Neuroimaging in Bipolar Disorder: What Have We Learned?

Andrew L. Stoll, Perry F. Renshaw, Deborah A. Yurgelun-Todd, and Bruce M. Cohen

New technologies are offering increasingly powerful means to obtain structural, chemical, and functional images of the brain during life, often without the use of ionizing radiation. Bipolar disorder, with its clear physiologic features, would appear to be a prime candidate for the application of current brain imaging; however, only a modest number of studies have been reported to date, and most studies have small sample sizes and heterogeneous subject groups. Nonetheless, there are a few consistent findings among these studies, including the following: 1) Structural imaging studies suggest an increased number of white matter hyperintensities in patients with bipolar disorder. These may be lesions unique to bipolar disorder and its treatment, or related to cardiovascular risk factors, which are more common in bipolar patients. Decreased cerebellar size and anomalies of cerebellar blood volume have also been reported. Increased sulcal prominence and enlargement of the lateral and third ventricles are less consistently observed findings. 2) Spectroscopic imaging suggests abnormalities of metabolism of choline-containing compounds in symptomatically ill bipolar patients and, possibly, treatment-induced changes in choline- and myo-inositol–containing compounds. Each of these groups of metabolites serves as a component of membrane phospholipids and cellular second-messenger cycles. 3) Metabolic and blood flow studies provide evidence for decreased activity of the prefrontal cortex (PFC) in bipolar patients during depression. It is not clear if these changes are restricted to particular subregions of the PFC, nor if they are reversed with mania.

No single pathophysiologic mechanism yet explains these findings, although all might be due to regional alterations in cellular activity and metabolism or changes in cell membrane composition and turnover.

The development of imaging technologies has far outpaced their use in bipolar disorder. The promise of future studies is great, with more powerful magnetic resonance scanners, additional ligands for positron emission tomography and single photon emission computed tomography imaging, and improved image generation and processing already available. Biol Psychiatry 2000;48:505–517 © 2000 Society of Biological Psychiatry

Key Words: Bipolar disorder, imaging, MRI, SPECT, PET

Introduction

Neuroimaging technologies are maturing rapidly. Earlier techniques, such as x-ray computed tomography (CT) and electroencephalography, have been joined by magnetic resonance imaging (MRI), magnetic resonance spectroscopy (MRS), functional magnetic resonance (fMR), positron emission tomography (PET), and single photon emission computed tomography (SPECT). In addition, these recent techniques have steadily become more sensitive, more reliable, and more affordable (Rauch and Renshaw 1995).

Increasingly in the last decade, brain imaging has been applied to the study of psychiatric disorders and, most notably, to research on schizophrenia and depression, leading to new clues on cause and treatment. By comparison, bipolar disorder has received less attention. This is unfortunate, as bipolar disorder is relatively common, often quite disruptive to normal living, and clearly mediated by biological factors.

Genetic studies have the most direct evidence of a biological basis for bipolar disorder, notably the concordance rates for monozygotic identical twins being twofold higher than those of same sex dizygotic (fraternal) twins. In fact, depending on definition of illness, identical twin concordance rates vary from 50% to nearly 100%, indicating a substantial role for inherited factors. Family and adoption studies confirm these findings (National Institute of Mental Health’s Genetics Workgroup 1999).

Further evidence of a biological etiology and pathogenesis in bipolar disorder stems from pharmacologic research, where specific drugs can mimic or ameliorate bipolar symptoms. For example, antidepressants, corticosteroids, and other classes of drugs can induce or exacer-
bate mania. Psychostimulants, such as d-amphetamine, cocaine, and others can induce hypomaniaclike states at low doses and maniclike psychosis at high and repeated doses. In contrast, mood-stabilizing and antimanic medications, such as lithium carbonate and valproate, and antipsychotic agents, such as haloperidol and clozapine, reduce or eliminate manic symptoms (Baldessarini 1996).

Clues to the neural substrate of affective symptoms in bipolar disorder come from studies of normal volunteers as well as subjects with unipolar major depression. Areas of the brain that appear to mediate both normal and abnormal mood include anterior limbic and paralimbic structures, such as the prefrontal cortex and anterior cingulate cortex; subcortical structures, such as the thalamus, basal ganglia, and nucleus accumbens; and temporal lobe structures, notably the amygdala and hippocampus (Davidson et al. 1999; Dougherty and Rauch 1997; Kennedy et al. 1997; Ketter et al. 1996; Soares and Mann 1997b). Studies of brain lesions, mostly stroke and tumors, show a relationship between left-sided frontal regions and depression and right-sided regions and mania, though appearance of the latter is less frequent than the former (Soares and Mann 1997a; Starkstein et al. 1991). Subcortical lesions, especially of the caudate and thalamus, can also present with mood dysregulation, with right-sided lesions again being more commonly associated with mania (Starkstein et al. 1991).

