ATTACHMENT A

CURRICULUM VITAE

Wayne Andrew Stillings, M.D.

PLACE & DATE OF BIRTH: Appleton, Wisconsin - January 23, 1949

EDUCATION: Oberlin College, B.S. 1967-1971
Washington University School of Medicine, M.D. 1971-1975

RESIDENCY: Barnes Hospital, Department of Psychiatry 1975-1978

HOSPITAL APPOINTMENTS: Assistant Psychiatrist, Barnes Hospital 1978 on
Assistant, Jewish Hospital 1978-1983
Assistant Attending, Jewish Hospital 1983 on

TEACHING APPOINTMENT: Instructor in Clinical Psychiatry, Washington University School of Medicine 1978-1983
Assistant Professor of Clinical Psychiatry Washington University School of Medicine 1983 on

PRIVATE PRACTICE: July 1, 1978

BOARD CERTIFICATION: National Board of Medical Examiners, 1975
American Board of Psychiatry & Neurology, 1979

LICENSE: Missouri, R6971, 1976

PROFESSIONAL SOCIETIES: American Medical Association
Eastern Missouri Psychiatric Society
American Psychiatric Association
American Association for the Advancement of Science

American Society of Law & Medicine
American Academy of Psychiatry & Law
American Academy of Clinical Psychiatrists

HONORARY SOCIETIES: Phi Beta Kappa
Sigma Xi
Alpha Omega Alpha

PUBLICATIONS

Scott, G.T. & Stillings, W.A.: Evidence for the release of MSH by phenothiazine ataraxics. Endocrinology 90:2, 545-551, 1972

Raichman, J.A., Martin, R.L., & Stillings, W.A.: Catatonic stupor: A diagnostically non-specific but distinct syndrome. J. Clinical Psychiatry 42:12, 477 478, Dec. 1981

Helzer, J.E., Stillings, W.A., et al: A control study of the association between ulcerative colitis and psychiatric disorders. Digestive Diseases and Sciences, Vol. 27, 513-518, 1982.

Helzer, J.E., Chammas, S., Stillings, W.A., et al: A study of the association between Crohn's disease and psychiatric illness. J. Gastroenterology 1984: 86: 324-30.

FORENSIC AND CONTINUING MEDICAL EDUCATION

1) American Academy of Psychiatry and the Law; Forensic Psychiatry Course: Board Review and Update.
   a) The Forensic Psychiatry Exam: An Overview.
   b) Involuntary Civil Commitment.
   c) The Battered Child.
   d) Personal Injury Action: The Psychiatrist's Role.
   e) Malpractice.
   f) Privilege and Confidentiality.
   g) Competence to Stand Trial and as a General Principle.
   h) Criminal Responsibility: Historical Perspective and Modern Application.

i) Videotape of Criminal Responsibility Examination.
j) Right to Treatment-Right to Refuse Treatment.
k) Child Forensic Issues.
l) Child Custody.
m) The Psychiatrist as Expert Witness.

2) Psychological Damages: Advocacy and Defense:
a) The Law and Psychic Trauma: Current Trends.
b) Evaluation of "Psychic Damages" in Negligence and Workers' Compensation Cases: An Overview of Strategies.
c) Psychological and Neuropsychological Testing: Strategies for Plaintiff/Strategies for Defenses.
d) Post-Traumatic Stress Disorder: Plaintiff and Defense.
e) Mock-Up of Consultation on a Post-Traumatic Stress Disorder Case.
f) Closed Head Injury: Plaintiff and Defense ("Shearing Injury" Case).
g) Mock-Up of Consultation on a Closed Head Injury Case.
h) An Introduction to Mock Jury Strategies in Civil Litigation.

3) Expert Witness in Psychic Stress Litigation.

4) The Treatment of Post-Traumatic Stress Disorder.

5) The Detection of Malingered Mental Illness.

6) Treatment of Panic Disorders and Agoraphobia.

7) Cognitive Therapy of Panic Disorders, 1989, 1992.

8) How To Do Child Custody Evaluations.

9) The Psychiatrist as an Expert Witness, 1988, 1989, 1992.

10) The Medical Letter and The Yale School of Medicine-CME exams #20, #21, and #22.

11) 1st Annual Premenstrual Syndrome Seminar.

12) Clinical Applications of the MMPI-2-Basic Course.

13) Clinical Applications of the MMPI-2-Advanced Course.

14) 1992 St. Louis Psychiatric Symposium.

15) Motivating the Chemically-Dependent Patient for Treatment.

16) Fifth Annual Forensic Conference-University of Southern Florida. The Psychiatric Expert-Courtroom Techniques.

17) Processing of Traumatic Memories.

18) Evolutionary Biology: A Foundation For Psychiatry.

19) Behavior Therapy in Psychiatry.

20) Insanity Defense Evaluations.

21) American Academy of Clinical Psychiatrists 1993 Program.

22) Seminars with the Experts.

23) Pain and Pain Management.

24) International Psychiatric Congress.

25) An Update on Briefer Therapies in the Managed Care World.

26) St. Vincent's Hospital and Medical Center of New York-Malpractice Risk Management Volume 3.

27) St. Vincent's Hospital and Medical Center of New York-Risk Management Volume 1.

28) Violence: Implications for Clinical Practice.

29) Diagnosis, Treatment Planning, Managing the Difficult Patient.

30) Rapid Stabilization of Acute Episodes in Bipolar Disorder Patients.

31) American Academy of Disability Evaluating Physicians, Eleventh Annual Scientific Session.

32) How to be an Effective, Successful, and Ethical Medical Witness.

33) Clinical Update on Anxiety Disorders.

34) Better Recognition and Treatment for Geriatrics, Women, Children and Adolescents.

35) An Update on Alcoholism, Substance Abuse, Schizophrenia and Comorbid Disorders.

36) Child and Adolescent Advanced Update.

37) Improved Treatment Strategies for Dementias, Delirium, and Depression.

SPEAKING ENGAGEMENTS AND SEMINARS

"Psychiatric Issues in the Personal Injury Case"
November 30, 1990
The Bar Association of Metropolitan St. Louis

"Detection of Malingering"
January 12, 1992
St. John's Mercy Medical Center

"Posttraumatic Stress Disorder"
July 14, 1992
St. John's Mercy Medical Center

"The Psychiatric Aspects of Pain"
October 21, 1992
Missouri Rehab Professionals Association

Updates in Occupational Medicine
"The Detection of Malingering"
May 12, 1993
St. John's Mercy Medical Center

"Posttraumatic Stress Disorder"
July 21, 1993
Case Management Society of St. Louis

"Spinal Disorders in the Work Comp System: A Psychiatrist's View"
May 12, 1995
St. Louis Spine Care Alliance

"Sexual Harassment: From the Boardroom to the Retail Store and Back"
November 16, 1995
University of Missouri-Kansas City
School of Law/Continuing Legal Education

"Process of Case Review in Psychiatric Causality"
May 10, 1996
St. Louis Spine Care Alliance

"Posttraumatic Stress Disorder"
February 5, 1998
Missouri Employers Mutual Insurance

"Dealing With the Difficult Patient"
March 6, 1998
Third Annual Conference on Occupational Health and Workers' Compensation

"The Quintessential Psychiatric Stress Injury: Posttraumtic Stress Disorder (PTSD)"
April 9, 1998
Sixth Annual Amelung, Wulff & Willenbrock, P.C. Law Seminar

"Psychiatric Challenges in the Workers' Compensation System"
July 31, 1998
Attorney Generals' Labor Division Seminar

"Preparing Your Worker's Compensation Program for the Next Millennium"
September 12-15, 1998
Missouri Self-Insurer's Association, 9th Annual Meeting, Panelist

Manic Episode

Episode Features

A Manic Episode is defined by a distinct period during which there is an abnormally and persistently elevated, expansive, or irritable mood. This period of abnormal mood must last at least 1 week (or less if hospitalization is required) (Criterion A). The mood disturbance must be accompanied by at least three additional symptoms from a list that includes inflated self-esteem or grandiosity, decreased need for sleep, pressure of speech, flight of ideas, distractibility, increased involvement in goal-directed activities or psychomotor agitation, and excessive involvement in pleasurable activities with a high potential for painful consequences. If the mood is irritable (rather than elevated or expansive), at least four of the above symptoms must be present (Criterion B). The symptoms do not meet criteria for a Mixed Episode, which is characterized by the symptoms of both a Manic Episode and a Major Depressive Episode occurring nearly every day for at least a 1-week period (Criterion C). The disturbance must be sufficiently severe to cause marked impairment in social or occupational functioning or to require hospitalization, or it is characterized by the presence of psychotic features (Criterion D). The episode must not be due to the direct physiological effects of a drug of abuse, a medication, other somatic treatments for depression (e.g., electroconvulsive therapy or light therapy) or toxin exposure. The episode must also not be due to the direct physiological effects of a general medical condition (e.g., multiple sclerosis, brain tumor) (Criterion E).

The elevated mood of a Manic Episode may be described as euphoric, unusually good, cheerful, or high. Although the person's mood may initially have an infectious quality for the uninvolved observer, it is recognized as excessive by those who know the person well. The expansive quality of the mood is characterized by unceasing and indiscriminate enthusiasm for interpersonal, sexual, or occupational interactions. For example, the person may spontaneously start extensive conversations with strangers in public places, or a salesperson may telephone strangers at home in the early morning hours to initiate sales. Although elevated mood is considered the prototypical symptom, the predominant mood disturbance may be irritability, particularly when the person's wishes are thwarted. Lability of mood (e.g., the alternation between euphoria and irritability) is frequently seen.

Inflated self-esteem is typically present, ranging from uncritical self-confidence to marked grandiosity, and may reach delusional proportions (Criterion B1). Individuals may give advice on matters about which they have no special knowledge (e.g., how to run the United Nations). Despite lack of any particular experience or talent, the individual may embark on writing a novel or composing a symphony or seek publicity for some impractical invention. Grandiose delusions are common (e.g., having a special relationship to God or to some public figure from the political, religious, or entertainment world).

Almost invariably, there is a decreased need for sleep (Criterion B2). The person usually awakens several hours earlier than usual, feeling full of energy. When the sleep disturbance is severe, the person may go for days without sleep and yet not feel tired.

Manic speech is typically pressured, loud, rapid, and difficult to interrupt (Criterion B3). Individuals may talk nonstop, sometimes for hours on end, and without regard for others' wishes to communicate. Speech is sometimes characterized by joking, punning, and amusing irrelevancies. The individual may become theatrical, with dramatic mannerisms and singing. Sounds rather than meaningful conceptual relationships may govern word choice (i.e., clanging). If the person's mood is more irritable than expansive,

Mood Disorders Specifiers

speech may be marked by complaints, hostile comments, or angry tirades.

The individual's thoughts may race, often at a rate faster than can be articulated (Criterion B4). Some individuals with Manic Episodes report that this experience resembles watching two or three television programs simultaneously. Frequently there is flight of ideas evidenced by a nearly continuous flow of accelerated speech, with abrupt changes from one topic to another. For example, while talking about a potential business deal to sell computers, a salesperson may shift to discussing in minute detail the history of the computer chip, the industrial revolution, or applied mathematics. When flight of ideas is severe, speech may become disorganized and incoherent.

Distractibility (Criterion B5) is evidenced by an inability to screen out irrelevant external stimuli (e.g., the interviewer's tie, background noises or conversations, or furnishings in the room). There may be a reduced ability to differentiate between thoughts that are germane to the topic and thoughts that are only slightly relevant or clearly irrelevant.

The increase in goal-directed activity often involves excessive planning of, and excessive participation in, multiple activities (e.g., sexual, occupational, political, religious) (Criterion B6). Increased sexual drive, fantasies, and behavior are often present. The person may simultaneously take on multiple new business ventures without regard for the apparent risks or the need to complete each venture satisfactorily. Almost invariably, there is increased sociability (e.g., renewing old acquaintances or calling friends or even strangers at all hours of the day or night), without regard to the intrusive, domineering, and demanding nature of these interactions. Individuals often display psychomotor agitation or restlessness by pacing or by holding multiple conversations simultaneously (e.g., by telephone and in person at the same time). Some individuals write a torrent of letters on many different topics to friends, public figures, or the media.

