation, as defined by at least a 40% reduction in HAM-D scores and "much improvement" on the Clinical Global Impression—Improvement scale. Significantly greater decreases in IBZM binding were noted in responders compared with nonresponders to sleep deprivation. In a subsequent study, the same group reported that responders to amitryptiline treatment (n = 5) had significant decreases in IBZM binding in both the right and left striatum compared to nonresponders (n = 5) [42].

In contrast, two studies reported increases in IBZM binding in treatment responders compared to nonresponders. Larisch and colleagues treated 13 patients with major depression with the selective serotonin inhibitors (SSRIs) paroxetine or fluoxetine [56]. Patients had IBZM scans at baseline and 40 days following the commencement of treatment. Overall, no difference in binding was noted between pre- and posttreatment conditions. However, when patients were divided into responders and nonresponders, 7 re-

sponders to treatment had significant increases in IBZM binding in the anterior cingulate and adjacent parts of the frontal lobe and striatum compared with the 6 nonresponders in this study. This study also found a significant correlation between clinical improvement and increases in IBZM binding. Similarly, Klimke and colleagues reported that treatment with paroxetine or fluoxetine for 6 weeks had no overall effect on IBZM binding; but when patients were stratified into responders and nonresponders, those who responded had increases in binding as compared with nonresponders. Furthermore, lower pretreatment IBZM binding predicted treatment response and that treatment response correlated with change in IBZM binding [44].

A PET study using [$^{18}$F]-FESP measured $D_2$ receptor binding in 15 drug-naïve patients with major depression. Of 15 patients, 9 completed a treatment trial with fluvoxamine for 4 weeks. $D_2$ binding in the basal ganglia was increased following treatment, but the difference was not statistically significant after correction for multiple comparisons [57].

To conclude, the effects of antidepressant treatment on $D_2$ receptors are inconsistent, with some studies suggesting an increase in $D_2$ density associated with treatment response while others showed a decrease in $D_2$ density related to response.

### 3.5 Effects of Antidepressant Treatments on Dopamine Function in Healthy Controls

In the only PET study to date in healthy human controls, Tiihonen and colleagues measured the effects of acute and subacute (14 days) citalopram treatment on raclopride binding [58]. Subacute but not acute citalopram treatment led to a significant decrease in raclopride binding in 8 healthy volunteers. The authors suggested that the decreased raclopride binding was likely to be a reflection of an increase in dopamine levels in the synaptic space and not due to changes in $D_2$ receptor density per se.

## 4 IMAGING STUDIES OF DOPAMINE FUNCTION IN BIPOLAR DISORDER

Both PET and SPECT have been widely used to assess dopamine function in schizophrenia. In contrast, few studies have examined dopamine function in bipolar patients. This is likely to be due to the inherent difficulties involved in recruiting and scanning drug-free acute manic patients.

### 4.1 Vesicular Monoamine Transporter

Zubieta et al. [59], in a PET study using carbon 11–labeled dihydrotetrabenazine, [$^{11}$C]DTBZ, as a tracer, measured the vesicular monoamine trans-

porter (VMAT2) in euthymic bipolar patients. The VMAT2 binding site mediates transport of monoamines from cytoplasm to the storage vesicles. This site is located exclusively in the membranes of presynaptic monoaminergic neurons. The VMAT2 concentrations do not appear to be modulated by short- or long-term administration of drugs that affect monoamine function or metabolism [60]. Therefore, any abnormalities in VMAT2 binding in euthymic bipolar patients would suggest that it is a trait marker for bipolar disorder.

Sixteen euthymic bipolar patients and the same number of matched healthy subjects underwent PET scanning with [$^{11}$C]DTBZ. Results showed no differences in binding between euthymic bipolar patients and healthy comparison subjects in dorsal or ventral caudate nuclei, an area rich in dopaminergic neurons. The VMAT2 protein in the caudate nuclei should reflect the concentration of synaptic vesicles in dopaminergic neurons in this region. These results indicate that bipolar patients do not have any abnormality in the concentration of VMAT2 protein, thus suggesting that transport of dopamine from cytoplasm to vesicles is intact in bipolar patients.

### 4.2 Dopamine $D_1$ Receptors

Using PET and [$^{11}$C]-SCH23390, Suhara and colleagues (1992) examined dopamine $D_1$ receptor density in 10 patients with bipolar disorder and 21 normal controls [61]. Patients were drug free from 2 to 36 days. Of the 10 patients, 6 were in the euthymic phase, 3 were in a depressive episode, and 1 was in a manic episode. The $D_1$ receptor density as measured by $D_1$ binding potential was significantly lower in the frontal cortex in bipolar patients compared with controls. The binding potential values fell outside the 95% confidence intervals of normal controls for 9 out of 10 patients. There were no differences in binding potential values between patients with and without symptoms. The $D_1$ density in the striatum, however, was not different in patients compared with controls.

These results suggest that decreased $D_1$ receptor density may be a trait marker for bipolar disorder. However, these results need to be replicated before firm conclusions can be drawn.

### 4.3 Dopamine $D_2$ Receptors

Wong et al. [39], using [$^{11}$C]NMSP as a tracer, measured $D_2$ receptor density in 16 patients with bipolar disorder, 13 patients with schizophrenia, and an unspecified number of normal controls. Of the 16 bipolar patients, only 3 were acutely manic at the time of scanning; 10 were on stable doses of lithium, 4 were drug-free for a month, and 2 had never received any psychotropic medication. There was no significant difference in $D_2$ receptor

density between patients with bipolar disorder and schizophrenia or normal controls. Similarly, Anand and colleagues found no difference in IBZM binding between 13 euthymic bipolar patients and the same number of age-matched healthy controls [62].

A lack of a significant difference in $D_2$ receptor density in the above studies may be due to euthymia, heterogeneity in clinical status, or medication status of patients with bipolar disorder. Indeed, in a subsequent study of acute patients with bipolar disorder [63], a significant increase in $D_2$ receptor density was observed in 7 psychotic patients with bipolar disorder and in 10 schizophrenic patients compared with 12 normal controls. However, this study failed to detect a significant increase in $D_2$ receptor binding in another 7 patients with nonpsychotic bipolar disorder compared with the healthy controls. Based on this, Pearlson et al. argued that increased $D_2$ receptor density is a marker of psychosis, as it was present both in psychotic bipolar patients and those with schizophrenia but not in those with nonpsychotic bipolar disorder. However, it is important to note that this study had only 5 nonpsychotic manic patients (the other two out of the 7 had nonpsychotic bipolar depression); of these, 3 had Young Mania Rating Scale (YMRS) scores under 15 (i.e., 14, 9, and 5) indicating minimal manic symptoms. Therefore, failure to find an elevation in $D_2$ receptors in nonpsychotic manic patients in this study is likely to be due to a small sample size (as it had only two manic patients with symptoms of moderate severity).

Previous studies, with the exception of the study by Pearlson et al. [64], did not separate nonpsychotic manic patients from psychotic manic patients. If the objective is to ascertain whether manic symptoms are related to increased dopamine transmission, this can be accomplished only by studying nonpsychotic manic patients. This is because, if an increase in dopamine transmission is found in psychotic manic patients, it would be difficult to know whether such abnormality is due to psychosis per se (since dopamine abnormalities are linked to psychosis as argued above) or manic symptoms. Hence, in order to explore this issue further, we examined $D_2$ receptor density in 13 first-episode neuroleptic and mood stabilizer—naïve nonpsychotic manic patients (defined by absence of delusions and hallucinations) and 14 age- and sex-matched healthy controls using PET scans and [$^{11}$C]raclopride.

The $D_2$ binding potential values for patients and controls are presented in Fig 1. There was no significant difference in $D_2$ binding potential between patients and controls. There was also no correlation between $D_2$ binding potential and YMRS scores in patients. This finding suggests that nonpsychotic manic patients do not have an elevation in $D_2$ receptor density. Alternatively, if nonpsychotic mania is associated with an increase in synaptic dopamine levels as well as an increase in $D_2$ receptors as would be predicted by the dopamine theory of mania, binding estimates of $D_2$ receptors with

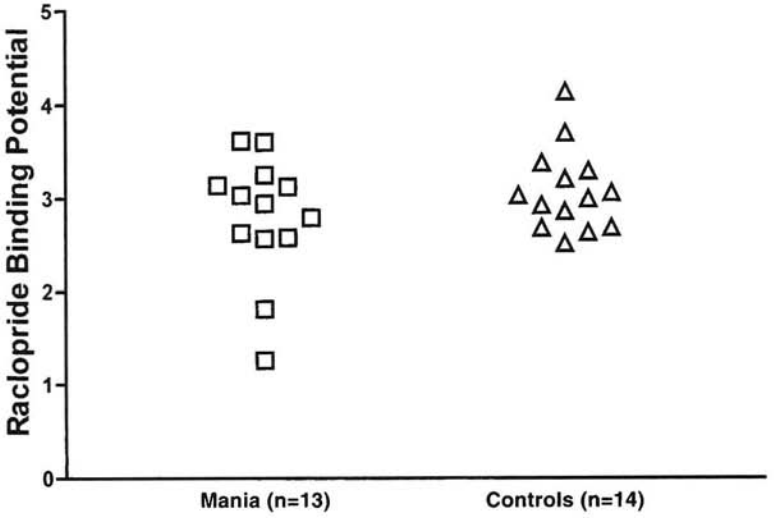


FIGURE 1 $D_2$ receptor binding in patients with mania and healthy controls.

[$^{11}$C]raclopride would not reveal an increase in $D_2$ binding in such a situation. This is because, as previously stated, binding estimates of $D_2$ receptors with [$^{11}$C]raclopride are sensitive to changes in endogenous dopamine levels. In other words, [$^{11}$C]raclopride will give an estimate only of $D_2$ receptors not occupied by endogenous dopamine. In a situation where there is excess dopamine as well as an increase in $D_2$ receptors, more dopamine receptors are occupied by excess dopamine leaving the similar number of unoccupied $D_2$ receptors as in healthy controls; this would result in a finding of no difference in [$^{11}$C]raclopride binding between patients and controls.

The above situation has been shown to be the case in schizophrenia as studies revealed no increase in $D_2$ receptors with [$^{11}$C]raclopride binding in schizophrenic patients compared with controls [65]. In order to resolve this issue, researchers in the schizophrenia field employed an AMPT challenge paradigm in combination with SPECT/PET. This strategy involves measuring $D_2$ receptors after depleting endogenous dopamine with AMPT in both patients and controls to get a true estimate of $D_2$ receptors. Indeed, AMPT/SPECT studies in schizophrenia confirmed both an increase in synaptic dopamine as well as an increase in $D_2$ receptor density [66]. Further studies employing the AMPT depletion paradigm with PET/SPECT in acute manic patients are therefore clearly needed in order to ascertain whether $D_2$ receptors are elevated in nonpsychotic mania.

### 4.4 Presynaptic Dopamine Function

In a PET study, we examined [$^{18}$F]-dopa uptake in 13 neuroleptic and mood stabilizer–naïve nonpsychotic manic patients and the same number of matched healthy controls [67]. Results of our study showed that there were no significant differences in [$^{18}$F]-dopa influx rate constants in the striatum, caudate, or putamen between manic patients and comparison subjects (Fig. 2). These findings indicate that manic patients do not have an increase in the activity of AADC, which may suggest that the rate of dopamine synthesis is not altered in mania. These findings, however, cannot exclude the possibility of an increased dopamine release from the presynaptic neurons into the synapse and a consequent increase in synaptic dopamine and dopamine transmission in mania.

Anand et al. [62] combined amphetamine challenge with SPECT and [$^{123}$I]IBZM to measure $D_2$ receptors and the extent of dopamine release from presynaptic neurons in 13 euthymic bipolar patients in comparison to 13 healthy subjects. There were no significant differences in $D_2$ receptors in the left or right striatum at baseline between bipolar patients and healthy subjects.

Amphetamine challenge led to a significant increase in behavioral symptoms in both healthy subjects and bipolar patients. The increase in

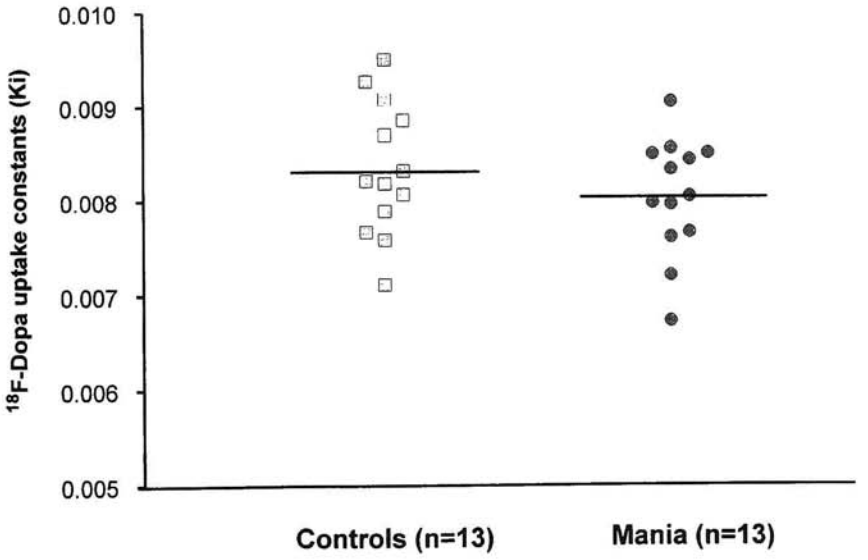


FIGURE 2 Dopa uptake rate constants in manics and controls.

behavioral symptoms as measured by changes in the YMRS and Brief Psychiatric Rating Scale was significantly greater in bipolar patients compared with healthy subjects. The $D_2$ receptor binding decreased in both bipolar patients and healthy subjects following amphetamine challenge. However, the change in $D_2$ receptor binding, which is supposed to reflect the extent of dopamine release from presynaptic neurons, was not significantly different between bipolar patients and healthy subjects.

The failure to detect a significant difference in change in $D_2$ receptor binding between patients and controls may suggest that the extent of dopamine release from presynaptic neurons was not different in bipolar patients compared with controls. However, this does not explain why patients had greater behavioral responses compared with controls following amphetamine release unless such was accompanied by an increase in dopamine release or dopamine receptors or an increased postdopamine receptor signaling pathway activity. One reason for failure to detect a significant difference in change in $D_2$ binding (and dopamine release) may have to do with the higher variance in percent change in $D_2$ receptor binding observed in this study's subjects (about 12.5, confidence intervals −29.4 to 21.6), thus affecting the study power. The higher variance may have been due to the heterogeneity in study population (e.g., 6 patients had a history of polysubstance abuse which affects neurotransmitters, especially dopamine, while 7 others did not; 7 patients were unmedicated while 6 were taking mood stabilizers, etc.). An alternative explanation may be that the abnormality in dopamine release in bipolar patients may be present only during the natural duration of a manic episode, which is usually between 3 to 6 months. If this were to be the case, one would not expect to find differences in change in $D_2$ binding in this study, as the SPECT scans were done on subjects after patients had been euthymic for an average duration of 2 years.

Therefore, due to the limitations discussed above, the possibility that bipolar patients release excess dopamine from presynaptic neurons compared with controls cannot be excluded.

### 4.5 Effects of Mood Stabilizer Treatment on Dopamine Function

In the only study to date to examine the effects of treatment with divalproex sodium (DVP) on dopamine function in mania, we measured $D_2$ receptor density with raclopride and presynaptic dopamine function with [$^{18}$F]-dopa in 10 neuroleptic and mood stabilizer–naïve manic patients before and after treatment with DVP.

If there were to be increased dopamine release from the presynaptic neurons in mania, effective treatment with mood stabilizers such as DVP

would be expected to lead to a decreased release. Our study did not measure the amount of dopamine release, but it did measure [$^{18}$F]-dopa uptake rate constants. This provides a measure of the activity of aromatic amino acid decarboxylase (AADC), which should provide some indication of the rate of dopamine synthesis. As expected, treatment with DVP led to a significant reduction in [$^{18}$F]-dopa influx rate constants in both the left and right striatum in manic patients (see Fig. 3). This would suggest that DVP treatment decreased the activity of AADC, which would be expected to lead to a decrease in the rate of dopamine synthesis. Decreased dopamine synthesis will likely limit the amount of dopamine available for release from presynaptic neurons. Therefore, the findings of our study are consistent with the hypothesis that mania is associated with increased dopamine release from presynaptic neurons. This, hypothesis, however, needs to be tested directly to confirm it.

DVP treatment did not lead to any change in [$^{11}$C]raclopride binding. In light of the evidence from our F-dopa study indicating that DVP is likely to decrease dopamine release, this finding suggests that DVP treatment may also lead to a decrease in $D_2$ receptor numbers. However, such an argument is indirect. A more direct assessment of intrasynaptic dopamine levels and the measurement of $D_2$ receptors following depletion of intrasynaptic dopamine with AMPT is more likely to be more informative.

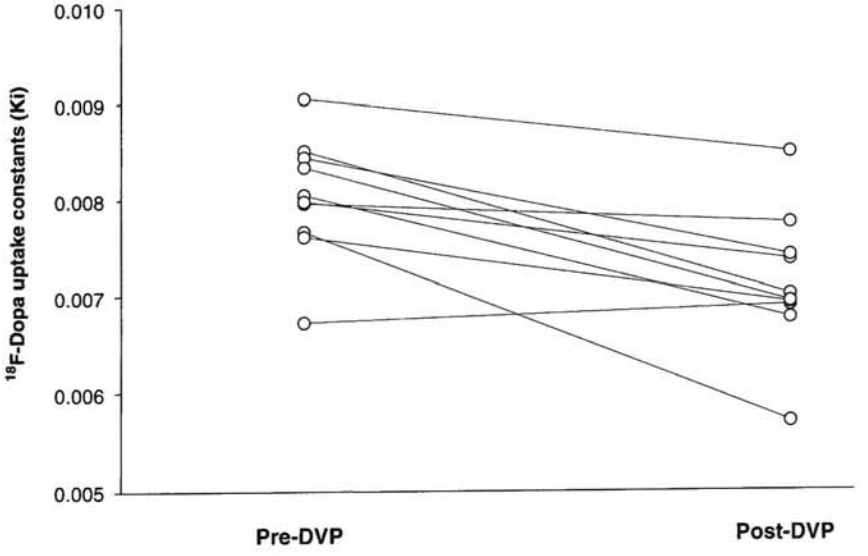


**FIGURE 3** Dopa uptakes rate constants in manic patients before and after treatment with DVP.

## 5 CONCLUSIONS

Brain imaging work on dopaminergic pathways in mood disorders is still in its infancy. Much of the work is preliminary and clearly needs replication. The work thus far provides some evidence for decreased presynaptic dopamine function in depression, but whether presynaptic dopamine function is increased in mania clearly requires further examination. Dopamine transporter appears to be increased in depression, but no studies to date have examined dopamine transporter in mania. The VMAT2 in bipolar disorder does not appear to be altered. There is no consistent evidence to date for any alteration in $D_2$ receptors either in depression or in mania. There is some suggestion for a decrease in $D_1$ receptors in bipolar patients, but this clearly needs to be replicated. The effects of antidepressant treatment on $D_2$ receptors is also inconsistent, with some studies reporting an increase and others a decrease associated with response. Valproate appears to reduce presynaptic dopamine function in manic patients, but this needs to be replicated.

## ACKNOWLEDGMENT

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# 8

# Brain Serotonergic Abnormalities in Affective Disorders

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## 1 OVERVIEW OF THE ROLE OF SEROTONIN

### 1.1 Anatomy

#### 1.1.1 Nuclei

The serotonergic nuclei lie in the brainstem. They can be divided into two groups: superior and inferior. The superior nuclei have efferents that project superiorly (see Table 1), and the inferior nuclei have efferents that project inferiorly. The nuclei that project superiorly are discussed briefly because they are relevant to brain imaging. In the nonhuman primate and the human, the superior group consist of the caudal linear nucleus, dorsal raphe nucleus, and median raphe nucleus [1,2].

The following descriptions are based on immunohistochemistry techniques using antibodies to tryptophan hydroxylase in humans [1]. (For more detailed information, see Refs. 1 and 2.) The superior nuclei consist of the caudal linear nucleus, dorsal raphe nucleus, median raphe nucleus, and rostral portion of the reticular formation [1]. They span from the level of rostral midbrain to the caudal third of the pons. The caudal linear nucleus is the most rostral and dorsal. This nucleus then merges caudally and dorsally along the midline within the midbrain into the dorsal raphe nucleus. Cau-

**TABLE 1** Serotonergic Efferents

| Nucleus | Tract | Structure |
|---|---|---|
| DRN | DRCT | Cortex |
| | | Basal ganglia |
| | DRAT | Ventrolateral geniculate nucleus |
| | | Substantia nigra |
| | | Suprachiasmatic nucleus |
| | DRPT | Midline thalamus |
| | DRPT + MFB | Periventricular |
| | DRFT | Substantia nigra |
| | | Midline thalamus |
| | | Basal ganglia |
| | | Amygdala |
| | | Suprachiasmatic nucleus |
| | | Hippocampus |
| | | Septum |
| MRN | MRFT | Midline thalamus |
| | | Septum |
| | | Hippocampus |
| | | Olfactory bulb |
| | | Preoptic area |
| | | Mammillary body |
| | | Interpeduncular nucleus |
| | RMT | Interpeduncular nucleus |
| | | Mammillary body |

*Key*: DRN, dorsal raphe nucleus; DRCT, dorsal raphe cortical tract; DRAT, dorsal raphe arcuate tract; DRPT, dorsal raphe periventricular tract; MFB, medial forebrain bundle, DRFT, dorsal raphe forebrain tract; MRN, median raphe nucleus; MRFT, median raphe forebrain tract; RMT, raphe medial tract.

dally the dorsal raphe nucleus becomes more ventrally located and merges into the median raphe nucleus at the caudal midbrain. The median raphe nucleus then extends ventrally along the midline to the rostral pons. Neurons within the reticular formation project both superiorly and inferiorly. Superiorly projecting serotonergic neurons are present in greater density at the level of superior pons and at lesser density at the mid pons [1].

### 1.1.2 Main Efferents from Superior Serotonergic Nuclei

The main efferents from the dorsal raphe (DRN) are the dorsal raphe cortical tract (DRCT), the dorsal raphe arcuate tract (DRAT), the dorsal raphe periventricular tract (DRPT) and the dorsal raphe forebrain tract (DRFT). The

major tracts from the median raphe are the median raphe forebrain tract (MRFT) and the raphe medial tract (RMT) (see Table 1) [2–4].

In nonhuman primates, efferents from dorsal and median raphe nuclei show an approximate rostrocaudal relationship between the neurons at cell bodies and their cortex projections [5]. The most rostral neurons of the dorsal raphe nucleus project to the dorsolateral prefrontal cortex. More caudally located dorsal raphe neurons and rostral median raphe neurons project to motor and somatosensory cortex. Median raphe neurons project to the occipital cortex.

### 1.1.3 Structures with Direct Efferents to Superior Serotonergic Nuclei

Structures sending efferents can be classified as those that seem to have both afferents and efferents (and have the potential to form a simple loop) and structures with efferents but no known afferents.

Structures with both afferents and efferents include the limbic system and linked structures: locus coerulus and subcoerulus [6,7], lateral habenula [6], bed nucleus of stria terminalis [6,7], diagonal band of Broca [6,7], and amygdala [8]; these have afferents and efferents to the superior serotoninergic nuclei [9]. Additional structures or groups of structures that also have both afferents and efferents to serotonergic nuclei include the serotoninergic nuclei themselves bilaterally [6,7,10–12], hypothalamus [6,10], substantia nigra [6,7,10], and prefrontal cortex [6,7]. In rats, it is mainly the medial prefrontal cortex rather than the dorsolateral prefrontal cortex that sends inhibitory efferents to the dorsal and median raphe nuclei [6,13].

Some structures send efferents to serotonergic nuclei but do not receive efferents in return. Efferents from the superior vestibular nucleus pass via the medial longitudinal fasciculus to release acetylcholine at the dorsal raphe nucleus (DRN) [11]. Efferents from the dorsal medulla release epinephrine to the DRN [10].

## 1.2 Physiology

### 1.2.1 Dorsal and Median Raphe Nucleus

Most studies are of the DRN. Evidence to separate firing rate of serotonin releasing neurons in the DRN from serotonin releasing neurons in other superior serotonergic nuclei is unavailable. Most efferents that project superiorly originate in the DRN or the median raphe nucleus (MRN) [5]. During waking states in cats, the DRN fires at a regular rate of 3 spikes per second. This firing rate declines during slow-wave sleep and stops during REM sleep [14].

The DRN may have a more specific role given its connections to the pedunculopontine (PPT) and laterodorsaltegmental (LDT) nuclei as well as the pontine reticular formation (PRF): During wakefulness DRN efferents inhibit firing of the PRF and PPT/LDT via release of serotonin [14–19]. During slow-wave sleep, the DRN has a decreased firing rate and at the onset of REM the firing of the DRN stops [14,20,21]. When the DRN is below a threshold firing rate, DRN efferents no longer inhibit the PRF and PPT/LDT [14,20–23]. The PPT/LDT and the PRF neurons start to fire at the onset of REM [14,22,23]. Efferents from the PPT/LDT to the PRF also induce firing of the PRF [14] The PPT/LDT has efferent projections to the thalamus and initiates pontogeniculoccipital waves [a characteristic electroencephalographic (EEG) pattern] that heralds the onset of rapid-eye-movement (REM) sleep [14]. (See Fig. 1 for an overview.)

### 1.3 Serotonin Synthesis and Metabolism

Serotonin does not cross the blood-brain barrier directly; rather, its precursor, tryptophan, crosses the blood-brain barrier. The synthesis and metabolism of serotonin in the brain is summarized in Fig. 2 [24].

### 1.4 5-HT Receptors in Humans

There are more than 11 different serotonin receptor types present in humans. Many have been cloned, yet a number of these receptors do not have selective antagonists. A partial list of receptor types and their associated effectors is presented in Table 2.

## 2 BRAIN IMAGING STUDIES OF MOOD DISORDERS

### 2.1 Studies of Serotonin Turnover

#### 2.1.1 L-Tryptophan Uptake

This may be measurable under conditions of low serum tryptophan using [$^{11}$C]alpha-methyl tryptophan positron emission tomography (PET) [25–27]. To date there are no studies examining this in either depression or bipolar disorder.

#### 2.1.2 Tryptophan Depletion

It is interesting that tryptophan depletion paradigms, which may lower brain serotonin concentrations [28,29], lower mood in humans [30]. The likelihood of mood lowering is greater in men with a family history of a mood disorder but not women with a family history of a mood disorder or patients with a past history of a mood disorder [31–33]. Tryptophan depletion is also re-

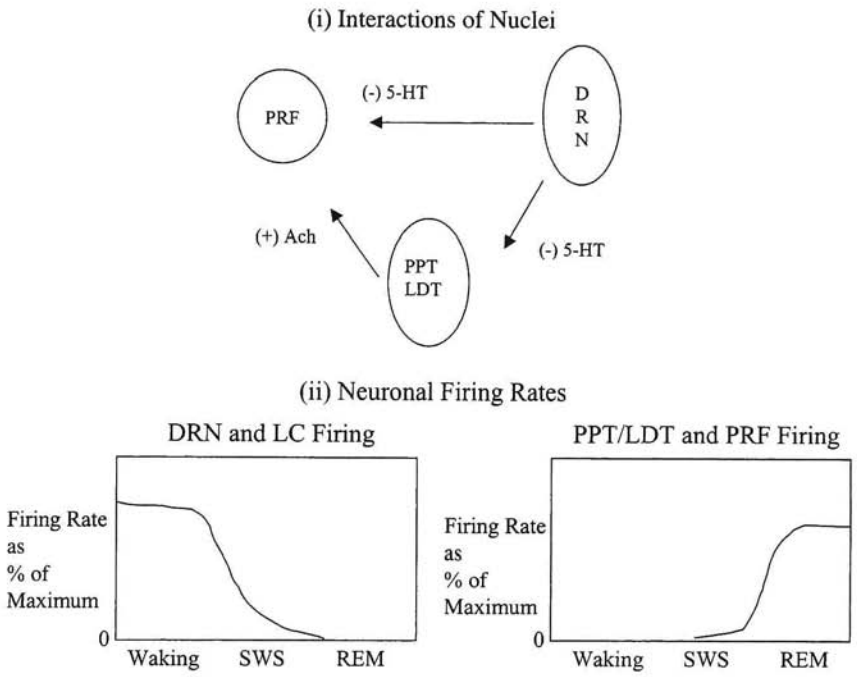


**FIGURE 1** Overview of rapid-eye-movement control.

ported to lower mood in patients with depression who have been treated with selective serotonin reuptake inhibitors (SSRIs) [32,34].

Several studies have examined the effect of tryptophan depletion upon either brain metabolism or regional cerebral blood flow. Bremner et al. [35] conducted the largest study with the most homogeneous sample: all subjects had major depression and were taking treatment with SSRIs. This group found decreased brain metabolism in the dorsolateral prefrontal cortex, thalamus, and orbitofrontal cortex in patients with a relapse of symptoms after tryptophan depletion. In addition, the severity of depressive symptoms was associated with these regional decreases in brain metabolism.

Another group examined the relationship between tryptophan depletion and performance on cognitive tasks as well as the relationship between levels of depression and brain activation [36]. They also found an association between the level of depression symptoms and activity in the orbitofrontal cortex. Activation in the anterior cingulate after a verbal fluency task was also attenuated. It is possible that the relationship between cognitive activation and tryptophan depletion could vary depending upon the task per-

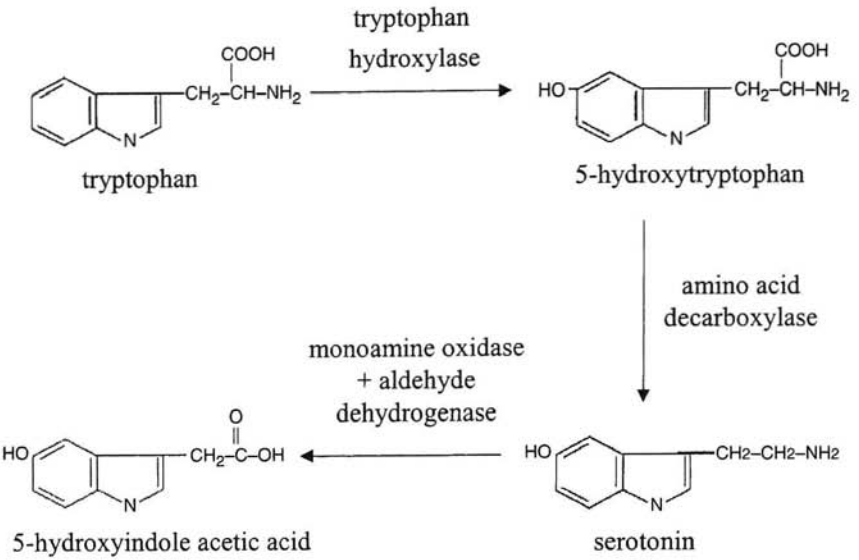


**FIGURE 2** Serotonin synthesis and metabolism. (From Ref. 24.)

formed. Many more investigations are needed to explore this challenging area.

There is only one report examining the relationship between tryptophan depletion and changes in a serotonin receptor binding potential. Yatham et al. reported a decrease in 5-$HT_{2A}$ binding potential (BP) after tryptophan depletion [37]. Usually, postsynaptic receptors increase affinity under conditions of acutely reduced neurotransmitter, so it is surprising that the 5-$HT_{2A}$ BP decreased. It may be that the mechanism of tryptophan depletion is more complicated than what was assumed previously. More receptor-ligand studies will be required to better understand the effects of tryptophan depletion.

### 2.1.3 5-HT Synthesis in Depression

Whole-brain 5-hydroxytryptophan (5-HTP) uptake as found by l-[$^{11}$C]5-hydroxytryptophan is reported to be low in depression with the exception of medial frontal cortex, where uptake was increased [38,39]. Since 5-HTP is also decarboxylated by aromatic acid decarboxylase in dopamine-releasing neurons, L-dopa uptake was also measured. L-dopa uptake was found to be unchanged both globally and within this region. Therefore the changes in 5-HTP uptake were attributed to abnormalities of serotonin turnover.

**TABLE 2** Serotonin Receptor Subtypes Found in Humans

| Name | Associated Second-Messenger changes [129] | Anatomical location | Associated behaviors |
|---|---|---|---|
| 5-$HT_{1A}$ | Inhibition of adenylate cyclase<br>Decrease cAMP [129] | Dorsal raphe autoreceptors, hippocampus, cortex [130,131]<br>Pyramidal cells and efferent terminals [132] | Increased density in cortex of aggressive mice |
| 5-$HT_{1D}$ | Inhibition of adenylate cyclase<br>Decrease cAMP [129] | Efferent terminals in cortex, raphe nuclei, basal ganglia, and nucleus accumbens [133,134] | |
| 5-$HT_{1E}$ | Inhibition of adenylate cyclase<br>Decrease cAMP [129] | Within cortex, caudate, putamen [135] | |
| 5-$HT_{1F}$ | Inhibition of adenylate cyclase<br>Decrease cAMP [129] | Dorsal raphe, hippocampus, cortex [129,135] | |
| 5-$HT_{2A}$ | Increase phospholipase C<br>Inositol phospholipid hydrolysis<br>$Ca^{2+}$ mobilization [129] | Apical dendrites of pyramidal cell neurons in cortex (III–V), interneurons (IV), raphe nuclei, CA1 hippocampus, claustrum [136–138] | Increased in prefrontal cortex of suicide victims |
| 5-$HT_{2C}$ | Stimulation of phospholipase C to increase phosphoinositol turnover [139] | Choroid plexus<br>Nerve terminals in basal ganglia, CA3 hippocampus [140,141] | |
| 5-$HT_3$ | Opens $Na^+$ and $K^+$ channels<br>Depolarization and influx of $Ca^{2+}$ [129] | Lower brainstem (dorsal vagus), area postrema<br>Cortex, hippocampus amygdala<br>Nucleus accumbens<br>Amygdala [142] | |
| 5-$HT_4$ | Increases cAMP<br>Decreases $K^+$ conductance in hippocampus [129] | Caudate nucleus, lateral pallidum, putamen, medial pallidum, temporal cortex, hippocampus, amygdala, frontal cortex, cerebellar cortex [143] | |
| 5-$HT_{5A}$ | Inhibits cAMP accumulation | Cortex, hippocampus, cerebellum, astrocytes [144,145] | |

**TABLE 2** Continued

| Name | Associated Second-Messenger changes [129] | Anatomical location | Associated behaviors |
|---|---|---|---|
| 5-$HT_6$ | Stimulates adenylyl cyclase activity in HEK 293 cells [129] | Rat cortex, nucleus accumbens, olfactory tubercle, striatum, hippocampus, anterior cortex | |
| 5-$HT_7$ | Stimulate cAMP in HLA cells [129] | Rat septum, globus pallidus, hypothalamus, centromedial amygdala, substantia nigra, periaqueductal gray, superior colliculus [146] | |

### 2.1.4 5-HT During Depression

While direct methods of measurement are not possible, some receptors may regulate in response to chronic changes in 5-HT levels. After 5-HT–depleting paradigms, 5-$HT_{2A}$ receptors increase in density [40,41]. An intact synapse may be important for these density changes to occur, because 5-$HT_{2A}$ receptors do not increase in density after lesions of serotonin neurons [42,43].