Bipolar disorder is not only typified by the affective symptoms of mania and depression. Physiologic and somatic symptoms of altered sleep, energy, and appetite suggest involvement of brain stem nuclei and the hypothalamus. By analogy to findings in schizophrenia, hallucinations and cognitive symptoms suggest involvement of the temporal cortex and temporal lobe structures as well as the parietal and prefrontal cortices, respectively.

Thus, there are numerous leads in the search for candidate neural substrates involved in the syndrome of bipolar disorder. The background evidence and the profound and often severe clinical presentation of patients with bipolar disorder suggest that sufficiently sensitive and specific brain imaging technologies will be able to detect the crucial brain substrate of bipolar illness.

In preparation for this article, a review of the literature was conducted using the software OVID to search the MEDLINE database. The subject heading bipolar disorder, combined with imaging, was searched for the years 1966–2000. In this review we will discuss some of the newer imaging technologies (specifically, MRI, MRS, fMR, PET, and SPECT), review data from the application of these techniques to the study of bipolar disorder, and provide recommendations on the use of current and developing imaging approaches in future research.

The purpose of this article is not to review individual articles, but to succinctly and clearly describe the most consistent findings among the neuroimaging studies in bipolar disorder (Table 1). In addition, this review focuses on the common methodological limitations and strengths of existing studies, design issues for future research, and emerging technology for this work.

Recent excellent reviews of individual study results are available for structural (Altschuler et al. 1995; Jeste et al. 1988; Norris et al. 1997; Soares and Mann 1997a; Videbech 1997; Yurgelun-Todd and Renshaw 1999), chemical (Kato et al. 1998; Moore and Renshaw 1997; Soares et al. 1996), and functional (Dougherty and Rauch 1997; Soares and Mann 1997b) brain imaging in bipolar disorder, and for affective disorders in general. Details of published studies and techniques can be found in these and the original sources cited.

### Imaging Technologies: An Overview

**MR Scanning**

Magnetic resonance scanning works by immersing tissues in a magnetic field. Due to their unpaired neutrons or protons, a number of atomic nuclei of biological relevance will line up with (in a lower, more stable energy state) or against (in a higher, less stable energy state) the static magnetic field. Brief radio frequency pulses are generated, which are absorbed by some of the lower energy nuclei, moving them into the higher energy, less stable state. When the radio frequency pulse is shut off, some of the nuclei that were shifted into the higher energy state revert back to the lower energy state, releasing radio frequency energy in the process. This released energy decays with two relaxation times, T1 and T2.

The T1 time represents the spin–lattice (or longitudinal) relaxation time and T2 is the spin–spin (or transverse) relaxation time. T1 measures the time required for nuclei as a whole to return to their baseline lower energy state in the magnetic field. The T2 relaxation time is the time between turning off the radio frequency pulse and lack of directionality to the sum of the individual nuclear spins.

### Table 1. Imaging Findings in Bipolar Disorder

<table>
<thead>
<tr>
<th>Finding</th>
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<tr>
<td>Increased white matter hyperintensities</td>
<td>Davidson et al. 1999; Dougherty and Rauch 1997; Kennedy et al. 1997;</td>
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<td>Ketter et al. 1996; Soares and Mann 1997b;</td>
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<td>Mild sulcal prominence and ventricular</td>
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*Note: This table is a simplified representation of the findings discussed in the text.*
The frequency and relaxation times of the atomic nuclei in tissues are dependent on the molecule containing each nucleus and the chemical milieu of each molecule. Therefore, the electromagnetic signal can be analyzed to yield anatomic (structural or MRI) data, chemical (MRS) data, or functional (blood flow and volume or fMRI) data.

MRI
Magnetic resonance imaging, a technique for structural or anatomic imaging of the brain, is based largely on signals from protons in water (H\textsubscript{2}O), the most prevalent chemical in the brain. The association of water with local lipids produces most of the regional signal differences in MRI scans. Magnetic resonance imaging has replaced x-ray CT in most clinical and almost all psychiatric neuroscience research applications. This is because MRI has superior contrast and soft tissue imaging capability, and because MRI does not expose the research subject to ionizing radiation. Therefore, subjects can be imaged repeatedly. Newer contrast agents, such as gadolinium, have improved the ability to differentiate certain pathologic processes, such as tumors, from normal tissue.