Expansiveness, unwarranted optimism, grandiosity, and poor judgment often lead to an imprudent involvement in pleasurable activities such as buying sprees, reckless driving, foolish business investments, and sexual behavior unusual for the person, even though these activities are likely to leave painful consequences (Criterion B7). The individual may purchase many unneeded items (e.g., 20 pairs of shoes, expensive antiques) without the money to pay for them. Unusual sexual behavior may include infidelity or indiscriminate sexual encounters with strangers.

The impairment resulting from the disturbance must be severe enough to cause marked impairment in functioning or to require hospitalization to protect the individual from the negative consequences of actions that result from poor judgment (e.g., financial losses, illegal activities, loss of employment, assaultive behavior). By definition, the presence of psychotic features during a Manic Episode constitutes marked impairment in functioning (Criterion D).

Symptoms like those seen in a Manic Episode may be due to the direct effects of antidepressant medication, electroconvulsive therapy, light therapy, or medication prescribed for other general medical conditions (e.g., corticosteroids). Such presentations are not considered Manic Episodes and do not count toward the diagnosis of Bipolar I Disorder. For example, if a person with recurrent Major Depressive Disorder develops manic symptoms following a course of antidepressant medication, the episode is diagnosed as a Substance-Induced Mood Disorder, With Manic Features, and there is no switch from a diagnosis of Major Depressive Disorder to Bipolar I Disorder. Some evidence suggests that there may be a bipolar "diathesis" in individuals who develop manic-like episodes following somatic treatment for depression. Such individuals may have an increased likelihood of future Manic, Mixed, or Hypomanic Episodes that are

not related to substances or somatic treatments for depression. This may be an especially important consideration in children and adolescents.

Associated Features and Disorders

Associated descriptive features and mental disorders. Individuals with a Manic Episode frequently do not recognize that they are ill and resist efforts to be treated. They may travel impulsively to other cities, losing contact with relatives and caretakers. They may change their dress, makeup, or personal appearance to a more sexually suggestive or charismatically flamboyant style that is out of character for them. They may engage in activities that have a disorganized or bizarre quality (e.g., distributing candy, money, or advice to passing strangers). Gambling and antisocial behaviors may accompany the Manic Episode. Ethical concerns may be disregarded even by those who are typically very conscientious (e.g., a stockbroker inappropriately buys and sells stock without the clients' knowledge or permission, a scientist misrepresents the findings of others). The person may be hostile and physically threatening to others. Some individuals, especially those with psychotic features, may become physically assaultive or suicidal. Adverse consequences of a Manic Episode (e.g., involuntary hospitalization, difficulties with the law, or serious financial difficulties) often result from poor judgment and hyperactivity. When no longer in the Manic Episode, most individuals are regretful for behaviors engaged in during the Manic Episode. Some individuals describe having a much sharper sense of smell, hearing, or vision (e.g., colors appear very bright). When catatonic symptoms (e.g., stupor, mutism, negativism, and posturing) are present, the specifier With Catatonic Features may be indicated (see p. 482).

Mood may shift rapidly to anger or depression. Depressive symptoms may last moments, hours, or more rarely, days. Not uncommonly, the depressive symptoms and manic symptoms occur simultaneously. If the criteria for both a Major Depressive Episode and a Manic Episode are prominent every day for at least 1 week, the episode is considered to be a Mixed Episode (see p. 533). As the Manic Episode develops, there is often a substantial increase in the use of alcohol or stimulants, which may exacerbate or prolong the episode.

Associated laboratory findings. No laboratory findings that are diagnostic of a Manic Episode have been identified. However, a variety of laboratory findings have been noted to be abnormal in groups of individuals with Manic Episodes compared with control subjects. Laboratory findings in Manic Episodes include polysomnographic abnormalities, increased cortisol secretion, and absence of dexamethasone nonsuppression. There may be abnormalities involving the norepinephrine, serotonin, acetylcholine, dopamine, or gamma-aminobutyric acid neurotransmitter systems, as demonstrated by studies of neurotransmitter metabolites, receptor functioning, pharmacological provocation, and neuroendocrine function.

Specific Culture, Age, and Gender Features

Cultural considerations that were suggested for Major Depressive Episodes are also relevant to Manic Episodes (see p. 324). Manic Episodes in adolescents are more likely to include psychotic features and may be associated with school truancy, antisocial behavior, school failure, or substance use. A significant minority of adolescents appear

Mood Disorder Specifiers

to have a history of long-standing behavior problems that precede the onset of a frank Manic Episode. It is unclear whether these problems represent a prolonged prodrome to Bipolar Disorder or an independent disorder. See the corresponding sections of the texts for Bipolar I Disorder (p. 352) and Bipolar II Disorder (p. 360) for specific information on gender.

Course

The mean age at onset for a first Manic Episode is the early 20s, but some cases start in adolescence and others start after age 50 years. Manic Episodes typically begin suddenly, with a rapid escalation of symptoms over a few days. Frequently, Manic Episodes occur following psychosocial stressors. The episodes usually last from a few weeks to several months and are briefer and end more abruptly than Major Depressive Episodes. In many instances (50%–60%), a Major Depressive Episode immediately precedes or immediately follows a Manic Episode, with no intervening period of euthymia. If the Manic Episode occurs in the postpartum period, there may be an increased risk for recurrence in subsequent postpartum periods and the specifier With Postpartum Onset is applicable (see p. 386).

Differential Diagnosis

A Manic Episode must be distinguished from a **Mood Disorder Due to a General Medical Condition.** The appropriate diagnosis would be Mood Disorder Due to a General Medical Condition if the mood disturbance is judged to be the direct physiological consequence of a specific general medical condition (e.g., multiple sclerosis, brain tumor, Cushing's syndrome) (see p. 366). This determination is based on the history, laboratory findings, or physical examination. If it is judged that the manic symptoms are not the direct physiological consequence of the general medical condition, then the primary Mood Disorder is recorded on Axis I (e.g., Bipolar I Disorder) and the general medical condition is recorded on Axis III (e.g., myocardial infarction). A late onset of a first Manic Episode (e.g., after age 50 years) should alert the clinician to the possibility of an etiological general medical condition or substance.

A **Substance-Induced Mood Disorder** is distinguished from a Manic Episode by the fact that a substance (e.g., a drug of abuse, a medication, or exposure to a toxin) is judged to be etiologically related to the mood disturbance (see p. 370). Symptoms like those seen in a Manic Episode may be precipitated by a drug of abuse (e.g., manic symptoms that occur only in the context of intoxication with cocaine would be diagnosed as Cocaine-Induced Mood Disorder, With Manic Features, With Onset During Intoxication). Symptoms like those seen in a Manic Episode may also be precipitated by antidepressant treatment, such as medication, electroconvulsive therapy, or light therapy. Such episodes are also diagnosed as Substance-Induced Mood Disorders (e.g., Amitriptyline-Induced Mood Disorder, With Manic Features; Electroconvulsive Therapy-Induced Mood Disorder, With Manic Features).

Manic Episodes should be distinguished from **Hypomanic Episodes.** Although Manic Episodes and Hypomanic Episodes have an identical list of characteristic symptoms, the disturbance in Hypomanic Episodes is not sufficiently severe to cause marked impairment in social or occupational functioning or to require hospitalization. Some Hypomanic Episodes may evolve into full Manic Episodes.

Major Depressive Episodes with prominent irritable mood may be difficult to

distinguish from Manic Episodes with irritable mood or from **Mixed Episodes.** This determination requires a careful clinical evaluation of the presence of manic symptoms. If criteria are met for both a Manic Episode and a Major Depressive Episode nearly every day for at least a 1-week period, this would constitute a Mixed Episode.

Attention-Deficit/Hyperactivity Disorder and a Manic Episode are both characterized by excessive activity, impulsive behavior, poor judgment, and denial of problems. Attention-Deficit/Hyperactivity Disorder is distinguished from a Manic Episode by its characteristic early onset (i.e., before age 7 years), chronic rather than episodic course, lack of relatively clear onsets and offsets, and the absence of abnormally expansive or elevated mood or psychotic features.

Criteria for Manic Episode

A. A distinct period of abnormally and persistently elevated, expansive, or irritable mood, lasting at least 1 week (or any duration if hospitalization is necessary).

B. During the period of mood disturbance, three (or more) of the following symptoms have persisted (four if the mood is only irritable) and have been present to a significant degree:

(1) inflated self-esteem or grandiosity
(2) decreased need for sleep (e.g., feels rested after only 3 hours of sleep)
(3) more talkative than usual or pressure to keep talking
(4) flight of ideas or subjective experience that thoughts are racing
(5) distractibility (i.e., attention too easily drawn to unimportant or irrelevant external stimuli)
(6) increase in goal-directed activity (either socially, at work or school, or sexually) or psychomotor agitation
(7) excessive involvement in pleasurable activities that have a high potential for painful consequences (e.g., engaging in unrestrained buying sprees, sexual indiscretions, or foolish business investments)

C. The symptoms do not meet criteria for a Mixed Episode (see p. 355).

D. The mood disturbance is sufficiently severe to cause marked impairment in occupational functioning or in usual social activities or relationships with others, or to necessitate hospitalization to prevent harm to self or others, or there are psychotic features.

E. The symptoms are not due to the direct physiological effects of a substance (e.g., a drug of abuse, a medication, or other treatment) or a general medical condition (e.g., hyperthyroidism).

Note: Manic-like episodes that are clearly caused by somatic antidepressant treatment (e.g., medication, electroconvulsive therapy, light therapy) should not count toward a diagnosis of Bipolar I Disorder.

Brain SPECT Imaging in Psychiatry

Daniel G. Amen, MD

INTRODUCTION

Brain SPECT (single photon emission computed tomography) imaging is a nuclear medicine study, utilizing minute doses of radioactive isotopes bound to neurospecific pharmaceuticals to study cerebral perfusion and thus, indirectly, brain metabolic activity.[1] SPECT can provide clinically useful information in several areas relevant to psychiatry. There are enough published articles, combined with extensive clinical experience, to substantiate its use in evaluating head trauma,[2-4] dementia,[5-7] cerebral vascular disease,[8,9] aggression,[10,11] and temporal lobe epilepsy.[12,13] Refractory suicidal behavior[14] and substance abuse[15,16] are also areas where SPECT can provide useful information. Unfortunately, the interface between psychiatry and nuclear medicine is uncommon and SPECT is underutilized.

With continued improvement in technology, brain SPECT image resolution is nearing the same realm as PET,[17] at less cost. SPECT scans are relatively easy to perform, requiring only an intravenous line; with the multiheaded cameras, the acquisition time for the scan is approximately 16 minutes. High-resolution SPECT cameras are also widely available. Unfortunately, there remain few trained physicians with extensive experience in reading brain SPECT images for neuropsychiatric indications. Some clinicians have reservations about the use of SPECT in children and teenagers, feeling that it may be unsafe. The radiation exposure from SPECT is about the same as that from a brain CT scan or an abdominal X-ray. Nuclear medicine, as a specialty, has been doing studies on children for over 30 years without untoward effects. Having an unresponsive or poorly understood psychiatric condition has many more risks than the risk of low-dose radiation exposure engendered by a SPECT scan. Chiron et al[18] have reported normative data for children, demonstrating that the brain of a two- to three-year-old child shows the same relative cerebral blood flow pattern as the adult brain.

Common SPECT radiopharmaceuticals used to study cerebral blood flow and indirectly cerebral metabolism include HMPAO (Ceretec), ECD (Neurolite), and 133-Xenon gas. HMPAO and ECD are considered to be equal in their capacity to reflect regional cerebral blood flow; the most clinical experience is with HMPAO.

HOW IS SPECT DISPLAYED AND INTERPRETED?