### 2.1.5 Monoamine Oxidase A Activity

No change in monoamine oxidase A activity within the dorsal raphe and locus ceruleus was reported in a postmortem study of depression [44]. No changes in monoamine oxidase A activity were reported in the frontal cortex of suicide victims [45–47]. As a result of these findings, interest in monoamine oxidase A has been minimal. Monoamine oxidase A density and activity has not been measured in mood disorders with brain imaging.

### 2.1.6 5-Hydroxyindoleacetic Acid (5-HIAA)

It could be useful to measure brain 5-HIAA in mood disorders. This metabolite of serotonin is sometimes [48,49] but not always [50,51] reported to be reduced in the brainstem of suicide victims. Similarly, 5-hydroxyindoleacetic acid is reduced in the frontal cortex of suicide victims in some [49,52,53] but not all reports [50,54,55]. It is not clear whether this reflects depression, suicidality, or impulsivity. People with depression and depression with suicidal ideation have low cerebrospinal fluid (CSF) 5-HIAA [45,56–62]; however, people with a history of childhood conduct disorder, impul-

sivity, incarceration, murder, arson, and those with previous alcohol abuse also have decreased CSF 5-HIAA [63–68].

Unfortunately there is no method of imaging 5-HIAA levels at this time.

### 2.1.7 d-Fenfluramine Challenge

Interest in imaging brain responsivity to d- or d,l-fenfluramine seemed like a promising approach because several studies found decreased hormone responses to d,l- or d-fenfluramine [69,70], a serotonin-releasing agent during depression [71–73]. This finding is more consistently associated with subgroups of depressed patients who have either more severe depression or a history of suicide attempts [74–77]. Blunted prolactin responses to intravenous tryptophan have been often reported in depression [78–81].

[$^{18}$F]fluorodeoxyglucose (FDG) PET is an index of neuronal metabolism, and neuronal responsivity to d,l-fenfluramine can be measured by comparing [$^{18}$F]FDG uptake postfenfluramine to [$^{18}$F]FDG uptake postplacebo. This method was first developed by Kapur et al. [82] and subsequently by Mann et al. [83].

This method was applied to 6 depressed patients and 6 healthy controls [84]. In healthy subjects, Mann et al. [84] found relative increases in left medial prefrontal cortex and left parietal-temporal cortex and relative decreases in right medial prefrontal and right parietal-temporal cortex. In depressed patients none of these changes occurred and it was concluded that responsivity to d,l-fenfluramine was dramatically reduced in depression [84].

Replication of this finding was important, given the small sample size used in this study. The specificity of d,l-fenfluramine for serotonin release was also a concern because l-fenfluramine induces dopamine release [70]. Meyer et al. [85] investigated changes in regional cerebral blood flow (CBF) using [$^{15}$O]$H_2O$ PET after administration of intravenous d-fenfluramine to 13 depressed and 18 healthy women. Differences between the depressed and healthy groups in change in regional CBF (mean postfenfluramine minus mean prefenfluramine) were analyzed. No significant differences in response to d-fenfluramine were found between depressed and healthy subjects; in fact, changes in regional CBF after intravenous d-fenfluramine were remarkably similar. The authors concluded that the degree of neuronal responsivity to d-fenfluramine is similar in depressed and healthy subjects.

Results between these two studies were dissimilar. Several factors that could account for the difference include greater specificity of intravenous d-fenfluramine to serotonin release, timing of scans, paucity of suicidal subjects in the second study, or greater variance in regional CBF from direct vascular effects of serotonin. Since this latter study, there have been no

further reports of the effect of d-fenfluramine on metabolism or regional CBF in mood disorders.

### 2.2 5-HT Transporter

Interest in the 5-HT transporter (5-HTT) in mood disorders increased after a very large postmortem study found decreased 5-HTT receptor density in several regions within the prefrontal cortex of patients with a history of depressive episodes [86]. Previous to this finding, there were some reports of decreased 5-HTT density in different brain regions; however, these results were not particularly consistent across studies [55,87–97].

With regard to neuroimaging studies, a recent β-CIT-SPECT study has reported decreased 5-HT transporter BP in the brainstem in depression [98]. There are a few confounds for this potentially significant finding. One is that β-CIT has a similar affinity for dopamine transporters and the substantia nigra is in close proximity to the raphe nuclei. A second confound is that the raphe nuclei are susceptible to partial volume effects [99]. The partial volume effect occurs when PET or single photon emission computed tomography (SPECT) is used to measure radioligand binding to small structures. The actual size of the structure influences the signal detected by the camera—i.e., smaller structures appear to have lower binding-potential values. Thus this finding could be consequent to decreased dopamine transporter binding potential or decreased size of either the substantia nigra or raphe nuclei.

A second β-CIT-SPECT study reported decreased 5-HTT BP in the thalamus in drug-free depressed subjects with seasonal affective disorder [100]. The thalamus is a considerably larger structure and the density of dopamine transporters is not detectable in in the thalamus [101,102], therefore this investigation avoided some of the confounds of the β-CIT-SPECT study by Malison et al. [98].

Several selective 5-HTT radiotracers that have a high proportion of signal attributable to specific binding have been recently developed [103, 104]. Thus imaging studies of the 5-HTT BP without confounds of selectivity will be feasible in mood disorders.

### 2.3 5-$HT_{1A}$ Receptors

In postmortem studies of suicide victims, increased 5-$HT_{1A}$ receptor binding in prefrontal cortex, including Brodmann's area 9, has been reported, but these findings are not always replicated [97,105–109]. Increased 5-$HT_{1A}$ receptor binding has been also found in suicide victims who had depression [110].

These postmortem findings have led to an interest in imaging 5-$HT_{1A}$ receptors. Using [$^{11}$C]WAY 100635 PET, Sargent et al. and Drevets et al. have reported decreased 5-$HT_{1A}$ receptor binding in depressed subjects in all brain regions examined [111,112].

## 2.4 5-$HT_{2A}$ Receptors

Postmortem studies investigating Brodmann's area 9 in suicide victims often find increased 5-$HT_{2A}$ receptor binding [89,90,113–116]. For most of these studies, the psychiatric diagnosis of the patients sampled is unknown. Depressive episodes from major depressive disorder is the most likely illness to explain the postmortem findings, because more than 50% of suicide victims are experiencing a depressive episode at the time of death [117,118]. Thus it is not surprising that increased 5-$HT_{2A}$ receptor binding was reported in the prefrontal cortex in postmortem samples of drug-free depressed patients [90,116].

Given the postmortem data, it seems odd that studies imaging 5-$HT_{2A}$ receptors in patients during depressive episodes find no consistent difference as compared to healthy subjects [119–124]. What appears even more discrepant is that a few studies actually find a significant decrease in 5-$HT_{2A}$ BP in orbitofrontal cortex [120], prefrontal cortex [119], and whole cortex [123]. This latter discrepancy appears to be explainable because all of the studies that report a significant decrease in 5-$HT_{2A}$ BP recruit subjects who have taken antidepressant medication as recently as 1 or 2 weeks prior to scanning [119,120,123]. Studies of drug-free subjects found no difference between depressed and healthy subjects [122,124]. It has been demonstrated that desipramine, a norepinephrine reuptake inhibitor with some affinity for the 5-$HT_{2A}$ receptor, lowers 5-$HT_{2A}$ BP in depressed subjects after chronic treatment [125]. Paroxetine, a SSRI, lowers 5-$HT_{2A}$ BP in younger depressed subjects (who have a higher, more detectable 5-$HT_{2A}$ BP) [126]. Nefazodone also lowers 5-$HT_{2A}$ BP [127].

It is more difficult to understand why there is a discrepancy between studies that find no difference in 5-$HT_{2A}$ BP between depressed and healthy subjects and studies of suicide victims. It is possible that suicide victims who have increased 5-$HT_{2A}$ density in prefrontal cortex do not have depressive episodes and have another illness. It is also possible that only the subset of subjects with depressive episodes who become victims of suicide have higher 5-$HT_{2A}$ receptor binding potential in prefrontal cortex. The idea of that there is a subgroup of patients with higher 5-$HT_{2A}$ BP is supported by a report that 5-$HT_{2A}$ receptor BP is higher in treatment-responsive depressed patients [128].

## 3 FUTURE PROSPECTS

Even though a number of investigations have been completed (see summary, Table 3), the imaging of serotonergic abnormalities in mood disorders is still at an early stage. The effect of tryptophan depletion upon activation patterns under different tasks has not been fully explored. Receptor binding potential has been measured for only a few receptor subtypes in depressed patients. The relationship between receptor binding potential measures and symptoms is still under investigation. Serotonin abnormalities have not been imaged in bipolar or dysthymic illnesses.

**TABLE 3** Summary of Imaging Studies in Mood Disorders

| Serotonergic measure | Sample | Result |
|---|---|---|
| Tryptophan depletion and metabolic/ blood flow change | History of depression, currently treated | Decreased orbitofrontal cortex metabolism [35]<br>Decreased anterior cingulate activation during task condition [36] |
| Fenfluramine challenge and metabolic/blood flow change | Current depression, major depressive disorder | Decreased metabolic response [84]<br>Unchanged blood flow response [85] |
| 5-HTP uptake | Current depression, major depressive disorder | Globally low but increased in medial prefrontal cortex [38,39] |
| 5-HTT | Current depression, major depressive disorder | Decreased in brainstem [98] |
| 5-HTT | Current depression, seasonal affective disorder | Decreased in thalamus [100] |
| $5\text{-HT}_{1A}$ receptors | Current depression, major depressive disorder | Decreased in cortex and amygdala [111,112] |
| $5\text{-HT}_{2A}$ receptors | Current depression, major depressive disorder | Unchanged in drug free [121,124]<br>Decreased in recently treated [119,120,123]<br>Increased in treatment responsive [128] |

For major depressive disorder, an interesting challenge lies ahead. Brain imaging techniques could translate postmortem findings into in vivo clinical situations. How reports of decreased 5-HTT density in the prefrontal cortex of depressed subjects and increased 5-$HT_{2A}$ density in the prefrontal cortex of suicide victims relate to specific symptoms and illness states should be answerable with receptor-ligand methods.

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# 9

# GABAergic Abnormalities in Mood Disorder: Magnetic Resonance Spectroscopy Investigation

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## 1 BACKGROUND

Despite high prevalence rates and tremendous emotional and financial costs to individuals and society as a whole, many questions remain unanswered regarding the pathophysiology of mood disorders. Initial work uncovered ties between the noradrenergic system and mood disorders, leading to the catecholamine deficit hypothesis of depression. Later findings prompted modification of this original hypothesis to include the indoleamines and related second-messenger signaling systems. However, little attention has been directed outside this broader biogenic amine model of depression until recently. Over the past two decades, increasing evidence suggests that the GABAergic system may contribute to the neurobiology of mood disorders. Yet the role the GABAergic system plays in the pathophysiology of mood disorders has not been thoroughly investigated. This has been due in large part to our previously limited understanding of amino acid neurotransmitter

physiology and the technological difficulties encountered in attempting to study theses systems. Recent advances in molecular pharmacology, genetics, and neuroimaging are now allowing this investigation to move forward. In this chapter we briefly review the physiology of the GABAergic system along with the existing evidence of GABAergic involvement in mood disorders and highlight the use of magnetic resonance spectroscopy as a method of investigation.

## 1.1 GABAergic Complexity

### 1.1.1 Ubiquitous and Abundant

Previous investigations into GABA's role in the pathophysiology and treatment of mood disorders have been limited in large part by the complexity of the system. GABA is ubiquitous and abundant in the human brain. It is estimated to serve as the primary neurotransmitter at 30–40% of all central nervous system (CNS) neurons and is present in concentrations of 1–2 mM/kg of tissue [1]. In contrast to the more discretely localized biogenic amine systems, the GABAergic system is widely distributed with the majority of GABAergic neurons serving as interneurons in dispersed local circuits [2].

### 1.1.2 Neurotransmitter and Metabolite

Further adding to the complexity of the GABAergic system is the fact that GABA appears to serve two major functions in the adult CNS: first, as the primary inhibitory neurotransmitter and, second, as an intermediate molecule in energy metabolism [3]. Thus, it is reasonable for the regulation of GABA metabolism to be tied to both its role as an inhibitory neurotransmitter and also to the demands of cellular energy metabolism. In fact, the dual identity of the amino acid neurotransmitter systems are likely to result in a functional coupling of neurotransmitter action and brain metabolism, making it difficult to distinguish between the two functions.

### 1.1.3 Multiple Regulators Metabolism

Considering GABA's central position in brain function, it is not surprising that the system is highly regulated through multiple levels of control. Glutamic acid decarboxylase (GAD) is the principal enzyme controlling GABA synthesis from glutamate. GAD is present in two molecularly distinct forms, termed $GAD_{65}$ and $GAD_{67}$. Each appears to have unique subcellular distributions and mechanisms of regulation. $GAD_{67}$ is present in both terminals and the cell body, where it may provide a nonsynaptic, intracellular GABA pool. In contrast, $GAD_{65}$ is primarily localized to nerve terminals. $GAD_{65}$ enzymatic activity is more subject to regulation by cofactor binding and

neuronal activity, consistent with its involvement in the production of synaptic GABA [4]. The fact that GAD activity is rapidly increased within the first few minutes after death makes postmortem measurements of GAD activity and GABA concentrations especially difficult to interpret. Synaptic GABA is stored in vesicles and is primarily released in a calcium-dependent manner [5]; however, more recent studies suggest other mechanisms may mediate tonic release of GABA at times of increased neuronal activity [6]. Once released, GABA is cleared from the synapse by transporters present on both neurons and glial cells [7]. GABA aminotransferase (GABA-T) then catalyzes the transfer of the amino group from GABA to $\alpha$-ketoglutarate to regenerate glutamate and produce succinic semialdehyde [8].

### 1.1.4 Receptor Complexity

GABA's neurotransmitter effects are mediated through two major receptor subtypes. The $GABA_A$ receptor is an ionotropic receptor that is predominantly involved in fast inhibitory synaptic transmission. Each receptor is composed of five subunits. The existence of at least 15 different subunits in the mammalian CNS with different pharmacological properties affords the ability to synthesize multiple receptor subtypes with heterogeneous pharmacological actions and distributions [9,10]. In addition to GABA, there are recognition sites for a number of other molecules present on the receptor complex, including benzodiazepines, picrotoxin, neuroactive steroids, barbiturates, alcohols, anesthetics, and bicuculline (see Ref. 2 for review) [2]. The benzodiazepine-binding site is most frequently associated with the clinical pharmacology of the $GABA_A$ receptor. The strong correlation between $GABA_A$ receptor affinity and the pharmacological potency of benzodiazepines indicates that the majority of behavioral responses produced by these agents are probably mediated through $GABA_A$ modulation. The $GABA_B$ receptor is a guanine-nucleotide-binding (G) protein-coupled receptor, which modulates synaptic transmission primarily by presynaptic inhibition, mediated through its action on $K^+$ channels, voltage sensitive $Ca^{2+}$ channels, and inhibition of adenylate cyclase [11]. Selective $GABA_B$ agonists possess muscle relaxant and antispastic properties, and $GABA_B$ receptors have been shown to modulate the generation of excitatory postsynaptic potentials and long-term potentiation in the hippocampus [12,13].

### 1.1.5 Interactions with Biogenic Amine Neurotransmitter Systems

The close association of the GABAergic and monoaminergic systems in several regions of the brain highlights the fact that pathophysiological models of mood disorders need not be exclusive to a single system. An example of this is the fact that serotoninergic axons in the prefrontal cortex synapse

predominantly on GABAergic interneurons [14]. These interneurons express 5-$HT_3$ and 5-$HT_{2A}$ receptors that modulate activity and increase GABA release [15–17]. 5-HT-induced modulation of GABAergic neurons has also been demonstrated in other brain regions, including the piriform cortex and the dentate gyrus [18,19]. Direct noradrenergic- [20–22] and dopaminergic-mediated [22–24] effects on GABAergic interneurons have also been demonstrated. Further demonstrating the complex interaction of these systems, serotonergic and noradrenergic inputs elicit a long-term facilitation of GABAergic interneurons in a manner that may be related to neuronal adaptation and synaptic plasticity [25].

In summary, GABA is abundant and ubiquitous in the CNS, serving various physiological roles. The major function of GABA in the CNS is that of an inhibitory neurotransmitter, where it acts through two classes of receptors. The complex physiology of the system has delayed investigators' attempts to fully characterize the multiple functions and regulatory mechanisms of the system. Dysregulation of the GABAergic system may be responsible for pathophysiological states resulting in several neurological and psychiatric disorders in humans.

## 2 EVIDENCE SUPPORTING GABAERGIC DYSFUNCTION IN MOOD DISORDERS

### 2.1 Preclinical Evidence of a GABAergic Contribution in Mood Disorders

Based largely on anecdotal tales of valproic acid's beneficial effects in the treatment of mood disorders, Emrich first proposed a GABAergic deficit hypothesis of mood disorders in 1980 [26]. In spite of the fact that little serious attention was given to the model, several lines of evidence supporting the general hypothesis have developed (see Lloyd [27], Petty [28], Shiah [29], and Sanacora [30] for complete reviews). Supporting evidence consists of rodent models that suggest adaptive changes in GABAergic function may contribute to the stress response by showing decreased rates of GABA synthesis, decreased GABA concentrations, and decreased $GABA_A$ receptor binding in response to both acute and chronic stress [31–39]. Moreover, other studies have demonstrated that some stressful early life events have long-lasting effects on GABA function that appear related to altered expression of adult behaviors [40]. Further support comes from reports of GABA-enhancing agents having antidepressant-like actions in several rodent models used as tests of antidepressant activity [27,35,41,42]. Based on these findings, a series of clinical trials using two GABA-mimetic compounds, progabide and fengabine (SL 79229), were conducted. The compounds ap-

peared to possess antidepressant properties, in some reports having equal efficacy to TCAs (see Bartholini et al., 1986, for compilation of studies) [43,44], but unfavorable side effect profiles halted the development of these compounds.

There is also evidence that standard antidepressant agents may have significant effects on GABA function. Several studies reported elevated GABA levels and enhanced GABA release in rat brains following high-dose acute administration of TCAs, monoamine oxidase inhibitors (MAOIs), and daily electroconvulsive stimuli [45–49]. Other studies, however, give inconsistent findings, adding some confusion to the picture [50,51]. In another series of animal studies, Lloyd et al. demonstrated enhanced $GABA_B$ receptor binding following chronic administration of all three classes of classic antidepressant agents—TCAs, selective serotonin reuptake inhibitors (SSRIs), MAOIs, and electroconvulsive therapy (ECT) [27]. However, again, the initial enthusiasm has been somewhat tempered by a series of contrasting findings that have also been reported [52–55].

## 2.2 Evidence Supporting a GABAergic Deficit in Depressed Subjects

The most convincing data suggesting GABAergic involvement in the pathophysiology of mood disorders come from the multiple studies showing reduced levels of GABA in the plasma, cerebrospinal fluid (CSF), and brain of individuals with major depressive disorders. Gold et al. [56] first reported reduced CSF GABA concentrations in a group of depressed patients that were compared to patients with other psychiatric or neurological diagnoses. Seven additional studies have been conducted since that time. In total, four studies found significantly lower GABA concentrations in depressed subjects compared to various control groups, and the other four found reduced GABA concentrations at trend levels. A metanalysis of these data shows the finding of GABA reductions in depression to be highly significant [57]. These studies also serve well to illustrate several of the difficulties encountered in this form of research. First, the study by Gerner et al. demonstrates how the results could vary based on what CSF aliquot is chosen for analysis [58], a finding that is likely related to the existing GABA gradient in the CSF column. The study by Roy highlights the need for accurate demographic and diagnostic assessment in studies of mood disorders. Roy's group found patients with a current depressive episode to have lower CSF GABA levels than healthy comparison subjects; however, when they covaried for age and gender, there was no significant difference. Only the subgroup of patients with unipolar melancholic depression had significantly lower GABA levels than all other groups [59]. Unfortunately, most of the studies included pa-

tients diagnosed with depressive episodes, and they either combined or did not specify unipolar and bipolar disorders. The effect of grouping unipolar and bipolar patients into a common class for analysis remains unclear. Three of the studies performed post hoc analysis between the two groups; two found no difference and one found bipolar depressed patients to have higher GABA levels compared to unipolar depressed subjects. However, the finding does seem to have relative specificity to depression. No significant differences were observed in schizophrenic, anorectic, or manic subjects [56,58,60,61].

GABA concentrations are also decreased in the plasma of depressed subjects. Multiple reports of decreased plasma GABA levels in individuals with affective disorders have been published. The majority of studies, however, are from only two laboratories [62–66]. In the largest of these, the mean plasma GABA levels were 10–15% lower in depressed patients compared to healthy controls, with a marked shift in the frequency distribution of plasma GABA levels of depressed subjects. Forty percent of depressed subjects had levels below 100 pmol/mL, while only 6% of healthy subjects had plasma GABA levels below 100 pmol/mL. The results remain somewhat inconsistent in relation to plasma GABA of bipolar patients, with early studies suggesting higher GABA levels in bipolar disorder, but later ones reporting levels similar to those in unipolar depression [66]. The findings are also inconclusive regarding state and trait dependence. Similar to the CSF studies, the lower GABA concentrations appear somewhat specific to mood disorders. Normal plasma GABA levels were observed in patients with schizophrenia, generalized anxiety disorder, eating disorders, and panic disorder [63,67–69], but lower plasma GABA levels were seen in alcoholism [70], Parkinson's disease [71], and premenstrual dysphoric disorder [72].

Postmortem studies comprising mostly of depressed suicide victims have not provided consistent evidence of GABAergic abnormalities. An initial postmortem study found no significant differences in brain GABA levels of suicide victims [73]; however, a study measuring GABA levels from cortex removed during psychosurgery revealed a negative correlation between GABA concentration and severity of depression [74]. Similar inconsistencies were observed regarding GABA synthesis rates and GAD activity levels. An initial study reported a significantly lower rate of GABA synthesis in several brain regions from elderly depressed patients compared to control subjects [75]. This appeared consistent with a finding of lower plasma GAD activity in depressed patients [76]. However, a later study failed to demonstrate significant reductions in brain GAD activity in depressed suicide victims [77], and Toth et al. recently reported a significant increase in $GAD_{67}$ expression in the prefrontal cortex of depressed patients [78]. As mentioned previously, it is important to consider that the rapid postmortem increase in

GAD activity confounds the findings of these studies and thus limits the ability to accurately interpret the results.

## 3 MRS STUDIES OF GABA IN DEPRESSION

### 3.1 Measuring GABA Concentrations with MRS

The development of magnetic resonance spectroscopy (MRS) has greatly enhanced the ability to probe the GABAergic hypothesis of mood disorders and, for the first time, affords the opportunity to make in vivo measures of GABA concentrations in the brain. Since Cady [79] first used the technique to study the human brain in 1983, its applications to clinical neuroscience have grown steadily. MRS has been successfully employed to obtain in vivo measurements of several neuronal substances with putative relations to neuropsychiatric disorders [80–82].

The molecular structure and relatively high concentrations of the amino acid neurotransmitters in the brain make them especially suitable for studies using proton spectroscopy ($^1$H-MRS). However, the practical implementation of $^1$H-MRS in this pursuit remains a challenge. $^1$H-MRS studies of GABA are limited by several complications, the most prominent being the fact that the GABA resonance frequency is in the same range as molecules such as glutamate, glutamine, choline, and creatine, which are present in higher concentrations in the brain. This gives rise to an overlap of resonance peaks, forming a single combined peak frequently referred to as Glx (Fig. 1), and makes it difficult to obtain isolated measures of GABA. New $^1$H-MRS techniques such as the double-quantum filter [83], and the difference-editing protocol [84] now allow measurement of brain GABA by eliminating confounding resonances from the spectrum. These measurements have successfully demonstrated decreased GABA levels in seizure disorder patients [85] and are sensitive to pharmacological manipulation of GABA levels [86].

### 3.2 Difference Editing Protocol

We have recently used the difference-editing protocol, a homonuclear J-editing method developed by Rothman et al. [1], to further investigate potential GABAergic involvement in depression (Fig. 2). Occipital cortex GABA concentrations were determined using a 2.1 Oxford magnet with a 1-m bore and equipped with a Bruker Avance spectrometer (Bruker Instruments, Billerica, MA). Homonuclear editing of the 3.0 parts per million (chemical shift scale; ppm) C4 GABA resonance was performed using the J-editing pulse sequence described previously. Spectral editing detects signals from hydrogen atoms that are J-coupled to hydrogen atoms on adjacent

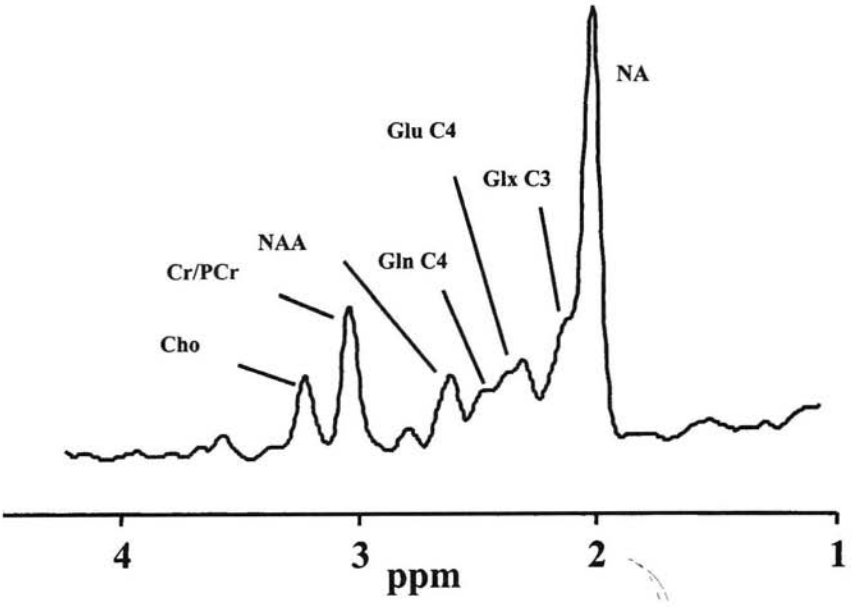
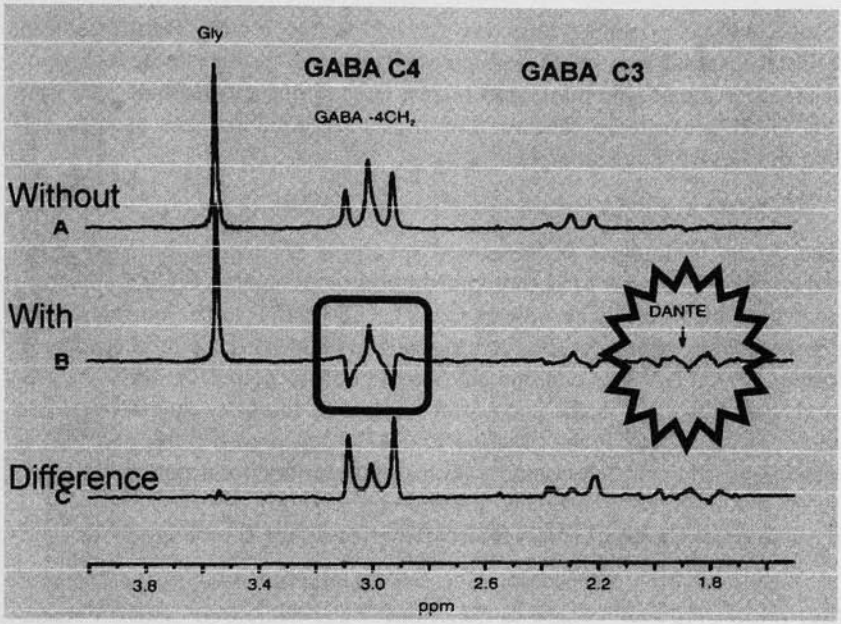
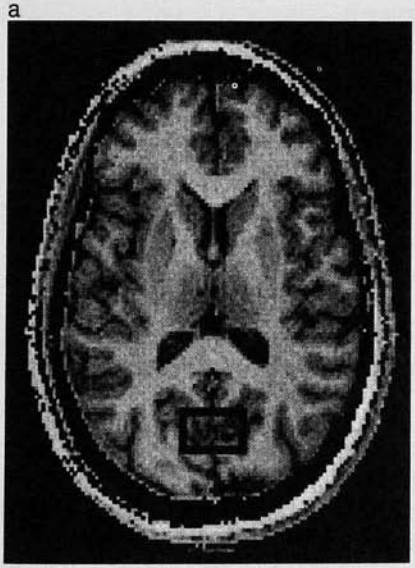



**FIGURE 1** $^1$H-MRS spectrum showing resonance frequencies in parts per million (ppm) for choline (Cho), creatine/phospocreatine (Cr/PCr), N-acetylaspartate (NAA), C4 resonances of glutamine and glutamate (Gln and Glu), Glx (overlapping C3 resonances of Glu, Gln, and GABA), and NA.

carbon atoms in the same molecule. In this case, the spin-spin J editing selected the GABA C4 triplet resonance at 3.0 ppm, which is coupled to the GABA C3 multiplet resonance at 1.9 ppm. Two subspectra, of 128 scans each, were subtracted to obtain a difference spectrum that isolates $GABA_{(Total)}$ (combined measure of GABA and the GABA containing dipeptide homocarnosine). The localization techniques included three-dimensional image-selected in vivo spectroscopy, with outer volume suppression, selective excitation, and use of a surface spoiler coil. The spectral acquisition parameters were as follows: repetition time, 3.39 sec; echo time, 68 msec; sweep width, 1500 Hz; and acquisition time, 510 msec. A chemical shift–selective 80-ms hyperbolic secant pulse followed by an inversion recovery delay and a 2-2 refocusing pulse were used for water suppression. Spectral editing of the GABA C4 resonance at 3.0 ppm was achieved by applying a Delays Alternating with Nutations for Tailored Excitations (DANTE) pulse to invert selectively the 1.9 ppm C3 resonance [1]. The 26.5-msec DANTE editing pulse was applied symmetrically in time about the center of the refocusing pulse sequence. The free induction decay was zero-filled to 32




a



b

**FIGURE 2** a. Top (A), 1H-MRS spectrum of solution containing GABA and glycine (gly) without application of the DANTE sequence; middle (B), the effects of the DANTE sequence; bottom (C), the difference spectrum. b. GABA measurements are obtained from a 13-mL region of interest in the occipital cortex.

K, and a 3-Hz exponential filter was applied before Fourier transformation. The GABA signal was integrated over a 0.30 ppm bandwidth at 3.00 ppm. The creatine signal was integrated over a 0.20 ppm bandwidth at 3.00 ppm in the GABA-inverted spectrum. The following equation was used to calculate the GABA concentration:

$$[\text{GABA}] = (G^*/Cr^* - M/Cr^*)(\text{ICF})(\text{EE})(3/2)[\text{Cr}]$$

where G* is the integral in the edited spectrum, Cr* is the integral of the creatine resonance, and M is the contribution to the edited GABA spectrum from edited macromolecule resonances [1,87,88]. ICF is the correction for the limited integral bandwidths determined from localized edited spectra of solutions of GABA and creatine line-broadened to match the in vivo processed linewidths, EE is the correction for loss of intensity due to imperfect editing efficiency, 3/2 is the creatine to $GABA_{(total)}$ proton ratio, and [Cr] is 9 mmol/kg—the creatine concentration in human occipital cortex [89].

### 3.3 Occipital Cortex GABA Concentrations Are Decreased in Depressed Subjects

In our initial study we sought to determine if the decreased GABA concentrations observed in the plasma and CSF of depressed individuals are also present in the brain. Occipital cortex GABA levels of 14 medication-free, moderately to severely depressed subjects were compared to those of 18 healthy control subjects. The results of this study were consistent with the peripheral studies, demonstrating a 52% reduction in GABA concentrations in the depressed subjects compared to the healthy controls (Fig. 3) [90]. This finding remained highly significant after controlling for the presence of age and gender effects (ANCOVA, $F1,28 = 83.0$, $p < 0.001$), and was most interesting in regard to the extremely limited degree of overlap between the two groups.