MRS
The physical chemistry governing MRI also applies to MRS. With some minor modifications, a standard MRI machine, instead of producing structural imaging data, can generate concentration data for a number of psychiatrically relevant compounds in a given volume (voxel) of brain tissue. The most common magnetic resonant nucleus used for MRS is hydrogen (\textsuperscript{1}H, or proton), since as with structural imaging, the high concentration of hydrogen in biological tissues and the great sensitivity of \textsuperscript{1}H in a magnetic field permits the detection of compounds in lower concentrations within the brain. Commonly measured compounds include those containing inositol, choline, creatine, or N-acetyl-aspartate. Phosphorous (\textsuperscript{31}P) MRS is also frequently used to measure phosphonoesters (PMEs) and phosphodiester (PDEs), including sugars and phospholipid-associated metabolic and catabolic components of cell membranes, as well as energy storage metabolites such as phosphocreatine (PCr) and nucleotide phosphates. Magnetic resonance spectroscopy technology has been applied to many other biologically important nuclei, including \textsuperscript{3}Li, the most abundant isotopic component of natural lithium, including lithium given as a medication, \textsuperscript{19}F, to detect the many fluorine-containing psychotropic drugs; and a low abundance form of carbon, \textsuperscript{13}C, to label biological compounds. \textsuperscript{23}Na, \textsuperscript{25}Mg, and \textsuperscript{39}K are also observable by MRS.

fMR
Functional magnetic resonance produces images related to cerebral blood flow or volume that, on average, correlate with the relative degree of activity of regions of the brain. Cerebral blood volume is based on the detection of the flow of intravenously administered paramagnetic tracers, such as gadolinium, through brain tissue, with measurements that can be made as frequently as one per second by a technique called dynamic susceptibility contrast MRI (DSCMRI; Belliveau et al 1991; Levin et al 1996; Rosen et al 1991). Alternatively, regional blood flow can be estimated by blood oxygenation level detection (Kwong et al 1992), which takes advantage of the fact that deoxyhemoglobin is paramagnetic, whereas oxygenated hemoglobin is not. Brain regions that are activated receive increased blood flow, delivering oxygen beyond their immediate needs, leading to a reduction of deoxyhemoglobin, greater regional coherence of the magnetic field, and a slightly greater MR signal, which identifies the activated region.

PET
Positron emission tomography scanning is based on compounds containing unstable isotopic forms of atomic nuclei (radioisotopes) that emit positrons when they disintegrate. When positrons encounter electrons, the two particles annihilate each other, releasing high energy gamma rays. The gamma rays radiate in opposite directions and can be detected by coincidence counters. Because the half-lives of these radioisotopes are brief, an on-site cyclotron or fast delivery from an off-site cyclotron is required to generate fresh isotopes on an as-needed basis. Positron emission tomography studies can be used to determine local brain activity through measurements of either regional cerebral blood flow or glucose utilization. As with fMR, PET works because blood flow and glucose metabolism are tightly linked to regional brain activity. The radioisotope-containing compounds typically used to estimate regional brain activity include \textsuperscript{11}C-glucose and \textsuperscript{18}F-deoxyglucose for metabolism and \textsuperscript{15}O-water for blood flow.

Positron emission tomography can also be used to detect and quantify radioisotope-containing ligands designed to bind to specific receptors and other sites of interest in the brain, such as neurotransmitter transporters or enzymes.

SPECT
Single photon emission computed tomography is based on compounds containing unstable radioisotopes that emit gamma rays on disintegration. No on-site linear accelera-
Brain Imaging Findings in Bipolar Disorder

MRI

The recurrent nature of bipolar disorder has often suggested a search for a chemical abnormality; however, structural anomalies can also potentially cause episodic illness or dyscontrol of mood. Although there are strikingly few postmortem studies of bipolar disorder, in vivo anatomic studies go back at least to the early 1980s, with some x-ray CT studies finding enlarged ventricles in subjects with bipolar disorder.

Magnetic resonance imaging provides high resolution, in vivo anatomic data, including separation of white and gray matter, and is well suited to identify structural abnormalities in psychiatric disorders. At least 30 MRI studies in patients with bipolar disorder have been published since 1987. Their most consistent finding is a higher than expected presence of white matter hyperintensities (WMHs). Two recent reviews (Altschuler et al 1995; Videbech 1997) document seven reports of a statistically significant increase of WMHs in patients with bipolar disorder. In fact, of 12 studies overall, all but two show at least a trend to an overall increase in the presence of WMHs. On average, the risk of having WMHs was elevated more than threefold in bipolar subjects.