Brain SPECT studies can be displayed in a variety of ways. Traditionally, the brain is examined in three different planes: horizontally, coronally, and sagittally. A normal study shows relatively symmetrical uptake of the isotope throughout the brain, with the cerebellum being the most active part of the brain. Overactive areas of the brain are indicated by an increase in color (depending on the color scale utilized), and decreased areas are shown by diminished color. With advancements in computer technology, the brain can be represented in three-dimensional images. *3D surface images* are one way to represent brain activity, by looking at the blood flow of the brain's cortical surface. These images are helpful in evaluating strokes, brain trauma, the effects from drug abuse, etc. A normal 3D surface scan shows good, full, symmetrical activity across the brain's cortical surface (Figures 1-3; PP8-16). *3D active brain images* compare average brain activity to the most active parts of the brain, typically the most active 15% in the author's clinic. These images are helpful for picking up areas of overactivity, as seen in active seizures, obsessive-compulsive disorder, bipolar disorder, etc. A normal 3D active scan

EDUCATIONAL OBJECTIVES:

- **Learn five ways that SPECT may be helpful in clinical practice**
- **Learn how SPECT imaging is helpful in obtaining compliance from patients**
- **Understand how SPECT studies are displayed**

Dr. Amen is director of the Amen Clinic for Behavioral Medicine in Fairfield, California.

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shows increased activity in the back of the brain (the cerebellum and visual or occipital cortex) and average activity everywhere else (Figures 4-6; PP8:17). Physicians are usually alerted that something is wrong in one of three ways: (a) too much activity in a certain area; (b) too little activity in a certain area; or (c) asymmetrical areas of activity that ought to be symmetrical or symmetrical areas of activity that are typically asymmetrical.

Following is a list of conditions where SPECT can be helpful in a neuropsychiatric practice.

HEAD TRAUMA

The impact of head trauma is often overlooked in psychiatry. Even minor head injuries to vulnerable parts of the brain can cause problems for years to come. SPECT is one of the best tools in evaluating functional deficits from head trauma that are often not seen by other studies, leading to more understanding and effective treatments for patients.[7] Typically, SPECT findings in head trauma include focal areas of decreased activity, often in a contra-coup pattern (such as decreased activity in the left anterior prefrontal cortex and right occipital lobe, or the anterior and posterior aspects of a temporal lobe) and, in some cases, marked hyperactivity over the site of the injury. In many cases, the author has seen increased "off center" cingulate gyrus activity after a head injury.

Here is a case example. The patient T, 15, had severe behavioral problems. He had already been arrested for shoplifting and selling drugs. He frequently cut school and was defiant and abusive toward his parents. He frequently used both marijuana and cocaine. He had already been in one drug treatment program and was on his way to a second program when his parents brought him for evaluation. He had tried numerous medications without success. When he was 18 months old, he had fallen down a flight of stairs. His mother reported that he was never quite the same after that. A SPECT study was ordered to evaluate the prior head trauma and his unresponsive behavioral problems. It showed severe damage to his left prefrontal cortex (Figure 7; PP8:18). Given the level of functional damage to his brain, he was placed on a combination of an anticonvulsant and a psychostimulant. This combination helped lessen his anger and improve his impulse control. Given the level of damage to his prefrontal cortex, it was felt that his chances for having full executive function were not promising—helpful information in the treatment planning process, necessitating that T be placed in a more highly supervised environment.

Documentation of head injuries is essential for several reasons. For school-age children and teenagers, it allows them to receive more specialized services. Knowledge of the injuries is often essential for legal/insurance reasons. Patient and family understanding of the effects of brain trauma enhances treatment compliance and a deeper understanding from family and support systems.

DEMENTIA

The SPECT pattern for Alzheimer's disease is typically bilateral hypoperfusion in the parietal and temporal regions of the brain, with frontal lobe hypoperfusion occurring later in the illness. Multi-infarct dementia is characterized

Image Preparation

SPECT cortical surface images are rendered by setting the threshold at 55%, looking at the most active 45% of brain activity.

SPECT active images are rendered by setting blue color at threshold set at 55%, looking at average brain activity compared to white threshold set at 85%, and looking at the most active 15%.

Figures 1-3 PP8:15

Normal Surface Images

Fig.1-Normal top-down surface view. Notice full, symmetrical activity.

Fig. 2-Normal left side surface view. Notice full activity

Fig. 3-Normal underside surface view. Notice full, symmetrical activity.

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Figures 4-6 PP8:16

Normal Active Images

Fig. 4-Normal top-down active view. Cerebellum most active area.

Fig. 5-Normal left side active view. Cerebellum most active area.

Fig. 6-Normal underside active view. Cerebellum most active area.

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by multiple areas of decreased perfusion. HIV dementia is typically seen by decreased patchy uptake across the cortex.[37] Frontal lobe dementias (as the name indicates) are often characterized by very poor frontal lobe perfusion.[38]

Here is an example of how SPECT can be useful in the evaluation and treatment of dementia-like presentations. When F entered his seventies, he became significantly forgetful. His family had significant problems coping with him. The SPECT study showed marked suppression across the entire brain, especially in the parietal and temporal lobes (Figures 8 and 9), PP8:19), a classic Alzheimer's disease pattern. Showing the family these images and pointing out the physiological cause of F's problems gave them a deeper understanding of this serious medical problem. Consequently, they were able to develop strategies to cope with the situation. In addition, F was immediately placed on donepezil, which slowed the course of his illness.

CEREBRAL VASCULAR DISEASE

SPECT is often helpful in the evaluation and management of cerebral vascular disease.[39] After an acute stroke, an early SPECT scan may depict the area of ischemia with greater accuracy than either computed tomography or magnetic resonance imaging. When the perfusion defect is large, the likelihood of hemorrhagic complications or herniation increases. Reperfusion of an arterial territory after thrombolysis can be documented more conveniently with SPECT than with angiography. SPECT before and after the injection of acetazolamide has been used to assess the vascular reserve in patients with severe stenosis of the proximal vessels of the cerebrovascular tree. Figure 10 (PP8:20) shows a typical stroke.

Figure 7 PP8:17

Head Trauma

Fig. 7-3D top-down surface view. Notice large defect in left midfrontal and prefrontal regions.

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Figures 8-9 PP8:18

Alzheimer's Disease

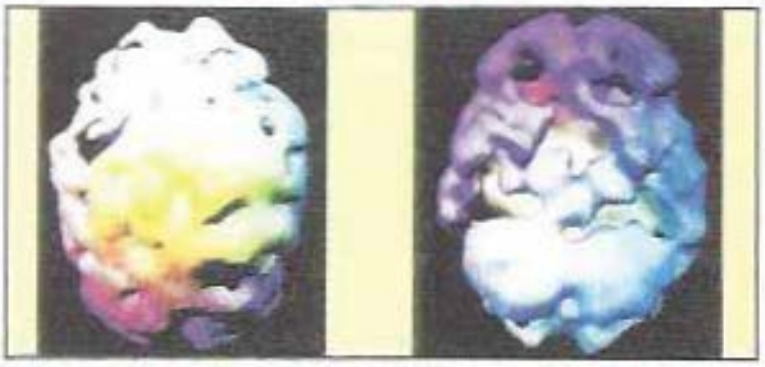

Fig. 8-Top-down surface view, marked decrease in activity in parietal lobes.

Fig. 9-Undersurface view, marked decreased temporal lobes.

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Figure 10 PP8:19

Stroke

Fig. 10-Left side surface view, marked decreased left frontal, temporal, and parietal lobe.

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Figure 11 PP8:20

Two Right Hemisphere Strokes with Depression as Presenting Symptom

Fig. 11-Top-down surface view, marked decreased right frontal, temporal, and parietal lobe.

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Here is a cerebral vascular case where SPECT was clinically helpful in psychiatry. N, a 59-year-old woman suffering from severe depression, had been nonresponsive to treatment. A SPECT study was ordered to evaluate her unresponsive condition. Because she had not experienced any neurological symptoms, it was surprising to discover two large right-hemisphere strokes (Figure 11; PP8:21). Her nonresponsive depression became clearer as 60% of the people who have frontal-lobe strokes experience severe depression. As a result of the SPECT study, immediate neurological consultation was obtained, and subsequently, N was placed on blood-thinning medication to prevent further strokes.

AGGRESSION

SPECT can be helpful in understanding and directing treatment for aggressive behavior. The author and colleagues have found a consistent triad of SPECT findings common in children, teenagers, and adults who exhibit aggressive behavior.[8,9] These findings are: (1) abnormalities (either increased or decreased activity) in the left temporal lobe, often the seat of aggressive thoughts; (2) increased activity in the anterior cingulate gyrus, which often causes problems with repetitive thoughts and shifting attention (a person may get stuck on the aggressive thoughts that are present); and (3) decreased activity in the prefrontal cortex, leading to poor internal supervision.

When these three findings are present, it is often helpful to intervene with anticonvulsant medication to stabilize temporal lobe abnormalities and decrease violent thoughts, a serotonergic agent to help decrease anterior cingulate activity and improve cognitive

Figures 12-13 PP8:21

Aggression, Before and After Treatment with Clomipramine and Divalproate

(3D top-down active views)

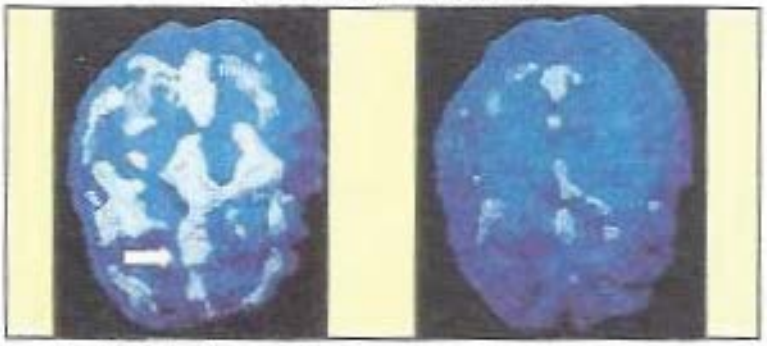

Fig. 12-**Before Treatment**
Marked increased cingulate activity.

Fig. 13-**After Treatment**
Normal cingulate activity.

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Figure 14 PP8:22

Temporal Lobe Epilepsy

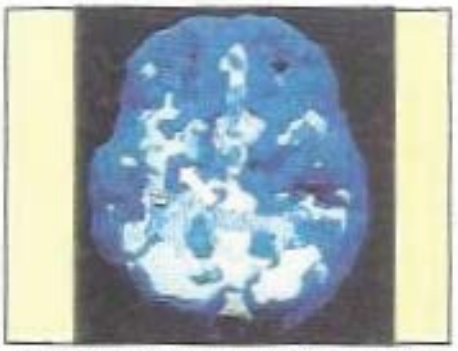

Fig. 14-3D underside active view. Increased activity deep in right temporal lobe (arrow).

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Figures 15-17 PP8:23

Depression

Fig. 15-3D underside active view; increased deep limbic activity.

Fig. 16-3D side active view; increased cingulate and deep limbic activity.

Fig. 17-3D underside surface view; marked decreased activity in left temporal lobe associated with serious suicidal thoughts.

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flexibility, and sometimes a psychostimulant to activate prefrontal cortex activity and enhance impulse control.

Here is an example of how SPECT can be helpful in aggressive behavior. A 48-year-old married man sought evaluation for obsessive thoughts, moodiness, irritability, periodic intense suicidal thoughts, and problems with anger control. His wife reported episodes where he would become upset about something, be unable to shift away from his upsetting thoughts, lose control, and exhibit aggressive behavior such as breaking furniture or putting holes in the walls. As part of his evaluation, a brain SPECT study was ordered. It revealed marked increased uptake in the cingulate gyrus and increased uptake in the medial aspects of the left temporal lobe (Figures 12-13; PP8:22). After the clinical evaluation and SPECT findings, the patient was placed first on divalproate (to stabilize left temporal lobe activity and decrease aggressive thoughts and behaviors), then clomipramine (to decrease cingulate activity and obsessive thoughts, and to improve cognitive flexibility). The patient and his family noted a marked positive response. He was less irritable, had good control over his temper, and had no suicidal thoughts. After 3 years of continued clinical improvement on these medications, a follow-up SPECT study was ordered to evaluate cerebral blood flow subsequent to treatment. It revealed a marked normalization of brain activity in the cingulate gyrus and left temporal lobe.