### 3.4 Occipital Cortex GABA Concentrations Are Increased Following Treatment

We next sought to investigate the effects of treatment on cortical GABA concentrations. To study the effects of antidepressant medication therapy on cortical GABA concentrations, we obtained pre and posttreatment $^1$H-MRS studies of 11 depressed subjects being treated with SSRIs. The pretreatment study was performed in a medication-free state of at least 2 weeks' duration. The posttreatment study was performed after a period of at least 5 weeks on the medication. The results show that posttreatment occipital cortex GABA concentrations (mean = 1.70, SD = 0.37) were significantly increased over pretreatment concentrations (mean = 1.27, SD = 0.30) [paired t-test, t

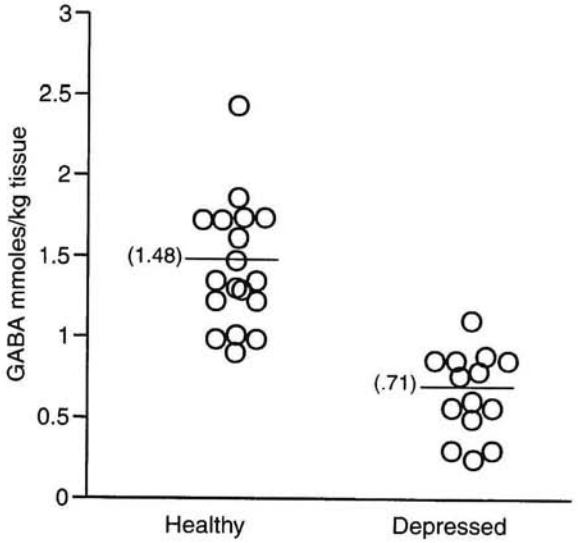



**FIGURE 3** Occipital cortex GABA concentrations are reduced in depressed males and females relative to respective controls (means and 95% confidence intervals). (From Ref. 90.)

= 2.61, df = 10, $p < 0.03$], with nine of the 11 subjects demonstrating elevated posttreatment concentrations [91] (Fig. 4). Other preliminary studies suggest that occipital GABA concentrations are also increased following a course of electroconvulsive therapy [92]. These findings are consistent with the older rodent studies, which showed increased brain GABA concentrations following chronic administration of several different antidepressant treatments, and suggest that modulation of GABAergic function may serve a common mechanism of action between classes and modalities of antidepressant treatment.

### 3.5 Comments and Caveats

$^{1}$H-MRS methodology has been especially useful in allowing further investigation into GABAergic contributions to the pathophysiology of depression. The initial studies are largely consistent with the GABA deficit hypothesis, and suggest that the system may be involved in a common mechanism of antidepressant action. However, there are several caveats that need to be considered when evaluating these studies. First, the initial studies have been limited to the occipital cortex due to the technical challenges presented with the use of a surface coil. The fact that reduced GABA concentrations are

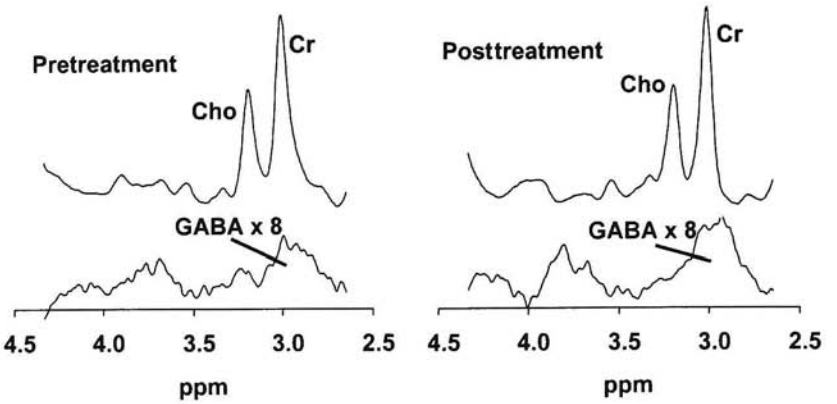



FIGURE 4 Representive spectra from a depressed subject prior to (left) and after (right) treatment with a selective serotonin uptake inhibitor. The top line for each subject depicts an unedited proton magnetic resonance spectroscopy spectrum. The lower line illustrates the difference spectrum obtained using the delays alternating with nutations-tailored excitations editing pulse.

found in this region as well as in the plasma and CSF of depressed subjects suggests a widespread disruption of GABAergic function may be associated with depressive episodes. However, the lack of any clear association between the occipital cortex and the regulation of mood and cognition makes it difficult to find any direct link between these findings and the classic cognitive, emotional, and behavioral signs and symptoms that are characteristic of depression.

It is also important to remember that the technique used in these studies is not yet able to distinguish between intraneuronal, synaptic, and nonneuronal stores. This issue is further complicated by the existence of multiple pools related to energy metabolism and neurotransmission. Therefore it is not possible to determine if the GABA concentrations measured in these studies are reflecting alterations of the vesicular pool, the more widely distributed cytosolic pool or even the extracellular pool. Without knowing the location of the altered GABA concentrations, it is difficult to determine its relationship to the underlying pathophysiology. Last, it is also necessary to note that the GABA measurements made in these studies also contain the dipeptide homocarnosine. Homocarnosine is an interesting molecule that appears to possess bioactivity on its own [93] and may be prove to be relevant to the regulation of inhibitory transmission.

## 4 FUTURE OF MRS STUDIES OF GABA IN THE NEUROBIOLOGY OF MOOD DISORDER

The current applications' $^{1}$H-MRS are limited to static measurements of GABA in single voxels of the brain in vivo; however, techniques are now under development that should dramatically improve the ability to interpret the meaning of the depression-related changes in GABA. The advances include (1) the acquisition of images of GABA levels [94], taking the measurements beyond the present stage of sampling a single volume of tissue, and (2) the measurement of absolute rates of synthesis of GABA and related neurochemicals, permitting the study of neurotransmitter and energetic pathways in vivo.

### 4.1 MRS Imaging

MRS measurements that are made simultaneously in multiple voxels are called MRS images (MRSI). Such images permit efficient regional analysis of differences in subjects by mapping the quantities of metabolites that are present in different brain regions. Shen et al. [94] demonstrated the first such method for the measurement of GABA in the human brain. Techniques of MRSI will be particularly useful in determining the regional specificity of observed GABA abnormalities and may provide clearer clinical-pathophysiological correlates.

### 4.2 Measurement of Rates of Synthesis

While the static $^{1}$H-MRS measurements are informative and help generate hypotheses about GABAergic systems in psychiatric disease, coupling them with measurements of synthesis will provide a means of hypothesis testing and fuller development of those hypotheses.

A method that yields the absolute rate of synthesis of GABA is $^{13}$C MRS detection of GABA turnover. In this approach, glucose labeled with $^{13}$C is injected into the bloodstream of a subject. The $^{13}$C-labeled substrate rapidly enters the brain and is converted—through glycolysis, the tricarboxylic acid cycle, and neurotransmitter release and reuptake—to glutamate, glutamine, and GABA. It is possible to detect the labeling of all of these compounds simultaneously in vivo. The time course of GABA labeling has been observed in the rat brain, where $\gamma$-vinyl-GABA was shown to reduce the rate of synthesis of GABA [95], as well as in experimentally induced hypothyroidism [96]. GABA labeling has also been observed in a preliminary in vivo study of depressed patients and healthy controls.

The ability to make regional measurements of GABA levels and kinetic measurements of the metabolism of GABA and related pathways is provid-

ing the means to study the biochemical details of mood disorders and their treatments.

## 5 CONCLUSION

The last three decades of research have emphasized the role of the biogenic amines and hypothalamic-pituitary-adrenal axis in the pathophysiology of depression. However, emerging evidence suggests that the GABAergic system may also contribute to the pathophysiology and pharmacological treatment of depression. The recent development of 1H-MRS techniques to measure cortical GABA concentrations has provided us with a mechanism to demonstrate that the decreased GABA concentrations previously reported in the plasma and CSF are also present in the brains of depressed subjects. It has also allowed us to show treatment-related effects on cortical GABA concentrations. Future studies utilizing MRSI and $^{13}$C-MRS studies of GABA and other amino acid neurotransmitters may significantly enhance our understanding of the complex neurobiology of depression.

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# 10

# Magnetic Resonance Spectroscopy as a Tool for Psychopharmacological Studies

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## 1 INTRODUCTION

Magnetic resonance spectroscopy (MRS) techniques offer the potential for in vivo measurement of a number of psychoactive drugs and for assessing the neurochemical effects of on these agents at their target tissue, i.e., the human brain. Two basic parameters establish practical limitations for the collection of useful magnetic resonance spectra of drugs. First, the drug must be "MRS visible" by virtue of containing an atom that can be detected by nuclear magnetic resonance with reasonable sensitivity (e.g., $^{1}H$, $^{19}F$, or $^{7}Li$). Second, the concentration of the drug in the brain must be sufficiently high to allow signal detection. With currently available and developing technology, these restrictive parameters can be overcome in these cases.

Lithium has a natural abundance of 93% and a relatively high MR visibility, 29% relative to hydrogen ($^{1}H$). As therapeutic serum levels are in the range of 1 mEq/L, brain lithium levels may be detected and quantified with relative ease [1]. This was first demonstrated by Renshaw and Wicklund

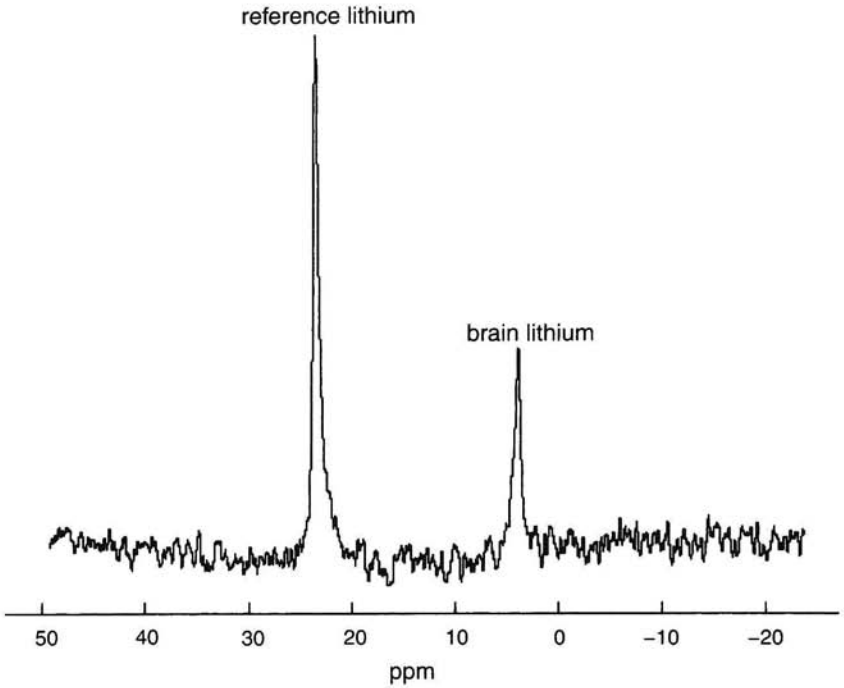


**FIGURE 1** $^{7}$Li-MRS. Lithium resonances from a 6-cm axial slice through the brain (center) and from an external standard (left). (Data from the McLean Hospital Brain Imaging Center.)

in 1988 [2] (Fig. 1); subsequently, a number of research groups have developed methods for measuring brain lithium levels [3,4]. In practice the major problems associated with measuring brain lithium levels are the hardware requirements for detection of the lithium-7 ($^{7}$Li) nucleus and the relatively slow relaxation rates of this weakly quadrupolar, spin 3/2 nucleus [5].

As with most psychiatric medications, lithium's mechanism of action is uncertain and it is only effective in approximately two-thirds of patients with bipolar disorder. Sachs et al. (1995) [6] have pointed out that there is considerable range in brain lithium levels for persons with similar serum lithium levels, which may contribute to the variable response observed with lithium therapy. In addition, lithium is one of the most dangerous drugs in the pharmacopeia, with serious toxicity occasionally resulting from modest elevations in serum levels [7]. Thus, for both therapeutic and safety reasons, $^{7}$Li-MRS may come to play an important role in clinical neuropsychiatry [4,8].

To date, MRS has been used for lithium pharmacokinetic studies

[2,6,9–18] and, to a limited degree, for pharmacodynamic characterization of lithium effects [10,19–21] (Table 1).

A surprisingly large number of psychiatric medications contain the fluorine-19 ($^{19}$F) nucleus, which is 100% naturally abundant and which has an MRS sensitivity of 83% relative to protons [1]. Fluorine-19 is a component of several psychotropic agents and is not normally detected in the human body. However, in vivo measurement of fluorinated drug levels by $^{19}$F-MRS has limitations since active drug levels may not be distinguished from those of active and inactive metabolites which contain $^{19}$F [22]. Spectra tend to have low signal-to-noise ratios (SNR), primarily due to low $^{19}$F-drug concentration. Fluorinated drugs include most of the selective serotonin reuptake inhibitors (SSRIs), which are among the most widely prescribed agents in the world today. For the most part, and in contrast to lithium, therapeutic serum drug levels are in the range of 1–20 $\mu$M, consequently limiting the sensitivity for measurement of these compounds. The brain tends to accumulate these agents at levels which are an order of magnitude higher than serum levels due to (1) their lipophilicity and (2) pH trapping in acidic vesicles [23], consequently making these compounds MRS-visible using clinical MR scanners (Fig. 2) [24,25]. Increasing the number of $^{19}$F atoms per molecule results in an increased sensitivity to detection [26]. Fluoxetine and fluvoxamine have three fluorine atoms and paroxetine has one, which explains the prevalence of 19F-MRS research on these trifluorinated drugs. Antipsychotics that have been approved for clinical use may have either one (e.g., haloperidol), two (e.g., pimozide), three (trifluoperazine, fluphenazine), four (trifluperidol), or five (penfluridol) fluorine atoms.

The accuracy of $^{19}$F-MRS for the measurement of brain drug levels has been validated in an animal model [27] and applied to studies of human subjects over the last decade [28]. $^{19}$F-MRS has also contributed to our understanding of the pharmacokinetics of fluorinated antidepressants, including fluoxetine [22,24,28–31], fluvoxamine [31–33], and paroxetine [30] (Table 2). The relationship between brain drug levels and clinical response, as well as possible mechanism of action have also been explored using $^{19}$F-MRS [30–32,34–36].

$^{19}$F-MRS has been used in animal and human studies of some fluorinated neuroleptics including fluphenazine and trifluroperazine [28,37–44].

Brain hydrogen ($^{1}$H) MRS and phosphorus ($^{31}$P) MRS studies in subjects with mood disorders have expanded our pharmacodynamic understanding of psychotropic medications, especially in areas of high energy and membrane metabolism [45,46] as well as second-messenger systems [21,47–50] in brain in vivo.

In the following section, we present an overview of (1) lithium MRS studies, (2) fluorine MRS studies, and (3) MRS pharmacodynamic studies.

**TABLE 1** In Vivo $^{7}$Li-MRS Studies in Mood Disorders

| Study | Subjects (*n*) | Mood state | Lithium dose (mg/day) | MRS methods (tesla, coil type, VOI) | Brain lithium concentration (mM/L) | Brain:Serum (correlation coefficient) | Peak after dose (hours) | Elimination half-life (hours) |
|---|---|---|---|---|---|---|---|---|
| Renshaw and Wicklund, 1988 [2] | Normal subjects (2)<br>Age: 26, 31<br>2 Male | Euthymic | 1200 | 1.8T<br>Surface coil (11.5 cm)<br>Occipital area | ~0.1–0.4 | 0.40 | >8 | Brain: 48<br>Serum: 30<br>Muscle: 24 |
| Komoroski et al., 1990 [9] | Schizoaffective disorder (1)<br>Bipolar disorder (1)<br>Normal subject (1)<br>3 male<br>Age: —, 38, 61 | Hypomanic<br>Hypomanic<br>Euthymic | 1200<br>900<br>900 | 1.5T<br>Surface coil (16 cm)<br>Occipital area | 0.45–0.84 | 0.61 (schizoaffective patient) (0.67) | >5 | — |
| Gyulai et al., 1991 [10] | DSM-III-R bipolar disorder (9)<br>6 male, 3 female<br>Age: 20–55 | Various | 900–1200 | 1.85T<br>Surface coil (11.5 cm)<br>Occipital area | 0.36 ± 0.1 | 0.35–0.70 (0.71, $p < 0.05$) | — | — |
| Kato et al., 1992 [11] | DSM-III-R bipolar disorder (10)<br>4 male, 6 female<br>Age: 19–50 | — | 600–1200 | 1.5T<br>Surface coil<br>Frontal area | ~0.1–0.9 | 0.5–0.6 (0.55, $p < 0.01$) | — | — |

| | | | | | | | | |
|---|---|---|---|---|---|---|---|---|
| Kushnir et al., 1993 [12] | Bipolar disorder (8)<br>5 male, 3 female<br>Age: 33–78 | — | 450–1200 | 2T<br>Surface coil (11.5 cm)<br>Left temporal area | 0.28–0.40 | 0.44–0.83 | — | — |
| Komoroski et al., 1993 [13] | DSM-III-R schizoaffective disorder (3), bipolar disorder (1)<br>Sex: —<br>Age: — | — | 600–1800 | 1.5T<br>Birdcage head coil<br>Frontal area | ~0.25–0.5 | 0.4–0.7 | 3–5 | 24–48 |
| Gonzalez et al., 1993 [15] | Bipolar disorder (10)<br>Sex: —<br>Age: — | — | 900–1575 | 1.5T<br>Volume coil (24 cm)<br>Transverse slice above corpus callosum | 0.52–0.87 | 0.50–0.97 | — | — |
| Kato et al., 1993 [14] | DSM-III-R bipolar disorder (7), schizoaffective disorder (1)<br>2 male, 6 female<br>Age: 19–44 | Various | 600–1000 | 1.5T<br>Surface coil (15 cm)<br>Frontal area | ~0.02–0.5 | 0.45 (0.66, $p <$ 0.01) | — | — |

**TABLE 1** Continued

| Study | Subjects (*n*) | Mood state | Lithium dose (mg/day) | MRS methods (tesla, coil type, VOI) | Brain lithium concentration (mM/L) | Brain:Serum (correlation coefficient) | Peak after dose (hours) | Elimination half-life (hours) |
|---|---|---|---|---|---|---|---|---|
| Kato et al., 1994 [19] | DSM-III-R bipolar disorder (14)<br>5 male, 9 female<br>Age: 19–51 | Hypomanic, manic | 600–1000 | 1.5T<br>Surface coil (15 cm)<br>Frontal area | 0.3 ± 0.16 | 0.56 ± 0.24 (0.57, $p <$ 0.05) | — | — |
| Plenge et al., 1994 [16] | Normal subject (2)<br>2 male<br>Age: 38–50 | Euthymic | 1000–1200 | 1.5T<br>Helmholtz head coil (17 cm)<br>Transverse slice above lateral vertricle | 0.45–0.93 | <24 hr: 0.5–1.0<br>>48 hr: <1.2 | <6 | Brain: 28<br>Serum: 16 |
| Sachs et al., 1995 [6] | Bipolar disorder (25)<br>11 male, 14 female<br>Age: 36.4 ± 10 | Various | —<br>(serum level: 0.16–1.2 mM/L) | 1.5T<br>Volume coil (24 cm)<br>6 cm thickness transverse slice around corpus callosum | 0.25–0.89 | 0.51–1.23 (0.68, $p <$ 0.001) | — | — |

| | | | | | | | | |
|---|---|---|---|---|---|---|---|---|
| Kato et al., 1996 [20] | DSM-III-R bipolar patients (15), bipolar disorder NOS (1), schizoaffective disorder (1)<br>6 male, 11 female<br>Age: 38.6 ± 9.6 | Various | 729 ± 117 | 1.5T<br>Surface coil<br>Frontal area | 0.39 ± 0.22 | — | — | — |
| Jensen et al., 1996 [17] | DSM-III-R bipolar disorder or depressive disorder (10)<br>9 male, 1 female<br>Age: 31–68 | Euthymic | Group I: 800 qd<br>Group II: 1200 qod | 1.5T<br>Coil type: —<br>Transverse slice above lateral ventricle | Group I: 0.31–0.80<br>Group II: 0.42–0.65 | Group I: 0.59–0.89<br>Group II: 0.77–1.10 (0.53, $p$ = 0.003) | — | — |
| Soares et al., 2001 [18] | DSM-III-R bipolar type I (8)<br>5 male, 3 female<br>Age: 21–43 | Euthymic: 7<br>Depressed: 1 | 750–1800 | 3T<br>Birdcage headcoil<br>6 cm thickness transverse slice around corpus callosum | 0.23–0.55 | 0.30–0.80 | — | — |

*Key*: VOI, volume of interest; —, not reported.

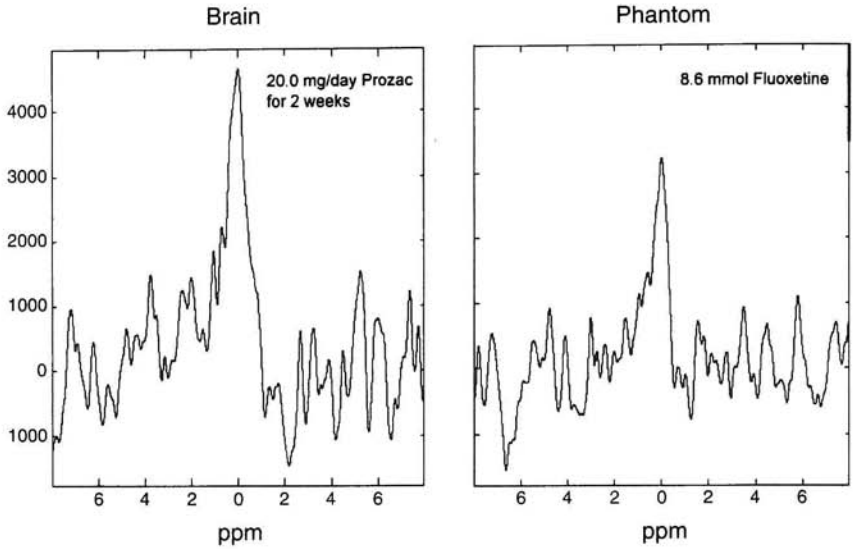


FIGURE 2 $^{19}$F-MRS. Comparison of spectra obtained from human brain (left) and a 2.0 l phantom containing 8.6 $\mu$M/L fluoxetine (right). (Renshaw, unpublished data.)

## 2 $^{7}$Li-MRS

### 2.1 Pharmacokinetic Studies with $^{7}$Li-MRS

The accumulation of lithium in the brain is slower than in serum, with peak brain concentrations observed 3–8 hr after oral administration of lithium and 0–2 hr after the peak serum concentration. Its elimination from the brain is also slower than from serum, with an elimination half-life after steady state of approximately 48 hr [2,9,13,16].

Renshaw and Wicklund (1988) [2] pioneered the first in vivo measurement of lithium in human brain using $^{7}$Li-MRS. Brain, muscle, and serum lithium accumulation and elimination were measured in two healthy subjects. During the first 8 hr following a single 1200-mg dose of lithium carbonate, serum lithium concentrations were higher than those measured in brain or muscle. In a multiple-dose experiment, 1200 mg of lithium carbonate was administered in two divided doses for 4 days. Over this time period, serum levels remained consistently higher than brain or muscle levels. Elimination kinetics, which were measured after taking a last dose, were similar between serum and muscle, with elimination half-lives of 30 and 24 hr. Elimination from the brain took longer, with a half-life of 48 hr.

Komoroski et al. (1990) [9] studied the pharmacokinetics of lithium uptake using $^{7}$Li-MRS to assess lithium concentrations in the brain and muscle of a normal subject and a patient with bipolar disorder. The lithium levels in brain and muscle were similar. These concentrations tracked the serum level but achieved lower concentrations. In a later study, this group reported that peak brain concentrations were observed approximately 0–2 hr after peak serum levels and that elimination from the brain took longer than from muscle. No lithium signal was detected after a period of 10 days from the last lithium dose [13].

Gyulai et al. (1991) [10] and associates reported that the brain lithium concentration, as measured by $^{7}$Li-MRS, ranged from 0.19–0.53 mEq/L in nine bipolar outpatients in remission. The mean Hamilton Depression Rating Scale and Young Mania Scale scores of the subjects were 11.0 ± 12.7 (range: 0–41) and 6.2 ± 3.3 (range: 1–10), respectively. An effective minimal maintenance brain lithium range of 0.2–0.3 mEq/L was suggested.

Kato et al. (1992) [11] performed serial measurements of brain lithium levels in 10 lithium-treated bipolar patients. A significant positive correlation was observed between serum and brain concentrations ($r = 0.55$, $p < 0.01$). Brain lithium concentrations were 50–60% of the serum levels when serum lithium levels were in the range of 0.5–0.9 mEq/L. They reported a similar correlation between brain and serum levels ($r = 0.66$, $p < 0.001$) in a subsequent study involving eight subjects with bipolar or schizoaffective disorder [14]. This correlation was stronger than brain:erythrocyte lithium correlations ($r = 0.44$, $p < 0.05$). There was no correlation between the length of lithium treatment and the brain:serum lithium ratio.

Gonzalez et al. (1993) [15] later refined the in vivo MRS quantification of lithium using several methodological enhancements. A larger cerebral volume was sampled to maximize the signal-to-noise ratio as well as adiabatic excitation pulses and longer interpulse delays. A volume coil was used rather than a surface coil. In addition, an image-selected in vivo spectroscopy (ISIS) sequence was employed [51]. Measured lithium levels were from 0.52–0.87 mEq/L and the brain:serum ratios ranged from 0.5 to 0.97 in 10 patients with bipolar disorder.

Plenge et al. (1994) [16] assessed brain and serum elimination pharmacokinetics of lithium in two healthy subjects. Each subject had taken 1000 and 1200 mg, respectively, of lithium for 8 days to ensure a steady state prior to discontinuation of medications. Brain and serum lithium concentrations were measured every second hour during the first 24-hr period following discontinuation and once again 48 hr later. Brain:serum lithium ratios undulated in a peak-trough pattern following the serum lithium profile, though in an attenuated form. Also, the investigators found that the brain:serum lithium ratios varied significantly, 0.5–1.3, during the 48-hr period and that this

**TABLE 2** In Vivo $^{19}$F-MRS Studies of Selective Serotonin Reuptake Inhibitors

| Author | Subjects (*n*) | Medication (mg/day) | MRS methods (tesla, coil type, VOI) | Brain concentration | Serum concentration | Brain:Serum (correlation coefficient) |
|---|---|---|---|---|---|---|
| Komoroski et al., 1991 [29] | Major depression (1) | Fluoxetine 40 | 1.5T surface coil occipital area | — | — | — |
| Karson et al., 1992 [28] | Major depression (2), bipolar disorder (1), posttraumatic stress disorder (3), dysthymia (1)<br>7 male<br>Age: 36–61 | Fluoxetine 20–40 | 1.5T conforming surface coil frontal area | 1.3–5.7 $\mu$g/mL | — | — |
| Renshaw et al., 1992 [24] | Major depression (3), obsessive-compulsive disorder (5)<br>4 male, 4 female<br>Age: 34 $\pm$ 8 | Fluoxetine 60–100 | 1.5T Surface coil | ~1.25–4.5 $\mu$g/mL | — | 2.6 (0.58, $p <$ 0.001) |

| | | | | | | |
|---|---|---|---|---|---|---|
| Karson et al., 1993 [22] | Bipolar disorder (1), major depression (6), posttraumatic stress disorder (4), obsessive-compulsive disorder (1), dysthymia (7), adjustment disorder (2)<br>15 male, 6 female<br>Age: 13–73<br>11 adults, 9 adolescents, 1 postmortem brain | Fluoxetine 20–40 | 1.5T Surface coil (flat and conforming) and birdcage coil | 4.24 ± 2.83 μg/mL | 0.20 ± 0.08 μg/mL | 20 (0.81, $p < 0.05$) |
| Miner et al., 1995 [34] | DSM-III-R social phobia<br>Responders (5), nonresponders (3)<br>5 male, 3 female<br>Age: 43.9 ± 8.4 | Fluoxetine 20–60 | 1.5T Birdcage coil | Responders: 7.9 ± 5.4 μM/L<br>Nonresponders: 1.6 ± 1.5 μM/L | — | — |
| Strauss et al., 1997 [32] | DSM-IV obsessive-compulsive disorder (8)<br>3 male, 5 female<br>Age: 18–65 | Fluvoxamine 100–300 | 1.5T Birdcage coil | 3.5–36.8 μgM/L (11.2 ± 26 μM/L) | 0.1–3.2 μM/L (0.7 ± 0.8 μM/L) | 24 ± 12 |
| Strauss et al., 1998 [33] | Obsessive-compulsive disorder (4), panic attack (1), depression (1)<br>5 male, 1 female<br>Age: 48 ± 16 | Fluvoxamine 100–300 | 1.5T Birdcage coil | 4.2–12.7 μM/L (9.8 ± 3.0 μM/L) | 0.31–0.79 μm/L (0.50 ± 0.18 μM/L) | — |

**TABLE 2** Continued

| Author | Subjects (*n*) | Medication (mg/day) | MRS methods (tesla, coil type, VOI) | Brain concentration | Serum concentration | Brain:Serum (correlation coefficient) |
|---|---|---|---|---|---|---|
| Christensen et al., 1999 [70] | Healthy obese women (12)<br>Age: 38–54<br>Body mass index: 28.4–37.4 | Dexfenfluramine 30 | 1.5T Quadrature volume head coil | Day 10: 3.9 ± 1.1 μM/L<br>Day 60: 3.6 ± 0.6 μM/L<br>Day 90: 3.9 ± 0.8 μM/L | Day 10: 0.23 ± 0.08 μM/L<br>Day 60: 0.27 ± 0.08 μM/L<br>Day 90: 0.25 ± 0.08 μM/L | — |
| Henry et al., 2000 [30] | Major depression (10)<br>Fluoxetine (1 male, 4 female), paroxetine (2 male, 3 female)<br>Age: Fluoxetine (31 ± 11), paroxetine 44 ± 16) | Fluoxetine 20<br>Paroxetine 20 | 1.5T Quadrature volume head coil | ~2–13 μM/L | — | — |
| Bolo et al., 2000 [31] | DSM-IV major depressive disorder (12)<br>Fluoxetine (1 male, 3 female), fluvoxamine (3 male, 5 female)<br>Age: fluoxetine (47 ± 4), fluvoxamine (47 ± 10) | Fluoxetine 10–40<br>Fluvoxamine 100–300 | 3T Birdcage coil | Fluoxetine and norfluoxetine: 13 ± 6 μM/L<br>Fluvoxamine: 12 ± 5 μM/L | Fluoxetine and norfluoxetine: 1.73 ± 1.0 μM/L<br>Fluvoxamine: 1.12 ± 0.31 μM/L | Fluoxetine and norfluoxetine: 10 ± 6 ($r^2$ = 0.94)<br>Fluvoxamine: 10 ± 2 (0.69) |

*Key*: VOI, volume of interest; —, not reported.

ratio was independent of serum lithium level. The results of this study suggested that the timing of brain lithium measurements following the last lithium dose is an important factor in the interpretation of $^{7}$Li MRS results.

Sachs et al. (1995) [6] studied 25 DSM-III-R bipolar disorder subjects, as identified by SCID-P, in various mood states. A 1.5-T scanner was used with an Alderman-Grant type volume coil and an ISIS pulse sequence to measure lithium levels in a 6-cm-thick axial brain slice including the corpus callosum. In general, this procedure was similar to the method developed by Gonzalez et al. (1993) [15]. Ranges of serum and brain lithium concentrations were 0.25–1.16 mEq/L and 0.25–0.89 mEq/L, respectively. However, a greater that twofold interindividual variation in brain:serum lithium ratios was observed (0.51–1.23). There was a relatively high correlation between brain and serum concentrations ($r = 0.68$, $p < 0.001$). Also, the euthymic group ($n = 15$) had a tendency to have a higher mean brain:serum lithium ratios as compared to nonеuthymic subjects ($n = 10$) (0.84 ± 0.21).

Most published studies have been conducted using 1.5-T magnets. More recently, Soares and colleagues [18] demonstrated the feasibility of human brain $^{7}$Li-MRS using a 3-T scanner. They studied eight bipolar disorder type I patients, who took a mean lithium dose of 1265 ± 442 mg/day, using a dual-tuned (1H and 7Li) echoplanar imaging compatible radiofrequency birdcage coil. Brain lithium levels ranged from 0.23–0.55 mEq/L (0.35 ± 0.11) and brain:serum ratios varied from 0.30–0.80 (0.52 ± 0.16). Subjects taking a single daily dose of lithium had greater brain:serum ratios compared with those on a twice-a-day divided schedule (0.61 ± 0.12; 0.37 ± 0.07, respectively). Though the $^{7}$Li-MRS method used in this study is based on Gonzalez et al. (1993)'s method [15], the reported brain:serum ratio is lower than that reported by Gonzalez et al. (1993) [15] (0.77 ± 0.14) or Sachs et al. (1995) [6] (0.80 ± 0.19). The reasons for this discrepancy are not entirely clear.

### 2.1.1 Intraindividual Variability

Komoroski et al. (1990) [9] serially measured brain and serum lithium levels in a patient with schizoaffective disorder over a 7-month period. A large intraindividual variation in brain:serum lithium ratios, ranging from 0.46–0.84, was found.

### 2.1.2 Brain:Serum Lithium Ratio May Vary with Clinical Status

The relationship between brain lithium concentrations and clinical status has been discussed in a limited number of studies [6,11,52], as most studies have been conducted with euthymic bipolar patients. Kato et al. (1992) [11] performed a serial measurement of brain lithium in 10 lithium-treated bipolar

patients. They reported that brain lithium concentrations increased markedly during the manic state while serum concentrations remained unchanged. Considering the fact that lithium ions enter through the sodium channel [53], this finding suggests that lithium is more actively taken into excitable neurons in the brain in the manic state compared to the euthymic states.

Sachs et al. (1995) [6] compared mean brain:serum lithium concentrations during maintenance treatment in 25 subjects with various mood states. The brain:serum lithium ratio tended to be higher in euthymic states (0.84 $\pm$ 0.21) than in depressed or mania/mixed states (0.59 $\pm$ 0.12, 0.71 $\pm$ 0.19, respectively). In addition, interindividual differences in brain:serum lithium ratios were 2.4-fold in euthymic patients ($n$ = 15), 1.7-fold in manic/mixed subjects ($n$ = 3), and 1.4-fold in depressed subjects ($n$ = 2). In other studies, these interindividual differences ranged from 1.4 [17] to 2.7 [18] in euthymic bipolar patients and 4.7 for hypomanic/manic patients [19].

This large interindividual variability suggests that brain lithium concentration may not be within the therapeutic range even if a patient is maintaining a therapeutic serum lithium concentration and that this may, in part, account for failure of lithium prophylaxis in some patients who have serum lithium levels in the therapeutic range.