White matter hyperintensities, best visualized with T₂-weighted images, are small areas where the signal intensity is high relative to the surrounding tissue. Most often seen in aging and cerebrovascular disorders, WMHs are extremely rare in healthy individuals without any personal history of psychiatric or neurologic illness who are under the age of 30–40 years (Steffens and Krishnan 1998). Demyelination, astrogliosis, or axonal loss as well as dilated perivascular spaces or diverticula of the lateral ventricles can also cause WMHs; however, the precise cause and relevance of WMHs in bipolar disorder are unclear, although data exist to suggest that the WMHs are present early in the course of illness (Botteron et al 1992; McDonald et al 1999), often at the first significant episode of illness (Strakowski et al 1993a), and are higher in bipolar patients at all ages (Woods et al 1995). Some studies have reported that WMHs are associated with a worse prior clinical course and a worse clinical outcome, but many have not (Altshuler et al 1995; Soares and Mann 1997). Whether the nature of the WMHs in subjects with bipolar disorder is similar to that of WMHs seen with aging has never been studied; however, bipolar patients have more alcohol and substance abuse (Strakowski et al 1998), more frequent smoking histories (Yates and Wallace 1987), and greater cardiovascular risk factors (such as hypertension) than healthy comparison subjects (Aylward et al 1994; Figiel et al 1991; Steffens and Krishnan 1998; Yates and Wallace 1987), all of which could lead to cerebrovascular lesions. Most patients with bipolar disorders do not have WMHs, nor is there a clear association between medications, such as lithium, that can alter lipid metabolism and lead to MR signal changes and the frequency of encountering WMHs (Figiel et al 1991; Norris et al 1997).

As with previous CT studies, some MRI studies have reported increased ventricular volume (Ellis et al 1995; Figiel et al 1991; Kato et al 1994; Raz and Raz 1990; Strakowski et al 1993b; Swayze et al 1990), including ventricle-to-brain volume ratio (VBR) and third ventricle volume (TVV; (Strakowski et al 1993b), in subjects with bipolar disorder. These results for VBR and TVV are not consistent across studies, with only six of 15 seeing statistically significant increases (Norris et al 1997; Soares and Mann 1997); however, most studies measuring VBR were modest in number of subjects, and increases in ventricular volume were small. Thus, inability to see an increase could reflect false negative results. Measurements of the brain regions surrounding the lateral and third ventricles show no decrease in gray matter volume (Zimpursky et al 1997). Nor are specific paraventricular nuclei clearly decreased in size. Small ventricular abnormalities
may be related to alterations in fluid homeostasis. Periventricular WMH, the most common WMH, might also be related to apparent VBR increases.

Many cortical and subcortical regions have been examined for a relationship to bipolar disorder. The most consistent report may be of a decrease in cerebellar size. Various studies using CT or MRI suggest cerebellar atrophy in psychosis, in general, and bipolar disorder, in particular (DellBello et al 1999; Heath et al 1979; Soares and Mann 1997a). Several studies observed statistically significant cerebellar atrophy, on average, in all or a subset of patients who were older or had multiple episodes of bipolar disorder (DellBello et al 1999; Nasrallah et al 1982a; 1982b; Yates et al 1987). All of the remaining studies of bipolar disorder show a substantial trend in the same direction (Loebel et al 1999; Weinberger et al 1982). Drug and especially alcohol abuse (Lippmann et al 1982), which can cause cerebellar atrophy, may be responsible for this finding. Lithium treatment may cause cerebellar changes as well (Roy et al 1998). If cerebellar abnormalities are illness rather than drug related, the pathophysiologic changes may be mediated, in part, by dysregulated cerebellar control over limbic and cortical regions (Schmahmann and Sherman 1998). Studies of the volumes of the striatum, amygdala, other temporal lobe structures, and the prefrontal cortex have yielded less consistent results. Drevets and associates (1997, 1998) have reported reduced volume and altered activity of the subgenual prefrontal cortex, an area activated during the production of normal moods, as well as a reduction of glial cells postmortem in bipolar subjects. Hirayasu and colleagues (1999) observed decreased subgenual cingulate cortex volume in subjects with first-episode affective psychosis, most of whom had bipolar disorder; however, the abnormality was only seen in patients with a family history of affective illness. Also, patients with schizophrenia had the same mean subgenual cingulate cortex volume as patients with affective illness and a positive family history of illness. These findings in the prefrontal cortex are well worth following up.