TEMPORAL LOBE EPILEPSY

Temporal lobe epilepsy is one of the most frequently encountered chronic epileptic disorders, and it is associated with many psychiatric symptoms, such as depressive mood, anergia, irritability, euphoric mood, atypical pain, insomnia, fear, and anxiety.[26] Problems in the temporal lobe typically are found in the medial aspects, which are difficult to find with routine EEG studies. SPECT findings in temporal lobe epilepsy, and epilepsy in general, reveal decreased activity in the interictal period and increased activity during the ictal phase.[4,13] Proper diagnosis of temporal lobe epilepsy, especially when it presents with psychiatric symptomatology, is essential for effective treatment.

Here is a case example. A 7-year-old boy became very upset when his mother read *Alice in Wonderland* to him. He said that he felt like Alice. "I have weird things happen to me," he told her. "I see things." During the day, he saw objects change shapes, often getting smaller, and at night, he saw green, shadowy ghosts. He had many anxiety symptoms. His mother brought him for evaluation. He had normal EEG. A SPECT study was ordered for further evaluation. During the scan he complained of having visual changes. The SPECT study showed increased activity in the medial aspects of his right temporal lobe (Figure 14; PP8:23). Within 2 weeks on divalproate the boy's strange experiences disappeared, and over the next 6 months his anxiety significantly lessened.

DEPRESSION

Decreased prefrontal cortex activity at rest, especially on the left side, is a consistent SPECT finding in depression.[26,27] The severity of depression is often related to the degree of frontal hypometabolism. Several studies have indicated that the hypometabolism normalizes after treatment if the

Figure 18 PP8:24

Manic Phase of Bipolar Disorder

Fig. 18-3D top-down active view; patchy increased uptake across the cortical surface.

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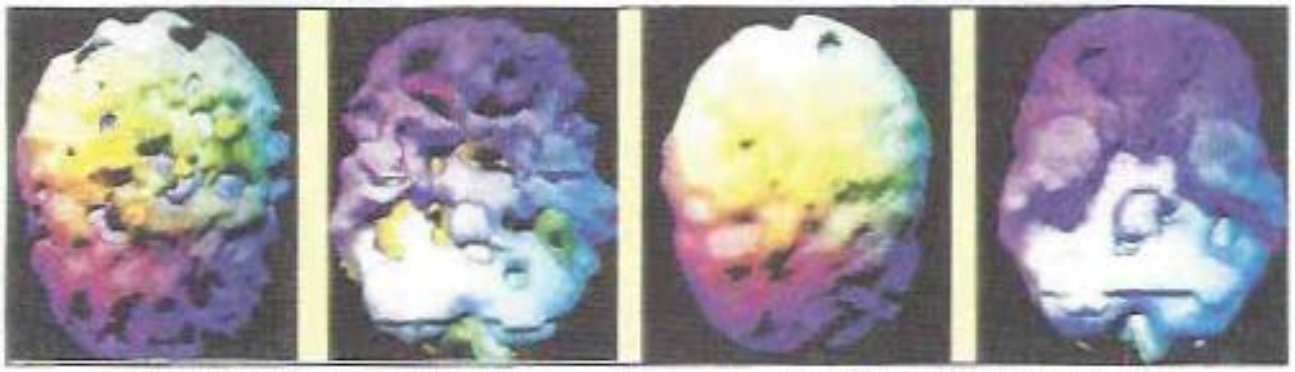
Figures 19-22 PP8:25

Paranoid Schizophrenia, Before and After Treatment with Risperidone

(3D top-down and underside surface views)

Before Treatment After Treatment



Figs. 19,20-Marked decreased activity throughout the cerebral cortex.

Figs. 21,22-Marked overall improvement throughout the cerebral cortex.

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patient's mood has improved. Researchers have also seen increased limbic system activity in depression (thalamus, amygdala, cingulate gyrus, and deep temporal lobes). When depressed patients perform a concentration task, the left prefrontal cortex often activates to normal levels, differentiating depression from attention deficit disorder, which often shows normal activity at rest and decreased prefrontal cortex activity with concentration.[9]

SPECT can be helpful in the diagnosis and treatment of complex or resistant depressive disorders by differentiating them from other disorders; by enhancing compliance from the patient, who is able to "see the changes in the brain"; and by subtyping depression. In the author's experience there are three SPECT subtypes of depression that appear to correlate with treatment responses.

(1) Decreased prefrontal cortex activity with increased deep limbic system (thalamus) activity (Figure 15; PP8:24). This subtype is often associated with moodiness, negativity, low energy, sleep and appetite problems, and poor concentration. It often responds best to dopaminergic or noradrenergic interventions such as bupropion, imipramine, or desipramine.

(2) Decreased prefrontal cortex activity, increased anterior cingulate (this part of the brain is heavily innervated with serotonergic nerve fibers), thalamus, and basal ganglia activity (Figure 16; PP8:24). This subtype is often associated with sadness, negativity, irritability, worrying, cognitive inflexibility, and getting stuck or locked into negative thought patterns. It often responds best to the serotonergic antidepressants such as fluoxetine, sertraline, paroxetine, and venlafaxine.

(3) Decreased prefrontal cortex activity with increased or decreased temporal lobe activity (Figure 17; PP8:24). This is often the most serious subtype, and it is often associated with sadness, irritability, rage (toward others or self in suicidal behavior), mild paranoia, atypical pain (atypical headaches or abdominal pain), and insomnia. The author has seen this subtype often made significantly worse by serotonergic medications; it is often helped by anticonvulsants, such as gabapentin or divalproate.

BIPOLAR DISORDER AND SCHIZOPHRENIA

Bipolar disorder has been characterized by increased activity across the cerebral cortex.[10] Clinically, during the manic phase the scans often look hyperactive, especially in the lateral frontal cortex, lateral parietal lobes, and lateral temporal lobes; focal increased uptake in the limbic system has also been noted (Figure 18; PP8:25). Differentiating the initial onset of bipolar disorder from schizophrenia is often a difficult task in an acutely psychotic individual. In schizophrenia, SPECT findings have frequently reported decreased activity, especially in the prefrontal cortex.[10,11] SPECT studies may provide helpful information in the differential diagnoses of these disorders. In addition, SPECT can provide useful information to patients to significantly improve compliance in disorders where compliance is a frequent serious problem.

Here is an example. A 35-year-old man who had been living on the street was brought in for an evaluation by his mother. He had previously been diagnosed on many occasions with paranoid schizophrenia, but refused medication. His SPECT study revealed marked overall decreased activity throughout the cerebral cortex. Being able to see his own brain activity, represented by the 3D surface SPECT study, was helpful for him. He agreed to take his medication under his mother's supervision. One month later, after significant clinical improvement on 4 mg/d of risperidone, a repeat SPECT study was performed which

Figures 23-26 PP8:26

Substance Abuse

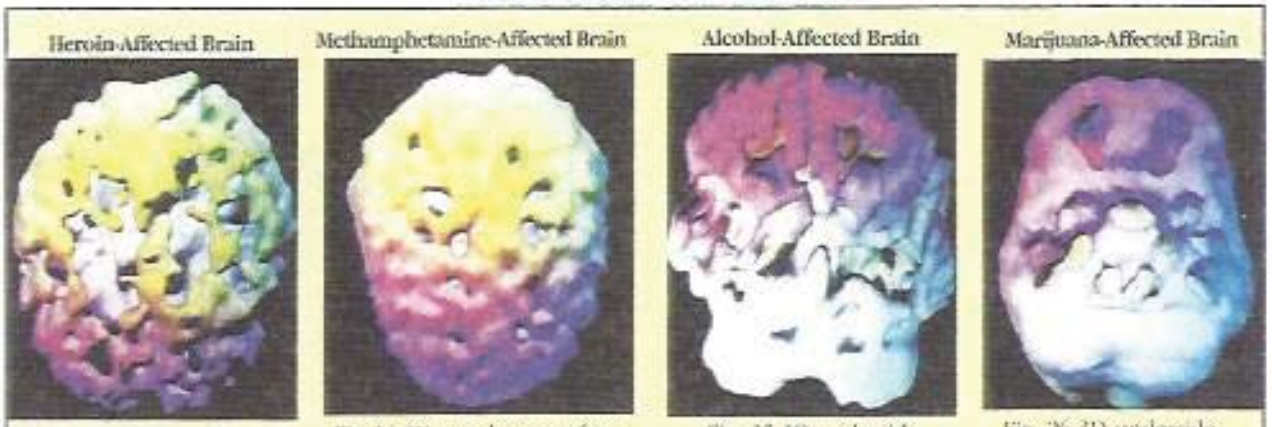

Fig. 23-3D top-down surface view; large areas of decreased perfusion.

Fig. 24-3D top-down surface view; multiple small areas of decreased perfusion.

Fig. 25-3D underside surface view; overall shriveled appearance.

Fig. 26-3D underside surface view; decreased activity, especially in temporal lobes.

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showed improved overall cerebral perfusion. Being able to see the before-and-after SPECT studies side by side on the imaging computer monitor again was very encouraging to the patient and helped significantly with compliance (Figures 19-22; PP8:26).

DRUG- AND ALCOHOL-RELATED DISORDERS

SPECT can be helpful in evaluating the effects of drugs and alcohol on the brain. On 3D surface images several substances of abuse appear to show consistent patterns. For example, cocaine and methamphetamine abuse appear as multiple small holes across the cortical surface[7,8]; heroin abuse appears as marked decreased activity across the whole cortical surface[8]; heavy marijuana abuse shows decreased activity in the temporal lobes bilaterally[8]; and heavy alcohol abuse shows marked decreased activity throughout the brain.[8,9] These findings tend to improve with abstinence, although long-term use has been associated with continued SPECT deficits seen after years of abstinence.

SPECT can be helpful in several ways in drug and alcohol abuse. First, 3D surface SPECT images of drug and alcohol abusers can be used in drug prevention education (Figures 23-26; PP8:27). Second, SPECT studies can help break through the denial that often accompanies substance abuse. When one is faced with one's own abnormal cerebral perfusion, it is hard to remain in denial. Third, SPECT may help evaluate whether there is an underlying neuropsychiatric condition that needs treatment.

Here is an example. A 34-year-old male was evaluated after he was discharged prematurely from a drug treatment program for psychotic thinking. The patient had gone voluntarily to the drug program trying to break a long-standing cocaine addiction. Initially, it was thought he had a cocaine psychosis, but after 4 months free from any drugs, his paranoia and aggressive behavior escalted. He refused medication. He consented to having a brain SPECT study after encouragement from his family. His brain SPECT study revealed significant decreased uptake in his left temporal lobe. With the clinical picture and the SPECT information, he was started on carbamazepine. Within 10 days, he felt calmer and was obviously less paranoid. Within a month, he returned to work at full function and felt more in control of his temper than even before he started using drugs.

OBSESSIVE-COMPULSIVE DISORDER AND OCD SPECTRUM DISORDERS

There are a number of SPECT studies that report hyperfrontality, increased anterior cingulate gyrus activity, and increased basal ganglia activity in obsessive-compulsive disorder[10-13] (Figure 27; PP8:26). Of interest, hyperactivity in the anterior cingulate gyrus has also been noticed in oppositional defiant disorder[14] and violence.[15] The anterior cingulate gyrus, which is heavily innervated by serotonergic fibers, has been postulated as being involved with shifting attention and cognitive flexibility, deficient in all of these disorders. Treatment with serotonergic antidepressants such as fluoxetine and clomipramine decreases the hyperactivity in these areas.[16,17]

ATTENTION DEFICIT DISORDER

SPECT studies in attention deficit disorder (ADD) often show normal activity at rest and then decreased activity in the prefrontal cortex and basal ganglia[15,18] while a concentration task is being performed. These findings reverse with stimulant medication treatment[18] (Figures 28-30; PP8:29). These studies are important as they highlight the underlying neurobiological nature of ADD, which has come under attack in the popular media as being a "fad" or a disorder of poor parents or teachers. ADD is primarily diagnosed by clinical history over a prolonged period of time,

with SPECT not needed to make the diagnosis. Yet, SPECT can be helpful in the diagnostic process when ADD is complicated by comorbid conditions, head trauma, or lack of responsiveness to traditional treatments.