### 2.1.3 Brain:Serum Lithium Ratio—General

The brain lithium concentration is, in general, moderately correlated with the serum concentration, with a brain:serum ratio of 0.40–0.80, across studies [6,15]. This correlation is reported to be weaker on a therapeutic serum range of 0.6–1.0 mEq/L [6]. Brain lithium uptake and elimination following oral intake shows displays a delayed course compared to those in the blood compartment [13]. However, the strength of these correlations is dependent on a number of factors, including clinical status [52], intraindividual variability [9], serum concentrations [6], interindividual variability [6], and the duration of treatment [54]. Therefore, brain lithium measurements may provide more useful information for therapeutic drug monitoring relative to the serum lithium measurement [8].

## 2.2 Clinical Efficacy and Side Effects

### 2.2.1 Minimum Effective "Brain" Concentration

Various lithium-related measures—such as brain lithium concentration, serum lithium concentration, brain:serum lithium ratios, and lithium dose:body weight ratio—have been assessed with regard to their relationship to clinical improvement [12,19].

There have also been a few studies regarding minimum effective brain lithium concentrations. Kushnir et al. (1993) [12] measured brain lithium

concentrations in eight bipolar patients. In the serum concentrations ranging from 0.28 to 0.86 mEq/L, they did not find any difference in brain lithium concentrations between responders and nonresponders. Kato et al. (1994) [19] reported that bipolar patients with brain lithium level less than 0.2 mEq/L showed a poor response to treatment.

### 2.2.2 Clinical Improvement: Reduction of Manic Symptoms

Kato et al. (1994) [19] studied correlations between clinical improvement of mania determined by the reduction in the Petterson Mania Rating Scale score 4 weeks after the initiation of lithium treatment and various lithium-related measures in 14 manic patients with bipolar disorder. Improvement in manic symptoms was significantly correlated with the brain lithium concentration ($r = 0.64$, $p < 0.05$) and the brain:serum lithium ratio ($r = 0.60$, $p < 0.05$). However, this measure of treatment response to lithium was not correlated with either the serum concentration ($r = 0.33$) or the lithium dose: body weight ratio ($r = 0.02$) [19].

### 2.2.3 Side Effects

Kato et al. (1996) [20] examined the relationship between lithium-induced side effects as determined by the UCLA General Side Effect Rating Scale For Lithium Treatment (GSE) and lithium concentrations in brain in 17 bipolar patients treated with lithium and other psychotropic drugs. There were no significant relationships between general side effects and brain lithium concentration ($r = 0.01$). Patients with hand tremor had significantly higher brain Li concentrations ($0.51 \pm 0.27$ mEq/L) than those without apparent tremor ($0.36 \pm 0.20$ mEq/L), even though there was no significant difference in serum lithium level between these two groups. Sachs et al. (1995) [6] has speculated that patients with tremor, sedation, and cognitive impairment were more likely to have relatively high brain lithium levels.

## 2.3 Technical Factors That Influence $^7$Li MRS Data

Although the lithium-7 nucleus has reasonable sensitivity, the calculation of accurate brain lithium levels is dependent upon knowledge of in vivo relaxation times for lithium-7. Unlike the case of the proton, the exact in vivo relaxation behavior of lithium is still not clear. Determination of T1 and T2 relaxation times also provides an information necessary for determining the optimal acquisition parameters, which, in turn, can maximize lithium resonance intensity.

Reported T1 relaxation times of $^7$Li in the human brain range from 3.4–6.6 sec [12,13,55]. Renshaw and colleagues (1986) [55] studied the longitudinal and transverse relaxation characteristics of lithium in cat brain.

T1 relaxation times were 3.5 and 6.6 sec. Both relaxation decays were observed to be biexponential, consistent with the behavior expected for a spin 3/2 quadrupole nucleus. T2 relaxation times were 80 and 320 msec. However, as subsequent studies on T1 of lithium-7 in vivo have reported a monoexponential decay [12,13,56], the biexponential T1 relaxation might be due to lithium resonances that arise from different tissue sources such as brain and muscle [13]. Ramaprasad et al. (1992) [56] studied lithium-7 T1 and T2 relaxation times in rat brains using a 4.7-T scanner. T1 demonstrated monoexponential relaxation curve (4.1 ± 0.3 sec) while T2 displayed biexponential time constants (32 and 630 msec).

## 2.4 $^{7}$Li-Magnetic Resonance Spectroscopic Imaging (MRSI)

Regional differences in brain lithium levels have been demonstrated in both animal studies [5–61] and human postmortem studies [61,63].

In line with the above observations, efforts to obtain magnetic MRS images of brain lithium concentration have been made [56,64–66]. Technical difficulties, including long acquisition times, must be overcome in order to obtain reliable lithium signals from different brain regions. However, with ongoing technological improvements [4] such as high field scanners [18], brain $^{7}$Li-MRSI may provide new insights into the relationship of the brain and serum lithium concentrations to clinical efficacy and side effects.

## 2.5 Prospects

The measurement of serum lithium concentration has limited value in predicting efficacy and side effects in a treated population owing to the fact that brain:serum lithium ratios have inter- and intraindividual variabilities. In addition, mood status also appears to influence brain:serum lithium ratios [6,11,19]. Further, ethnic differences in lithium pharmacokinetics that have been observed in brain [19] are in line with studies of erythrocyte Na/Li countertransport [67,68].

Ongoing technical development will enable reliable and rapid measurement of brain lithium concentrations in humans. These methods, once disseminated, should allow clinicians to optimize treatment with lithium and minimize untoward effects. Over time, studies may also permit determination of the minimum effective concentration of brain lithium in both acute and maintenance treatment phases. In time, this information can be used to shed light on lithium's mechanism of action. Furthermore, region-specific lithium concentrations, which will be made possible by the $^{7}$Li-MRSI, will enable researchers to better understand the action site of lithium in manic episodes.

## 3 $^{19}$F SPECTROSCOPY

### 3.1 $^{19}$F-MRS Studies of Fluorinated Antipsychotics

Komoroski et al. (1989) [44] initially demonstrated the feasibility of detecting a fluorinated neuroleptic in human brain in vivo. Komoroski et al. (1991) [29] succeeded in obtaining an acceptable spectrum of trifluoperazine in 13–20 min of scanning in one subject with schizoaffective disorder who was taking trifluoperazine at a dosage of 120 mg/day. They reported that the signal from the occipital area was greater than that from the frontal area, possibly due to neuroleptic concentration in the fat and muscle tissue at the back of the head. Brain trifluoperazine concentration was estimated to be in the range of 0.01–0.03 $\mu$M.

Durst et al. (1990) [42] conducted a study to detect fluphenazine in the brain of a schizophrenic patient who had been taking 350 mg of fluphenazine decanoate every 17 days for over a year. A fluphenazine signal was detected from the frontal lobe immediately after injection. However, the signal in the frontal lobe decreased markedly after 5 days and was undetectable after 11 days. Furthermore, there were no detectable signals from the occipital lobe at any time point. This variation in serum:brain drug ratios in fluphenazine signal may hamper the usefulness of in vivo $^{19}$F-MRS measurement of fluorinated antipsychotics.

Bartels et al. (1991) [41] conducted a $^{19}$F-MRS study in an effort to detect a fluphenazine resonance in one subject who had received 37.5 mg of fluphenazine decanoate on the preceding day. Using a 3-T magnet and a 10-cm diameter surface coil placed over the frontal region, a broad signal was obtained.

More recently, Karson et al. (1992) [28] measured brain concentrations of various fluorinated antipsychotic drugs using $^{19}$F-MRS in eight male patients with schizoaffective disorder. They could not detect any signal from neuroleptics for subjects who were taking fluphenazine decanoate or haloperidol. However, $^{19}$F resonances were detected in several patients who were taking either oral fluphenazine or trifluoperazine. However, in one subject who was taking 120 mg of trifluoperazine daily, there was no detectable peak on MRS.

All of the above $^{19}$F-MRS studies demonstrate the feasibility of measuring in vivo concentrations of fluorinated antipsychotics. However, the lack of consistent findings also points out the difficulty in reliably evaluating the brain levels of fluorinated antipsychotics. These inconsistencies in results between studies of fluorinated antipsychotics, compared to those of fluorinated antidepressants may be due to low serum and drug levels of antipsychotics relative to antidepressants [29] (Table 2). Consequently, $^{19}$F spectra from antipsychotics have far lower SNR than antidepressants. In addition,

antipsychotics may be localized rather than globally accumulated in brain [29,37,42]. Employing high-field MRS scanners and adopting a priori hypothesis of specific brain localization of antipsychotics may enhance $^{19}F$ MRS measurements of these drugs.

### 3.2 $^{19}F$-MRS Studies of Fluoxetine

Komoroski et al. (1991) [29] first demonstrated the feasibility of detecting fluoxetine in human brain. They recorded a spectrum from the occipital region in a patient receiving 40 mg of fluoxetine daily. These data were obtained using a 1.5-T scanner with a flat 16-cm surface coil. A distinct fluoxetine peak was identified, as signals from fluoxetine and its metabolite, norfluoxetine, with both containing $^{19}F$, cannot be distinguished from each other [22]. This pioneering research was followed by a number of studies evaluating brain concentrations of fluoxetine [22,24,28,30,31,34].

Renshaw et al. (1992) [24] studied three depressed and five subjects with obsessive-compulsive disorder (OCD) who were taking 60–100 mg of fluoxetine daily. A 1.5-T system and a cylindrical coil with a 21-cm internal diameter were used to acquire spectra from the upper half of the head. Brain fluoxetine/norfluoxetine concentrations ranged from 2–5 $\mu$g/mL and the mean brain:serum drug ratio was 2.6. These findings suggest that fluoxetine accumulates in the brain during chronic treatment, possibly due to its lipophilic nature. A mean 5% test-retest difference was observed in three subjects, indicating good test-retest reliability.

Karson et al. (1992) [28] studied six psychiatric patients with various psychiatric disorders taking 40 mg of fluoxetine daily. Signal detection on a volume of approximately 800 mL from the anterior cerebral cortex was enhanced by conforming the surface coil to the contour of the subject's forehead; consequently the spectral acquisition time was reduced. The reported brain concentration range was 1.3–5.7 $\mu$g/mL. Karson et al. (1993) [22] studied 22 subjects with various psychiatric diagnoses who were taking 20–40 mg of fluoxetine per day. Different head coils were used as the study progressed, and a volumetric coil was found to be more sensitive compared to flat surface or conforming coils. Concentrations of fluoxetine and norfluoxetine in brain ranged from 0–10.7 $\mu$g/mL. Plasma levels of fluoxetine and norfluoxetine were approximately ~0.05–0.33 $\mu$g/mL as determined by liquid chromatography with fluorescence detection.

At earlier time points during the course of treatment (8–150 days), brain levels correlated better with plasma levels (Pearson $r = 0.81$, $p < 0.05$) than with cumulative dose (Pearson $r = 0.57$, $p > 0.10$). However, at later time points (150–730 days), brain concentrations were more strongly associated with cumulative dose than plasma levels. At steady state, after 6–

8 months of treatment, brain concentrations were about 20 times higher than those measured in plasma. In addition, direct measurement of brain slices from a deceased subject confirmed the source of the fluoxetine/norfluoxetine (F/NF) signal, i.e., brain tissue.

Miner et al. (1995) [34] studied nine subjects with social phobia, who were taking 10–60 mg of fluoxetine for 8–20 weeks. A 1.5-T scanner with a quadrature cylindrical birdcage design was used. A spherical polypropylene phantom was used to measure absolute concentrations. Brain concentrations of fluoxetine/norfluoxetine ranged from 0 (undetectable) to 16.54 $\mu$M/L. Response to treatment was defined as scores of 1 (very much improved) or 2 (much improved) on the Clinical Global Impression scale after treatment. Responders had a tendency to have higher F/NF concentrations as compared to nonresponders (7.96 vs. 1.61, $p < 0.10$). In the multiple regression model to predict brain concentrations (independent factors: dose, age, weight, sex), only weight was a significant predictor (inverse relationship).

Henry et al. (2000) [30] studied brain elimination kinetics of fluoxetine and paroxetine in eight patients with remitted major depression. These patients, who were taking 20 mg/day of either fluoxetine or paroxetine from 6 months to 3 years, underwent placebo substitution for 3 days. At day 3, 88% of brain fluoxetine (plus fluorinated metabolites) signals remained as compared to baseline, while only 38% of paroxetine (plus fluorinated metabolites) signals were detected. With respect to serum concentrations at day 3, 75% of fluoxetine/norfluoxetine remained, whereas only 12% of paroxetine remained. The number of adverse events during placebo substitution was positively correlated with the brain drug level before substitution with placebo.

Bolo et al. (2000) [31] studied steady-state concentrations and washout of fluoxetine in brain in 12 subjects with major depression. Using a 3-T scanner, conventional MRS and MRSI were done in order to measure SSRI levels in different brain regions at multiple time points. Fluoxetine doses of 10–40 mg daily were administered for 3–12 months. Brain and plasma fluoxetine and norfluoxetine levels at steady state were 13 $\pm$ 6 $\mu$M/L (0.71–1.75) and 1.73 $\pm$ 1.0 $\mu$M/L (0.3–2.6), respectively. Brain/plasma ratios of fluoxetine plus norfluoxetine were 10 $\pm$ 6. Brain and plasma half-lives were 382 $\pm$ 48 and 406 $\pm$ 172 hr, respectively.

Strauss et al. (2001) [69] measured in vivo the relative contribution of unbound versus bound fluoxetine and metabolites to the "MRS-visible" signal in human brains by applying magnetization transfer methods. Signals from the bound form of fluoxetine/norfluoxetine were about 14.2% relative to signal derived from the unbound form of fluoxetine/norfluoxetine. This result implies that actual brain drug concentrations may be higher relative

to the measured concentrations using the conventional MRS technique, which does not detect the bound form of the drug.

### 3.3 $^{19}$F-MRS Studies of Fluvoxamine

Strauss et al. (1997) [32] conducted a prospective, open-label treatment trial of fluvoxamine in eight subjects with OCD to quantify brain fluvoxamine levels. Fluvoxamine was started at 100 mg per day and doses ranged from 100–300 mg/day during treatment. Brain fluvoxamine levels were serially measured over a period of 25 weeks using a quadrature cylindrical birdcage coil. Brain concentrations were 3.5–36.8 $\mu$M/L (range: 11.2 $\pm$ 26 $\mu$M/L) and plasma concentrations were 0.1–3.2 $\mu$M/L (range: 0.7 $\pm$ 0.8 $\mu$M/L). Brain:plasma ratios were 24 (SD: 12). They also found that steady-state brain fluvoxamine levels correlated with plasma fluvoxamine levels but not with fluvoxamine dose.

Strauss et al. (1998) [33] subsequently measured, for up to 10 days, brain and plasma fluvoxamine levels after discontinuation of fluvoxamine in six psychiatric subjects with OCD ($n$ = 4), panic disorder ($n$ = 1), and depression ($n$ = 1). Before fluvoxamine withdrawal, study subjects were receiving 100–300 mg/day (mean 217 $\pm$ 68) for at least 5 weeks. Brain fluvoxamine concentrations were 4.2–12.7 $\mu$M/L (9.8 $\pm$ 3.0 $\mu$M/L) and plasma fluvoxamine levels were 0.31–0.79 $\mu$M/L (0.50 $\pm$ 0.18 $\mu$M/L). Brain elimination half-life was determined to be significantly longer than plasma half-life (58 $\pm$ 15 and 26 $\pm$ 9 hr, respectively; mean ratio 2.4). Brain fluvoxamine levels were not correlated with daily dose. Withdrawal symptoms such as sweating, dizziness, headache, and nausea, occurred in the interval between one and two brain elimination half-lives. Brain as well as plasma elimination followed first-order kinetics.

Bolo et al. (2000) [31] studied steady-state and washout brain concentrations of fluvoxamine in brain in 12 depressed subjects. Fluvoxamine at doses of 100–300 mg per day was administered for 1–12 months. Brain and plasma fluvoxamine levels at steady state were 12 $\pm$ 5 $\mu$M/L (6–24) and 1.12 $\pm$ 0.31 $\mu$M/L (0.3–2.6), respectively. Brain/plasma ratios of fluvoxamine were 10 $\pm$ 2. No correlations were found between brain fluvoxamine level and treatment dose, duration, and cumulative dose of fluvoxamine. Brain and plasma half-lives were 79 $\pm$ 24 and 35 $\pm$ 8 hr, respectively.

### 3.4 $^{19}$F-MRS Studies of Other Fluorinated Serotoninergic Drugs

Dexfenfluramine, an anorectic drug, is another "MRS-visible" serotonergic drug. Christensen has performed a series of 19F-MRS studies both in pri-

mates [27] and humans [70] to evaluate brain concentrations of dexfenfluramine. In primates, 19F-MRS estimates of dexfenfluramine/dexnorfenfluramine concentrations were similar to those detected using the gas chromatography method [27]. The same group [70] subsequently conducted a $^{19}$F-MRS study of dexfenfluramine in 12 healthy obese women who were taking 30 mg dexfenfluramine daily. Serial measurement results are as follows: Brain dexfenfluramine + dexnorfenfluramine levels were 3.9 ± 1.1 $\mu$M (day 10), 3.6 ± 0.6 $\mu$M (day 60), and 3.9 ± 8 $\mu$M (day 90). Serum dexfenfluramine + dexnorfenfluramine levels were 0.23 ± 0.08 $\mu$M (day 10), 0.27 ± 0.08 $\mu$M (day 60), and 0.25 ± 0.08 $\mu$M (day 90). These results also demonstrate the feasibility of quantifying fluorinated drugs in brain using $^{19}$F-MRS at concentrations below 10 $\mu$M.

### 3.5 Prospects

So far, the feasibility of $^{19}$F-MRS in detecting several fluorinated antidepressants is well established in different psychiatric populations (major depression, OCD, and social phobia). Some pharmacokinetic properties (such as brain:serum ratio, brain elimination half-life, and minimum therapeutic brain concentrations) and their relationships with clinically important events (e.g., withdrawal symptoms) have been reported. More standardized and robust technical approaches involves high-field scanners, are expected to provide new opportunities to apply $^{19}$F-MSR in clinical research.

## 4 MRS PHARMACODYNAMIC STUDIES IN MOOD DISORDER: MEDICATION EFFECTS ON BRAIN

Proton MRS studies of human brain generate spectra at 1.5 T with resonances derived from cytosolic choline (Cho), creatine plus phosphocreatine (Cr-PCr), *N*-acetyl aspartate (NAA), Glx (glutamate, glutamine, GABA), and myo-inositol (Inos). It is technically more difficult to determine absolute metabolite concentrations. The Cr and PCr levels are known to be relatively constant throughout the brain, though they are slightly higher in cerebral cortex than in white matter [71]. Consequently, brain MRS measures are often expressed as metabolite ratios such as Cho/Cr, NAA/Cr, which are useful in assessing metabolic changes in brain. The NAA resonance is the largest after water suppression, and the intensity of this resonance has been used as a neuronal viability marker [72]. The 1H-MRS Cr resonance derives from Cr as well as PCr while the $^{31}$P MRS resonance is just from PCr. PCr is a high-energy phosphate and alterations in the level of this neurochemical suggest changes in brain energy metabolism [73]. The choline signal is primarily derived from phosphocholine and glycerophosphocholine, precursors and catabolites of phosphatidylcholine [74,75].

### 4.1 Pharmacodynamic Studies of Depressive Disorder

Several lines of evidence suggest that alterations in brain choline metabolism may be associated with the pathophysiology of depressive disorders [35,36,76–78]. First, cholinergic agonists and antagonists have been shown to affect mood [79,80] and an imbalance between adrenergic and cholinergic systems is one etiologic theory of depression [81]. Thus, changes in brain levels of choline, a precursor of the neurotransmitter acetylcholine, may play a role in depression. Second, choline is incorporated into two phospholipids in the neuronal membrane, i.e., phosphatidylcholine and sphingomyelin [82,83]. Since phosphatidylcholine is an important substrate for second-messenger generation, alterations in this choline-containing phospholipid may result in change in intracellular signal transduction [84]. Third, the choline resonance may be related to changes in local metabolic rates required to drive the incorporation of cytosolic choline-containing compounds into phospholipids [85]. Reduced metabolism and blood flow in depressed subjects have been consistently reported [86,87].

Alteration of Cho/Cr by antidepressant administration is the most frequently reported finding in MRS studies of depressive disorder [35,36,76]. Charles et al. (1994) [76] evaluated the influence of oral nefazodone treatment on the brain metabolite ratios of Cho/Cr, NAA/Cr, and NAA/Cho in seven depressed subjects before and after treatment of nefazodone up to 500 mg daily for 2–3 months. A single-voxel proton MRS revealed that subjects with major depression had increased levels of Cho/Cr relative to healthy comparison subjects at baseline ($1.27 \pm 0.29$ and $1.08 \pm 0.06$, respectively) and that this increased level of Cho/Cr decreased significantly following treatment ($0.79 \pm 0.16$).

Renshaw and colleagues have also used $^{1}$H-MRS to perform pharmacodynamic studies in mood-disordered subjects [35,36] (Table 3). Renshaw et al. (1997) [36] measured *N*-acetylaspartate/creatine (NAA/Cr) and choline (Cho)/Cr ratios within an 8-cm$^3$ voxel, centered on the head of the left caudate and the putamen in 41 major depressive disorder (MDD) subjects and 22 healthy comparison subjects using hydrogen-1 MRS ($^{1}$H-MRS). The diagnosis of depression was based on DSM-III-R criteria and 17-item Hamilton Depression Rating Scale (HDRS) scores were $\geq 16$ ($20.8 \pm 3.8$). Responders ($n = 18$) in MDD subjects were defined by a 50% reduction in HDRS measures and a posttrial score <7 after 8 weeks of treatment with fluoxetine 20 mg daily. MRS metabolitesconcentrations were calculated using the ratios of peak areas (NAA/Cr, Cho/Cr) and the contributions of gray and white matter compositions were taken into account.

Depressed subjects had a lower area ratio of choline resonance (Cho/Cr) than comparison subjects. This difference was more pronounced in the

treatment responders than in the nonresponders. Considering that there was no difference in the relative volumes of gray matter or white matter in the voxel used for proton spectroscopy, this finding is likely to represent differences in metabolites measured.

The same group [35] extended the research by repeating the MRS measurements after treatment in the depressed group ($n = 15$) and employing pattern analysis in defining a true treatment response group ($n = 8$) and a placebo-pattern response/nonresponse group ($n = 7$). A significant difference in degree of change in Cho/Cr ratios between the true drug response group and the placebo pattern response/nonresponsive group were found. There was no difference in demographic factors (age, gender) and HDRS scores. True drug response showed a 20% (0.14) increase [from 0.69 (SD = 0.16) to 0.83 (SD = 0.11)] whereas placebo pattern response/no response group exhibited 12% (0.09) decrease [from 0.74 (SD = 0.09) to 0.65 (SD = 0.19)]. However, there were no differences in NAA/Cr ratios between the two groups after 8 week of treatment.

These studies describe MRS pharmacokinetic studies designed to link changes in levels of brain metabolites with treatment efficacy. These results, if replicated, could serve as markers for predicting treatment response.

### 4.2 Pharmacodynamic Studies of Bipolar Disorder

Both $^{1}H$ and $^{31}P$-MRS studies have been performed in bipolar patients. Most of the $^{1}H$-MRS studies have focused on the myo-inositol depletion hypothesis. $^{31}P$-MRS have been adopted to measure the change of phophomonoester (PME), phophodiester (PDE), phosphocreatine (PCr), inorganic orthophosphate (Pi), and adenosine triphosphate (ATP).

PME arise from the primary anabolites of the membrane phospholipid (phosphocholine, phosphoethanolamine, and sugar phosphate) or second-messenger system (inositol 1,4,5-triphosphate). The physiological role of PDE is still obscure and regarded to reflect membrane catabolites, such as glycerophosphocholine and glycerophosphoethanolamine, as well as mobile phospholipids. Levels of ATP, PCr, and Pi reflect the state of cerebral energy metabolism [88].

The myo-inositol depletion hypothesis is one of the most important theories to explain lithium's pharmacological effects [21,47–50]. Lithium is known to uncompetitively inhibit the conversion of inositol phosphate to myo-inositol, which results in the decrease of membrane phophoinositides available for second-messenger generation (phosphatidylinositol cycle). $^{1}H$ and $^{31}P$ MRS provide the noninvasive and accurate methods to measure the level of myo-inositol and its precursor, inositol-1-phosphate.

Results from most animal [89,90] and human studies [47–49] have supported the myo-inositol hypothesis while other studies have not [21,50].

**TABLE 3** In Vivo $^{1}H$ and $^{31}P$-MRS Pharmacodynamic Studies in Mood Disorders

| Author | Subjects (*n*) | Medication (mg/day) | MRS methods (tesla, coil type, VOI) | Findings |
|---|---|---|---|---|
| Charles et al., 1994 [76] | DSM-III-R major depression (7), control (10)<br>Age: major depression (63–76), control (65–75) | Nefazodone 500 | 1.5T<br>3rd ventricle level | *Cho/Cr at baseline and after treatment*<br>Major depression: 1.27 ± 0.29 → 0.79 ± 0.16 ($p$ = 0.026) |
| Renshaw et al., 1997 [36] | Major depression (20 male, 21 female), control (12 male, 10 female)<br>Fluoxetine responders (18), fluoxetine nonresponders (23)<br>Age: major depression (39 ± 10), control (41 ± 10)<br>*Correlation study between baseline choline levels and diagnostic/clinical variables | Fluoxetine 20 | 1.5T<br>Left caudate and putamen | *Cho/Cr at baseline*<br>Responders: 0.71 ± 0.17 $\mu$M/L<br>Nonresponders: 0.76 ± 0.10 $\mu$M/L<br>Control: 0.81 c 0.11 $\mu$M/L<br>Decreased baseline Cho/Cr in major depressive patients than control subjects (more pronounced difference in responders) |
| Sonawalla et al., 1999 [35] | Major depression (15)<br>Responders (8), placebo pattern responders (4), nonresponders (3)<br>*Correlation study between choline level changes and diagnostic/clinical variables | Fluoxetine 20 | 1.5T<br>Left caudate and putamen | *Cho/Cr at baseline and after treatment*<br>Patients with true drug response: 0.69 → 0.83 ($\mu$M/L, 20% increase)<br>Patients with placebo pattern or no response: 0.74 → 0.65 ($\mu$M/L, 12% decrease)<br>Significant difference in delta Cho/Cr ratio |

| | | | | |
|---|---|---|---|---|
| Silverstone et al., 1996 [50] | Healthy volunteers (17)<br>Lithium group (13), placebo group (4)<br>Age: 18–35 | Lithium 1200 (for 7 days) | 1.5T<br>Circumscribing head coil<br>Temporal area | *Myo-Inositol before and after lithium treatment*<br>No significant change<br>*PME/PCr before and after lithium treatment*<br>No significant change |
| Silverstone et al., 1999 [47] | Healthy volunteers (16)<br>Lithium group (7 male, 3 female), placebo group (5 male, 1 female)<br>Age: lithium (25.3 ± 1.7), placebo (26.1 ± 2.6) | Lithium 1200 (for 7 days) | 3T<br>Surface coil<br>Temporal area | *Myo-Inositol before and after lithium treatment*<br>No significant change |
| Silverstone et al., 1999 [47] | Healthy volunteers (16)<br>Lithium group (5 male, 5 female), placebo group (4 male, 2 female)<br>Age: lithium (22.9 ± 0.8), placebo (23.0 ± 1.7) | Lithium 1200 (for 7 days) (dextroamphetamine stimulation study) | 3T<br>Surface coil<br>Temporal area | *PME/β-ATP before and after dextroamphetamine administration*<br>Lithium group: 1.24 ± 0.30 → 1.69 ± 0.45 ($p = 0.005$)<br>Placebo group: 1.41 ± 0.54 → 1.37 ± 0.40<br>Increased PME/β-ATP in lithium group |
| Moore et al., 1999 [48] | DSM-IV bipolar disorder<br>5 male, 7 female<br>Age: 22–56 | Lithium (serum level: 0.8–1.3 mM/L) | 1.5T<br>Right frontal, left temporal, central occipital, left parietal | *Myo-Inositol levels, baseline, after 5–7 days and after 3–4 weeks of lithium treatment*<br>Right frontal lobe: ($p = 0.04$): ~4.1 (baseline) → ~2.7 (after 5–7 days) → ~2.9 (after 3–4 weeks) |

**TABLE 3** Continued

| Author | Subjects (*n*) | Medication (mg/day) | MRS methods (tesla, coil type, VOI) | Findings |
|---|---|---|---|---|
| Moore ef al., 2000 [21] | DSM-IV bipolar disorder (5 male, 7 female), control (3 male, 6 female)<br>Age: bipolar disorder (22–56), control (18–48) | Lithium (dosage not specified, for 4 weeks) | 1.5T<br>Right frontal, left temporal, central occipital, left parietal area<br>*Gray matter volumetry | *NAA before and after lithium treatment*<br>4.5% increase from baseline (after chronic lithium treatment) ($p = 0.022$)<br>No significant difference between bipolar disorder and control<br>*Correlation between NAA and gray matter volume*<br>Positive correlation between NAA and gray matter volume ($r = 0.967$, $p = 0.33$) |
| Moore et al., 2000 [95] | DSM-IV bipolar I disorder (5 male, 4 female), control (6 male, 8 female)<br>Age: bipolar I disorder (37.9 ± 9.7), control (36.1 ± 10.5)<br>Lithium (5), valproate (4) | Lithium<br>Valproate | 1.5T<br>Anterior cingulate | *Right anterior cingulated Cho/Cr at baseline*<br>Bipolar I disorder patients: 0.86 ± 0.23<br>Control: 0.63 ± 0.12<br>*Cho/Cr at baseline and after treatment*<br>No difference<br>Increased baseline right anterior cingulate Cho/Cr in bipolar I disorder ($p < 0.005$) |

| | | | | |
|---|---|---|---|---|
| Kato et al., 2000 [45] | DSM-IV bipolar I disorder (32)<br>Responders (5 male, 3 female), nonresponders (8 male, 16 female)<br>Age: responders (42.1 ± 9.6), nonresponders (39.9 ± 11.5) | Lithium (0.3–1.0 mM/L) | 1.5T<br>Surface coil<br>Frontal area | *Intracellular pH at baseline*<br>Responders: 6.988 ± 0.036<br>Nonresponders: 7.027 ± 0.044<br>*PDE at baseline*<br>Responders: 19.3 ± 3.4<br>Nonresponders: 20.8 ± 2.6<br>Decreased baseline intracellular pH and PDE in disorder |
| Murashita et al., 2000 [46] | DSM-IV bipolar I disorder (3 male, 16 female), control (12 male, 13 female)<br>Responders (1 male, 8 female), nonresponders (2 male, 8 female)<br>Age: responders (50.7 ± 12.0), nonresponders (42.3 ± 12.0), control (37.0 ± 14.0) | Lithium (9)<br>Lithium + other medication (6)<br>Other medication (3)<br>No medication (1) (photic stimulation study) | 1.5T<br>Surface coil<br>5 cm-thick transverse slice including occipital lobe | *PCr during photic stimulation*<br>Significant effect of diagnosis during photic stimulation<br>*PCr before and after photic stimulation*<br>Decreaed PCr after photic stimulation in nonresponders |
| Davanzo et al., 2001 [49] | Adolescent bipolar disorder (11)<br>9 male, 2 female<br>Age: 7–17<br>Age, gender-matched control (11) | Lithium 300–600 | 1.5T<br>Anterior cingulate (frontal interhemispheric fissure, 8 mL) | *Myo-Inositol/Cr*<br>Bipolar patients: 1.092 ± 0.612 → 0.820 ± 0.279<br>Control: 0.821 ± 0.152 (baseline only)<br>Decreased myo-Inositol/Cr after lithium treatment ($p = 0.047$) |

*Key*: VOI, volume of interest; Cho, choline; Cr, creatine; PME, phosphomonoester; PDE, phosphodiester; ATP, adenosine triphosphate; NAA, N-acetylacetate.

Silverstone et al. (1996) [50] evaluated the myo-inositol/Cr and PME/PCr ratios before and after treatment with lithium 1200 mg daily for 7 days in healthy volunteers. There were no significant differences in levels of both metabolites between before and after lithium treatment. The same group [47] tested the "inositol depletion hypothesis" of lithium efficacy again after activating the phosphatidylinositol cycle by administering amphetamine to study subjects. Lithium and placebo groups were treated with lithium of 1200 mg daily and placebo, respectively, for 1 week. At day 8, 20 mg of amphetamine was orally administered to stimulate the phosphatidylinositol cycle. A single-voxel ($2 \times 2 \times 3$ cm) in the temporal lobe was measured by multinuclear MRS of proton and phosphorus using a 3-T scanner. There was no change in myo-inositol levels before and after lithium treatment, as measured by $^1$H-MRS. However, lithium-treated subjects had a greater increase in phosphomonoester/$\beta$-adenosinetriphosphate (PME/$\beta$-ATP) ratios after amphetamine intake compared to placebo-treated subjects. These results are in accord with the hypothesis that lithium blocks the conversion of inositol monophosphates to myo-inositol.

Moore et al. (1999) [48] measured myo-inositol levels in 8-mL voxels of right frontal, left temporal, central occipital, left parietal in 12 lithium-treated bipolar subjects after a 2-week drug washout period. Subjects with bipolar disorder received oral lithium and their serum lithium levels were 0.8–1.3 $\mu$M during the course of treatment. In serial measurements made at baseline, 5–7 days, and 3–4 weeks after starting lithium, decreased myo-inositol was observed in the frontal lobe at 5–7 days and thereafter. Depressive symptoms, as measured by the HDRS, significantly decreased during the course. However, this decrease in the myo-inositol level occurred prior to any change in clinical symptoms. The authors viewed this discrepancy as evidence against the relationship between lithium-related myo-inositol change and therapeutic response.

Davanzo et al. (2001) [49] measured changes in $^1$H-MRS-visible metabolites after lithium treatment in 11 subjects with bipolar disorder and 11 age, and gender-matched controls. Study subjects were in manic, hypomanic, or mixed episodes. An 8-mL voxel was centered on frontal inter-hemispheric fissure. Myo-inositol/creatine ratios (Ino/Cr) after treatment ($0.820 \pm 0.279$) were significantly smaller than levels before treatment ($1.092 \pm 0.612$). However, there were no differences in other measures of Cho/Cr, Glx/Cr, and NAA/Cr.