MRS

By its origins, MR scanning is a technique for chemical identification, and MRS has the potential to measure the concentrations of various endogenous and exogenous compounds in the brain. Most studies in bipolar disorder have used $^1$H or $^{31}$P MRS technology.

Choline is highly visible with $^1$H MRS and, as a precursor and metabolite of membrane phospholipids, second-messenger compounds, and the neurotransmitter acetylcholine, is among the more interesting compounds to study. Overall, several studies suggest a modest increase in choline concentration in the basal ganglia (Kato et al 1998; Moore and Renshaw 1997; Sharma et al 1992) and, possibly, the anterior cingulate (Soares et al 1999) in mania or depression, but not during euthymia.

Several groups using $^{31}$P MRS agree that there are elevations in PMEs, most likely in the frontal lobes in symptomatic patients with bipolar disorder (Deicken et al 1995; Kato et al 1998; Ketter et al 1996). Evidence has been reported for abnormal levels of other compounds readily observed by $^1$H MRS or $^{31}$P MRS, including myo-inositol, phosphocreatine, and PDEs, but these findings have not been repeatable across studies (Kato et al 1998; Moore et al 1999; Soares et al 1996).

The choline resonance by $^1$H MRS represents combined signals from several choline-containing compounds, including phosphocholine and glycerophosphocholine. Similarly, the PME resonance by $^{31}$P MRS, often taken to be a measure of precursors for membrane lipids, contains signals from numerous metabolites, including phosphocholine, phosphoethanolamine, and phosphoinositol (Moore and Renshaw 1997). It is possible that increased choline and PME resonances represent alternative measures of higher concentrations of the same molecule, phosphocholine, as its signal appears in each peak. No direct test of this possibility has yet been performed. It is also possible that both increases in choline and PME resonances are due to lithium treatment. Lithium inhibits choline transport, increases choline-containing metabolites in cells (Stoll et al 1992), and inhibits the breakdown of inositol monophosphate (IMP), leading to an intracellular increase in IMP (Berridge et al 1989). Both of these effects have been observed in nonhuman studies as well as in some in vivo studies in human subjects (Silverstone et al 1999; C.M. Demopoulos et al, unpublished data).

The ability to see changes in the choline and PME resonances in vivo is notable, as MRS can only observe compounds present in micromolar quantities. Such compounds, due to high concentration, serve as osmolytes, and can only show limited change without being balanced by alterations of other highly concentrated substances. A candidate for such changes would be taurine (Pasantes-Morales et al 1998), but while visible by MRS, its levels have not been studied in bipolar disorder. The substantial and consistently reported increases found for choline and PME may simply reflect changes in membrane turnover or cellular metabolism, activities that may be greatly altered regionally during the symptomatic phases of bipolar disorder.

fMR

Given its versatility and safety, it is perhaps surprising that there are few studies utilizing fMR in the study of bipolar
disorder. In fact, our search found only one. It noted decreased cerebral blood volume (measured by DSCMRI) in bipolar versus schizophrenic or healthy comparison subjects in each of nine regions measured, regionally significant for the cerebellar tonsils (Loeber et al 1999). Other studies have suggested reduced cerebellar volume (see above). Functionally, the cerebellum participates in regulation of numerous areas thought to be associated with control of mood and the symptoms of affective illness, including limbic and paralimbic brain regions and the monoaminergic nuclei of the midbrain (Loeber et al 1999; Soares and Mann 1997a, 1997b).

**PET**

Positron emission tomography has been used predominantly in metabolic ($^{18}$F-fluorodeoxyglucose) studies in bipolar disorder. Studies mixing subjects with unipolar and bipolar depression, with most subjects having unipolar illness, have tended to see a reduction of metabolism in the prefrontal cortex (Soares and Mann 1997b), which may correlate with severity of illness (Soares and Mann 1997b). For bipolar depression or mania, alone, no consensus of findings suggests altered metabolism in the brain as a whole or in the prefrontal cortex or its constituent parts (Ketter et al 1996; Soares and Mann 1997b). Single studies, without independent reports of replication, have observed increased metabolism in basal ganglia and the thalamus in bipolar depression (Baxter et al 1989) and increased metabolism in the left amygdala in mania (Al-Mousawi et al 1996). A single cerebral blood flow study with $^{15}$O suggested increased activity in the subgenual prefrontal cortex during mania (Drevets et al 1997).

**SPECT**

Cerebral blood flow studies, performed with $^{133}$Xenon, IMP, or $^{99}$Te tend, like metabolic studies, to suggest a reduction in prefrontal cortex with depression, but most studies mixed patients with unipolar and bipolar illness. No consistent, or replicated, differences have been reported for bipolar patients for the whole brain, temporal lobe structures, subcortical nuclei, or lateralized activity in the brain (Dougherty and Rauch 1997; Ketter et al 1996; Soares and Mann 1997b).