CAUTIONS

Even though the knowledge and technology exist to use SPECT in day-to-day clinical psychiatric practice, it is still considered as only a research tool by many. Typically, clinicians and researchers have criticized SPECT on several fronts. It has been said that there is not enough information on "normative samples" to make SPECT studies clinically useful. Yet, with experience, the differences between good overall brain perfusion and the disorders discussed in this paper are clear. In addition, many of the published research studies on SPECT in neuropsychiatry have used normal control groups for comparison. To further clarify this issue, the Society of Nuclear Medicine is sponsoring a "normal SPECT database" that will be housed at Yale University and will be available over the Internet to interested physicians.

Another criticism of SPECT is the uncertainty over false-positive and false-negative readings. The actual statistical significance of these false readings is unclear at this time and needs more research. In the author's experience, reading over 5,000 SPECT studies in the past 8 years, there have been few studies where there have been defects that were not related to head trauma, cysts, or strokes; few studies of severely violent patients that were normal; and few studies that showed intense cingulate hyperactivity that was not related to overfocus symptomatology. No medical test, including SPECT, should be used in isolation. It is very important to relate what is seen on SPECT with a patient's clinical history and examination. SPECT studies should not be used in isolation to make medical decisions.

The reading variability between SPECT raters can be a significant problem. In clinical practice SPECT studies are read by visual inspection, and there is a wide variety of color scales and ways to read them. The author has personally seen studies that were read by other physicians as normal, but when read by more experienced eyes, the studies showed clear areas of concern. Experience and finding more standard ways to read the studies are important if SPECT is to yield consistent results. Rater variability is a concern in reading most imaging studies.

SPECT cameras also vary in sophistication. The older single- or double-headed cameras do not give the same level of resolution, and the studies take longer to perform, making them less helpful for neuropsychiatric indications than the newer triple-headed systems. In order to utilize the technology effectively, it is important to have a high-resolution SPECT camera, such as a triple-headed camera, a nuclear medicine physician skilled in reading brain studies for neuropsychiatric reasons, and a psychiatrist who understands how to utilize the technology properly. Given those three elements, SPECT is a powerful diagnostic tool for many patients.

Figure 27 PP8: 27

Obsessive-Compulsive Disorder

Fig. 27-3D front on active view; hyperfrontality, especially in the cingulate gyrus.

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continued on page 94

Figures 28-30 PP8: 28

Attention Deficit Disorder, Before and After Treatment with Adderall

Fig. 28-Undersurface view; rest: mild decrease in prefrontal area.

Fig. 29-Undersurface view; concentration: marked decrease in prefrontal cortex and left temporal lobe.

Fig. 30-Undersurface view; with Adderall: overall marked improved activity.

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Imaging in Psychiatry

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Neuroimaging Bipolar Illness With Positron Emission Tomography and Magnetic Resonance Imaging

by MONTE S. BUCHSBAUM, MD;
TOSHIYUKI SOMEYA, MD;
JOSEPH C. WU, MD;
CHEUK Y. TANG, MS; and
WILLIAM E. BUNNEY, MD

Can brain imaging distinguish the psychosis of schizophrenia from the psychosis of bipolar disorder? Because as many as one half of all patients with bipolar disorder may exhibit psychotic symptoms (see review by Dieperink and Sands[1]), the clinical distinction during acute episodes, especially early in the course of the illness, may be difficult. If the choice between lithium, carbamazepine, and valproate on the one hand and neuroleptics on the other is to be made on a scientific basis rather than trial and error, information about the functional state of the neural circuits involved in the illness seems to be a promising clinical tool. Pulmonologists have chest radiographs to provide additional diagnostic information on patients whose history and symptoms of breathlessness and cough do not fully differentiate among many pathophysiologic possibilities. They weigh imaging results with other clinical findings in planning the first treatment course. In bipolar illness, the modulation of sensory input, organizing sustained future plans, and inhibiting action appear to be key functions that are disturbed during mood episodes; can we image their anatomic sites in the brain?

Dr. Buchsbaum and Mr. Tang are from the Department of Psychiatry, Mt. Sinai School of Medicine, New York. Dr. Someya is from Shiga University of Medical Science, Otsu, Japan. Drs. Wu and Bunney are from the Department of Psychiatry and Human Behavior, University of California, Irvine.

Address reprint requests to Monte S. Buchsbaum, MD, Department of Psychiatry, Mt. Sinai School of Medicine, Box 1505, New York, NY 10029-6574.

THE THALAMUS, FRONTAL LOBE, AND STRIATUM

The thalamus, "gateway to the cortex,"[2] may also be seen as a castle portal and drawbridge under the control of monumental feedback projections from cortical projection areas. Sensory information flows from the thalamus to primary cortical sensory areas and from them to prefrontal executive areas. Prefrontal executive areas communicate primarily unidirectionally to the striatum and globus pallidus, and receive returns via the thalamus. In the fortress analogy, the prefrontal region is a throne room for strategy and long-range planning; the striatum-pallidum, the keep where knights flex their muscles; and the ventral anterior and medial dorsal thalamus, the courtyard adjoining the portal where pages, courtiers, and nobles mingle to relay messages back up to the throne room. It is in these reciprocal communication lines to the executive that the disordered behavior and its varieties may lie.

Although the frontal lobe is unlikely to be the "primary" site of bipolar disorder, findings of abnormality have been frequent enough to suggest the value of a wider focus on the role of the frontal lobe, not in isolation, but as part of the sensory modulation fronto-striatal-thalamic circuitry. The role of fronto-striatal-thalamic loops in sensory gating or modulation[3,4] and subsequent sensory overload with attendant cognitive disorganization and psychotic symptoms has been stressed by many authors as important in understanding imaging results in affective disorder,[5,6] obsessive-compulsive disorder,[7] and schizophrenia.[8-12] For example, fronto-striatal-thalamic circuits were implicated in a study of patients with mania secondary to strokes; frontal white matter, internal capsule, striatum, and thalamus were frequently involved, especially on the right side.[13] Fronto-striatal circuit deficits in depression were also suggested by the finding that rel-

ative metabolic activity in the inferior frontal lobe and striatum was associated with depression in patients with Parkinson's disease.[14] Also, interestingly, a reduced frontal metabolic rate was observed in depressed but not nondepressed patients with complex partial seizures.[15]

It has been proposed that in schizophrenia,[16,17] psychosis is a disorder of dopamine and glutamate activity that results in impaired control of arousal and of the filtering of sensory signals to the cortex via the thalamus. The primary site of dysfunction in this model is a cortico-striato-thalamic circuit, extending the initial proposals of Kim and colleagues[18] of deficits in dopaminergic to glutamatergic balance. A deficiency of cortico-striatal glutamatergic activity, possibly secondary to frontal cortical developmental impairment, is hypothesized to decrease striato-pallidal inhibitory GABAergic tone. This decreased striato-pallidal inhibition is proposed to increase pallido-thalamic GABAergic tone, resulting in a disinhibition of the thalamic filter, which allows sensory information to overwhelm the cortex, thus in part generating manic and psychotic symptoms, defocusing attention, and disturbing cognitive processes that require sensory quiet, such as retaining and recalling items from memory. Thus, hypofrontality and/or fronto-striatal disconnection could indicate reduced frontal glutamatergic activation of the striatum and thalamic filter failure. Alternatively, reduced ventral striatal metabolism without hypofrontality might implicate dysfunctional striato-pallido-thalamic circuits under inhibitory control of striatal dopamine opposing the corticostriatal glutamatergic system.

We believe that understanding how these circuits function in normal individuals and recognizing whether they are missing, interrupted, or abnormally connected in patients with schizophrenia will provide important information about individual differences in medication response, symptom expression, and illness severity. The multineurotransmitter basis of these loops makes the high-resolution, regional metabolic rate imaging that is possible using ^{18}F-deoxyglucose (FDG) an incisive technology for understanding these circuits and the implications of their disturbance for pharmacologic treatment in humans.

IMAGING BIPOLAR AFFECTIVE DISORDER

In the earliest positron emission tomography (PET) study of bipolar disorder, we[19,20] found that patients with the disorder had reduced metabolic rates in their frontal cortex compared with in the occipital lobe, in contrast to individuals without bipolar disorder, whose frontal lobes were relatively more active than their occipital cortex. Cortical surface statistical probability mapping at that time[19-21] also suggested areas of metabolic increase in the superior temporal gyrus in patients with bipolar disorder, with decreases at the temporal pole, relative to subjects without the disorder. Differences between patients with schizophrenia and those with bipolar disorder were not found in analysis of variance contrasts of regions of interest, but statistical probability mapping suggested significantly lower temporal lobe activity in schizophrenic patients than in normal subjects. However, higher activity in patients with affective disorders could be one possible explanation for this finding. Baxter and colleagues[22] compared five bipolar depressed patients with 11 unipolar patients and found that manic bipolar patients had lower metabolic rates in most parts of the brain but did not demonstrate regional decreases for prefrontal cortex, caudate, cingulate, or thalamus. However, subsequent larger studies tended to show frontal lobe decreases in both bipolar and unipolar patients. In a study involving a group of mainly bipolar patients (seven bipolar, three unipolar), Martinot and colleagues[23] found decreased frontal cortical but not temporal or striatal metabolism in depressed patients. Other studies of patients with affective disorder[21,24-28] have also found relatively reduced frontal lobe function. Ketter and colleagues[6] reviewed 36 controlled studies of cerebral blood flow and reported that decreased activity in the frontal lobe was found in primary depression in 27 studies. In a recent study of patients with affective disorder who underwent FDG uptake tests while sleeping in the non-REM state,[29] hypofrontal function was also found, which suggests that neither task performance nor active mentation is essential for this finding.

These PET findings are more uniform for the relatively large prefrontal cortex and show more variation for the other structures in the fronto-striato-thalamic loop—the caudate/putamen and thalamus. These smaller subcortical structures were not uniformly assessed in all studies, and many of the methods used for identifying the regions of interest depend on assessment at coordinates placed visually or stereotaxically in the regions of interest. Methodologic problems may reduce or distort the strength of the differences found between patients and control subjects. First, region-of-interest placement by tracing directly on the PET or single photon emission computed tomography scan may confound activity and region of interest size, minimizing group differences. Second, statistical stereotaxic procedures with bounding box proportions[30] (linear adjustment in proportion to brain height and width) may blur or lump together different nuclei with different functions. Individual differences in the size, shape, and position of the region-of-interest structure contribute further noise. For precise comparison of regions of interest, an individual anatomic template from co-registered magnetic resonance imaging (MRI) is valuable to assure reliable identification of structures. Because the thalamus is a key link in the hypothesized circuit and has been the least studied, we began with an

emphasis on the thalamus and its component regions in the study reported below.

PET STUDY OF UNMEDICATED PATIENTS WITH BIPOLAR DISORDER

The subjects were 9 patients with bipolar affective disorder (4 men and 5 women; mean age [+SD], 32.3+8.9 years) and 36 patients with unipolar depression (15 men and 21 women; 32.3+11.4 years) recruited from referral through the clinical and research programs of the University of California, Irvine. Twenty-three age- and sex-matched volunteers (10 men and 13 women, 43% male; mean age = 31.5, SD = 9.2) served as control subjects.

All depressed subjects met DSM-III-R criteria for bipolar disorder, depression, or (unipolar) major depression. The mean score on the Hamilton Rating Scale for Depression at the time of scanning was 17.1+12.2 for bipolar depression and 22.8+5.4 for unipolar depression. Neither the patients nor the controls had taken psychoactive medications for at least 2 weeks before the study. All subjects were right-handed and judged to be in good health on the basis of medical history, physical examination, and laboratory measures. No subject had an abnormal blood glucose level. All subjects received a drug screen on the day of the PET scan. Control subjects were excluded if they had a family history of psychiatric illness in self or first-degree relatives as assessed by structured interview.

Task and PET Procedure

Before the scanning, an individually molded, thermosetting plastic head holder was made for the subject to minimize head movement during scanning and also to minimize head-positioning error between PET and MRI scan. For the PET scan, two intravenous lines were inserted, one in the right arm for the administration of ^{18}FDG and another in the left arm for withdrawal of blood samples. Subjects were then seated in a comfortable chair in a darkened, acoustically attenuated isolation room and instructed about the procedure and the Continuous Performance Task[31] (CPT) to be performed. A 5-minute practice session was given, the task was restarted, and then an injection of 148 to 192 mBq (4.0 to 5.2 mCi) of ^{18}FDG was administered.[32] After 30 to 35 minutes of FDG uptake, the subject was transferred to the adjacent scanning room.