O'Donnell et al. (2000) [90] reported in an animal study of rats that both lithium and sodium valproate administration decreased the concentration of myo-inositol and increased the concentration of inositol monophosphates. These results suggest the possibility that lithium and sodium val-

proate may share a common mechanism of action, through actions on a phosphatidylinositol cycle, in the treating subjects with bipolar disorders.

In contrast to findings on brain myo-inositol, results of $^{1}$H-MRS studies in subjects with bipolar disorder where brain Cho/Cr levels were measured are somewhat inconsistent. Stoll et al. (1992) [91] measured Cho/Cr and Cho/NAA levels in lithium-treated euthymic bipolar disorder patients (7 males) and normal volunteers (6 males) using 1.5-T $^{1}$H-MRS. There were no significant difference in these metabolites between the groups.

Silverstone et al. (1999) [92] studied the effect of lithium administration on brain Cho/Cr ratios in 16 healthy volunteers. Ten volunteers (lithium group) had orally taken 1200 mg of lithium for 7 days and six volunteers received placebo (placebo group). Ratios of Cho/Cr in the temporal lobes were measured by $^{1}$H-MRS. Cho/Cr ratios were not different before and after lithium treatment and were not different between the two groups after lithium treatment.

Moore et al. (2000) [21] studied Choline/Cr and Inositol/Cr ratios in nine DSM-IV bipolar I disorder subjects and 14 comparison subjects, before and serially after treatment (mean 3.1 $\pm$ 1.3 examinations) with either lithium ($n$ = 5) or valproate ($n$ = 4). At baseline, the right cingulate choline levels in the bipolar group were greater than in the control group (0.86 $\pm$ 0.23 and 0.63 $\pm$ 0.12, respectively). In addition, the bipolar subjects' depression ratings correlated positively with MRSI measures of Cho/Cr in the left cingulate cortex. However, inositol/Cr ratios in the anterior cingulate cortex were not different at baseline and after treatment.

Lithium has shown to have neuroprotective effects, possibly by protecting neurons from excitatoxicity effects of glutamate and *N*-methyl-D-aspartate (NMDA) [93,94]. Currently, only a few studies have evaluated possible effects of lithium on NAA using $^{1}$H-MRS [48,49]. Moore et al. (1999) [48] measured brain NAA levels in 12 bipolar subjects and nine healthy comparison subjects. There was no significant difference in NAA levels between patient and control subjects. Total brain NAA levels significantly increased after lithium administration. Also, there was a positive correlation between increased NAA level and voxel gray matter content ($r$ = 0.967, $p$ = 0.033). Considering that voxel content within each ROI remained unchanged across the two time points, this correlation implies that NAA increases mainly in the CNS gray matter. Davanzo et al. (2001) [49] measured changes in NAA/Cr ratios following lithium intake. There was no change in NAA/Cr ratios after treatment.

Kato and colleagues performed a series of pharmacodynamic studies using 31P-MRS [45,46]. Kato et al. (2000) [45] conducted a $^{31}$P-MRS study in 32 DSM-III-R bipolar disorder subjects to identify predictors of treatment response to lithium. In the logistic regression model (response to lithium as

a dependent variable; age, sex, age at onset, subtype of bipolar disorders, and measures by $^{31}$P-MRS including PME, PDE, intracellular pH, PCr as predictor variables). Intracellular pH was inversely correlated with treatment response. Although the meaning of this finding remains unclear, the decreased intracellular pH was implicated to be related to the pathophysiology of lithium responsive bipolar disorder.

Murashita et al. (2000) [46] conducted a $^{31}$P-MRS study to evaluate the photic stimulation–related changes in brain metabolites in 19 euthymic subjects with DSM-IV bipolar disorder and 25 healthy comparison subjects. White light flashing at 10 Hz emitted by a metal halide lamp was used for photic stimulation and brain metabolites were measured at the 5-cm-thick transverse slice including occipital lobes. There were no significant differences in brain metabolites between lithium-responsive, lithium-resistant, and control groups. In the lithium-resistant group, PCr levels in the two post-stimulation periods were significantly smaller than the prestimulation levels. This finding implies that mitochondrial function may be impaired in the lithium-resistant bipolar group.

### 4.3 Prospect

Currently, a decreased level of brain myo-inositol after the lithium intake is the most consistent finding in MRS studies in subjects with bipolar disorder. Studies on other metabolite studies, such as NAA and Cho levels, have reported inconsistent results, which may be partially due to the current limitations of MRS techniques.

MRS can measure only relatively mobile compounds and thus the receptor bound form of medications cannot be measured using MRS. More importantly, the low concentration of receptors put receptor studies within the domain of SPECT and PET. However, MRS has the capability of measuring various brain metabolites in vivo and in a noninvasive way. Using a high field scanner, standardization of MRS techniques, and employing provocation methods may overcome some of the current limitations associated with MRS pharmacodynamic studies.

## 5 CONCLUSION

MRS studies are likely to greatly enhance our knowledge on the relationship between brain drug concentration and the medication/side effects as well as pharmacokinetic properties in brain and plasma. With ongoing developments in technology, local distribution of lithium and fluorinated drugs along with changes after treatment in brain chemistry will be better clarified. This will improve our understanding of how the psychoactive drugs work and, hopefully, of the pathophysiology of affective disorders.

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# 11

# Positron Emission Tomography and Single Photon Emission Computed Tomography Imaging of Antidepressant Treatment Effects in Major Depression

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## 1 INTRODUCTION

The incorporation of neuroimaging methods into clinical trials represents a potentially powerful approach to understanding the neurobiological basis of variability in response to antidepressant treatmen—in particular the neurobiological substrates that underlie treatment resistance. The ultimate goal of these studies is to inform the development of novel treatments and augmentation strategies in order to improve the clinical management of depression. The application of neuroimaging methods in this manner has been facilitated both conceptually and practically by programmatic initiatives at the National

Institute of Mental Health (NIMH) that have led to the development of intervention research centers. This chapter will focus on the application of functional neuroimaging methods, specifically positron emission tomography (PET) and single photon emission computed tomography (SPECT) to the evaluation of antidepressant treatment effects in major depression. The reason for this particular emphasis is that, at present, PET and SPECT are the best available methods to visualize functional neuroanatomical pathways and neurochemical substrates. This review includes a discussion of the clinical and methodological considerations that are important in interpreting the literature, followed by a critical review of the literature concerning acute and chronic pharmacological interventions and electroconvulsive therapy (ECT). Potential future directions in the neuroimaging of antidepressant treatment effects are discussed.

## 2 THE NEUROBIOLOGY OF MAJOR DEPRESSION

The dominant hypothesis guiding research and drug development in major depressive disorder is that of decreased monoaminergic function, particularly regarding serotonin and dopamine [1,2]. The evidence supporting the role of *serotonin* in depression includes (1) studies of the brain at postmortem examination that have demonstrated reductions in serotonin transporter binding, 5-HT1A and 5-HT2A receptor binding, (2) a blunted neuroendocrine response to acute pharmacological interventions of the serotonin system, and (3) the effect of pharmacological manipulations of serotonin systems on mood in depressed patients (improvement with increased serotonin and worsening with reduced serotonin concentrations, as reviewed in Refs. 3 through 8). The role of the *dopamine* system in depression has been the subject of several reviews (e.g., Refs. 9 and 10). There are several lines of evidence to support dopamine dysfunction in depression, including (1) neuropharmacological evidence for the improvement of depressive symptoms (by administration of dopamine agonists and antidepressants that act through a dopaminergic mechanism), (2) the induction of depressive symptoms by the pharmacological depletion of dopamine (using alpha-methylparatyrosine a monoamine synthesis inhibitor that depletes dopamine to a greater extent than other monoamines), and (3) reductions in cerebrospinal fluid (CSF) measures of homovanillic acid [10].

Due to advances in radiotracer chemistry, it is now possible to test the monoamine hypothesis of depression directly by evaluating components of the serotonin (e.g., serotonin metabolism, serotonin transporter, 5-HT1A and 5-H2A receptors) and dopamine systems (dopamine metabolism, dopamine transporter, D1 and D2 receptors). While there is great interest in evaluating the noradrenergic system, particularly due to the efficacy of the new antidepressant agents that inhibit norepinephrine reuptake, radiotracers with suit-

able imaging properties are still in development. Thus far, the neuroreceptor studies performed in patients with depression compared to normal controls have shown decreases in serotonin transporter binding and 5-HT1A receptor binding, but no differences in 5-HT2A binding [11–13]. However, no striking differences have been noted in serotonin or dopamine receptor binding, nor have the receptor binding measures been shown to be predictive of antidepressant treatment response. These findings have led investigators also to pursue more dynamic measures of monoaminergic function, such as the examination of monoamine metabolism, cerebral glucose metabolism, and, most importantly, the combination of measures of cerebral glucose metabolism with acute and chronic pharmacological interventions. As described in this chapter, these imaging approaches have been applied to evaluate the functional neuroanatomical and neurochemical substrates underlying the mechanism of action of antidepressant medications.

## 3 THE STATUS OF APPROACHES FOR THE IN VIVO IMAGING OF CEREBRAL FUNCTION AND NEUROTRANSMISSION

In the design of a neuroimaging study, the selection of the appropriate imaging modality is influenced by the scientific question. PET and SPECT imaging, for example, uniquely provide information about neurotransmitters that are in relatively low concentrations, such as the monoamine systems. However, magnetic resonance imaging (MRI) can visualize neurotransmitters in the brain in relatively high concentrations, such as the amino acid neurotransmitters [e.g., gamma aminobutyric acid (GABA), glutamate]. In addition, MRI has superior spatial and temporal resolution and has advantages for cognitive and affective activation studies. The integration of neuropharmacological and activation paradigms is a powerful strategy for understanding neurochemical modulation of specific brain functions.

Radiotracer development for neuroreceptor systems is a complicated and expensive process. For the dopamine system, tracers with suitable binding characteristics are available for the dopamine transporter, D1 and D2 receptors, and the measurement of dopamine synthesis (as reviewed in Ref. 14). Thus far, it has been possible to image synaptic dopamine concentrations using radiotracers that bind to the striatal D2 receptor combined with acute pharmacological interventions to image the competition between D2 radiotracer binding and endogenous dopamine concentrations. The imaging of extrastriatal dopamine concentrations is an active area of investigation for which suitable radiotracers continue to be evaluated (e.g., Ref. 15). The development of radiotracers for the serotonin system has been extremely difficult, primarily because many of the radiotracers have high levels of nonspecific binding due to radiolabeled metabolites that enter the brain and

hinder quantification of specific radiotracer binding (as reviewed in Refs. 16 and 17). For the serotonin system, radiotracers are available for imaging of the serotonin transporter, 5-HT1A and 5-HT2A receptors, and serotonin synthesis (as reviewed in Ref. 4). There is not as yet a suitable radiotracer available to measure endogenous serotonin concentrations. The 5-HT2A radiotracers [18F]-altanserin and [18F]-setoperone have been evaluated [18,19]. The studies of the sensitivity of [18F]-altanserin binding to alterations in serotonin concentrations were difficult to interpret, as changes in the specific and nonspecific binding components were observed with the administration of citalopram [18]. [18F]-setoperone binding has not been shown to be sensitive to changes in endogenous serotonin after the acute oral administration of a selective serotonin reuptake inhibitor (SSRI) [19]. Given the constraints of the available serotonin radiotracers, we have developed an alternative approach to image the dynamic aspects of serotonin function in vivo. The acute administration of an SSRI (citalopram, the most potent and pharmacologically selective SSRI) has been combined with measures of cerebral glucose metabolism (Smith et al., submitted). The development of radiotracers for such potentially relevant sites as the norepinephrine transporter, the corticotrophin releasing factor receptor, and second-messengers are in development [20–22]. Radiotracer development for the amino acid neurotransmitters has also been extremely difficult [23]. However, as mentioned earlier, magnetic resonance spectroscopy (MRS) measurements of such amino acid neurotransmitters as GABA, glutamate, and choline and are feasible. Thus, the combination of PET/SPECT and MRS methods would provide complementary data that would be extremely informative.

## 4 CLINICAL CONSIDERATIONS

There are many clinical aspects of the subjects enrolled in neuroimaging studies that might contribute variability to the results reported. For both patients and comparison subjects, it is important to take into consideration the following: age and gender matching, comorbid psychiatric or neurological disorders, family history of psychiatric or neurological disorders, medical conditions that might affect brain function (e.g., hypertension, diabetes), and concomitant use of any medications, dietary or hormonal supplements, tobacco, alcohol, or drugs of abuse. Medical history and medications are especially critical to consider in the study of elderly individuals. In addition, it is important to consider the state of the patient at the time of scanning (severity of mood and anxiety symptoms), whether this is a first episode or recurrent affective disorder, age at onset of first episode, previous treatment with psychotropic medications [including electroconvulsive therapy (ECT)

or repetitive transcranial magnetic stimulation (rTMS)], treatment response history, and treatment at the time of scanning (medication status at baseline, duration of treatment, type of medication and concurrent treatment for comorbid psychiatric disorders). The characterization of other aspects of symptomatology—such as suicidality, level of disability, perceived stress, and neuropsychological function—might serve to enhance the interpretation of the neuroimaging data.

## 5 METHODOLOGICAL CONSIDERATIONS

In the evaluation of the PET literature, there are many issues in the conduct and analysis of the studies that may affect the results obtained and their interpretation. Many of these issues were taken into consideration in summarizing the literature presented in the tables. Regarding the conduct of the PET studies, there is potential variability introduced by the following:

The specific PET scanner used

The data acquisition mode (two- versus three-dimensional)

Whether or not the study was quantitative (i.e., venous or arterial blood samples obtained to measure radioactivity/metabolite concentrations) and the procedures used (number or timing of blood samples relative to radiotracer injection)

The state of the subjects during scanning ("resting"—eyes and ears open or covered or performing a standard sensory or motor task)

Regarding the analysis of the PET data, the main issues involve

Whether the data are analyzed using a region-of-interest approach or a voxel-by-voxel approach (e.g., statistical parametric mapping)

Whether structural brain scans are used for anatomical definition or atrophy correlation

Whether absolute values or normalized data are analyzed as well as the methods for normalization and the statistical procedures used (e.g., analysis of variance, principal component analysis)

There are additional considerations pertinent to neuroreceptor studies. In performing neuroreceptor studies prior to and following treatment, the primary considerations include the effects of the intervention (acute or chronic) on

Ligand delivery (particularly with respect to high-affinity ligands)

The metabolism of the radiotracer or radiolabeled metabolites of the ligand

Endogenous neurotransmitter concentrations (if the radiotracer is sensitive to alterations in neurotransmitter concentrations)

The ability to interpret the data obtained is largely determined by the degree to which the radiotracer has been characterized.

In regard to the design of the intervention paradigm, the pharmacological profile of the intervention agent must be considered, in addition to the time course of the acute (minutes to hours) or chronic (weeks) neuropharmacological effects. In this context, the incorporation of plasma levels of the intervention agents and neuroendocrine measures may enhance the interpretation of the neuroimaging data. Measures of the effects of the interventions on cognition and mood may provide useful information with respect to interpretation of the neuroimaging data.

## 6 NEUROIMAGING STUDIES OF ACUTE INTERVENTION EFFECTS

Relatively few studies performed in depressed patients have incorporated acute neuropharmacological interventions or experimentally induced alterations in mood states with neuroimaging methods. As mentioned previously, the integration of such approaches represents a powerful method of understanding the functional neuroanatomy and neurochemical substrates of mood states and dysregulation in affective disorders. The representative studies are summarized in Table 1.

The effects of increases in serotoninergic function in depressed patients have been evaluated. The effects of the acute administration of the SSRI and releasing agent fenfluramine have been conducted [24,25]. A blunted response to fenfluramine administration was reported by Mann et al. [24] in patients compared to normal controls in that there was a lesser degree of increase (prefrontal temporal and parietal cortices) and of decrease (right prefrontal, temporal, and parietal cortices) in glucose metabolism. Meyer et al. [25] observed a blunted response to fenfluramine only in the right medial frontal cortex, whereas the other changes in cortical and thalamic metabolism observed with fenfluramine in the controls were similar to the changes observed in the patients. The differences between the findings across studies may be attributable to the fact that the Mann et al. [24] study involved the oral administration of fenfluramine and measurements of glucose metabolism, while the Meyer et al. [25] study involved the intravenous administration of d-fenfluramine (which is more pharmacologically selective) and the measurement of regional cerebral blood flow (rCBF). As reviewed previously, the differences in aspects of symptomatology between the patients enrolled in the two studies may also account for the different results.

Several studies have examined the effects of tryptophan depletion on cerebral metabolism/blood flow [26,27]. Bremner et al. [26] evaluated depressed patients who responded to SSRI treatment. The patients underwent

two scans, after either placebo administration or tryptophan depletion. The patients who relapsed in response to tryptophan depletion demonstrated elevated metabolism in prefrontal and limbic regions at baseline. The patients who relapsed showed decreased metabolism in dorsolateral prefrontal cortex, thalamus and orbitofrontal cortex (anterior cingulate metabolism was not reported in this study). The increases in Hamilton Depression Rating Scale score correlated with the decrease in metabolism in these regions. In another study involving tryptophan depletion that measured rCBF at rest and during a verbal fluency task. Smith et al. [27] reported that depressive relapse was associated with decreased rCBF in ventral anterior cingulate gyrus, caudate, and orbitofrontal cortex and with rCBF task activation in dorsal anterior cingulate cortex. Thus, the studies conducted to date indicate that acute alterations of serotoninergic function result in detectable differences in depressed patients and controls but may be even more useful in making comparisons between subgroups of depressed patients. The tryptophan depletion studies support the observation that measures of cerebral metabolism/blood flow are sensitive to state-dependent changes in depressive symptoms. An important future direction of this work is the combination of the tryptophan depletion paradigm with measures of alterations in neuroreceptor availability. In normal control subjects, Yatham et al. [28] reported a decrease in cortical 5-HT2A receptor availability with tryptophan depletion. The application of this paradigm to patients with depression would be very informative with respect to whether depressive relapse is associated with alterations in 5-HT2A binding.

Concerning the dopamine system, Parsey et al. [29] conducted a SPECT study of endogenous striatal dopamine concentrations using the D2 radiotracer [$^{123}$I]iodobenzamide (IBZM) in unipolar depressed patients. No differences were observed in baseline striatal D2 binding or the amphetamine induced reduction in striatal D2 binding, indicative of endogenous dopamine concentrations. The majority of studies have failed to find differences in striatal D2 binding between depressed patients and controls. These results are consistent with the findings of Anand et al. [30] in studies using the same paradigm in euthymic, bipolar depressed patients.

Few studies have been conducted to evaluate the noradrenergic system. Pharmacological studies of the noradrenergic system in humans are difficult to conduct due to the potentially serious side effects of administering agents of this class, particularly effects on blood pressure. The availability of the selective noradrenergic reuptake inhibitors will facilitate research in this area. Fu et al. [31] combined rCBF measurements of an attentional task with the administration of the alpha$_2$ agonist clonidine. Depressed patients demonstrated a similar increase in metabolism as controls in the insular cortex and right prefrontal cortex; however, the patients demonstrated decreased

**TABLE 1** Summary of Studies Designed to Examine the Effects of Mood Induction and Acute Antidepressant Interventions on Cerebral Glucose Metabolism

| Author/date | Subjects | Method | Analysis | Results |
|---|---|---|---|---|
| Parsey et al., 2001 [29] | 9 patients<br>Mean age 36<br>Major depression<br>10 healthy controls<br>Mean age 30 | Between subjects: Normal controls vs. patients and within subject: pre and post d-amphetamine infusion.<br>Protocol: Subjects are scanned before and 5 min after d-amphetamine infusion.<br>SPECT<br>[123I]IBZM<br>Quantitative | ROI | Patients did not differ from controls in baseline or d-amphetamine induced change D2 receptor availability. |
| Fu et al., 2000 [31] | 6 patients<br>Mean age 30.8 years<br>Major depression<br>6 healthy controls<br>Mean age 29.5 | Between subjects: Normal controls vs. patients and within subject: pre- and postclonidine infusion.<br>Protocol: Subjects are scanned before and 25–30 min after an intravenous clonidine infusion while performing a sustained attention task.<br>PET<br>[15O]water<br>Quantitative | SPM | rCBF in the control group increased bilaterally in the insular cortices and decreased in the left angular gyrus and right superior prefrontal cortex.<br>rCBF in the depressed group increased bilaterally in the insular and right superior prefrontal cortices and decreased bilaterally in the cerebellum. |

| | | | | |
|---|---|---|---|---|
| Mayberg et al., 1999 [32] | 8 patients<br>Mean age 44 years<br>Major depressive episode (unipolar)<br>8 normal controls<br>Mean age 36 years | Within subjects: Pre- and postmood change/ treatment.<br>Protocol 1: rCBF was measured in two mood states: sad and neutral. Rehearsed autobiographical scripts were used to induce sadness. Patients achieved the desired mood in 8–10 min, were scanned, and then allowed to return to a normal mood state.<br>Protocol 2: Patients were scanned pre- and post–6 weeks of treatment with either fluoxetine or placebo.<br>PET<br>[15O]water (protocol 1) and [18F]fluorodeoxyglucose (FDG) (protocol 2)<br>Semiquantitative | SPM | During induced sadness, as compared to rest, patients showed increases in ventral limbic and paralimbic sites (subgenual cingulate and ventral, mid-, and posterior insula). Decreases were seen in dorsal cortical regions (right dorsal prefrontal, inferior parietal, dorsal anterior cingulate and posterior cingulate).<br>Recovered depressed patients showed an involvement of the same regions, but in an inverse pattern. Increases were seen in dorsal cortical regions and decreases in ventral limbic and paralimbic sites. |
| Meyer et al., 1998 [25] | 13 patients<br>18–30 years old<br>Major depressive episode (unipolar and bipolar)<br>18 healthy controls | Between subjects: Normal controls vs. patients.<br>Protocol: Patients were scanned pre- and postfenfluramine infusion.<br>PET<br>[15O]water<br>Quantitative | SPM | In normal controls, increased activity was observed bilaterally in the medial frontal cortex and decreased activity was found in the bilateral posterior temporal cortex and in the left thalamus. In depressed patients, increased activity was found in the left medial frontal cortex and decreases were found bilaterally in the inferior parietal-superior temporal cortex. |

**TABLE 1** Continued

| Author/date | Subjects | Method | Analysis | Results |
|---|---|---|---|---|
| Bremner et al., 1997 [26] | 21 patients<br>18–65 years old<br>Major depressive disorder | Between subjects: Those who experienced a tryptophan depletion-induced relapse, and those who did not.<br>Protocol: Patients undergo two scans, one after tryptophan depletion and one after placebo.<br>PET<br>F18-fluorodeoxyglucose<br>Quantitative | ROI | Tryptophan depletion resulted in a decrease in brain metabolism in the middle frontal gyrus, thalamus, and orbitofrontal cortex for those who relapsed, but not for those who did not. |
| Mann et al., 1996 [24] | 6 patients<br>Mean age 29.7 years old<br>Major depressive episode (unipolar and bipolar)<br>10 healthy controls (no medication on either scan)<br>Mean age 25.4 years<br>6 healthy controls (placebo on day 1 and fenfluramine on day 2)<br>Mean age 26.7 | Between subjects: Patients vs. healthy controls.<br>Protocol: Patients are scanned after receiving placebo on day 1 and fenfluramine on day 2.<br>PET<br>Fluorodeoxyglucose (FDG)<br>Quantitative | SPM and ROI | Patients demonstrated less of an increase in the left lateral prefrontal and temporal cortex, and bilaterally in medial aspects of the prefrontal and parietal cortex compared to healthy controls. They also showed blunted decreases in the right prefrontal, superior temporal, and parietal regions. |

rCBF in the cerebellum, which was not observed in the controls. Thus, in this study, differences in the acute noradrenergic modulation of cortical function were not observed between depressed patients and controls. This may be attributable to the small sample size of the study and perhaps to particular characteristics of the subject sample. For example, if normal cortical noradrenergic responsiveness is related to treatment response and the subject sample comprised treatment responders only, this might explain the results obtained.

Studies of mood induction combined with neuroimaging methods represent a powerful approach to understand the neural circuitry underlying mood states and how this circuitry may be altered in patients with depression. Mayberg et al. [32] used a mood-induction paradigm involving rehearsed autobiographical scripts combined with neuroimaging methods in depressed patients prior to and following treatment. Prior to treatment, patients demonstrated increased metabolism during induced sadness in ventral brain regions (subgenual cingulate gyrus and insular cortices) and decreased metabolism in dorsal regions (right dorsal anterior and posterior cingulate, prefrontal, and inferior parietal cortices). An inverse pattern of activation was observed in patients that had recovered after antidepressant treatment. These results indicate that sadness is associated with limbic activation and deactivation of cortical regions known to be associated with attentional processes. This important study indicates that the mechanism of action of antidepressant interventions involves altering the functional interactions between cortical regions. Thus, the application of brain network analysis methods such as structural equation modeling to neuroimaging data sets may be especially revealing in evaluating the function interactions altered with antidepressant [33–35]. Finally, the evaluation of changes in neuroreceptor binding during induced mood states would represent an informative approach to evaluate the neurochemical substrates underlying these functional neuroanatomical circuits.

## 6.1 Future Directions

Although relatively few studies have been performed to combine pharmacological or emotional activation paradigms with neuroimaging methods in depression, the available studies indicate that this is an extremely powerful approach for evaluating the pathophysiology and mechanisms of action of antidepressant treatment. Perhaps the most important application of such an approach would be to evaluate patients prior to and following treatment, as done in the study by Mayberg et al. [32], to determine whether the pretreatment findings have predictive value with respect to subsequent treatment outcome. In this manner, neuroimaging studies might be potentially useful

in determining the appropriate treatment for a given patient prior to treatment or to identify individuals in advance who would require more intensive treatment. To evaluate whether the modulation of brain function by neurotransmitters implicated in depression is affected, the acute effects of relevant pharmacological agents for other aspects of the serotonin system (e.g., 5-HT1A agonists) or for other neurotransmitter systems should be studied (e.g., dopamine, glutamate, opiates). This is especially important for certain neurotransmitter systems for which suitable receptor or transporter imaging agents are not yet available (e.g., norepinephrine, glutamate, GABA).

In regard to the measurement of acute neuromodulatory effects as neuroimaging predictors of treatment outcome, we are currently conducting a study to measure the cerebral metabolic effects of the administration of a single intravenous dose of the selective antidepressant citalopram and to rescan the patients during a course of treatment (at 8 weeks) with the oral medication to determine whether the initial metabolic response to citalopram relates to treatment outcome after a 12-week clinical trial. An example of a patient enrolled in the study is shown below. This patient demonstrated a progressive decrease in glucose metabolism in the anterior cingulate, medial frontal, and anterior temporal regions after the initial administration of citalopram as compared with 8 weeks of chronic treatment (Fig. 1). When a sufficient number of patients have been enrolled in the study, we will be able to evaluate the hypothesis that alterations in cerebral glucose metabolism will be greater in the treatment responders than nonresponders after both acute and chronic citalopram treatments. The acute metabolic response will have predictive value with respect to the clinical and metabolic response to chronic treatment.

## 7 NEUROIMAGING STUDIES OF CHRONIC ANTIDEPRESSANT TREATMENT

### 7.1 Neuroreceptor Studies

The evaluation of neuroreceptor changes with antidepressant treatment has focused on serotonin and dopamine systems. A summary of the studies discussed is shown in Table 2. In an early study, Agren et al. [36] reported lower uptake of [11C]-5-hydroxytryptophan, a radiolabeled precursor for serotonin synthesis, in depressed patients. In patients with depression, cortical 5-HT2A binding has not been shown to be altered compared to control subjects; however, 5-HT1A binding (cortex) and serotonin transporter binding (midbrain) have been reported to be reduced [11–13,37]. Several studies have evaluated the effects of antidepressant treatment on 5-HT1A and 5-HT2A binding. 5-HT1A binding was not shown to be altered by SSRI treat-

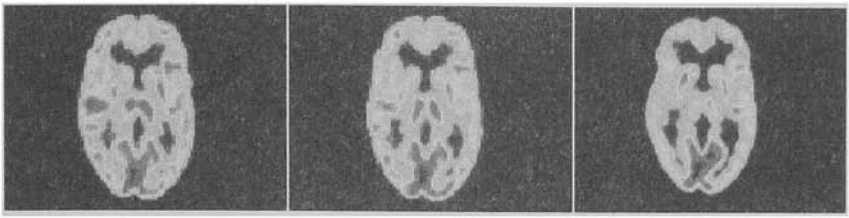

**FIGURE 1** PET scans of cerebral glucose metabolism (baseline, acute citalopram, and chronic citalopram, respectively, from left to right) at the level of the basal ganglia for a representative subject (SS). Note the progressive decrease in glucose metabolism in frontal and anterior temporal cortices and the thalamus. The corresponding Hamilton Depression Rating Scale scores for the baseline and week 8 conditions are 25 and 10.

ment [12] and neither study demonstrated correlations between baseline 5-HT1A binding and treatment outcome. PET and SPECT studies are being performed to evaluate serotonin transporter binding, which may be more revealing as this is the initial target site of the SSRIs [38,39]. For example, reduced serotonin transporter binding in the midbrain (including the raphe nuclei) has been reported in depressed patients using SPECT imaging [11]. Meyer et al. [13] reported that a decrease in 5-HT2A receptor availability after 6 weeks of paroxetine treatment was observed only in younger depressed patients (under age 30). Several studies have reported increased cortical binding to the 5-HT2A receptor with antidepressant treatment in depressed patients [40–42], but one study reported a decrease [43]. In the study by Zanardi et al. [40], the investigators reported that the magnitude of increase in binding was significantly greater in responders than in nonresponders. One of the main reasons for the discrepancy across studies is that, in the Yatham et al. [43] study, desipramine was administered, which binds directly to the 5-HT2A receptors, whereas SSRIs were used in the other studies. It is possible that serotonin radiotracers used in these studies may have radiolabeled metabolites that enter the brain, and if the antidepressant treatment alters the metabolism of the radiotracer, this could affect the results. It has not been well established whether the binding of the radiotracers used in these studies is sensitive to changes in endogenous serotonin or whether an upregulation of 5-HT2A receptors is the primary explanation of the results obtained. Therefore the interpretation of the available data concerning alterations of 5-HT2A receptors by antidepressant treatment in PET studies is highly complex.