**Ligand Binding Studies**

There are individual, unreplicated reports in patients with bipolar disorder of 1) decreased frontal lobe but not striatal dopamine ($D_1$) binding sites (Suhara et al 1992), 2) no difference in $D_2$ binding sites versus control subjects (Wong et al 1985), or 3) an increase in $D_2$ binding sites in subjects with psychosis versus those without psychosis (Pearlson et al 1995). A recent report observed a decrease in serotonin ($5HT_{1A}$) binding sites in various brain regions in 17 subjects with mood disorders ($N = 4$ subjects with bipolar disorder; Drevets et al 1999); however, postmortem studies show no consistent decrease in $5HT_{1A}$ receptors in affective disorders. Neither do genetic studies show an association or linkage between structural genes for dopamine or serotonin receptors and bipolar disorder. Perhaps any in vivo abnormalities are related to changes due to medications or the course of illness.

**Summary of Findings**

Whether for anatomic, biochemical, or functional questions, the current data on bipolar disorder are from a modest number of studies, often differing in design and technical approaches and spanning different regions of the brain. Despite the preliminary nature of these data, some themes arise and some results appear replicable (Table 1).

Structurally, it appears highly likely that there is an increase in WMHs in bipolar patients, even when they are young. This increase may be related to illness per se; medication, alcohol, or smoking; or cardiovascular factors. Bipolar patients may, on average, have a modest increase in ventricular size, an effect that seems to be generalized. Among brain regions, there may be anomalies of the cerebellum, which again may be related to drugs as well as illness.

Biochemically, there appear to be altered levels of compounds containing choline and PMEs in basal ganglia and the frontal cortex. These alterations could represent detection of the same molecule or closely related ones as measured by $^1$H MRS and $^{31}$P MRS, respectively. Here, too, the alterations could be a consequence of treatment as well as underlying pathophysiology.

Glucose metabolic and blood flow studies suggest decreased frontal cortical activity in depression, whether unipolar or bipolar. Of interest, WMHs may be most common in frontal white matter or in periventricular regions in the frontal pole (Viedbech 1997). Individual studies of other regions thought to mediate mood, although not replicated, show abnormal metabolism in blood flow in various temporal lobe and subcortical nuclei.

No specific pathophysiologic mechanism has been demonstrated that could underlie or unify all of these findings. Abnormalities of membrane composition or turnover could explain increased WMHs as well as alteration of choline-containing compounds and PMEs, which are involved in membrane metabolism. Structural and functional abnormalities are observed in areas thought to be associated with cerebral tone (thalamus, cerebellum), emotional reactivity (amygdala and cingulate cortex), and high level
cognition and behavioral control (prefrontal cortex), all of which are altered in bipolar disorder. Future, more targeted studies can address these findings through the testing of hypotheses regarding specific molecular and functional abnormalities (see below).

Limitations in Interpreting Findings

Anyone who performs clinical psychiatric research will confirm that these studies are very difficult to design, complete, and interpret. While technologic advances make such studies more powerful, they do not necessarily make them easier, as they add complexity and an element of constant change through upgrades of techniques. The study of bipolar disorder by imaging technology is further confounded by historically low funding that cannot cover the cost of dedicated subject recruitment and evaluation staff or the full expense of scans and scan analysis. For these reasons, numerous caveats must be considered in the interpretation of existing studies.

By and large, sample sizes in the studies reported were small, often under 10 subjects, leading to a high likelihood of missed findings (false negative or type II error). By comparison, measures were often many, leading to a likelihood of findings by chance alone, a false positive or type I error.

These issues are compounded by the fact that bipolar disorder is likely heterogeneous in etiology and pathophysiology and is certainly heterogeneous in course, illness phase, and treatment response. Most studies do not or, given their small size, cannot control for these factors. Treatment is highly variable, and medications can affect brain volume as well as chemistry and function. The enlarged caudate in patients treated with neuroleptics illustrates this point well (Chakos et al 1994). Past or recent medication is often not documented, but drug effects can last weeks to years after exposure (Cohen et al 1992). Alcohol and substance use are also relevant, although are rarely documented, and dietary supplements, from stimulants to membrane precursors, such as ω-3 fatty acids, choline, and inositol, can potentially change brain structure and function to a degree detectable by current brain imaging technologies.