Thalamic Metabolism Measured by Magnetic Resonance Imaging Template Method

With the use of MRI templates, significant differences in thalamic metabolic patterns among patients with bipolar disorder, those with unipolar depression, and in control subjects emerged (Table 1). Bipolar patients had the greatest decreases relative to control subjects in the medial areas, especially the block containing the region of the medial dorsal nucleus (Figure 1). In contrast, changes in unipolar patients were more pronounced in the lateral regions, although anteriorly both lateral and medial areas were decreased. Absolute metabolic rates did not show significant group differences or interactions. There was no significant difference in the size of the thalamus between groups ($F=2.66$; $df=2.65$; $P=0.08$), although the mean area of the thalamus was about 9% larger in patients with unipolar depression than in those with bipolar depression or in controls.

Cortical Metabolism

As compared with other parts of the frontal lobe, the middle frontal gyrus was significantly decreased in bipolar depressed patients as compared with controls (Table 2). Relative rates in the temporal lobe of bipolar depressed patients were significantly higher than in controls ($F=6.65$; $df=1.30$; $P<0.02$), although the differential contrast of the major temporal gyri did not reach significance (group by gyrus interaction, $F=2.23$; $df=3.90$; $P=0.12$). No significant difference was found between patients with unipolar depression and control subjects.

Striatum and Limbic Areas

The entire striatum (caudate, putamen, and globus pallidus summed across all slice levels) showed higher relative metabolic rate in bipolar patients (1.23, SD=0.04) than in control subjects (1.17, SD=.10; $t=2.07$; $P<0.05$). However, the putamen on the left had significantly lower values in bipolar patients (1.14, SD=0.06) than in control subjects (1.22, SD=0.08; $P<0.05$).

Bipolar patients also showed significantly lower metabolic rates in the cingulate gyrus (combined across levels, 1.03, SD=0.07) than control subjects (1.10, SD=0.06; $t=2.15$; $P<0.05$). An exploratory survey of 66 stereotaxic areas revealed reduced metabolic rates in bipolar patients in the left frontal white matter (0.73, SD=0.06 vs 0.83, SD=0.10, $t=2.54$; $P<0.05$), but rates in parietal, occipital, cerebellar, and brain stem areas were not significantly different.

FRONTO-STRIATO-THALAMIC CIRCUITS

An overview of these pilot exploratory analyses reveals that areas in the frontal lobe tend to be hypometabolic, consistent with other studies (see Ketter and colleagues[5] for review). The list of other regions found significantly different comprises way-stations in this pathway. Significant reductions were found in the cingulate gyrus, the frontal white matter, the putamen, and a thalamic box in the region of the medial dorsal nucleus. The frontal reduction is similar to that found in unmedicated patients with schizophrenia, in whom deficits in this circuit have also been suggested. However, the patients with schizophrenia tended to have low values throughout the caudate and putamen, unlike the left putamen decrease shown in patients with bipolar disorder. Putamen-specific decreases in size in depressed patients have also been observed.[36] Although there is conflicting evidence about the role of dopamine in bipolar

Table 1

Thalamus Metabolism as Measured Using Positron Emission Tomography

	Bipolar Depression				Unipolar Depression				Control			
	Left		Right		Left		Right		Left		Right	
	lat.	med.	lat.	med.	lat.	med.	lat.	med.	lat.	med.	lat.	med.
Metabolic rate, μmol/100 g/min												
Anterior	21.2	20.3	21.5	23.1	23.1	23.4	25.2	25.5	25.7	25.9	26.1	27.8
Middle	20.8	16.8	19.8	19.7	22.8	21.0	23.2	21.8	24.5	22.7	24.2	23.9
Posterior	15.1	12.6	14.0	14.2	17.6	15.7	17.4	15.8	18.7	15.8	18.2	16.9
Relative rate*												
Anterior	1.19	1.13	1.20	1.28	1.09†	1.11†	1.18	1.20†	1.20	1.22	1.24	1.30
Middle	1.15	0.93†	1.11	1.08	1.08	1.00	1.09	1.03	1.15	1.08	1.13	1.11
Posterior	0.83	0.68	0.77	0.78	0.83	0.73	0.81	0.74	0.87	0.76	0.84	0.78

*Relative metabolic rate analysis of variance: group effect: $F=3.63$, $df=2,65$, $P<0.05$; group effect at left hemisphere: $F=3.89$, $df=2,65$, $P<0.05$; group effect at anterior position: $F=6.31$, $df=2,65$, $P<0.01$. Between bipolar depression and control, significant group by hemisphere by lateral-medial position interaction ($F=4.24$; $df=1,30$; $P<0.05$) was found. T-test results († is $P<0.05$ compared with controls) revealed that patients with unipolar depression had significantly lower relative metabolism at the anterior (especially in anterior-medial) position, and patients with bipolar depression had significantly lower relative rates at the region of the left medial thalamus than normal control subjects. Follow-up multivariate analysis of variance between two groups revealed no differences between unipolar depression and normal controls (group effect: $F=7.12$, $df=1,57$, $P<0.01$, group effect at left hemisphere: $F=7.18$, $df=1,57$, $P<0.01$, group effect at anterior position: $F=11.73$, $df=1,57$, $P<0.005$).

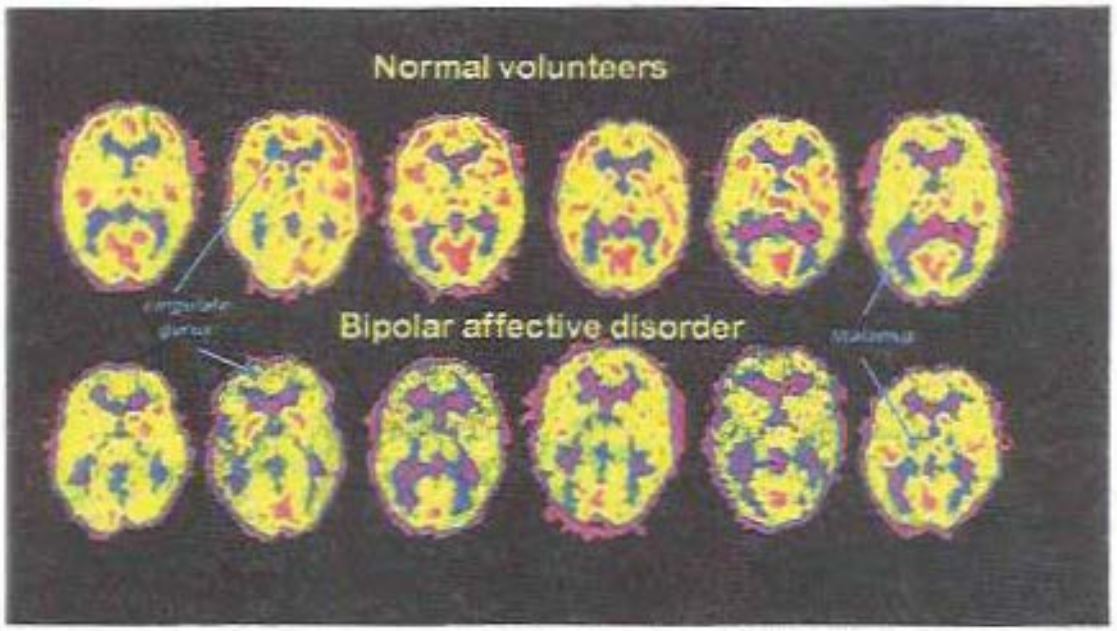

Figure 1. Mid-thalamic slice level PET scans in six control subjects and six patients with bipolar affective disorder. Images from each person are scaled relative to whole-slice mean to facilitate comparison across subjects. Note decreases in relative metabolic rate in frontal lobes, cingulate gyrus, and thalamus, confirmed by statistical analysis (see text).

affective illness, the finding that the "rush" and "high" of cocaine were associated with frontal and striatal decreases in blood flow,[36] a pattern similar to that in bipolar patients, supports the linking of these two structures in affect regulation. Dopamine receptor density was found elevated in the striatum both in psychotic patients with bipolar disorder and in patients with schizophrenia,[37] further linking striatal abnormality to bipolar disorder.

In the thalamus, patients with schizophrenia had lower values in anterior and right-sided regions,[33] whereas patients with bipolar illness had left-sided differences in the middle medial

Table 2
Cortical Metabolic Rate, μmoles/100 g/min

	Bipolar Depression		Unipolar Depression		Control	
	Left	Right	Left	Right	Left	Right
Frontal						
Superior	18.6 (1.07)	18.2 (1.05)	22.7 (1.08)	22.4 (1.06)	22.6 (1.06)	22.3 (1.05)
Middle	18.2* (1.06)	19.4 (1.12)	23.3 (1.11)	24.4 (1.15)	23.5 (1.10)	24.2 (1.15)
Inferior	20.0 (1.16)	20.3 (1.18)	23.9 (1.14)	24.1 (1.15)	24.0 (1.14)	24.1 (1.15)
Precentral	20.0 (1.15)	20.6 (1.18)	25.1 (1.19)	25.7 (1.22)	25.2 (1.20)	25.6 (1.21)
Parietal						
Postcentral	19.4 (1.12)	18.8 (1.08)	23.8 (1.13)	23.8 (1.13)	24.0 (1.14)	23.4 (1.11)
Supramarginal	18.7 (1.07)*	20.0 (1.14)	23.8 (1.13)	24.7 (1.18)‡	23.5 (1.11)	23.7 (1.13)
Angular	19.3 (1.10)	20.0 (1.13)	24.2 (1.15)	25.3 (1.21)	24.3 (1.14)	25.2 (1.19)
Superior	17.8 (1.01)	19.4 (1.10)	23.4 (1.11)	24.3 (1.16)	23.1 (1.08)	23.4 (1.10)
Temporal						
Superior	16.8 (0.98)	18.7 (1.09)*†	19.8 (0.95)	21.8 (1.04)	20.0 (0.95)	21.8 (1.03)
Middle	17.5 (1.02)	17.6 (1.03)	20.3 (0.98)	20.6 (0.99)	20.8 (1.00)	21.0 (1.00)
Inferior	15.6 (0.93)	16.5 (0.96)	18.4 (0.89)	19.0 (0.92)	18.6 (0.89)	19.2 (0.93)
Posterior	14.3 (0.84)†	14.2 (0.83)	15.9 (0.77)	16.5 (0.80)	15.5 (0.75)	15.8 (0.76)
Occipital						
Area 19	18.3 (1.06)	18.6 (1.08)†	22.2 (1.06)	22.0 (1.05)	22.0 (1.06)	21.7 (1.04)
Area 17	20.6 (1.17)	22.4 (1.27)	25.4 (1.21)	26.7 (1.27)	25.6 (1.22)	26.0 (1.24)
Area 17(2)	19.3 (1.12)	20.9 (1.20)	24.2 (1.16)	24.8 (1.19)	23.8 (1.14)	23.9 (1.15)
Area 18	17.8 (1.04)	18.9 (1.10)	20.9 (1.01)	21.3 (1.03)	21.1 (1.02)	21.2 (1.02)

Relative metabolic rates are shown in parentheses.
Analysis of variance: bipolar vs controls; group by region interaction at frontal lobe on relative rate: $F=3.11$, $df=2.46,73.83$, $P<0.05$ (on absolute rate: $F=2.54$, $df=2.14,61.98$, $P<0.09$); group effect at temporal lobe on relative rate: $F=6.65$, $df=1.30$, $P<0.02$; *t* tests; *bipolar vs unipolar ($P<0.05$); †bipolar vs control ($P<0.05$); ‡unipolar vs control ($P<0.05$).