Several imaging studies of antidepressant effects on the dopamine system have been performed. Changes in striatal D2 binding after total sleep

**TABLE 2** Summary of Studies Designed to Examine the Effects of Chronic Antidepressant Treatment on Cerebral Glucose Metabolism and Neuroreceptor Binding

| Author/date | Subjects | Method | Analysis | Results |
|---|---|---|---|---|
| | | Neuroreceptor Studies | | |
| **A. Serotonin system** | | | | |
| Meyer et al., 200 [13]1 | 19 patients<br>18–41 years old<br>Depressive disorder<br>19 healthy controls<br>18–41 years old | Between subjects: Patients vs. controls<br>Within subjects: Pre- vs. post-treatment.<br>Protocol: Patients scanned pre- and post–6 week treatment with paroxetine (20 mg per day).<br>PET<br>[18F]setoperone<br>Quantitative | SPM and ROI | Younger depressed patients showed a decrease in binding potential after treatment while older patients did not.<br>Higher binding potentials in responders compared to healthy controls. |
| Zanardi et al., 2001 [40] | 37 patients<br>Mean age 42.6<br>Major depression | Between subjects: Responders compared to nonresponders.<br>Protocol: Patients are scanned 4 weeks after initiation of paroxetine treatment; 18 patients subjected to a second PET scan 2 weeks later.<br>PET<br>[18F]-fluoro-ethyl-spiperone ([18F]-FESP)<br>Quantitative | ROI | [18F]-FESP binding index showed greater increases in the frontal cortex of treatment responders compared to nonresponders. |
| Sargent et al., 2000 [12] | 25 patients<br>19–69 years old<br>Major depressive disorder<br>18 healthy controls<br>27–56 years old | Between subjects: Healthy controls vs. treated and untreated depressed patients.<br>10 depressed patients pre- and post-treatment.<br>Protocol: 5 unmedicated patients are scanned; 10 patients are scanned prior to and then after SSRI treatment; 10 patients are scanned during SSRI treatment.<br>PET<br>[11C]WAY-100635<br>Quantitative | ROI and SPM | Binding potential values were significantly reduced across most brain regions except for the occipital cortex in both medicated and unmedicated depressed patients compared to controls. |

| | | | | |
|---|---|---|---|---|
| Moresco et al., 1999 [41] | 15 patients<br>22–54 years old<br>Major depressive disorder | Within subjects: Pre- and post–fluvoxamine treatment.<br>Protocol: Patients undergo a PET study before and after a minimum of 4 weeks of fluvoxamine treatment. Starting dose was 50 mg once a day and then rapidly increased to 50 mg twice a day for nearly 10 days. After this patients reached the maximum dose of 150 mg twice a day.<br>PET<br>[18F]FESP<br>Semiquantitative | ROI | Binding increased in the frontal and occipital cortex and to a lesser extent in temporal cortex, anterior cingulate, and basal ganglia. |
| Yatham et al., 1999 [43] | 11 patients (10 completed study)<br>Mean age of 40.6<br>Major depression | Within subjects: Pre- vs. post-treatment.<br>Protocol: Patients undergo a PET scan before and another after 3 to 4 weeks of treatment with desipramine.<br>PET<br>[18F]-setoperone<br>Semiquantitative | SPM | Depressed patients showed a significant reduction in [18F]-setoperone binding in frontal, temporal, parietal, and occipital cortical regions. Decreases highly significant in left medial and orbitomedial frontal gyri, left inferior frontal gyrus, left middle and inferior temporal gyri, right inferior frontal gyrus, right lingual gyrus, and right middle occipital gyrus. |
| Massou et al., 1997 [42] | 6 patients<br>20–57 years old<br>Major depression<br>8 control depressed patients | Between subjects: Treated depressed patients vs. untreated depressed patients.<br>Protocol: Patients were scanned during SSRI treatment. Controls are scanned after at least 5 weeks of no treatment.<br>PET<br>[18F]-setoperone<br>Quantitative | ROI | The mean frontal/cerebellar ratios tended to be higher in treated than untreated patients.<br>Increase in frontal [18F]-setoperone specific binding in treated patients compared to untreated depressed patients. |

**TABLE 2** Continued

| Author/date | Subjects | Method | Analysis | Results |
|---|---|---|---|---|
| **B. Dopamine system** | | | | |
| Klimke et al., 1999 [45] | 15 patients<br>29–71 years old<br>Major depression<br>Patients do not sufficiently respond to treatment with standard tricyclics<br>17 normal controls | Pre- and post–6-week SSRI treatment.<br>Patients vs. normal controls.<br>Protocol: Scan pre- and post–6-weeks of treatment with a SSRI; 13 patients received 0.3–0.7 mg/kg of paroxetine per day and 2 patients received 0.4–0.8 mg/kg of fluoxetine per day.<br>SPECT<br>[123I]-IBZM<br>Semiquantitative | ROI | Responders had a lower baseline D2 receptor availability compared to either nonresponders or control subjects.<br>With treatment, D2 receptor availability increased in responders and decreased in nonresponders. |
| Ebert et al., 1994 [44] | 10 patients (5 TSD responders and 5 nonresponders)<br>Mean age of 33.4<br>Bipolar II course with at least one previous major depressive episode and one hypomanic episode<br>5 controls (not healthy volunteers)<br>Mean age 34.8 | Between subject: Patient vs. control.<br>Protocol: Patients were studied with IBZM SPECT scans after a night of normal sleep and again after all-night sleep deprivation. Controls are studied only once after a night of normal sleep.<br>SPECT<br>[123I]IBZM<br>Semiquantitative | ROI | TSD responders show a significant decrease in striatal D2 receptor availability compared to nonresponders. |

**C. Glucose metabolism/cerebral blood flow studies**

| | | | | |
|---|---|---|---|---|
| Martin et al., 2001 [52] | 28 patients<br>30–53 years old<br>Major depressive episode | Within subject: Pre- and post-treatment.<br>Between subjects: Patients treated with venlafaxine or IPT.<br>Protocol: After baseline scan, patients are assigned to different treatments; 13 patients had 1-h weekly sessions of IPT; 15 patients had 37.5 mg twice daily dose of venlafaxine. Scans repeated after 6 weeks of treatment.<br>SPECT<br>[99Tc]-HMPAO<br>Semiquantitative | SPM | Venlafaxine group showed right posterior temporal and right basal ganglia activation, while the IPT group had limbic right posterior cingulate and right basal ganglia activation. |
| Brody et al., 2001 [49] | 24 patients<br>Major depressive disorder<br>Average age 38.9<br>Treated with paroxetin or interpersonal psychotherapy (based on patient preference)<br>16 normal controls<br>Average age 35 | Within subject: Pre- and post-treatment.<br>Between subjects: Normal controls vs. patients.<br>Protocol: Patients scanned before and after 6 weeks of treatment with either paroxetine or interpersonal psychotherapy (based on patient preference).<br>PET<br>[18F]-FDG<br>Semiquantitative | SPM and ROI | Before treatment patients had higher normalized metabolism than controls in the prefrontal cortex and lower metabolism in the temporal lobe. After treatment they showed metabolic changes in the direction of normalization. |

**TABLE 2** Continued

| Author/date | Subjects | Method | Analysis | Results |
|---|---|---|---|---|
| Kennedy et al., 2001 [50] | 13 male patients<br>24–58 years old<br>Major depressive disorder<br>24 male controls<br>Mean age 31.7 years | Within subject: Pre- and post-treatment.<br>Between subject: Depressed patients and normal controls.<br>Scans performed pretreatment and then after a mean of 42 days of paroxetine therapy.<br>Protocol: PET scans performed before and after 6 weeks of paroxetine treatment.<br>PET<br>[18F]-FDG<br>Semiquantitative | SPM | Increased glucose metabolism in prefrontal cortex, parietal cortex, and dorsal anterior cingulate. Decreased metabolism in anterior and posterior insular regions, hippocampal and parahippocampal regions.<br>More regions in left hemisphere showed increased activity and more regions on the right displayed decreased activity. |
| Mayberg et al., 2000 [48] | 17 male patients<br>Mean age 49<br>Unipolar depression | Within subject: Pre- and post-treatment.<br>Protocol: Baseline PET scan; antidepressant treatment initiated; second PET scan at end of first week; third PET scan at end of 6-week treatment course. Treatment is randomized to either fluoxetine or a placebo.<br>PET<br>[18F]-FDG<br>Semiquantitative | ROI | At 1 week, increases were observed in hippocampus, medial temporal and putamen and decreases in posterior cingulate, a reverse of this effect was observed at 6 weeks.<br>Sustained changes from one to 6 weeks; increases were observed in pons, premotor cortex and inferior parietal decreases in medial thalamus, insula, parahippocampal gyrus, cerebellum.<br>At 6 weeks, increases in anterior cingulate, prefrontal and decrease in subgenual cingulate cortex. |

| | | | | |
|---|---|---|---|---|
| Nobler et al., 2000 [53] | 20 patients<br>Mean age 67.8<br>Major depressive episode<br>20 normal controls<br>Mean age 67.3 | Within subject: Pre- and post-treatment.<br>Between subjects: Patients vs. controls.<br>Protocol: Patients are treated with either nortriptyline or sertraline. Resting regional cerebral blood flow is assessed by the xenon-133 inhalation technique after a medication washout and following 6 to 9 weeks of antidepressant treatment.<br>Novo cerebrograph<br>Xenon 133<br>Quantitative | ROI | At baseline, the depressed patients had reduced rCBF in frontal cortical regions.<br>After treatment, responders show reduced rCBF in frontal regions. |
| Buchsbaum et al., 1996 [51] | 17 patients<br>Mean age 38.5<br>Major affective disorder<br>Meet criteria for major depression<br>28 healthy volunteers<br>Mean age 27.7 | Within subject: Pre- and post-treatment.<br>Protocol: Patients are scanned before and after 10 weeks of treatment with sertraline or a placebo.<br>PET<br>[18F]-FDG<br>Quantitative | ROI | Increased metabolic activity in middle frontal gyrus, right parietal lobe and in left occipital area after sertraline treatment.<br>Decrease in right occipital area. |

deprivation (TSD) and antidepressant treatment have been reported that distinguish responders from nonresponders [44,45]. An increase in striatal and anterior cingulate D2 receptor binding in responders and a decrease in nonresponders after SSRI treatment has been observed in two studies [45,46]. In a study of the effects of total sleep deprivation, Ebert et al. [46] reported a decrease in striatal D2 binding in responders compared to nonresponders. These discrepant findings may be attributable to the fact that acute (TSD) compared to chronic treatment effects were evaluated and also to the fact that TSD has multiple neurochemical effects—as reviewed in Smith et al. [29]. Thus, the net effect on the dopamine system of TSD compared to antidepressant treatment may be different. Also, the acute TSD effect may be different from the effects of chronic treatment. Thus, based on neuroimaging studies, there is some suggestion of dopaminergic dysfunction in depressed patients and some indication that alterations in dopamine function may be related to treatment response.

### 7.2 Cerebral Glucose Metabolism/rCBF Studies

Several studies have examined the effects of SSRI treatment on cerebral metabolism/perfusion/rCBF, as shown in Table 2, part B. The course of the cerebral metabolic effects of fluoxetine treatment was evaluated by Mayberg et al. [48]. The investigators observed sustained changes over time in terms of an increase in pons–rostral brainstem, premotor, and inferior parietal cortices and a decrease in caudate, medial thalamus, insula, parahippocampal gyrus, and cerebellum. The initial increase in hippocampus, medial temporal cortex, and putamen and decrease in posterior cingulate demonstrated a reversal of the direct effect at 6 weeks. The changes that occurred later in treatment included increases in anterior cingulate and ventral and dorsal prefrontal cortex and decreases in subgenual cingulate cortices. Treatment resistance was associated with a persistence of the changes observed after 1 week of treatment and the absence of change in prefrontal and subgenual cingulate cortices. The treatment responders showed increased metabolism in the right dorsal anterior cingulate and dorsal prefrontal and bilateral inferior parietal cortices and decreases in bilateral insulan and right subgenual anterior cingulate. The investigators concluded that the inability to demonstrate adaptive changes over the course of treatment might underlie the inability to respond to treatment. Given the effects of fluoxetine on several monoamine systems (serotonin, dopamine, and norepinephrine), it would be of interest to observe how these metabolic alterations relate to the time course of alterations in these neurochemical systems.

In a treatment study with paroxetine, Brody et al. [49] demonstrated similar decreases in metabolism in the insula, hippocampus, and parahip-

pocampal gyrus and increases in prefrontal, parietal, and anterior cingulate cortices, as observed by Mayberg et al. [48]. The results of the paroxetine treatment study by Kennedy et al. [50] were consistent with the findings of Mayberg et al. [48]. In the study by Kennedy et al. [50], efforts were made to control for gender (only males were studied), type of treatment, and concomitant medications The investigators commented that increases in metabolism with SSRI treatment were observed in the left hemisphere, whereas decreases were observed in the right hemisphere. We have observed a similar laterality of findings in our studies of the acute effects of citalopram on cerebral glucose metabolism. Finally, sertraline treatment was also shown to be associated with increased metabolism in frontal and parietal cortices [51].

Several studies have been conducted to examine the neurometabolic effects of other classes of antidepressants and psychotherapy. A study with the mixed serotoninergic/noradrenergic reuptake inhibitor venlafaxine demonstrated an increase in cerebral perfusion in the right posterior temporal and right basal ganglia [52]. In the same report, interpersonal therapy was shown to produce an increase in perfusion in the right basal ganglia in addition to the right posterior cingulate cortex. In another study that investigated the effects of interpersonal therapy compared to medication (paroxetine), Brody et al. [49] reported a normalization of baseline hypermetabolism in prefrontal cortex and anterior cingulate gyrus and an increase of baseline hypometabolism in the left temporal cortex. The differences in the direction of the effect across these studies suggests that the direction of change in perfusion/metabolism after treatment may be related to whether the patients have increased or decreased brain function compared to controls at baseline. It is interesting that the effects of interpersonal therapy on brain function are comparable to those of medication in the Brody et al. [49] study. The investigation of the effects of different forms of psychotherapy on brain function is an understudied and important area of investigation.

Few studies have been conducted in late-life depressed patients. In elderly depressed patients, Nobler [52] observed a decrease in frontal cortex rCBF at baseline and a further reduction in frontal rCBF after treatment with either sertraline or nortriptyline. In our studies using PET studies of cerebral glucose metabolism to evaluate the functional neuroanatomy of total sleep deprivation and antidepressant treatment, we have observed increased cortical metabolism at baseline and a predominant pattern of reductions in metabolism after TSD and paroxetine treatment [47,53,54]. These discrepant findings indicate that such issues as the coupling between flow and metabolism and potentially greater clinical and further neurobiological heterogeneity in late-life depressed patients must be evaluated (due to factors such as early versus late illness onset, antidepressant treatment history, comorbid

medical and psychiatric conditions, comorbid medications, cognitive impairment, cerebrovascular disease, age-related alterations in monoamine systems, and cerebral atrophy). The discrepancies between these studies are another example of how baseline brain function in the patients may determine the direction of the treatment effect.

### 7.3 Future Directions

A logical future direction for neuroimaging studies of antidepressant treatment effects is whether the difference between treatment responders and nonresponders can be attributed to differential occupancy of the serotonin transporter. Similar to the situation for the antipsychotic agents [55], it is not clear if there is a therapeutic window of serotonin transporter occupancy at which a therapeutic response is observed. Due to difficulties in radiotracer development and quantitating serotonin transporter binding, such studies have only recently become feasible. Other potentially relevant neuroreceptor imaging studies include the examination of the time course of effects of the SSRIs on serotonin and dopamine transporter and receptor binding. The recent availability of high-affinity D2 radiotracers to image extrastriatal sites, as well as improved D1 radiotracers, would provide a more comprehensive characterization of the effects of treatment on the dopamine system [56,57]. Additional neuromodulatory systems that would be of interest include the noradrenergic system, opiates, and second-messenger systems (e.g., arachidonic acid metabolism, phosphoinositide turnover). In addition, preclinical studies have shown that SSRI treatment induces the expression of trophic factors in the brain—e.g., brain-derived neurotrophic factor [58]. It would be extremely interesting to be able to visualize the primary or secondary effects of the expression of these trophic factors. Such in vivo studies would potentially enable us to understand the neurochemical cascade of events that may account for the delayed onset of antidepressant effects. The effects of other antidepressant intervention on such measures such as repetitive transcranial magnetic stimulation, total sleep deprivation, and forms of psychotherapy would be informative, as well.

As pointed out in the discussion, a systematic assessment of the time course of cerebral metabolic effects of different classes of antidepressant medications is important, particularly controlling for gender effects and comorbid medications. A rigorous comparison of treatment responders and nonresponders and a consideration of treatment-naïve compared to previously medicated subjects would also be informative. It is important to evaluate whether the functional neuroanatomy of the remission of depressive symptoms is similar across treatment modalities or whether treatment-specific neuroanatomical changes are observed.

## 8 NEUROIMAGING STUDIES OF ECT

A summary of the studies concerning the effects of ECT on cerebral function is presented in Table 3. With several exceptions, the majority of studies, performed across several functional imaging modalities and in both unipolar and bipolar depressed patients, have demonstrated that ECT induces both global and focal reductions in cortical glucose metabolism and blood flow/perfusion. The studies that have reported no change in cerebral function were studies that either measured the effects of unilateral ECT only [59] or evaluated a mixed group of treatment responders and nonresponders [60]. The results using region of interest (ROI) or statistical parametric mapping (SPM) analysis methods revealed relatively consistent results. Reductions in cerebral function were noted most consistently in the frontal cortex, bilaterally (superior, dorsolateral, and prefrontal regions) [61–63]. Decreased frontal lobe perfusion after a course of bilateral ECT was also reported in patients with bipolar disorder who also had psychotic symptoms [64]. Other regions that have demonstrated reductions in metabolism/flow/perfusion after a course of bilateral ECT treatment include left inferior and medial temporal cortices and the parietal cortex (some studies reporting bilateral changes and some reporting left hemisphere changes). It is interesting to note that only two studies have reported reductions in cerebral function in aspects of the cingulate gyrus—anterior cingulate gyrus [61] and posterior cingulate gyrus [65]—in contrast to studies of antidepressant medication effects on cerebral function in which the cingulate gyrus has been consistently implicated. This may be attributable to the fact that the majority of medication studies have used PET technology that has relatively better spatial resolution than SPECT or rCBF methods. The one study that examined the acute effects after a single bilateral ECT treatment reported reduced radiotracer uptake in the inferior anterior cingulate cortex [65]. Another study observed changes in the cingulate after a course of ECT [61]. This indicates that there may be a temporal course for the effects of ECT on cerebral function in the cingulate gyrus. Finally, increased metabolism in the occipital cortex was reported after a course of ECT treatment in one study but not in an earlier study with a relatively smaller sample size [61,63].

### 8.1 Summary and Future Directions

There are number of implications of the studies described in this section. Despite significant clinical and methodological differences across studies, the findings are remarkably consistent. These studies highlight several important points with respect to data analysis and interpretation. Since the majority of studies are limited by a small sample size, it is difficult to compare the effects of treatment responders to that of nonresponders. Most stud-

**TABLE 3** Summary of Studies Designed to Examine the Effects of Electroconvulsive Therapy on Cerebral Glucose Metabolism and Cerebral Perfusion

| Author/date | Subjects | Method | Analysis | Results |
|---|---|---|---|---|
| Nobler et al., 2001 [61] | 10 patients<br>Mean age 45.5<br>Depression (unipolar and bipolar | Within-patient comparison: Pre- and posttreatment.<br>Protocol: Patients are scanned before and 5 days after a course of bilateral ECT. All patients are medication-free for at least 2 weeks before treatment.<br>PET<br>[18F]-FDG<br>Semiquantitative | SPM and ROI | Decreased glucose metabolism in the bilateral superior frontal lobe, dorsolateral and prefrontal cortices, parietal cortex, posterior cingulate gyrus, left medial temporal lobe and the left inferior temporal lobe.<br>Significant increases in occipital cortex. |
| Henry et al., 2000 [62] | 6 patients<br>Age 30–53<br>Depression (unipolar and bipolar) | Within patients: Pre- and posttreatment.<br>Protocol: Patients are scanned pre- and post–bilateral ECT treatment. All patients are medication-free at time of study.<br>PET<br>[18F]-FDG<br>Quantitative | ROI and SPM | Significant decreases in the right parietal region, right anterior frontal region and left posterior frontal region. |
| Milo et al., 2000 [60] | 15 patients<br>Age 25–77; mean age of 54 years<br>Major depression<br>11 normal controls<br>Age 21–51 years | Within subject: Pre- and posttreatment and between subject: patients vs. controls.<br>Protocol: Patients are scanned 2–3 days before and 4 days after a mean of 9.3 bilateral ECT treatments. All patients are medication-free for 5–7 days before treatment. | ROI | Patients had significantly higher count densities than controls in the left and right inferior frontal subregions and the right anterior temporal cortex.<br>No changes within patients from pre- and posttreatment. |

| | | | | |
|---|---|---|---|---|
| Nobler et al., 1994 [53] | 68 depressed patients<br>Mean age 56.8<br>Major depression<br>10 manic patients<br>Mean age 36<br>Bipolar disorder | SPECT<br>$^{99m}$Tc HMPAO<br>Nonquantitative<br>Within subjects: Pre- and posttreatment.<br>Protocol: Measure CBF 30 min before and 50 min after a single treatment of ECT and during the week following ECT. Some patients undergo unilateral ECT while others receive bilateral ECT. All patients are medication-free.<br>Novo cerebrograph<br>Xenon-133 technique | ROI (analyses of covariance) | Depressed patients showed higher $P_{CO_2}$ values after treatment and decreased global CBF. |
| Scott et al., 1993 [65] | 15 patients<br>Age 50–74<br>Major depression | Within patients: Pre- and posttreatment.<br>Protocol: Patients are scanned before and 45 min after a single bilateral ECT treatment. All patients are medicated at time of study.<br>$^{99m}$Tc Exametazime<br>Nonquantitative | ROI | Decreased tracer uptake in the inferior anterior cingulate cortex.<br>Reductions also seen in the caudate and putamen bilaterally but these did not reach statistical significance. |

**TABLE 3** Continued

| Author/date | Subjects | Method | Analysis | Results |
|---|---|---|---|---|
| | | SPECT<br>$^{99m}$Tc Exametazime<br>Semiquantitative | | |
| Guze et al., 1991 [59] | 4 patients<br>Age 19–51<br>Bipolar depression | Within patients: Pre- and posttreatment.<br>Protocol: Patients undergo a scan before a course of right unilateral ECT and again immediately after it. Two of the patients were unmedicated through course of treatment.<br>PET<br>[18F]-FDG<br>Quantitative | ROI | No change in glucose metabolism in the middle frontal gyri or the parahippocampal gyrus. |
| Rosenberg et al., 1988 [64] | 10 patients<br>Age 29–72<br>Manic-depressive psychosis, endogenous type<br>10 healthy volunteers | Within patient: Before, during, and after treatment.<br>Protocol: Patients are scanned 2 days before the first bilateral ECT treatment, after the third treatment, and then again after the final treatment. Eight patients had taken medication during ECT treatment.<br>SPECT<br>Xenon-133 inhalation<br>Semiquantitative | ROI | Frontal/occipital ratio decreased with treatment.<br>Hemispheric CBF values decrease with treatment. |

| | | | | |
|---|---|---|---|---|
| Volkow et al., 1988 [63] | 4 patients<br>71–84 years old<br>Unipolar depression | Within patients: Pre- and posttreatment.<br>Protocol: Patients scanned before bilateral ECT treatment and again 24 hr after its completion. All patients are medication-free for at least 8 days before treatment.<br>PET<br>15O-water and [18F]-FDG<br>Semiquantitative | ROI | Decreased glucose metabolism in the left and right frontal cortex.<br>No change in glucose metabolism in occipital cortex.<br>Two patients showed decreased CBF in the frontal cortex and one showed an increase; latter underwent fewest treatments. |

ies include patients with either a unipolar or bipolar diagnosis who are scanned in the depressed state. It would be of interest to evaluate whether there are differences in cerebral function with ECT between the two diagnostic subgroups. Since ECT induces global alterations in cerebral metabolism and blood flow, the procedures for normalization of the data must be considered carefully, and it might be more instructive for investigators to present absolute as well as normal values. Another extremely interesting and potentially clinically meaningful issue is the time course of effects of ECT on cerebral function and whether the acute effects after a single or several treatments represent a biological marker of subsequent treatment response. In addition, the evaluation of the baseline neuroimaging data with respect to predictors of treatment outcome may also be important. Finally, conceptually similar to the approach that we have used to evaluate the effects of TSD on cerebral metabolism [47], it would be interesting to evaluate the time course of the resolution of subtypes of clinical symptoms relative to the specific neural networks that might be related to the symptom expression.

In reviewing the literature concerning the effects of ECT on cerebral function, there appears to be limited data available concerning the in vivo neurochemical effects of ECT. Using MR spectroscopy, investigators have demonstrated increased GABA concentrations in the occipital cortex after ECT [66]. MRS methods represent a unique opportunity to examine the time course of alterations in amino acid neurotransmitter over the course of ECT. Because the MRS method does not involve exposure to radiation, the time course of effects can be more rigorously evaluated compared to studies using PET and SPECT methods. However, the monoamine neurotransmitters cannot be imaged with MRS due to the relatively low concentration of these substances in the brain; thus PET and SPECT methods must be used. An important future direction for neuroimaging research in ECT is to evaluate the acute and chronic effects on such parameters as monoamine metabolism and transporter and receptor availability using radiotracers that are available to image these potentially relevant sites.

## 9 SUMMARY

Given the potential clinical and methodological differences across studies, there is a remarkable degree of convergence across studies with respect to the changes in brain function secondary to antidepressant treatment.

The acute intervention studies performed thus far demonstrate some evidence for a blunted serotonergic response in depressed patients and a greater responsiveness of the serotonin system in depressed patients using the tryptophan depletion paradigm [24–26]. However, endogenous dopamine concentrations are not altered in depressed patients compared to con-

trols [29]. The combination of mood induction paradigms and neuroimaging has provided important information into the functional neuroanatomy of mood states in normal controls and depressed patients [32]. Acute intervention methods performed in the context of a clinical trial may be very useful in developing early biologic markers of treatment outcome. This is the goal of the acute intervention studies that we are conducting with citalopram and total sleep deprivation.

In regard to neuroreceptor imaging, the studies cited in this review show reductions in 5-HT2A binding (although there are some exceptions as discussed) and 5-HT1A binding with antidepressant treatment (primarily the SSRIs). The regional localization of these changes in 5-HT2A and 1A binding are diffuse, some studies showing greater alterations in frontal compared to other cortical areas, and there are no systematic laterality effects observed across studies. For the dopamine system, increased striatal D2 binding is observed in treatment responders and decreased binding in nonresponders.

Neuroimaging studies of ECT effects consistently demonstrate reductions in perfusion/metabolism with ECT. Acutely, decreased perfusion in the anterior cingulate gyrus is observed. After chronic treatment, reductions are consistently observed in aspects of the frontal (superior, inferior, and dorsolateral prefrontal), temporal (anterior, inferior, and medial) and parietal (precuneus) cortices. In regard to the laterality of the effects, the findings are not consistent across studies.

Regarding medication and psychotherapy studies, increases in metabolism in anterior cingulate, prefrontal, premotor, and parietal (inferior parietal) cortices are fairly consistently reported, in contrast to decreases in insula, hippocampus, thalamus and cerebellum. The increases in cortical metabolism are in contrast to the findings of ECT and TSD studies in which cortical metabolism is decreased. The most likely explanation of these contradictory findings would involve different mechanisms of action and magnitudes of neurochemical effects. Both ECT and TSD produce multiple neurochemical effects acutely and these effects may be relatively greater in magnitude compared to medications (particularly the SSRIs) that have a relatively selective mechanism of action and a lesser magnitude of neurochemical effects. A common finding across all of these treatment is the reduction in metabolism in limbic-paralimbic regions. Thus, the remission of depressive symptoms across treatments may be related to a reduction in limbic-paralimbic metabolism and the cortical changes may reflect another adaptive process.

These neurometabolic data, in addition to preclinical and postmortem neurochemical studies were integrated to develop a functional neuroanatomic model of antidepressant effects [32,48,66,67]). In summary, increased metabolism is observed in dorsal structures and decreased metabolism in

ventral structures. Cortical increases in metabolism are observed in the anterior and posterior cingulate and dorsolateral prefrontal, premotor, and parietal cortices and the posterior insula as well as subcortical structures including the pons. Limbic-paralimbic reductions in metabolism are observed in the subgenual cingulate, hypothalamus, anterior insula, hippocampus, and parahippocampal gyrus/medial temporal cortex. Reductions are also observed in subcortical structures including the basal ganglia and thalamus.

Although not systematically observed across studies, Kennedy et al. [50] observed increased metabolism in the left and decreased metabolism in the right hemisphere. As mentioned previously, we have observed a similar laterality in our studies of the acute effects of citalopram on cerebral glucose metabolism. Both neuroimaging studies of the 5-HT2A receptor in stroke patients and animal models of brain injury have shown that greater changes in binding are observed after damage to the right hemisphere [68,69]. These findings may indicate that the compensatory ability of the serotonin system is different across hemispheres.

Finally, Mayberg et al. [48] note that "the metabolic change pattern seen in responders is not merely the correction of pretreatment abnormalities, but rather a more complex combination of effects involving both normalization of cortical hypometabolism and new adaptive changes in certain specific subcortical and paralimbic regions without previous metabolic anomalies." Thus, antidepressant treatment may induce changes in functional connectivity across brain regions rather than simply making the depressed brain function like the normal brain. This issue underscores the importance of applying network modeling approaches to understanding the changes in brain function with antidepressant treatment and also the importance of incorporating knowledge from basic neuroanatomical and neurochemical methods into data interpretation.

## 10 FUTURE DIRECTIONS

Neuroimaging studies of antidepressant treatment effects in major depression have demonstrated alterations in functional neuroanatomy and neurochemistry with treatment and some differences have been reported in treatment responders compared to nonresponders. As indicated in the discussion, the discrepancies across studies may be attributable in part to the composition of treatment groups comprising responders and nonresponders. However, it is difficult to make such comparisons without relatively large samples of subjects.

The integration of other neurobiological measures into the neuroimaging studies could be potentially informative. The measurement of specific genetic polymorphisms may help to account for some of the variability in

the responsiveness of monoamine systems. For example, the short form of the serotonin transporter promoter has been associated with a slower rate of treatment response [70]. Thus, the short form of the allele may be associated with decreased serotonin responsiveness as evidenced by a blunted cerebral metabolic response to the SSRI. Plasma levels of the drug evaluated as well as neuroendocrine measures (cortisol, prolactin, growth hormone, for example) are measures independent of the neuroimaging studies that may also explain the variability in response.

Neuroimaging studies of treatment effects in other types of affective disorders would be extremely informative. Some important areas include bipolar disorders (characterization of the effects of lithium, anticonvulsants, and other mood stabilizers) as well as the mechanism of action of olanzapine in treatment refractory depression [71] and bereavement-related depression (comparing individuals who have had a bereavement experience who develop depression to those who do not develop depression).

An understudied area is that of late-life depression. For example, the integration of functional and structural imaging approaches represents a unique opportunity to understand the neurochemical consequences of cerebrovascular disease on depression. The depression-dementia continuum is another opportunity to incorporate structural and functional neuroimaging techniques—for example, to examine the neurochemical concomitants of hippocampal atrophy.

In regard to understudied treatment modalities, mood stabilizers (including anticonvulsants and lithium) have not been the focus of many neuroimaging studies. Nor have nonpharmacological treatments such as total sleep deprivation, psychotherapy and rTMS been extensively studied. Some studies have been conducted that may have implications for antidepressant augmentation strategies such as total sleep deprivation [47], estrogen [72], stimulant—e.g., methylphenidate [73]—and pindolol [74]. Neuroimaging characterization of potential augmentation strategies may be very informative.

In conclusion, functional imaging studies, particularly PET scanning, have been incorporated into clinical trials and have begun to provide new insights into the functional neuroanatomy of treatment response and the mechanism of action of antidepressant medication. There are numerous exciting future applications of this approach such as the incorporation of structural and functional imaging methods, the use of new radiotracers that have been developed for potential treatment targets, and the extension of this approach to a greater extent to other patient groups (e.g., bipolar disorder, geriatric depression) and other forms of treatment (TSD, psychotherapy). The application of neuroimaging methods in this manner will further our knowledge regarding the neurobiology of treatment resistance and will in-

form the development of more effective antidepressant agents and adjunctive treatments.

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# 12

# Human Brain Imaging in the Development of Psychotropics: Focus on Affective and Anxiety Disorders

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## 1 INTRODUCTION

The development of human brain imaging in the last decade has resulted in a number of techniques that allow unprecedented insights into the in vivo metabolic and neurochemical processes of the brain. Some of these techniques are now mature, while others are at earlier stages of development. Perhaps surprisingly, these tools have been used sparingly by the pharmaceutical industry in the discovery and development of new psychotropics. There are a number of reasons for this:

- The robustness of the techniques is sometimes questioned. This concern has been reinforced by the equivocal methodology employed by some of the researchers in the field.
- There is a paucity of suitable radioligands that can be used to investigate binding in vivo at new as well as traditional targets.
- Some of the parameters generated are measures that need cross validation with more traditional in vitro or ex vivo measures.
- The investment, both capital and revenue, needed in the technology is seen as very expensive.

The economic advantages of using human imaging in the processes of drug development and discovery are as yet not quantified.
At present plans for imaging are often made at the beginning of the human phase of development, when the traditional philosophy of the pharmaceutical industry becomes dominated by concerns over regulatory issues and by reluctance to generate additional information unless required to do so.

This chapter explores the possible uses of imaging in the discovery and development of psychotropics for affective and anxiety disorders, giving existing examples where pertinent. Three areas germane to the discussion are discussed first:

A brief review of the imaging techniques available and of what they measure
A brief introduction to the necessary steps in drug discovery and development in order to define a new molecule as a potential psychotropic
The steps of drug discovery and development that can be aided by human imaging

Each step that can be aided by imaging is then discussed in detail. Finally, the chapter examines the organization steps necessary to implement these strategies in the future.

## 2 IMAGING TECHNIQUES

There are three families of techniques that can be used: magnetic resonance imaging (MRI); radionuclide tomography, such as single photon emission computed tomography (SPECT) and positron emission tomography (PET); and recordings of brain electrical activity such as electroencephalography mapping and magnetoencephalography. The last of these is not discussed in this chapter.

### 2.1 MRI

The principles of MRI are as follows:

A powerful magnetic field aligns all magnetic nuclei (in most cases water) parallel or antiparallel to the magnetic field.
Aligned nuclei are excited by radiofrequency pulse protocols that are spatially varied in order to provide spatial resolution.

Radio waves are turned off.
Signals are emitted from the brain.
Signals are received, recorded, and reconstructed to obtain a map, spectrum, or picture.

MRI can be used to

Obtain anatomical information, in particular to separate white and gray matter, assess ventricular volume, and detect areas of abnormal signal intensity, as in demyelination.
Measure diffusion of molecules in the tissue.
Assess changes in regional brain perfusion. Exogenous contrasts can be used, such as gadolinium, but the most powerful technique has been the detection of changes in deoxyhemoglobin concentration that occur with activation or deactivation of brain regions. This removes the need for an exogenous contrast agent and therefore can be potentially repeated hundreds of times.
Measure blood flow to an area. This can be done by injecting a contrast agent or by the technique of arterial spin labeling (ASL), whereby endogenous protons in the vasculature are excited when in transit through the neck arteries.
Measure concentrations of diamagnetic naturally occurring molecules in the brain, such as GABA, lactate, *N*-acetyl aspartate and choline. These can provide indices of neuronal or glial integrity and of metabolic or pharmacological processes.
Measure the concentration of exogenous diamagnetic molecules such as fluorinated pharmacological agents (e.g., fluoxetine).
Map white matter tracts within the brain.

All these functions can be used for central nervous system (CNS) drug development, with perfusion and spectroscopic measurement being most relevant for psychotropics.

## 2.2 Single Photon Emission Tomography (SPECT) or Positron Emission Tomography (PET)

The principles of radionuclide tomography are as follows:

A suitable ligand is labeled with a photon- or a positron-emitting nucleus.
The radioligand is injected.
The signal from the decay of the radioactive nuclei is detected from the tissues of interest with an appropriate camera. The signal is the

sum of radioactivity in the volume of interest over the time frame of acquisition.

A suitable model is applied to the recorded data in order to generate parameters of interest, such as metabolism, receptor density, or enzyme concentration.

These techniques can measure perfusion, blood flow, regional glucose or glucose analog transport, receptor density, transport of neurotransmitter precursors—such as fluorodopa and $\alpha$-methyl tryptophan, reuptake site density and function, and neurotransmitter release.