Matching of populations is also crucial for ensuring valid results, but is difficult to control. Few studies matched for sociodemographic conditions, IQ, ethnicity, or even age or gender, though these can have profound effects on all brain measures and cognitive/functional performance.

Similarly, on the technologic side, a variety of machines and techniques were used, as were a variety of analytic programs. This is partly an irreducible consequence of instrumentation and technical advance. Nonetheless, in comparing and interpreting findings it is important to recall that brain images are extensively processed through multiple stages of analysis, are highly dependent on machine type and analytic assumptions, and are not direct pictures of the brain.

Structural imaging by MRI produces high resolution scans, but boundaries between regions are often uncertain or arbitrary. Measures used vary between line, area, and volume.

Chemical imaging by MRS currently provides information only on compounds at very high concentrations in the brain. These compounds tend to have multiple functions as precursors, metabolites, and osmolytes. Seemingly individual MRS resonance peaks almost always contain signals from multiple related compounds, as well as unrelated compounds with overlapping resonance. The interpretation of changes in peak height or area are often oversimplified and inadequately blinded. Not only may they not take into account the numerous underlying sources of signal, but they also rarely take into account changes in the rate of disappearance (relaxation) of signals that may reflect aspects of tissue unrelated to concentration of the compound observed. Thus, a change in peak area or height may not mean a change in concentration of substances contributing to the peak.

Functional imaging represents a set of techniques variously measuring regional blood flow, blood volume, metabolism, or radioisotope binding. None of the techniques are equivalent measures nor are their signals a direct measure of neuronal firing, receptor level, or activity. Resolution on in vivo functional brain imaging combines information from many different cell groups, not a single coordinated group of cells. In addition, regional and whole brain activity is highly dependent not only on illness, but also on medication and on whatever the patient is thinking or doing. Cognitive state or task is controlled in very few studies.

These limitations suggest clear guidelines for improvement in future studies, including larger sample sizes, more thorough assessment, better matching, and greater attention to subject characteristics and analysis and interpretation of findings. Nonetheless, for a small number of studies, existing data provide both clear leads and a good reason to believe more specific hypotheses will be generated and tested. Advances in technology suggest the same.

Future Studies

The future of brain imaging in bipolar disorder is exceptionally bright. In part this is because technologic advances continue at a rapid pace (Table 2). In addition, existing studies suggest clear directions for optimizing and expanding future work. Taking into account advances in
both brain imaging techniques and design, some areas of future promise are listed here.

**MR Scanners**
- Most current studies are performed on 1.5-T clinical magnets. Increasingly 3-T, 4-T, and even 7-T magnets with bore sizes large enough for human heads or entire bodies are becoming available. These machines will improve all MR scanning, providing higher resolution structural and functional MRI and greater separation of compounds and sensitivity to compounds at lower concentrations by MRS.

**MRI**
- Past studies have concentrated on volumetric (size) analysis, but abnormalities may only affect part of a brain region or nucleus. Increasingly, analytic techniques are available for sophisticated morphometric (shape) analysis of nuclei, which may reveal previously unseen disease-related phenomena.
- No studies have compared in vivo to postmortem findings in the same individual. Also, structural MRI and histologic analysis can both be performed on a postmortem brain. In this fashion, the nature of WMHs or other anomalies seen by MR in bipolar disorder can be associated with a lesion at the cellular or molecular level.

**MRS**
- Proton decoupling (Luyten et al 1989; Murphy et al 1993), spectral editing (Mescher et al 1998; Rothman et al 1992), double quantum filtering (Keltner et al 1997; Thompson and Allen 1998) and two-dimensional MRS (Hurd et al 1998; Ryner et al 1995) can separate resonances from different compounds that normally appear in a single peak, thus allowing changes to be associated with individual metabolites or with metabolites that could not previously be studied.
- Diffusion-weighted imaging and diffusion tensor imaging take advantage of constraints imposed on molecular movement by cell membranes and axons to study cellular integrity and define white matter tracts in the brain (Rowley et al 1999; Shimony et al 1999).
- Chemical shift imaging (Nelson et al 1997; Vikhof-Baaz et al 1999) allows spectroscopic information to be rapidly obtained from large regions of the brain, with subsequent processing leading to the analysis of chemical signals from smaller, specific localized volumes.
- $^{13}$C can be used to label naturally occurring compounds (Bluml 1999; Petersen et al 1999) to follow brain metabolism of nutrients such as choline, inositol, or $\omega$-3 fatty acids, thus allowing the study of cell membrane turnover and second-messenger signaling.
- Many psychotropic drugs contain one or more fluorine atoms, which may make them visible by MRS with high-field strength magnets (Christensen et al 1998; Strauss et al 1998).
- Magnetic resonance signals contain far more information than is extracted. In MRS studies, peak amplitudes are usually measured at one particular time following excitation; however, different compounds under the same peak, as well as the same compound in different tissues or chemical backgrounds, can show very different rates of signal disappearance (relaxation time). These delay characteristics can be responsible for significant signal differences and can provide a new window on tissue abnormalities in bipolar disorder or other illnesses.