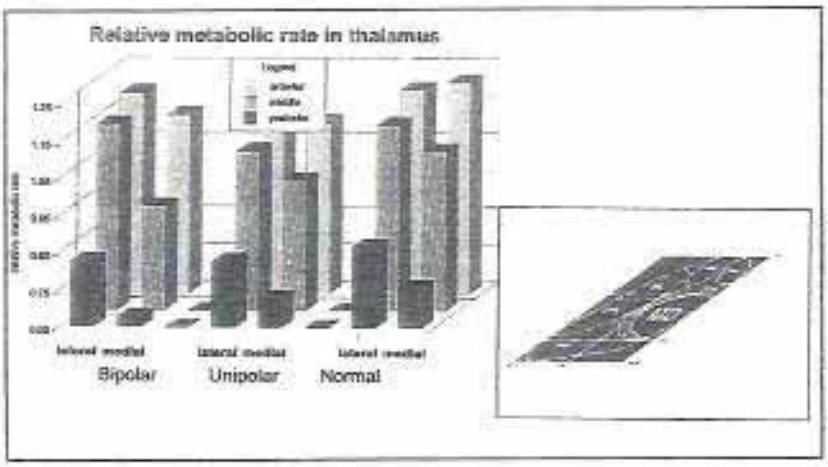

Figure 2. Relative metabolic rate in six divisions of the left thalamus in patients with bipolar affective disorder (n=9), patients with unipolar affective disorder (n=36), and control subjects (n=23). Data are organized so that the left thalamus is viewed as if looking down at the thalamus from the rear of the head; the anterior section is at the back and the posterior portion in the front. Note the low middle medial bar in bipolar patients (region of the medial dorsal nucleus) and that the two anterior bars in the unipolar group (region of the ventral anterior nucleus) have relatively low values in comparison with control subjects.

box, which was calculated to be centered on the medial dorsal nucleus. This finding may be of special interest because the medial dorsal nucleus contains about half glutamatergic excitatory cells and half GABAergic or inhibitory cells; could the medial dorsal nucleus be the unstable switch center with a bipolar potential to activate or inhibit? In our sample, the unipolar patients had thalamic changes in the anterior and lateral regions of the thalamus, areas that might lack this bidirectional potential.

The metabolic rate decrease in the anterior cingulate gyrus in patients with bipolar disorder is of interest because of the structure's important role in affect and attention, probably related to its rich connections to the medial dorsal thalamus and frontal cortex.[38] Ingvar[39] divides the cerebral correlates of willful acts into the inner representation of future events (prefrontal) and emotional/motivational or value aspects of volition (anterior cingulate cortex). Imaging has suggested lower metabolic rates in patients with schizophrenia than in control subjects,[40] but no changes in size.[41] The role of the

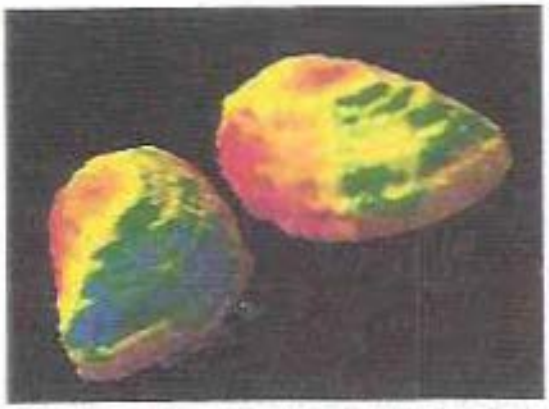

Figure 3. The metabolic surface of the thalamus. The image is generated from 33 new normal individuals scanned with high-resolution PET and 1.2-mm thick coregistered MRI. The thalamus has been traced on 11-15 axial levels, morphed to the average normal outline, and a surface view of relative metabolic rate generated (red is high metabolic activity; blue is low). The thalamus is viewed from the back of the head looking slightly down on the brain.

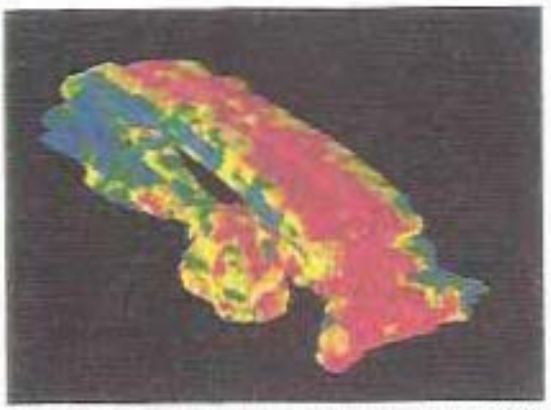

Figure 4. The surface relative metabolic rate of the cingulate gyrus and thalamus in 3D view. The cingulate gyrus was traced as above on coregistered MRI. The structures are viewed from the back of the head, so the anterior cingulate is at the top of the picture and the posterior cingulate at the bottom left.

anterior cingulate in affect and interpersonal interaction is suggested by other imaging studies. Individuals without affective disorders induced to feel happy or sad showed associated changes in cerebral activation in limbic structures, including the cingulate.[42,43] Recognition of novel faces, a task with clear affective significance, also activated the cingulate.[44]

The temporal increases in the superior temporal gyrus region in bipolar illness that we observed in our initial early data[19,20] contrast with findings of decreased metabolic rates and decreased size in the temporal lobe in patients with schizophrenia.[45] Matched imaging studies of this area in patients with bipolar disorder and those with schizophrenia might yield more specific diagnostic indicators.

Comparisons between disparate clinical groups are difficult to interpret. Bipolar and schizophrenic patients differ in their lifetime exposure to neuroleptic drugs, which may leave long-lasting functional and anatomical changes in the striatum and other brain areas. The recruitment of groups of remitted and off-medication schizophrenic patients to provide information for comparison with the remitted and off-medication bipolar patients is also a nearly impossible clinical task. Nevertheless, these metabolic changes taken together with the findings in schizophrenia suggest that the major psychoses are functionally related to this circuit system. Higher resolution PET and MRI studies will be necessary to better resolve thalamic nuclei and regions within the cingulate gyrus (Figures 3 and 4) and striatum to bring together basic animal studies of mammalian brain circuitry and imaging in individual patients.

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Brief Reports

Hippocampal Volume Reduction in Major Depression

J. Douglas Bremner, M.D., Meena Narayan, M.D., Eric R. Anderson, Lawrence H. Staib, Ph.D., Helen L. Miller, M.D., and Dennis S. Charney, M.D.

Objective: Elevated levels of glucocorticoids in depression have been hypothesized to be associated with damage to the hippocampus, a brain area involved in learning and memory. The purpose of this study was to measure hippocampal volume in patients with depression. **Method:** Magnetic resonance imaging was used to measure the volume of the hippocampus in 16 patients with major depression in remission and 16 case-matched nondepressed comparison subjects. **Results:** Patients with depression had a statistically significant 19% smaller left hippocampal volume than comparison subjects, without smaller volumes of comparison regions (amygdala, caudate, frontal lobe, and temporal lobe) or whole brain volume. The findings were significant after brain size, alcohol exposure, age, and education were controlled for. **Conclusions:** These findings are consistent with smaller left hippocampal volume in depression.

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Major depression is a common psychiatric disorder that is associated with considerable morbidity. Depressive episodes are associated with high levels of cortisol in about 40%–50% of patients (1). Elevated levels of glucocorticoids seen in stress have been associated with damage to hippocampal neurons, and the diagnosis of posttraumatic stress disorder (PTSD) has been associated with hippocampal volume reduction and deficits in declarative memory function (2, 3). Hippocampal dysfunction may contribute to verbal declarative memory deficits in depression (4, 5). Few studies, however, have examined hippocampal volume in patients with depression. Neuroimaging findings in affective disorders include ventricular enlargement, widening of the cortical sulci (6), and smaller volumes in the right hippocampus (7), left amygdala (8), and temporal lobe (9) in bipolar disorder and increased subcortical white matter areas of increased signal intensity (10), smaller caudate and putamen volumes (11), alterations in hippocampal T_1 relaxation time (12), and reductions in gray matter in the left temporal lobe (13) in unipolar depression. Studies of hippocampal volume in unipolar depression have had conflicting findings; some studies of amygdala/hippocampal volume (combined) found no difference in comparison with control subjects (14), and others found a reduction (15). The purpose of the current study was to compare hippocampal volume of patients with treated unipolar depression and nondepressed subjects.

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METHOD

The study group consisted of 16 patients with a history of depression based on the Structured Interview for DSM-IV currently treated on an outpatient basis with antidepressant medication (paroxetine, fluoxetine, or desipramine). Ten of the patients were men, and six were women. Patients were excluded according to criteria described elsewhere (16); in addition, patients with a history of PTSD or current medication use other than antidepressant were excluded. Depressed patients had a mean of three inpatient hospitalizations (SD=4, range=0–10), they had been in remission from depression for a mean of 11 weeks (SD=33, range=0–120), and they had experienced an average of two previous episodes of depression (SD=1, range=0–10).

TABLE 1. Volume of the Hippocampus and Other Brain Regions in 16 Patients With Major Depression and 16 Nondepressed Comparison Subjects

	Volume (mm³)					
	Patients With Major Depression		Comparison Subjects		Analysis	
Area	Mean	SD	Mean	SD	F (df=1, 30)	p
Hippocampus						
Left	940	208	1,166	248	7.78	0.009[a]
Right	982	269	1,113	194	2.29	0.13
Mean	961	239	1,140	221	5.23	0.03
Caudate						
Left	2,668	710	2,767	571	0.19	0.67
Right	2,712	765	2,802	613	0.13	0.72
Mean	2,690	738	2,785	592	0.16	0.70
Amygdala						
Left	1,652	455	1,347	448	3.64	0.07
Right	1,699	493	1,335	450	4.75	0.04[b]
Mean	1,676	474	1,341	449	4.33	0.05[b]
Frontal lobe						
Left	140,856	41,597	154,267	24,141	1.24	0.27
Right	143,101	45,265	164,471	27,150	2.62	0.12
Mean	141,979	43,431	159,369	25,646	1.95	0.17
Temporal lobe						
Left	17,931	4,170	18,227	1,791	0.07	0.80
Right	18,207	4,260	19,475	2,707	1.01	0.32
Mean	18,069	4,215	18,851	2,249	0.45	0.51
Whole brain	1,404,586	179,994	1,390,789	153,948	0.05	0.82

[a] Significant difference after correction for multiple comparisons ($p<0.03$) and covarying for whole brain size.
[b] Difference was not statistically significant after difference in whole brain size was controlled for ($p>0.05$).

Comparison subjects (N=16) were case-matched to patients for sex and handedness. There were no differences between patients and comparison subjects in age (mean=45 years, SD=8, versus mean=45 years, SD=10), years of alcohol abuse (mean=4, SD=7, versus mean=3, SD=5), or years of education (mean=14, SD=2, versus mean=15, SD=2). One of the patients had a past history of alcohol dependence, three had a past history of alcohol abuse, and two had a past history of polysubstance abuse. One of the patients had current panic disorder without agoraphobia. All patients and comparison subjects gave written informed consent before participating in the study.

Magnetic resonance images were obtained and analyzed by using methods described in detail elsewhere (3), including measurements of a mid-hippocampal segment performed by two blind raters. Volumetric assessments were also made of other regions (table 1) for purposes of comparison and to determine if volume changes were specific to the hippocampus as previously reported (3). Frontal lobe measurements were performed by measuring the frontal lobe on all coronal slices anterior to the anterior commissure. There was a high level of interrater reliability for hippocampal volume measurements between the two independent raters for the left hippocampus ($r=0.93$, $df=31$, $p<0.05$) and the right hippocampus ($r=0.94$, $df=31$, $p<0.05$).

Repeated measures analysis of variance (ANOVA) with side (left versus right hemisphere) as the repeated factor was performed to compare left and right hippocampal volume (as well as comparison regions) between patients and nondepressed subjects. Univariate statistics were used to compare left and right hippocampal volume; a level of significance of $p<0.03$ was applied to correct for multiple comparisons. Multiple linear regression was used to examine the relationship between hippocampal volume and diagnosis while controlling for potential confounders.