The methodology for many of these techniques needs to be rigorous. This is because the recorded signal is made up of various components such as bound and free radioligand metabolite in blood, labeled metabolites (if present), radioligand in interstitial fluid in the tissue, and specifically and nonspecifically bound radioligand. However unlike ex vivo or in vitro experiments the tissue cannot be treated or washed in order to eliminate the unwanted signals. Hence appropriate models have to be constructed to dismantle the total signal in its components (Fig. 1). If any of the assumptions

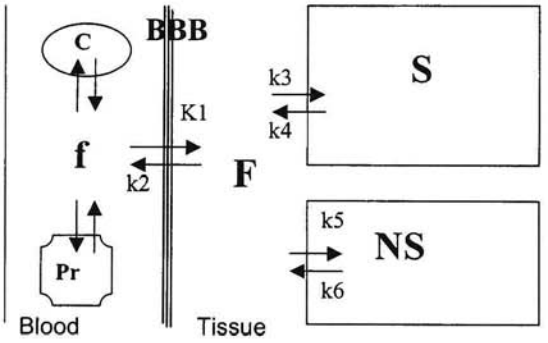


**FIGURE 1** Signal constituents for each brain voxel and rate constants relating "compartments." BBB, blood brain barrier; C, cells; Pr, proteins; F, free radioligand in tissue; S, specifically bound radioligand in tissue; NS, nonspecifically bound radioligand in tissue; f, unbound radioligand in blood. K1/k2 represents the equilibrium from plasma to brain, and k3/k4 represents the specific binding equilibrium whereby k3 = $k_{on}$. $B_{max}$ and k4 is $k_{off}$. k5/k6 represents the equilibrium with nonspecific binding in the brain.

on which the modeling relies are violated, then the signal becomes uninterpretable. A few important examples include

- Ensuring that only tracer quantities of ligand are injected so that significant occupancy is not achieved. In practice, occupancy above 1–5% significantly violates the assumptions necessary for tracer kinetics and the equations used for modeling become invalid.
- Scanning at appropriate times or with appropriate reference data to allow separation of delivery of the ligand to the tissue from binding within the tissue. This has often not been achieved in SPECT studies, where scanning may be performed too early after injection of radioligand, thus invalidating the assumption that comparisons reveal differences in binding density [1].
- Ensuring that labeled metabolites do not bind to the tissue and are measured in the plasma. The presence of radiolabeled metabolites in the tissue of interest invalidates many types of modeling, as in the difference between the different o-methyl and carbonyl label positions for [$^{11}$C]WAY 100635, a 5HT1A receptor PET radioligand [2].
- Ascertaining that the reference area and model used are apposite for the binding characteristics of the radioligand employed [3–5].

## 3 DISCOVERING AND DEVELOPING A PSYCHOTROPIC

Traditional discovery and development started from existing knowledge about neurotransmitters or brain receptors. Molecules would be developed that bound to the known receptors and function would be determined in vitro and then through behavioral pharmacology using models appropriate to the disease areas. Psychotropics have always been more difficult to develop because adequate animal models, based on the effects of known effective medicines, have little predictive validity. This is so because, while the effects of a sudden or progressive occlusion of brain vasculature or of progressive degeneration of a particular subcortical structure can be mimicked in experimental animals, anxiety disorders, affective disorders and schizophrenia cannot be simulated. The process for psychotropics has led to a number of seemingly false starts, such as 5HT3 antagonists, which were at one time touted as treatments for many psychiatric conditions, from anxiety to schizophrenia. Reliance on inappropriate behavioral tests of activity, such as the motor effects of a dopamine D2 antagonist in the basal ganglia as predictors of antipsychotic activity, also has its problems; it is of interest that if clozapine had been discovered 5 to 10 years later, it would have been

rejected as a potential antipsychotic because of its poor performance on such tests. Since brain imaging has a clear role in the investigation of the relationship between known brain chemistry and pathological states, an understanding of the detail of the pharmacokinetic and pharmacodynamic effects of medicines directly on human brain disease is likely to be very helpful in providing valid measures of psychotropic drug activity in decreasing traditional development time as well as providing leads of new applications in particular disease areas.

Contemporary drug discovery has, at least in significant part, moved away from known neurochemical systems, as targets often evolve from genomic leads based on the code sequence and the likely structure of the resulting proteins. Over two-thirds of brain protein is as yet undiscovered, and new receptors can now be assembled in the laboratory directly from the genetic code. Initially, the anatomy of expression of these receptors will be unknown, but even identification in particular brain structures does not predict function or probable therapeutic action. Yet this is often all the information that is available, and the shape of the total behavioral pharmacology package employed is influenced by considering whether the receptor of interest is distributed in particular locations such as, for example, the limbic system. Thus the current situation is that through genomics, combinatorial chemistry, and high-throughput screening, series of molecules are discovered that have high affinity for a particular type of receptor but whose function is completely unknown at system and sometimes lower levels. Human genomic mapping, when complete, may come to the rescue in this area, as the associations between polymorphisms and particular disorders are discovered. However, so far, these associations account for only a small percentage of the variance and cannot take account of the ontogenetic and environmental factors that are thought to be so important in the etiology and maintenance of psychiatric disorders. Brain imaging, on the other hand, is one of the tools operating at the posttranslational level, thus allowing the investigation of brain chemistry and new targets in vivo as shaped by environmental as well as genetic factors as well as the investigation of changes linked with disease, not only of predisposing factors.

In both the above models of discovery, early predictors of the path of development are essential. The function of such markers is to strengthen the odds of commercial success for particular molecules, so that resource can be channeled effectively. Brain imaging, in particular in humans, is one of these tools, as it has the potential to allow early discovery of target variation in disease at a time when the development course of a particular molecule can be influenced. Further, brain imaging can investigate a number of important areas for drug development, where more accurate information should

lead to more informed decisions in the development process. This is discussed below.

## 4 STEPS OF DRUG DISCOVERY AND DEVELOPMENT THAT CAN BE AIDED BY HUMAN IMAGING

The information that can be obtained by imaging comprises the following:

Brain penetration
Body distribution
Tissue kinetics
Targets distribution and density in health and in disease
Occupancy
Pharmacokinetic/pharmacodynamic (PK/PD) parameters
Pharmacodynamic effects
Measures of disease process modification

The first four types of information can be obtained *before* the first administration of pharmacological doses of the compound in development provided that a suitable radiolabeled form of the molecule has been synthesized.

### 4.1 Brain Penetration

Brain entry is a necessary prerequisite for psychotropic action. Most of the molecules recently synthesized by combinatorial chemistry are lipophilic and therefore likely to cross the blood-brain barrier. However, this step cannot be assumed. Further, many molecules are actively extruded from the brain by p-glycoproteins [6]; therefore entry is not the only criterion for brain penetration.

If a radiolabeled molecule is synthesized that can be used for either SPECT or PET, then brain entry can be assessed for that molecule quantitatively (PET) or semiquantitatively (SPECT). (SPECT measures are always effectively relative, as it is not possible to correct fully for attenuation and scatter of the signal.) The achievement of this step is easier than assessing detailed tissue kinetic parameters, as the *total* signal comprising free, specific and nonspecific binding is sufficient, thus eliminating the need for specific binding to be at least twice nonspecific binding (see below). The information can be obtained well in advance of "first administration in humans," since the total doses of radiotracer administered are in the picomolar (or less) range; therefore toxicological requirements are far less stringent.

An understanding of brain entry is, of course, important in the development of all psychotropics, but particularly when novel targets are ex-

plored. For instance, an understanding of the brain penetration of L 365260, a putative anxiolytic that is a CCK-B antagonist, would have been important in its early development. The compound failed to progress, since clinical tests showed it not to be effective in reducing anxiety in patients [7]. However, it is to date unclear whether this effect is a result of the target (CCK-B receptors) being irrelevant in anxiolysis or whether, as appears more likely, the compound did not achieve significant enough concentrations in the brain. Examples from currently fashionable targets may include corticosteroid receptor antagonists, as such molecules may be actively extruded from the brain [8].

### 4.2 Body Distribution

Information on the body distribution of a radioligand can be obtained by either moving the person in the scanner so that different organs are investigated or by using multiple detectors such as in the multiple organs coincidences counter [9]. An example of the distribution of [$^{11}$C]flumazenil and radiolabeled metabolites is shown in Fig. 2, and of the effects of blocking serotonin reuptake sites on the kinetics of [$^{11}$C]RTI55, a mixed serotonin and dopamine reuptake inhibitor, in Fig. 3. As in total brain entry, this information can be obtained early in the cycle and prior to first administration of pharmacological doses in humans.

An understanding of compound distribution in the body has advantages in terms of aiding calculations of likely total dose administration, of predicting possible interactions, and of toxicology. On the whole, this type of information is often available in animal pharmacokinetic studies but has not been available in human ones. Therefore possible benefits in terms of shortening the odds of making a successful medicine or in terms of decreasing development time will have to be demonstrated.

### 4.3 Tissue Kinetics

Nuclear medicine imaging with a radioligand with characteristics that allow identification of specific binding can give information on the kinetics of binding in the brain. This information is useful in determining the frequency of dosing and in understanding whether there is an association between kinetic properties and therapeutic action.

An interesting example comes from the antipsychotic quetiapine. Its plasma half-life is of the order of 3–5 hr, too short for reliable dosing in humans. However, using PET and the D2 ligand [$^{11}$C]raclopride and the 5HT2 ligand [$^{11}$C] N methyl spiperone Gefvert et al. [11] demonstrated that the brain half-life for D2 receptors is 12–15 hr, while the half-life at the 5HT2 receptor is over a day long. This information allowed continued de-

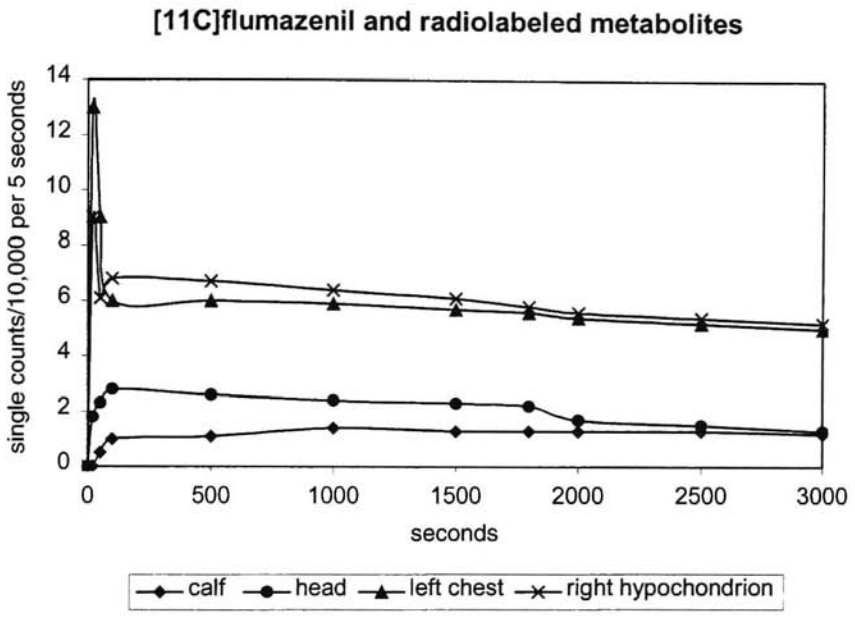


**FIGURE 2** Body distribution of radioligand after injection. Note that the signal also includes radiolabeled metabolites, hence the early "hump" in the data from the right hypochondrium. Note also that the signal from the head is rapidly decreased by the injection of 1 mg cold flumazenil at 1800 sec. This reflects specific binding in the brain. The other tissues are not affected. (From Ref. 9.)

velopment aiming for twice-daily dosing. This information was obtained after the first studies in humans, as the kinetics of the new molecule was studied by observing displacement of the reference radioligands for the targets of interest. However, this process can be performed before the first administrations in humans if the molecule of interest is itself radiolabeled.

### 4.4. Targets Distribution and Density in Health and in Disease

Brain imaging has allowed the discovery of changes in receptor density in disease, such as decreased benzodiazepine binding in panic disorder [12], decreased 5HT1A binding in depression [13], and increased peripheral benzodiazepine receptor brain expression in Alzheimer's disease [14]. These observations have been carried out in vivo and would not have been feasible in autopsy tissue because of the effects of medication, disease progress, other

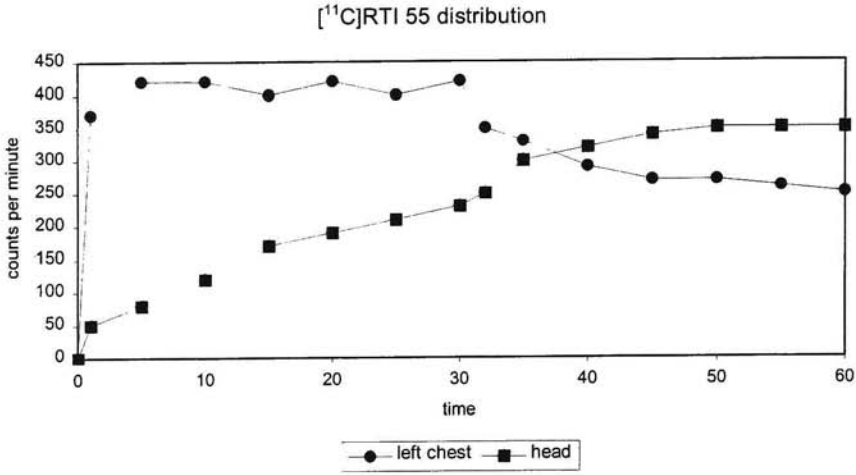


**FIGURE 3** Interaction between organs. Displacement of radioligand from lung results in more rapid accumulation in brain. RTI-55 binds to dopamine and serotonin transporters. Displacement from lung serotonin transporters by injection of clomipramine 10 mg IV at 30 min results in more rapid access to the brain, where the dopamine transporter is unaffected by the clomipramine injection. (From Ref. 10.)

diseases, and, in some cases, uncertain diagnosis when studies are carried out postmortem.

Availability of radioligands to carry out this type of studies with new targets would be of great value and should change the way that decisions are made on the potential therapeutic applications of new series of molecules, especially for novel pharmacological targets. Currently information on protein expression in vivo in psychiatric disorders is lacking. However, if radioligand development started with the discovery of a series for a molecular target, information on target expression in vivo in key diseases could be available when drug development investment decisions are made.

## 4.5 Occupancy

Occupancy can be measured by using nuclear medicine techniques. Clearly this can be achieved only once pharmacological doses can be administered and therefore cannot occur before phase I. This approach has been quite useful in clarifying the pharmacokinetics of antipsychotics and of pindolol as antagonists at D2, 5HT2, and 5HT1A receptors respectively [15–18].

The pindolol example is worth expanding on. It has been suggested that blockade of the 5HT1A somatodendritic receptors in the raphe would speed up and augment serotoninergic antidepressant action. This is because stimulation of these receptors by increased serotonin in the synaptic cleft decreases raphe firing, thus decreasing cortical release of serotonin. This effect is maximal soon after the initial administration of a serotoninergic release inhibitor but decreases after some days or weeks as the raphe 5HT1A receptors desensitize. Pindolol is a beta blocker that also has affinity for the 5HT1A receptor, where it acts as antagonist or a weak partial agonist. Pindolol therefore has been used in a number of clinical studies that have evaluated this theory in practice. The results have been equivocal in terms of its efficacy. The findings could indicate that the theory is inadequate in human depression or that the experiments did not achieve consistent blockade of the 5HT1A raphe receptors.

A key experiment using [$^{11}$C]WAY 100635 PET [18] demonstrated that doses of pindolol equivalent to most doses used in the clinical studies occupy about 20% of cortical receptors and about 40% of raphe receptors at peak plasma pindolol levels, that at trough the occupancy figures are diminished by about 5%, and that "superdosing" at four times the usual dose achieves raphe occupation of 60% and cortical occupation of 40%. The level of desirable occupancy is still a matter of debate; however, even conservative estimates would suggest that at least 50% occupancy is needed for effective antagonist action. If considerable receptor reserve is present, the level would have to be in the upper 90%. Therefore a conclusion from this study is that the clinical studies that have examined the role of pindolol as an augmenter did not test the hypothesis sufficiently, as they failed to achieve occupancy levels that would do so. It is also possible that where the effects were obvious, pharmacokinetic or pharmacogenetic factors contributed to achieving an effective brain concentration. Further, the study results in a subsidiary question. Differential occupancy was demonstrated between cortical and raphe receptors with pindolol, while pure antagonists may not have this effect in humans; would, therefore, the administration of the pure antagonists achieve clinical efficacy, given that any increase in serotonergic release in the cortex would be counterbalanced by blockade of the very cortical receptors that are thought to be important for clinical effect?

Another interesting example comes from antipsychotics. Investigation over the last 10 years has demonstrated that D2 occupancy in the striatum greater than 80% causes extrapyramidal side effects; that conventional antipsychotics need to achieve at least 60% occupancy of D2 receptors in the patients in which they are effective; but that this threshold does not explain their lack of efficacy in some patients and that, interestingly, the atypical antipsychotics clozapine and quetiapine achieve their effects at much lower

occupancy. The beneficial effects of these two drugs at lower occupancy has been the source of much debate, especially since clozapine has superior therapeutic properties that are not shared by other antipsychotics. Recently the idea that the effects may be due to differential occupancy of limbic D2 receptors has been discounted [19], but preliminary data from Kapur et al. [17] have helped to put forward the hypothesis that the differences are related to the brain kinetics of these molecules, which achieve high occupancy but only very transiently. These intriguing data question the assumptions that have determined the ideal dosing characteristics for psychotropics and may signal that, in future, development should aim toward pulsatile rather than tonic blockade of receptors.

These examples clearly demonstrated that determination of occupancy as part of future development packages of antagonists will be essential to make them more effective. Agonists often act at low levels of occupancy; therefore it is, at present, less clear whether this strategy has much to offer for their development.

### 4.6 Pharmacokinetic/Pharmacodynamic (PK/PD) Parameters

The measure of occupancy in the human brain in vivo allows the determination of pharmacokinetic/pharmacodynamic relationships (e.g., Ref. 20). This could be of use in the development of new medicines if the pharmacodynamic parameters are surrogate endpoints, as these may be achieved in disease at different occupancy than in health; further measures of occupancy can be used to validate particular pharmacodynamic measures as valid expressions of tissue kinetics.

For example, prolactin elevation can been used as an index of D2 occupancy in the brain. However, the receptors that control prolactin secretion are in the anterior pituitary and outside the blood-brain barrier; therefore the use of prolactin measures as an index of central D2 receptor occupancy can be deemed invalid as being remote from the site of interest. Thus, in order to be able to use this simple and cheaper measure in individual studies, the PK/PD relationship of prolactin elevation with central occupancy has to be established by using SPECT or PET, which will allow the plasma data to become a valid measure of brain pharmacology. Further, since medicines cross the blood-brain barrier differentially, this relationship has to be worked out for each individual pharmacological agent. If this is done, prolactin elevation is a useful quantitation of central D2 antagonism even with medicines such as quetiapine, which have minimal effects on prolactin elevation [17].

### 4.7 Pharmacodynamic Effects

Apart from the physiological effects described above, medicines have effects on brain metabolism and activation patterns. For instance, it has been demonstrated that antidepressants modulate prefrontal and cingulate cortex metabolism in depressed patients [21–24]. Further, it is postulated that patients in whom metabolic changes do not occur in the cingulate are not going to respond to antidepressants [23]. If this observation holds to robust scrutiny, then a potential tool for phase IIa will have been discovered. This is because this type of measure allows for more robust statistical comparisons when compared with traditional clinical measures, since there is less variance; in this case 12–20 patients per dosing arm would be sufficient as compared with 80–100 for traditional clinical measures. Further, the measure can be obtained in 1 week rather than 12, thus decreasing the time to decision as well as the cost.

### 4.8 Measures of Disease Process Modification

The use of imaging as a measure of disease progress modification is traditionally associated with degenerative or inflammatory disorders such as Alzheimer's or multiple sclerosis. However, the discovery of altered numbers of neurons and glia in brains of patients with depressive and psychotic disorders [25,26] suggests that measures of glial function during affective episodes are needed. If altered, these could represent a worthwhile target and an activity whose modulation may be essential in preventing recurrence.

## 5 CONCLUSION

Brain imaging has become a mature tool for the investigation of the effects of drugs on the brain. Some of the investigations can be carried out with pico- or fentomolar concentrations of drugs and therefore can take place before administration of pharmacological doses and with limited toxicology. Other strategies can be applied later in the process, when they are likely to improve the quality of available information at the time of making a decision on which compounds to back. Even by the time molecules are administered to humans, only 1 in 10 make it to the end of the discovery/development pyramid, and it is essential that the development of compounds that are more likely to fail is stopped before hundreds of millions of dollars are spent on them. However there are two obstacles that prevent the extensive use of these technologies currently: (1) a low uptake of these technologies in industry and (2) a paucity of radioligands for existing and new targets.

It is unlikely that this field will progress without the necessary investment from the big pharmaceutical companies, as the expenditure needed to

establish robust baseline data is too large for grant-giving organizations, while it represents only a fraction of the profits generated by one block-busting drug.

Further, industry is in a unique position to generate radioligands, as it can test the suitability of hundreds of molecules with good affinity for a target at a time when its chemists are concentrating on producing the best molecules for a particular receptor. In the future, drug discovery and development is likely to benefit from the intensive use of imaging, but the time to invest has now come.

## ACKNOWLEDGMENTS

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# 13

# Differential Brain Mechanisms in Bipolar and Unipolar Disorders: Considerations from Brain Imaging

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## 1 INTRODUCTION

In 1957, Leonhard distinguished unipolar depression from bipolar disorder by the presence of mania during the course of the latter [1]. In general, this distinction has been quite useful, since patients with bipolar disorder preferentially respond to lithium and other mood stabilizers that are relatively ineffective in unipolar depression [2]. In contrast, antidepressants, which are effective in 70–80% of patients with unipolar depression, may worsen the course of bipolar disorder by inducing mania or accelerating affective cycling [3]. Nonetheless, these two classes of affective disorders do not always separate neatly. For example, patients with recurring unipolar depression may respond to lithium despite not having a history of mania, and patients with hypomania and depression (i.e., bipolar type II disorder) may remain stable on antidepressants alone [2–4]. Distinguishing agitated unipolar depression from a bipolar mixed state is clinically difficult (cross-sectionally) if not impossible in many patients [5]. The similarity in symptoms during some phases of these illnesses as well as similar treatment responses (in

some cases) suggest that, despite their distinctiveness, bipolar and unipolar disorders may share a similar functional neuroanatomy.

During the past 15 years, the neurophysiology of affective disorders has received increasing attention, largely related to the development of effective neuroimaging technologies. As these technologies have been applied to patients with unipolar depression or bipolar disorder, the utility of the nosologic distinction between the two conditions has come under discussion, as many, particularly older imaging studies tended to combine unipolar and bipolar disorders into a single group. The validity of this approach has been challenged [6], but the specific neurophysiological distinctions between unipolar and bipolar disorders have been relatively little addressed. The aim of this chapter is to examine neuroimaging studies of affective disorders in order to identify similarities and differences in the functional neuroanatomy of unipolar depression and bipolar disorder.

## 2 NEUROANATOMY

Magnetic resonance imaging (MRI), and, historically, computed tomography (CT), permit the *in vivo* study of the neuroanatomy of bipolar disorder and unipolar depression. In these studies, it is assumed that the behavioral abnormalities observed will be reflected in brain structure, although it is entirely possible that normal-appearing brain regions function abnormally (or the converse). This is a significant potential limitation of morphometric imaging studies. Nonetheless, the identification of neuroanatomical abnormalities in affective disorders provides potential neural substrates to inform neurophysiological hypotheses of these illnesses.

### 2.1 Structural Imaging in Bipolar Disorder

In bipolar disorder there have been few consistently replicated structural neuroimaging findings. It appears that bipolar patients do not typically exhibit gross neuroanatomic abnormalities (e.g., significant cortical atrophy). However, differences from healthy subjects and, to a lesser extent, other psychiatric patient populations have been observed in brain regions associated with the modulation of mood, including the prefrontal cortex, basal ganglia, and amygdala [7].

The prefrontal cortex is a complex structure that consists of several histologically and functionally discrete brain regions which are difficult to demarcate from each other using structural imaging. As a result, most imaging studies of the prefrontal cortex in bipolar disorder looked at large anterior brain regions (e.g., all tissue anterior to the genu of the corpus callosum), which combined many different prefrontal and frontal brain areas.

These studies typically did not observe differences between bipolar and healthy subjects in these "prefrontal" volumes [7]. An exception to this was reported by Sax et al. [8], who found decreased prefrontal volumes in bipolar patients compared with healthy subjects that correlated with poor performance on the Continuous Performance Test (CPT), which is a measure of attention. This correlation provided clinical support for the validity of the finding, but unfortunately it has not been replicated.

Prefrontal structural abnormalities in bipolar disorder might be more consistently identified if functionally distinct subregions of the prefrontal cortex were examined separately. Drevets et al. [8] studied the relatively small subgenual prefrontal cortex (SGPFC), since this portion of the anterior cingulate is thought to modulate human mood states [8]. They found that patients with bipolar disorder and unipolar major depression who had a family history of affective illness exhibited smaller left SGPFC volumes than healthy subjects. These groups did not exhibit differences in other anterior cingulate regions. This finding was replicated by Hirayasu et al. [10], who also found that patients with first-episode psychotic affective illness (bipolar and unipolar combined) *and* a family history of affective illness had small left SGPFC volumes compared with healthy subjects, patients with schizophrenia, and patients with affective illness *without* a family history of affective illness. These two studies suggest that structural abnormalities in the left SGPFC may be specific for familial affective illness. However, neither study found that SGPFC volumes distinguished bipolar disorder from unipolar depression.

Several investigators observed increased size of basal ganglia in patients with bipolar disorder compared with healthy subjects [11–14], and there are no papers reporting decreased volumes in these brain regions [7]. Aylward et al. [11] reported caudate enlargement in male bipolar patients, and we observed similar enlargement in the striatum more generally [12]. Recently, we extended this finding by comparing first- and multiple-episode bipolar patients and healthy subjects. We found that both the putamen and caudate were enlarged in both patient groups (although the enlargement in the latter structured was restricted to men), suggesting that this abnormality is not a result of illness chronicity or medication exposure [13]. Noga et al. [14] found enlarged caudate volumes in both affected and unaffected monozygotic twins discordant for bipolar disorder as compared to the healthy subjects. This finding suggests that caudate enlargement may be a heritable vulnerability factor for developing bipolar disorder, which in and of itself is not sufficient to cause the condition.

The amygdala has been reported to be enlarged in bipolar patients compared with healthy subjects [12,15] and patients with schizophrenia [15]. Neither of these studies observed differences between bipolar and compar-

ison subjects in the nearby hippocampal volume, suggesting a relative specificity for amygdala dysmorphology. However, the amygdala finding has been inconsistent, as other groups observed no differences between healthy subjects or patients with bipolar disorder [16] or found the amygdala to be reduced in patients [17]. We recently failed to replicate our original finding of amygdala enlargement in bipolar patients [13], but by comparing the data from the two studies, we deduced that differences in patient- and healthy-subject sampling methods contributed to the different finding between the studies. This effect of clinical and demographic variables suggests that enlargement of the amygdala may occur only in a subgroup of bipolar patients, but so far the defining characteristics of this subgroup remain uncertain.

The cerebellum is strongly interconnected with limbic brain regions [18], and several older CT studies noted decreased cerebellar volumes in bipolar disorder [7]. However, these studies had many limitations in sample selection and imaging methods, and in a recent MRI study we did not observe differences between bipolar and healthy subjects in cerebellar hemispheric volumes. Instead, we found that bipolar patients with multiple prior affective episodes had vermal atrophy (particularly in area III) compared with first-episode patients and healthy subjects [19]. We have recently replicated this finding and extended it to include vermal area II [13]. Significant correlations between vermal volumes and prior treatment exposure in this study suggest that, at least in part, this finding may be iatrogenic.

Approximately half of the studies that examined ventricular volumes reported that bipolar patients had enlarged lateral and third ventricles as compared with healthy subjects, although this difference was typically not as marked as has been reported in schizophrenia [7]. Unfortunately, the meaning of ventricular enlargement is unclear, because ventriculomegaly does not appear to be associated with a reduction in the size of periventricular structures in bipolar disorder. As noted, the basal ganglia, which surround the lateral ventricles, are typically enlarged in bipolar disorder. This paradox suggests that periventricular white matter is reduced, but this possibility has not been directly studied. Nonetheless, in a study of first-episode mania, we observed an increased gray/white matter ratio in bipolar patients (particularly women), consistent with the notion that decreased white matter might explain the ventriculomegaly of bipolar disorder [20]. Additionally, white matter abnormalities in the form of T2-signal hyperintensities are among the most replicated imaging findings in bipolar disorder [21].

## 2.2 Structural Imaging in Unipolar Depression

Like bipolar disorder, unipolar depressive disorder has generally not been associated with significant global brain changes [6]. Also similar to bipolar

disorder, the left subgenual prefrontal cortex (SGPFC) appears to be smaller in depressed patients with familial affective illness than in those without a family history of affective illness or in healthy subjects [9,10]. However, unlike those with bipolar disorder, patients with unipolar depression may be more likely to exhibit decreased volumes in the prefrontal lobes more generally as well as smaller basal ganglia when compared with healthy subjects [6].

Decreased prefrontal lobe size, even using relatively imprecise measurements of the "prefrontal lobe," has been reported in several studies of unipolar depression [6]. Coffey et al. [22] found that patients with unipolar depression exhibited a 7% decrease in frontal lobe mean volume compared with healthy subjects, and other investigators, although not all, have observed similar reductions [23–26,33]. Kumar et al. [25] extended this work by noting that prefrontal volumes were inversely correlated with the severity of the depression. This clinical association adds validity to the neuroanatomical finding by suggesting that it has functional relevance. Finally, in addition to the studies examining total frontal lobe size, Lai et al. [26] studied the orbital frontal cortex specifically in elderly patients with unipolar depression and found it to be significantly smaller than in age-matched healthy subjects. Together, these studies suggest that patients with unipolar depression have structural abnormalities in several distinct prefrontal subregions. This finding may be more common in elderly than young depressed patients [6].

A number of investigators observed decreased basal ganglia volumes in patients with unipolar depression as compared to healthy subjects [6], which is in direct contrast to the basal ganglia enlargement reported in bipolar disorder. Decreased basal ganglia volumes in depression may be associated with increased illness severity [27]. In contrast to bipolar disorder, this basal ganglia reduction may also explain the typically modest lateral ventricular enlargement observed in unipolar depression, although this possibility has not been studied directly [6].

As in bipolar disorder, MRI T2-signal hyperintensities are common in patients with unipolar depression. However, unlike bipolar disorder, in which these lesions are observed throughout the life span, in unipolar depression they appear to be more common in late-onset patients [28]. These MRI T2-signal hyperintensities have been associated in postmortem studies with areas of arteriosclerosis, white matter necrosis, and axon loss and are likely the result of cardiovascular illness [29,30]. Therefore the presence of these MRI hyperintensities might identify a subgroup of unipolar depression in which the illness is initiated by brain injury due to cardiovascular disease [31]. In these patients, the hyperintensities are commonly observed in the basal ganglia; they may therefore contribute to the decreased volumes observed, at least in older patients [6,31].

Finally, again in at least partial contrast to studies in bipolar disorder, studies of the amygdala in unipolar depression have typically failed to find differences with healthy subjects [6]. In contrast, several recent studies of the hippocampus have suggested that its volume is decreased in depressed patients [33–35]. Sheline et al. [35] found that the loss of hippocampal volume was associated with the total duration of depression rather than patients' age, so that this abnormality may be related to the course of illness. These findings led several investigators to speculate that hippocampal atrophy results from the neurotoxic effect of elevated glucocorticoids, which may occur during depression [36,37]. This hypothesis has not been directly supported, however.

## 2.3 Neuropathology

Several recent histopathological studies identified cellular morphometric abnormalities in affective disorders. Specifically, two research groups reported a reduction in glial cell number and density in several prefrontal brain regions in both unipolar depressed and bipolar subjects [38–40]. To follow-up to their finding of left SGPFC volume reduction on MRI [9], Öngür et al. [38] examined the subgenual prefrontal cortex in two sets of brain specimens from patients with affective disorders. They found a reduction in the number of glial cells in this brain region, particularly in the familial cases of affective disorder. This same abnormality was not observed in the somatosensory cortex. Subsequently, Rajkowska et al. found decreased glial density in both unipolar depressed [39] and bipolar [40] patients. Decreased neuron density and glial enlargement were also observed in dorsolateral and orbital prefrontal cortex. However, there have been few studies in other, nonprefrontal brain areas, so that the regional specificity of these abnormalities is not yet established. Benes et al. [41] found a decreased density of nonpyramidal neurons in the CA2 region of the hippocampus in bipolar and schizophrenic patients as compared to healthy subjects. This abnormality has not been reported in major depression. To date, no specific histopathological differences between unipolar depression and bipolar disorder have been identified.

## 2.4 Summary of Neuroanatomy

Morphometric neuroimaging has identified different abnormalities in unipolar depression and bipolar disorder. Whereas unipolar depression has been associated with volume reduction in several prefrontal cortical areas, albeit somewhat inconsistently [6], in bipolar disorder this reduction may be limited to the left subgenual prefrontal cortex and restricted to familial cases of illness. There are too few studies of prefrontal subregions in either dis-

order to make definitive statements, unfortunately. Unipolar depressed patients commonly exhibit decreased volumes in basal ganglia, in contrast to basal ganglia enlargement seen in bipolar disorder. The basal ganglia have a central role in modulating mood, and injuries to basal ganglia can produce depression or cycling affective conditions [42]. Therefore this structural imaging finding may be relevant for distinguishing bipolar and unipolar disorders. Unfortunately, to my knowledge, basal ganglia volumes have never been directly compared between bipolar and unipolar disorders. The amygdala may be enlarged in bipolar disorder, at least in some patient subgroups, but this is not observed in unipolar depression. In contrast, hippocampal volume appears normal in bipolar disorder but is decreased in depression. Together, these findings suggest a differential neuroanatomic substrate for these two affective disorders.

The small number of histopathological studies of affective illness, particularly of subcortical structures, significantly limits how these morphometric imaging studies should be interpreted. Both unipolar and bipolar disorders appear to exhibit similar reductions in glia in prefrontal areas, but whether this occurs in other brain regions is less certain. Clearly more histopathological studies are needed. Nonetheless, in addition to histopathology, functional and spectroscopic studies of affective disorders may clarify the meaning of structural findings.

## 3 NEUROFUNCTION

Positron emission tomography (PET), single photon emission computed tomography (SPECT) and, more recently, functional magnetic resonance imaging (fMRI) all provide in vivo methods for defining the anatomy of brain function. These technologies produce brain maps that correspond to either changes in metabolism or blood flow at rest or during activating cognitive tasks. A number of investigators have used these technologies to study patients with affective illnesses in order to clarify the functional neuroanatomy of these disorders.