**Functional Imaging**
- For all forms of functional imaging, fMR, PET, or SPECT, cognitive tasks can be applied that activate specific brain circuits. Using such tasks adds addi-
tional controls over subject state and provides data on system responsivity, not just baseline regional activity.

- For SPECT, multiple-head cameras and dedicated ring-detector brain cameras have increased signal resolution (Noto and Scheiner 1999).
- New scintillators are under development for more sensitive γ-ray signal detection for both PET and SPECT (Noto and Scheiner 1999).

**Ligand Binding**

- Radioisotope-labeled ligands are available for PET scanning of dopamine D<sub>1</sub> and D<sub>2</sub> receptors and the dopamine transporter (Ouchi et al. 1999); brain uptake and metabolism of DOPA (Ito et al. 1999); 5-HT<sub>2</sub> (Attar-Levy et al. 1999) and 5-HT<sub>1A</sub> receptors; the serotonin transporter (McCann et al. 1998; Szabo et al. 1999); brain uptake and metabolism of tryptophan (Benkelfat et al. 1999); opioid receptors (Duncan 1999; Smith et al. 1999; Zubieta et al. 1999); histamine (H<sub>1</sub>) receptors (Kim et al. 1999); γ-aminobutyric acid A (GABA<sub>A</sub>) receptors (Weber et al. 1999); and levels of acetylcholinesterase (Namba et al. 1999). Single photon emission computed tomography ligands are available for D<sub>2</sub> receptors (Kuenstler et al. 1999), the dopamine transporter (Booij et al. 1999), and the GABA<sub>A</sub> receptor (Morimoto 1999).
- Positron emission tomography ligands under development include agents binding to muscarinic (Kiesewetter et al. 1999) and nicotinic acetylcholine (Valette et al. 1999) receptors and the N-methyl-D-aspartate glutamate receptor (Ametamey et al. 1999).
- Single photon emission computed tomography ligands under development include agents binding to the serotonin transporter (Dresel et al. 1999) and nicotinic acetylcholine receptors (Musachio et al. 1999).

**Study Design**

Many design issues have already been mentioned in the section on the limitations of current studies and techniques. Among them, attention to control and documentation of past and current medication, drugs of abuse, alcohol, smoking, and dietary supplements is very useful. Larger numbers of subjects are desirable in imaging studies and can help produce subgroups with some homogeneity by state, symptoms, clinical history, and drug response. Matching for age, gender, and ethnic, socioeconomic, and educational background are essential, though varying degrees of difficulty.

Other design issues worth considering include the following:

- Magnetic resonance techniques, particularly those involving no ionizing radiation, are ideal for longitudinal studies of structure, chemistry, or function through time, treatment, and different stages of illness. There is great power gained on state-related phenomena when a subject can be his or her own control subject.
- Similarly, MR techniques are well suited for use in children, either those who have early-onset illness or those at risk for illness. Including only the more severe presentations, lifetime risk to a first-degree relative of an individual with bipolar disorder is approximately 25%. Adding less severe manifestations, like cyclothymia, brings the risk close to 50%. Longitudinal studies of relatives can provide crucial information on those who will develop illness but who are currently asymptomatic or minimally symptomatic and are untreated.
- Bipolar disorder appears, as noted, to be a disease of heterogeneous origin and presentation. For this reason, it is wise not to look just at mean differences between subject groups, but to look 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 numbers aid in such an analysis.

Finally, it is important to recognize that brain imaging requires multidisciplinary teams of clinicians, scientists, and technologists. Often these collaborators do not understand the strengths and limitations of one another’s fields. Thus, the clinician may not appreciate the degree to which imaging data require postimage processing. The nonclinical technologist may have little appreciation of the difficulties and importance of high quality clinical recruiting, evaluation, and classification.

Ultimately, imaging studies are most powerful if a team of experts, including pharmacologists, epidemiologists, and generalists as well as clinicians and imaging specialists, is involved. Collaborations need not be on site, but they should involve as much information sharing and longer term association as possible.

We hope this review will serve to enhance such sharing in this young and promising field.

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