### 3.1 Functional Imaging in Bipolar Disorder

Functional imaging studies of bipolar patients are relatively scarce. Most have concentrated on patients during the depressed phase, although a few have compared bipolar and unipolar depression directly. Despite the relative paucity of data, these studies provide some support for regional brain dysfunction in areas that may be structurally abnormal in bipolar disorder.

Functional imaging studies of prefrontal brain regions generally reported decreased metabolism and perfusion in depressed bipolar patients

compared to healthy subjects [9,43–47]. Typically, these decreases have been observed in the dorsolateral prefrontal cortex (particularly on the left) and the anterior cingulate. Drevets et al. [9], in a series of linked studies, found that the subgenual prefrontal cortex specifically exhibited decreased blood flow and metabolism in bipolar depression, although during mania (in a small subsample), metabolism increased to above normal. Blumberg et al. [48] also found increased blood flow in the anterior cingulate during mania, including the region of the SGPFC. However, other investigators have not observed increased prefrontal glucose metabolism or cerebral blood flow during mania [44,46,49,50]; in fact, they have even reported decreased cerebral perfusion in selective frontal and temporal brain regions during mania [51–53]. Limiting all studies of mania, of course, is the fact that the more severely ill patients are typically unable to complete imaging studies. Yet in some ways, these are the patients that most differentiate bipolar and unipolar disorders.

Nonetheless, together, these studies suggest that changes in prefrontal metabolism and blood flow are state-dependent during the course of bipolar disorder. Specifically, activation appears to decrease during bipolar depression and then may increase during mania, although the latter is less clear. As noted previously, the prefrontal cortex is a heterogeneous, functionally complex brain region, so studies of relatively discrete anatomical areas within this larger region are needed to clarify the activation patterns of both bipolar mania and depression so as to determine whether some of the discrepancy, particularly in mania, may be due to differential activation among different prefrontal subregions [53].

In addition to studies of prefrontal cortical activation, there is evidence of functional abnormalities in basal ganglia in bipolar disorder. Specifically, Baxter et al. [44] reported decreased caudate metabolism in *depressed* bipolar patients compared with healthy subjects, although this was less clear after adjusting for hemispheric metabolism. O'Connell and colleagues [54] found increased basal ganglia blood flow, right greater than left, in *manic* bipolar patients. This latter finding was partially replicated by Blumberg et al. [48], who found increased cerebral blood flow in the left head of the caudate in manic patients compared with healthy subjects. These results suggest that state-dependent changes may occur in basal ganglia during the course of bipolar disorder that mirror those in the prefrontal cortex [49].

A somewhat contrasting finding was provided by Ketter et al. [55], who examined cerebral metabolism in depressed, treatment-resistant rapid-cycling patients. They found decreased prefrontal and paralimbic cortical metabolism, which correlated inversely with ratings of depression. In contrast, ventral striatum, thalamus, and amygdala demonstrated increased metabolism, positively correlated with depression ratings. These findings sug-

gest an affective state-dependent loss of prefrontal activation that produces disinhibition of limbic subcortical structures, leading to affective symptoms. Additionally, the investigators observed increased cerebellar metabolism that appeared independent of mood state, disorder subtype, or cycle frequency, which might be a trait or vulnerability factor.

There have been few studies of medial temporal structures in bipolar disorder [52,56]. Recently, Yurgelun-Todd et al. [56] found that the amygdala was activated by a facial affect-discrimination task, with a corresponding reduction in activation of the dorsolateral prefrontal cortex, in bipolar patients but not healthy subjects. This fMRI study is one of only a very few that have used cognitive activation paradigms in bipolar samples to study brain networks thought to underlie this illness. It suggests that a loss of prefrontal cortical control might be associated with increased amygdala activation; therefore it is somewhat consistent with the findings of Ketter et al. [55].

### 3.2 Functional Imaging in Unipolar Depression

Unipolar depression has been studied more commonly than bipolar disorder using functional imaging. Therefore there are a number of studies that unfortunately, often report discrepant findings. Nonetheless, suggestions of the underlying functional anatomy of unipolar depression are provided by these studies. Particularly, functional imaging has identified abnormalities in prefrontal regions as well as subcortical structures in unipolar depression.

Studies of depression focusing on the prefrontal cortex (PFC) illustrate the functional heterogeneity of this brain region, as different subregions have been observed to demonstrate different abnormalities. In the dorsolateral and dorsomedial PFC (particularly on the left), studies have typically observed decreased blood flow and metabolism in unipolar patients at rest and during cognitive activation [57]. Several studies observed that these changes appear to be affective state–dependent. Since these brain regions are associated with verbal memory and executive function tasks, it is thought that the decreases associated with depression represent disruption of these cognitive networks by the affective symptoms, perhaps by intrusion of the affective networks [58]. Drevets and colleagues [59] observed increased blood flow in unipolar depression in the ventrolateral prefrontal cortex [Brodmann areas 11, 45, and 47], a brain area that overlaps in part with the dorsolateral prefrontal cortex [Brodmann areas 9, 10, 45, and 46]. Paradoxically, the degree of overactivation was *inversely* related to the severity of depression in the ventrolateral PFC, suggesting that the most depressed patients approach normal levels of metabolism and blood flow in these brain areas. This association is difficult to understand mechanistically. Similarly, although the anterior

cingulate in general appears to be underactivated both at rest and in response to cognitive tests [57], the subgenual region of the anterior cingulate exhibited increased blood flow and metabolism after controlling for the reduced gray matter volume [31].

Moreover, the cognitive set of the patient may dictate the relative activation of prefrontal regions during depression. For example, Biver et al. observed increased activation in orbital frontal cortex in depressed versus healthy subjects at rest [60], but this brain region was less responsive to activation paradigms, thereby appearing underactivated. These factors—plus differences in patient samples, imaging techniques, and image resolution—are all likely to contribute to seemingly discrepant blood flow and metabolism findings during depression [31]. Moreover, these findings suggest that functionally distinct prefrontal areas are differentially activated during depression. Future studies might choose to focus on the pattern of prefrontal activation at rest and in response to specific tasks rather than looking at subregions in isolation in order to clarify these complex relationships.

In addition to changes in prefrontal metabolism and blood flow, two studies reported decreased basal ganglia activation in unipolar depression. Baxter et al. [44] found relatively decreased metabolism in the head of the caudate in unipolar but not bipolar depressed patients *after* adjusting for overall hemispheric metabolism. Drevets et al. [59] also observed decreased caudate blood flow in unipolar depressives with familial depressive disorder. Neither of these studies controlled for the possibility that the caudate volumes were decreased. Primarily preliminary studies have also reported increased amygdala blood flow and metabolism in unipolar (and bipolar) depression [31].

One approach to validate abnormalities observed at rest or during cognitive challenges in unipolar depression is to study changes in cerebral regional blood flow and metabolism in response to effective (and ineffective) antidepressant treatment. Mayberg et al. [58] found that successful treatment with fluoxetine resulted in increased metabolism in the dorsolateral PFC and dorsal anterior and posterior cingulate, with an associated decreased metabolism in the subgenual prefrontal cortex (SGPFC; Brodmann area 25), insula, hippocampus, and hypothalamus. In general, the change in metabolism associated with improved mood in response to fluoxetine treatment resulted in "normalization" of cerebral activation. Moreover, the changes in metabolism seen with successful antidepressant treatment were reciprocal to those seen during induced sadness in healthy volunteers [58]. Similar but not entirely consistent findings followed treatment with paroxetine [52,63], venlafaxine [64], interpersonal therapy [63,64], and sleep deprivation [65].

Mayberg et al. [61] examined changes in metabolism in patients with unipolar depression after 1 and then 6 weeks of fluoxetine treatment. Many

of the metabolic changes observed at 1 week did not persist or were reversed by the sixth week of treatment. Those changes that persisted and the new changes that occurred between 1 and 6 weeks included increased metabolism in the anterior cingulate (BA 24b), dorsolateral and ventral PFC, hippocampus, insula, and posterior cingulate as well as decreased metabolism in the SGPFC. Patients also demonstrated decreased metabolism in the caudate, thalamus, and parahippocampal regions that did not correlate with treatment changes. Differences in brain activation between 1 and 6 weeks after treatment are consistent with the relatively delayed onset of antidepressant therapy, in which a cascade of changes occur over time to induce improvement in depressive symptoms.

## 3.3 Summary

Functional imaging studies report abnormalities in regional brain metabolism and blood flow in both unipolar and bipolar disorders, although the former are better studied. In unipolar depression, patients typically demonstrate decreased metabolism or blood flow in dorsolateral and dorsomedial prefrontal cortex, anterior cingulate (posterior and superior to the subgenual cingulate), and basal ganglia, particularly caudate. Increased metabolism or blood flow is observed in the subgenual prefrontal cortex (BA 25), ventral prefrontal cortex, orbitofrontal cortex, and amygdala. Although many of the studies are fairly consistent with regard to this pattern, there are exceptions—e.g., Brody et al. [63]. Responses to antidepressant treatment, psychotherapy and sleep deprivation add validity to the notion that these general patterns occur in depression, as investigators typically report reciprocal changes with improvement in many of these same regions, although, again, with exceptions [63]. The prefrontal and basal ganglia functional abnormalities (decreased flow) are consistent with the decreased volumes in these regions observed in the previously reviewed morphometric studies. A limitation to most of the functional studies, however, is the failure to account for the effects of structural differences between unipolar depressed and control groups when regional metabolism and blood flow are calculated.

Decreases in prefrontal metabolism and blood flow similar to those seen in unipolar depression occur during the depressed phase of bipolar disorder, although increases in activation in some of these regions may occur during mania. In general, the studies have examined dorsolateral or dorsomedial PFC and have not delineated other specific subregions of the prefrontal cortex in bipolar disorder, as has been done in depression. Decreased basal ganglia metabolism has also been reported in bipolar depression, as in unipolar depression, that again may be state-dependent, as increased metabolism has been observed, albeit inconsistently, during mania. In the one

direct comparison of unipolar and bipolar depression, Baxter et al. [44] did not observe relatively decreased basal ganglia in bipolar depression, although this was present in the unipolar patients (after controlling for whole-brain activation). As noted, the results from Ketter et al. [55] suggest an affective state-dependent loss of prefrontal activation, leading to a disinhibition of limbic subcortical structures that is associated with the severity of affective symptoms, and the results from Yurgelun-Todd et al. support this assertion. However, the lack of studies of euthymic bipolar patients makes it difficult to identify potential trait functional brain abnormalities, as opposed to affective state–dependent changes, that might characterize this condition.

## 4 NEUROCHEMISTRY—SPECTROSCOPY

Magnetic resonance spectroscopy (MRS) is a technique that permits the in vivo study of brain chemistry in patients with affective disorders. Proton MRS provides a measure of cellular chemical activity by studying regional neurotransmitter and amino acid concentrations [7]. Typical compounds studied include *N*-acetyl aspartate (NAA), creatine (Cr), phosphocreatine (PCr), choline-containing compounds (Cho), myo-inositol (Ino), and a composite of a number of related amino acid neurotransmitters including GABA, glutamate, and glutamine (Glx). Phosphorus MRS provides a means to measure products of cellular metabolism such as adenosine triphosphate (ATP), PCr, phosphomonoesters (PME), and phosphodiesters (PDE). Of the imaging modalities, this technique has been the least applied to affective illness, but it may nonetheless have the greatest potential, as it might be used to test specific mechanistic hypotheses.

### 4.1 MRS in Bipolar Disorder

As recently reviewed [7], a number of MRS studies identified abnormalities in choline concentration in the basal ganglia of bipolar patients. In the oldest report, Sharma et al. [66] found elevated Cho/Cr-PCr ratios in the basal ganglia but not occipital lobes of lithium-treated bipolar patients. They also observed elevations in NAA/Cr-PCr and Ino/Cr-PCr in the same region. Subsequent investigators found elevated basal ganglia choline in bipolar patients that could not be secondary to lithium treatment [67,68]. Hamakawa and colleagues [69] found similar elevations in Cho/Cr-PCr ratios in both depressed and euthymic bipolar patients, suggesting that this abnormality might be a trait rather than state marker. These investigators also observed decreased Cr-PCr concentration during depression, suggesting a state-related change in Cr metabolism. This latter finding raised the important point that

MRS studies that use ratios (e.g., Cho/Cr-PCr) need to be careful when interpreting results, since an apparent elevation of the numerator compound (e.g., Cho) may simply reflect a decreased concentration of the denominator.

As a test of the hypothesis that the effects of lithium on inositol metabolism are responsible for its therapeutic efficacy in bipolar disorder, Moore et al. [70] used MRS to study changes in frontal lobe myo-inositol during lithium treatment of bipolar depression. They found that myo-inositol levels decreased after both acute (at 5–7 days) and chronic (3–4 weeks) lithium administration. Similar changes were observed for choline. However, these chemical changes were observed prior to improvement in depression ratings. The authors suggested that changes in myo-inositol and perhaps choline as well may initiate a cascade in cellular second-messenger systems leading to clinical improvement but were themselves not directly responsible.

A second group [71] studied bipolar patients at several time points longitudinally to determine whether choline and inositol measurements from the anterior cingulate change over the course of illness. Cho/Cr-PCr was elevated in the right anterior cingulate compared with healthy subjects at baseline, whereas changes in Cho/Cr-PCr levels in left anterior cingulate correlated with changes in depression ratings. No differences in Ino/Cr-PCr ratios were observed between bipolar and healthy subjects or within bipolar subjects over time. Lithium and valproate use were not associated with choline or inositol measurements, although patients receiving antidepressants (in addition to a mood stabilizer) demonstrated lower Cho/Cr-PCr ratios than patients not on antidepressants. However, unlike the study by Moore et al. [70], the patients in this study were on mood stabilizers prior to the first MRS scan, which might explain some of the apparent discrepancies.

Most of the phosphorus MRS studies in bipolar disorder have been reported by Kato and colleagues in Japan. In several studies, they observed elevated PME concentration in depressed *and* manic bipolar patients compared with euthymic patients and healthy controls [72–74]. In general, they also observed lower frontal lobe PME concentrations in euthymic bipolar patients compared with healthy subjects [74–76], as have Deicken et al. [77].

When ATP is consumed, PCr transfers its high-energy phosphate group to ADP, thereby replenishing ATP. This consideration led Kato et al. [78] to hypothesize that since secondary depression is associated with left frontal injury and secondary mania with right frontal dysfunction, depressed and manic bipolar patients would exhibit decreased PCr in the left and right frontal lobes respectively. Consistent with their hypothesis, Kato et al. [78] observed lower PCr in the left frontal lobe of depressed bipolar patients and higher PCr in the right frontal lobe of manic and euthymic patients. How-

ever, Deicken et al. [77,79] found the opposite pattern, so that laterality differences remain unclear.

### 4.2 MRS in Unipolar Depression

There have been only a handful of studies using MRS in unipolar depression, and nearly all of these used proton spectroscopy. In the earliest study, Charles et al. [80] reported that Cho/Cr levels were increased in the basal ganglia and thalamus of depressed compared with control subjects, and that this elevation decreased with effective treatment. However, Hamakawa and colleagues compared unipolar depressives to their patients with bipolar disorder and found that the increased choline resonance observed in bipolar depressed and euthymic patients was greater than in the unipolar depressed and unipolar euthymic patients [69]. Moreover, the unipolar patients did not significantly differ from healthy subjects. However, there was a nonsignificant trend for an increased Cho/Cr ratio in the unipolar depressed patients compared to the healthy subjects. In contrast, Renshaw and colleagues [81] observed lower Cho/Cr ratios in unipolar depressed compared to healthy subjects. In contrast to the fairly consistent observation of increased choline in bipolar patients in the basal ganglia, in unipolar depression it remains to be determined whether any spectroscopic abnormalities in this brain region are present and, if so, in which direction they occur.

Several research groups used MRS to study the neurochemistry of frontal brain regions in unipolar depression. Frey et al. [82] found no differences in myo-inositol (mI/Cr) in frontal brain between depressed and healthy subjects. However, the groups were poorly matched demographically and, after adjusting for age, the patients demonstrated a lower mI/Cr ratio than healthy subjects, which was also associated with current antidepressant treatment. This study was confounded by including a small number of bipolar patients in an otherwise predominantly unipolar sample. Steingard and colleagues [83] examined adolescents with unipolar depression and observed increased Cho/NAA and Cho/Cr ratios compared with healthy subjects in the orbitofrontal cortex.

Taking a different tack, Auer et al. [84] reported decreased amino acids (Glx) generally and glutamate specifically in the anterior cingulate but not the parietal lobe of patients with unipolar depression compared with healthy subjects. The contribution of GABA to this finding could not be determined. Moreover, in a recent study, GABA levels were measured in the occipital cortex of medication-free patients with unipolar depression and healthy subjects [86]. The depressed patients exhibited a 52% reduction in GABA levels compared to the healthy subjects with virtually no overlap in measurements between groups. This study suggests that patients with unipolar depression

may have abnormally low GABA concentrations, which may explain the low Glx and possibly low glutamate findings of Auer et al. [84], previously noted. However, limiting the study to the occipital cortex raises complex questions of whether this is a nonspecific, global cortical finding, since there has been little to suggest that the occipital cortex is dysfunctional during depression.

## 4.3 Summary

In bipolar disorder, studies have fairly consistently observed elevations in choline concentration in basal ganglia. In unipolar depression, changes in choline in these brain regions are less consistent, and the one study that compared bipolar to unipolar patients found that the bipolar patients exhibited significantly greater choline elevation during both depression and euthymia. Consistent with the previously reviewed structural and functional data, these results suggest that basal ganglia pathology is different in unipolar and bipolar disorders.

The specific meaning of choline elevation in the basal ganglia in bipolar disorder is unclear. The choline peak in MRS is constituted primarily of glycerophosphocholine and phosphocholine [87]. Lithium is known to inhibit choline membrane transport and thereby increases choline concentration in human erythrocytes [88]. However, lithium's effects on the inositol second-messenger system are more pronounced through its inhibition of inositol monophosphatase, thereby increasing inositol monophosphate levels and decreasing inositol levels in the brain, among other effects [89]. With this in mind, Stoll et al. [90] hypothesized that during lithium-refractory mania, some patients may "escape" from lithium-induced suppression of the phosphatidylinositol system by activating the phosphatidylcholine second-messenger system, which is less affected by lithium. They proposed that by inhibiting both systems (by adding choline to lithium treatment), a more effective treatment for lithium-refractory mania would be possible [90]. They tested this hypothesis by augmenting lithium treatment with choline in a small group of treatment-refractory rapid-cycling bipolar patients, who demonstrated clinical improvement with an associated increase in the MRS choline resonance in the basal ganglia.

Other spectroscopic findings in both unipolar and bipolar disorder require replication and the field has been limited by investigators using very different methods to study different brain regions and different compounds. However, promising areas of research in myo-inositol and its relationship to lithium treatment [70] and GABA and its role in unipolar (and bipolar) disorders [86] suggest that MRS will continue to inform hypotheses of mood disorders.

## 5 SYNTHESIS

Within the imaging literature, there are both differences and similarities in the functional neuroanatomy of bipolar and unipolar disorders. Both patient groups exhibit structural, functional, and possibly spectroscopic abnormalities in prefrontal regions. During unipolar depression, decreased cerebral activation is observed in prefrontal cortical areas that are associated with attentional and cognitive processes (e.g., dorsolateral PFC) with concurrent increased activation in limbic prefrontal regions (e.g., subgenual cingulate and orbital frontal cortex) [58]. This pattern of activation suggests a loss of "cognitive" prefrontal control over "emotional" brain regions, which is consistent with the clinical experience of depressed patients. These functional abnormalities are accompanied by decreased structural volumes in many of these same prefrontal regions, a phenomenon that appears to be secondary to decreased glial and neuronal density [38–40]. What remains unclear is whether these histological abnormalities precede the onset of depressive symptoms, thereby potentially representing an etiologic factor, or instead are a sequela of being depressed. Studies in new-onset untreated patients would answer this question directly, but completing such a study will be difficult or impossible, since brain specimens from these types of patients are typically unavailable.

The pattern of abnormal prefrontal activation during depression is generally corrected by effective treatment, independent of the type of treatment (i.e., antidepressants, psychotherapy, or sleep deprivation). This suggests that effective antidepressant treatments ultimately work through a common neural mechanism to correct prefrontal cortical dysfunction. However, not all of the brain regions are normalized. The subgenual prefrontal cortex (SGPFC), which appears normally activated or overactivated during depression, becomes underactivated following symptom remission [61]. This subnormal SGPFC activation could identify a specific neural risk factor for depression and may directly contribute to the functional abnormalities in other prefrontal regions by virtue of the SGPFC's many connection throughout frontal brain. This risk factor may be minimized only when SGPFC activity is suppressed [31].

The SGPFC has extensive reciprocal connections throughout the limbic system. The orbitofrontal cortex is strongly connected to the SGPFC and, similarly, is overactivated during depression. Similar overactivation occurs in anxious and obsessive states [91]; it may therefore underlie some of the ruminative and cognitive aspects of depression. The SGPFC also receives and sends projections to the amygdala, and both structures project to the hypothalamus. Hypothalamic dysfunction is well described in depression, particularly in the hypothalamic-pituitary-adrenal axis, and it is likely that

the hypothalamus modulates neurovegetative symptoms. The SGPFC is reciprocally connected with several brainstem nuclei such as the substantia nigra, dorsal raphe, and locus ceruleus [31,92]. Therefore the modulatory neurotransmitters serotonin, dopamine, and norepinephrine can affect and be affected by SGPFC activity [31]. Finally, as discussed in more detail below, the striatum is connected with the SGPFC, and differential striatal abnormalities may be the most distinguishing neuroimaging features between unipolar depression and bipolar disorder.

Whether dysfunction of the SGPFC or any other prefrontal region is *specific* for unipolar depression has not been demonstrated. In fact, functional, structural, and histopathological studies suggest similar abnormalities in the SGPFC and several other prefrontal cortical regions in both unipolar and bipolar depression. This observation suggests that rather than being etiological, these prefrontal abnormalities may be nonspecific epiphenomena resulting from other distinct neural processes that cause each of the disorders. What these processes are is unknown, but the imaging data reviewed suggest that, in contrast to the findings in prefrontal regions, bipolar and unipolar patients exhibit differential abnormalities in the basal ganglia.

In bipolar disorder, the basal ganglia have been reported to be enlarged, to exhibit abnormally elevated choline resonances, and to be overactivated during mania and relatively overactivated during depression [44]. In contrast, in unipolar depression, the basal ganglia appear to have reduced volume, are typically underactivated, and may have increased choline concentration, although the last point is unclear. The basal ganglia are topographically connected to the prefrontal cortex, such that several independent but interconnected prefrontal-striatal-thalamic networks have been described [93]. Separate prefrontal-striatal-thalamic networks control emotional, social, cognitive, and motor functions, so that disruption in one network—e.g., the orbital frontal network, which modulates social and emotional responses—can occur without disruption in other networks—e.g., motor function. Indeed, a number of investigators have proposed that dysfunction within selected prefrontal-striatal-thalamic networks underlies the expression of mood disorders [6,7,31,42,94], since injury to structures within these networks produces affective symptoms [42]. Starkstein et al. [95], found that specific injury to the right caudate head may precipitate mood cycling, similar to that observed in bipolar disorder, whereas injury to prefrontal or basotemporal regions is associated with fixed pathological mood states [42]. The neural basis of bipolar disorder, then, may differ from that of unipolar depression in the type of abnormality or dysfunction that occurs in the striatum. Despite this difference, because the striatum is only one component of a complex neural network that modulates human social and emotional responses, much of the neural substrate involved in the two disorders will be

similar, consistent with the observation that the two disorders share many affective and neurovegetative symptoms.

In fact, it is unlikely that any affective disorder will localize to abnormalities in a single structure, since the brain is not organized into discrete independent functional packets but, instead, consists of complex, interconnected neural networks. Therefore dysfunction in any part of the network can reverberate throughout the brain in complex and, at least at this time, unpredictable ways. Although recent histopathological studies implicate specific abnormalities in prefrontal cortex and potentially hippocampus, the limited number of these studies precludes comments about other brain regions. Additionally, a number of other important structures that appear to modulate emotional responses (e.g., amygdala) have been inconsistently observed to be structurally or functionally abnormal in imaging studies but are likely to be involved in the expression of mood symptoms, at least in some patients.

Nonetheless, taken together, these studies suggest that, in mood disorders, there may be relatively diminished prefrontal modulation of subcortical structures within the anterior limbic network, (e.g., amygdala, anterior striatum, and thalamus) that results in dysregulation of mood. Whether this dysregulation results in relatively fixed mood states or instead mood lability and cycling may depend on the specific type of abnormalities within these subcortical structures, particularly in the striatum. Future studies focused on these specific relationships might clarify the differential functional neuroanatomy of different affective disorders.

## 6 FUTURE RESEARCH DIRECTIONS

From this discussion, several consideration arise that might guide future studies. To begin, despite the many similar brain abnormalities in both unipolar and bipolar disorders, the observation that there are possible differences in brain structure, function and chemistry between these disorders suggests that the practice of combining patients with both disorders into a single sample is generally a mistake. For example, the decreased basal ganglia volume observed in a sample of unipolar depressed patients if combined with the increased basal ganglia volumes observed in a bipolar sample could lead to the incorrect interpretation that no differences exist in basal ganglia volumes between healthy and mood-disordered subjects. Instead, efforts to create even more homogeneous patient groups—e.g., by limited the subjects to first-episode patients or only those with a family history of the specific disorder—are likely to produce more consistent imaging findings. Importantly, there are relatively few studies directly comparing subgroups of affective disorders. These are sorely needed to better elucidate the neuro-

physiological differences between the different types of affective illness (e.g., unipolar and bipolar disorders).

As noted, it is unlikely that any affective disorder will be isolated to a single structure. Nonetheless, most approaches to brain imaging studies analyze brain regions as either independent packets or neural network models are needed that can approach patterns of neuroanatomical abnormalities to produce a more sophisticated interpretation of brain imaging findings in affective disorder. Using network models, it may be possible to identify how abnormalities within certain subcortical structures—e.g., ventromedial caudate—are specifically associated with changes in specific prefrontal cortical areas as well as other limbic structures.

Studies of patients during affective states provide important clues to what may have gone awry neurophysiologically to produce mood symptoms. However, in order to separate epiphenomena caused by the mood symptoms from neural abnormalities that are causative, patients need to be studied during periods of remission or recovery to compare with those in acute affective episodes. Perhaps even more informative are studies of patients at risk for developing mood disorders (e.g., children of bipolar parents), who will presumably have the neural risk factors without the confounds of treatment or affective symptoms.

Clearly, psychiatric treatments alter human brain function in patients with affective disorders. More research is needed in patients at the time treatment is initiated and then over the course of treatment to identify nonspecific and specific effects [61]. Since most psychiatric treatments do not work quickly, only longer-term studies that identify associations between neurophysiological measures and treatment response will have any real clinical meaning. Long-term studies that monitor changes in brain structure, function, and chemistry with clinical course may better inform hypotheses of which brain changes are relevant for different mood symptoms and states.

Neuroimaging continues to provide important advances for understanding the neurophysiology of affective disorders. Studies to date have identified important neural networks that need additional study in refined patients samples and over time to clarify the significance of abnormalities observed. The rapid advances in neuroimaging technologies bode well for the possibility that we will someday soon describe the neuropathology of different affective disorders.

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# 14

# Mood Disorders: Current Status and Prospects for Advances

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A series of major questions are raised (and to the extent possible also addressed) by various chapters in this book detailing how neuroimaging methodologies can shed light on the nature of pathological changes associated with mood disorders:

1. *What are the pathophysiological changes associated mood disorders and where in the brain do they occur?*

Answering this question relies on a prior understanding through investigation of the circuits implicated in the generation and maintenance of normal moods and emotions. The most reasonable working hypothesis in patients with mood disorders, is that predictable abnormalities occur in the overlapping realms of cerebral structure, function, neurochemistry, metabolism, neurotransmitters, and neuroreceptors. It is clear from existing research that the "mood circuits" referred to above are phylogenetically old and comprise connected brain regions including the insula; hippocampus; amygdala; parahippocampal gyrus; dorsal lateral prefrontal, anterior cingulate, posterior cingulate, parietal, and subgenual prefrontal cortices; hypothalamus; basal ganglia; and thalamus. Neuroimaging technologies provide direct in vivo probes of structure and function of these regions in mood disorders. To provide but

one example, these circuits can be probed functionally using functional magnetic resonance imaging (fMRI) or positron emission tomography (PET) in normal subjects and those with mood disorders, using a variety of paradigms including mood induction by simulated emotions and visual stimuli employing emotional facial expressions. There is, however, little integration of data across different methods of investigation—for example, neurochemistry and metabolism—in part due to the elaborate and expensive nature of these research studies.

2. *How are vulnerability genes for mood disorders manifesting in the brain?*

There are clearly liability genes for mood disorders, although affective illnesses are genetically complex illnesses—akin to type 2 diabetes, hypertension, and obesity—where multiple vulnerability genes of weak effect interact with environmental factors. In order to reveal the effect of genes in the brain, it is most straightforward to start with homogeneous clinical subtypes (e.g., psychotic depression, depression with anxiety) to see whether these are reliably associated with the changes in the brain circuits mentioned above. Studying unselected and heterogeneous clinical subtypes is much less likely to be informative, while having brain imaging investigators collaborate with clinical geneticists is a strategy more likely to benefit both types of studies.

3. *How can we distinguish state versus trait issues?*

By gathering data through the types of studies suggested above, one could gain useful information regarding state versus trait issues by determining the extent of brain abnormalities in unaffected individuals who are first-degree relatives of probands with mood disorders. This would address the question of what is necessary versus what is sufficient for the illness to manifest clinically and would help highlight the importance of critical environmental triggers.

4. *How can we understand the actions of medications used to treat mood disorders?*

Elucidating the therapeutic impact of mood-stabilizing and antidepressant medications on the circuits mentioned in queston 1 and the abnormalities associated with them is a powerful way to answer some of the above questions. Determining predictors of response and of relapse would have important implications for individualizing and guiding treatments. Similar considerations apply to the actions of electroconvulsive therapy and repetitive transcranial magnetic stimulation.

5. *What is the specificity of brain changes associated with mood disorders versus those seen in schizophrenia?*

Until relatively recently, few studies concentrated on elucidating the issue of specificity of brain alterations associated with affective disorder compared to those seen in schizophrenia. As there can be considerable symptomatic overlap between the two syndromes, it is important to determine whether there are associations between symptom complexes and brain changes and which (if any) pathologies segregate exclusively with only a single disorder.

6. *What can we learn from assessment of brain regions and circuits involved in neurodegenerative and cerebral vascular disorders?*

In such diseases, changes in moods and emotions are commonly seen and the associated pathology and/or genetics are often much better understood than those of affective disorders. Examples include Parkinson's and Huntington's diseases and stroke. The possibility is strong that these disorders might provide important clues regarding the etiopathology of "idiopathic" mood disorders and thus could be used to generate guiding hypotheses.

In approaching the above six questions, there are several major difficulties:

1. *The basic etiology and pathogenesis of mood disorders are essentially unknown.*

While studies of the brain in mood disorders have identified abnormalities in multiple, disparate regions, it is clear that circuits rather than regions must be involved. Returning to the first question above, proceeding from coherent hypotheses based on existing knowledge of such circuits and their role in maintaining normal mood states is more likely to be informative regarding etiology and pathogenesis than a less directed search. A conceptually related issue is that in attempting to maintain comparability among different studies attempting to unify investigations across a range of syndromes, one must heed the multiple methodological pitfalls that affect compatibility and quality of imaging studies, such as those listed by Schlaepfer and Pearlson (1997), some of which are discussed in detail in the chapter by Smith et al.

2. *There is extreme clinical heterogeneity of mood disorder syndromes.*

The current classification of mood syndromes is based essentially on phenomenology and some 10 diverse forms of the disorders are listed (see, for example, Schlaepfer and Pearlson, 1997). It is unclear whether clinically

separate syndromes represent different symptomatic manifestations of a single underlying biological problem or whether there are multiple subtypes of mood disorders each associated with its own biology. This question is seldom addressed by researchers but has important consequences for study design and analysis. At the very least, we need careful phenomenological descriptions of study populations to see whether study findings can be replicated.

3. *It is uncertain whether mood disorders that begin in childhood, early to midlife, and late life are variants of the same underlying etiological and pathogenic process or whether they are biologically separate.*

Studies of major depression with onset in later life strongly imply a vascular etiology for at least this subtype of the disorder. There is relatively little information on whether other identifiable etiological/risk factors exist for other possible affective subsyndromes; many research studies certainly focus on one life period rather than comparing across the life cycle. The issue of unity versus diversity deserves more detailed examination.

4. *Importance of secondary symptoms and signs.*

What are generally considered "primary" affective symptoms of mood, vegetative, and self-attitude changes are surrounded by a penumbra of perhaps equally important abnormalities in cognition, neuroendocrine function, etc. The cerebral basis for these syndromes also needs to be clarified in order to determine their relationship to other pathophysiological changes.

5. *Comorbidity and related issues.*

Alcohol and drug abuse are common accompaniments of mood disorders. When combined with effects of current and prior treatments and chronicity, these represent significant potential confounds to imaging studies.

6. *Neurotransmitter interactions are complex and current experimental designs too simple to capture much of this complexity.*

As stressed by Smith et al., in general, most scientific investigations into neurotransmitter systems in mood disorders have focused on single neurochemicals in isolation. Under real-world circumstances, neurotransmitters interact and mutually regulate each other's functioning; in fact, disturbances in just such regulatory mechanisms may underlie mood disorders. Thus PET investigations of neurotransmitters and receptors in affective syndromes would be improved by an ability and willingness to assess interactions between different systems.

Some suggestions for solutions to the above problems:

In the future, imaging studies in affective syndromes would be aided by more hypothesis-driven studies that focus on combined and integrated approaches—for example, overlapping two or more avenues of investigation from those discussed above. Attention to clinically homogeneous, genetically studied samples would reduce variance, but cognizance of the limitations of phenomenology as the basis for classification also needs to be kept in mind. Recording comorbidities and attending to "secondary" endocrine and cognitive changes would also be desirable. It is straightforward to see how brain imaging studies carried out longitudinally through illness, treatment, and recovery can clarify state versus trait issues and possible therapeutic mechanisms. Comparison studies across schizophrenia and mood disorders and across different age ranges will help address specificity issues.

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