RESULTS

Repeated measures ANOVA with side (left versus right hemisphere) as the repeated factor showed a significant main effect for diagnosis (table 1) and no significant main effect for side or side-by-diagnosis interaction. Univariate analyses showed a statistically significant 19% smaller volume of the left hippocampus in the depressed patients than the comparison subjects; the difference remained significant after differences in whole brain volume were controlled for, but a 12% difference in right hippocampal volume between the groups was not significant (table 1). There were no differences in volume in the comparison regions with the exception of the right amygdala, which was related to a larger volume of the right amygdala in depression (table 1). This effect was not significant, however, after differences in whole brain volume were controlled for.

There was no correlation between left hippocampal volume and clinical variables, including number of weeks in remission, number of previous episodes of depression, or number of hospitalizations for depression. Multiple linear regression to control for possible confounds that may affect hippocampal volume, including age, years of education, and years of alcohol abuse, continued to show differences in left hippocampal volume between patients and comparison subjects when these potential confounders were entered in the model.

DISCUSSION

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Patients with remitted major depression in this study had a 19% smaller volume of the left hippocampus than matched comparison subjects. There were no differences in volumes of comparison regions between the groups in the temporal lobe, caudate, frontal lobe, or whole brain.

There are several possible explanations for our findings of hippocampal volume reduction in depression.

Elevated levels of glucocorticoids during depressive episodes could cause hippocampal damage, leading to a reduction in volume. In this model, chronic repeated episodes of depression may lead to progressive hippocampal atrophy over time, possibly increasing the risk for subsequent depressive relapse. Other factors, such as reductions in neurotrophins, could also be responsible for hippocampal volume reduction. However, the current study did not include measures of cortisol during depressive episodes, and future studies are needed to evaluate the relationship between cortisol and hippocampal volume in depression. It is also possible that smaller hippocampal volume from birth, or secondary to some premorbid environmental factor, is a risk factor for depression.

Amygdala volume was larger in depression but not significantly larger after we controlled for brain size. The meaning of these findings is unclear and should be replicated. It may account for the finding of Axelson et al. (14) of no difference in combined amygdala/hippocampal volume in patients with unipolar depression.

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The Genetics of Bipolar Disorder

by JOHN R. KELSOE, MD

Although heredity has long been implicated in the causation of mood disorders, it has only been in the last seven decades that a variety of epidemiologic data and family studies have lent scientific support to this notion. Such studies provide convincing evidence that affective disorders are both familial and genetic, and hence, provide a powerful theory for their biologic cause. More recently, molecular genetic methods have made possible the identification of specific genes for genetic disorders. The epidemiologic data provides the rationale for such gene-mapping studies, and a guide to the pitfalls and complexities facing such efforts. This epidemiologic data is briefly reviewed here, and the reader is referred to several recent excellent reviews.[1-3] The current status of linkage studies and the search for specific genes will then be discussed.

FAMILY STUDIES

Epidemiologic support for the genetic cause of bipolar disorder derive primarily from three different types of studies: family, twin, and adoption. In family studies, rates of mood disorders are determined in the first-degree relatives of probands with bipolar disorder. Table 1 summarizes 18 family studies of bipolar disorder conducted over nearly 30 years. Because of the wide range of diagnostic and epidemiologic methods employed, any combined analysis of such data must be qualified. Together these studies indicate an approximately 6.5% risk for bipolar disorder and an approximately 10% risk for unipolar disorder. Population rates[3,4] and rates derived from family studies of control probands[5,6] are approximately 1% and 5% for bipolar and unipolar disorders, respectively. The risk for bipolar disorder is, therefore, elevated nearly sevenfold, and for unipolar disorder, it is doubled. Together, these data indicate that bipolar disorder is familial, and suggest that some forms of unipolar disorder may be an alternate expression of the same underlying diathesis. These studies do not, however, prove that bipolar disorder is genetic. Family studies are unable to separate "nature" from "nurture," and hence, exclude the possibility of environmental transmission. Theoretically, parents might unwittingly teach their children to be bipolar, create an environment conducive to bipolar disorder, or share a common environmental factor, such as a toxin or virus.

TWIN STUDIES

To address these issues, twin and adoption studies provide powerful experimental designs to separate genetic from environmental influences. In twin studies, both monozygotic (MZ) and same-sex dizygotic (DZ) twin pairs are identified in which at least one member of the pair has bipolar disorder. Theoretically, because the twin pairs are raised together, they are exposed to the same environmental and rearing factors. The twin pairs differ in that monozygotic pairs share all their genes, whereas dizygotic pairs share only half their genes as with any sib-pair. The concordance rate is defined as the percentage of twin pairs in which both twins are affected. Differences in the rates of concordance between the monozygotic and dizygotic twin pairs can, therefore, be attributed to genetic rather than environmental influences. Table 2 summarizes eight twin studies conducted since 1930. Again, because of the range of methods employed, any combined analysis of such data must be qualified. Nevertheless, these results

Dr. Kelsoe is from the Department of Psychiatry, University of California, San Diego.

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Address reprint requests to John R. Kelsoe, MD, Dept. of Psychiatry, 0603, University of California, San Diego, La Jolla, CA 92093-0603.

TABLE 1
Family Studies of Bipolar Disorder*

Study	Relatives at Risk	Morbid Risk (%)	
		Bipolar	Unipolar
Perris, 1966[74]	627	10.2	0.5
Winokur and Clayton, 1967[75]	167	10.2	20.4
Mendlewicz and Rainer, 1974[35]	606	17.7	22.4
Goetzl et al, 1974[76]	212	2.8	13.7
Helzer and Winokur, 1974[38]	151	4.6	10.6
Gershon et al, 1975[42]	341	3.8	6.8
James and Chapman, 1975[77]	239	6.4	13.2
Johnson and Leeman, 1977[78]	126	15.5	19.8
Petterson, 1977[79]	472	3.6	7.2
Smeraldi et al, 1977[80]	172	5.8	7.1
Trzebiatowska-Trzeciak, 1977[60]	289	11.4	0
Angst, 1980[81]	400	2.5	7.0
Dunner, Go, and Fieve, 1980[82]	1199	4.2	8.2
Taylor, Abrams, and Hayman, 1980[83]	600	4.8	4.2
Gershon et al, 1982[6]	598	8.0	14.9
Tsuang et al, 1985[84]	169	5.3	12.4
Rice et al, 1987[20]	557	5.7	23.0†
Sadovnick et al, 1994[85]	1102	3.5	5.7
Total relatives and weighted means of risks‡	8027	6.5	9.9

*Risk to first-degree relatives of bipolar probands. Adapted and updated from Nurnberger JI, Gershon ES. Genetics of affective disorders. In: Post RM, Ballenger JC, eds. *Neurobiology of Mood Disorders*. Baltimore, Md: Williams & Wilkins; 1984:76-101.
†Observed rates rather than morbid risk.
‡Means weighted according to number of relatives studied. This summary of studies must be carefully qualified because of the variety of diagnostic and other methods employed by these studies.

indicate a concordance rate of approximately 67% among monozygotic twins and 25% for dizygotic twins. This substantial increase in risk for monozygotic twins is perhaps the strongest data available for the role of genetics in bipolar disorder. Several interesting points are made in the report by Bertiesen.[7] MZ concordance is higher for the bipolar probands (80%) than the unipolar probands (59%), and 78% of pairs were concordant for polarity, ie, bipolar-bipolar or unipolar-unipolar. The observation regarding higher concordance for bipolar disorder is confirmed in the study by Kendler et al,[8] who observe a greater than 10-fold increase in concordance between MZ and DZ twins for bipolar-bipolar pairs.

ADOPTION STUDIES

Adoption studies provide another avenue to the separation of nature and nurture. These studies are typically conducted in one of two ways. Most commonly, ill and well adoptees are identified as probands, and the rates of illness are determined in both their biologic and adoptive parents. Alternatively, ill and well parents may be identified as probands, and the rates of illness determined in their adopted children. These studies are difficult to perform because informative individuals are relatively rare, and biologic parents difficult to locate. For these reasons, many such studies have been conducted in Scandinavian countries where centralized medical and adoption records facilitate proband ascertainment.

Of the five such studies that have been reported, two provide strong evidence of genetic transmission, and three only weak or no evidence. Using the adoptee as proband strategy, Mendlewicz and Rainer[9] reported more than a threefold increase in the rate of bipolar disorder in the biologic versus the adoptive parents of bipolar probands. Similarly, they observed a twofold increase in unipolar disorder. Wender et al[10] conducted an adoptee-as-proband study in a Danish population and reported more than a threefold increase in unipolar illness in the biologic relatives of mood-disordered adoptees. They also observed a sixfold increase in the rate of completed suicide in the biologic relatives. Three other studies have been less convincing of genetic transmission. In a study using parents as probands, Cadoret found a nonsignificant trend for increased unipolar disorder among the adopted children of affectively ill mothers.[11] Using adoptees as probands, Von Knorring et al[12] found no significant evidence for genetic transmission in a Swedish sample. Similarly, in a second study by Cadoret et al,[13] using adoptees as probands, no significant evidence for genetic transmission was obtained. Adoption studies, therefore, provide some support for genetic factors, but results are mixed, and further work is required using this difficult but powerful methodology.

TABLE 2
Twin Studies of Affective Disorder*

Study	Monozygotic Twins		Dizygotic Twins	
	No. Twin Pairs	Concordance (%)	No. Twin Pairs	Concordance (%)
Luxenberger[86]	4	75.0	13	0.0
Rosanoff et al[87]	23	69.6	67	16.4
Slater[88]	7	57.1	17	23.5
Kallman[89]	27	92.6	55	23.6
Harvald and Hauge[90]	15	66.7	40	5.0
Allen et al[91]	15	33.3	34	0.0
Bertelsen[7]	55	58.3	52	17.3
Kendler et al[8]	154	69.7	326	34.9
Totals	300	67.5	604	25.3

*Adapted and updated from Nurnberger JI, Gershon ES. Genetics of affective disorders. In: Post RM, Ballenger JC, eds. *Neurobiology of Mood Disorders*. Baltimore, Md: Williams & Wilkins; 1984:76-101.

MODE OF TRANSMISSION

Given that genetics plays some role in the cause of bipolar disorder, what can be inferred from epidemiologic data regarding the mode of genetic transmission? This question is addressed by a statistical approach to family data referred to as segregation analysis. To illustrate with a simple example, under a mendelian, dominant model of transmission, only one copy of a disease allele is required for an individual to be affected. Therefore, half of the children of one affected parent should also be affected. Similarly, under a recessive model, two copies of the disease allele are required for illness, and one quarter of the children of two unaffected carrier parents should be affected. Therefore, in the simplest case, one can infer the genetic mode of transmission by counting the affected children within families. In practice, such analyses are quite involved, and require mathematical fitting of a complex model to the observed family data. Furthermore, exacting care must be given to the ascertainment of subjects to prevent bias in the families studied.

In bipolar disorder, the results of such studies have been inconsistent. Many segregation analyses have been unable to reach any conclusion regarding a mode of transmission.[14-16] Several studies, however, have supported an autosomal-dominant mode of transmission.[17-21] Two of these studies, by Rice et al[20] and Spence et al,[21] are particularly important because they employ relatively large general population samples, and, more recently, developed statistical methodology. In addition to testing for genes of large effect, or major loci, other analyses have focused on a model in which multiple genes contribute to an overall liability to affective disorder. Unfortunately, such multifactorial polygenic models have similar limited success.[4,18,22] It is unclear exactly what conclusions to draw from these conflicting results. A likely explanation is the presence of multiple genetic forms with different modes of transmission. In fact, recent attempts to model the interaction of two or more genes has met with some success in predicting risks to bipolar disorder.[23]

THE COMPLEXITIES OF COMPLEX DISORDERS

A variety of factors likely contribute to the complexity of the genetics of bipolar disorder. Together these factors have confounded efforts to identify a mode of transmission and will similarly complicate the identification of specific loci by linkage analysis. One of these factors is reduced penetrance. Penetrance refers to the probability that a person will manifest the disease given that they have the gene. The strongest evidence of reduced penetrance is the observation that the concordance rate for monozygotic twins is less than 100%. The unaffected identical twin must carry the gene but not express it. The likely presence of phenocopies further complicates bipolar genetics. A phenocopy is a person who has the disease but not the gene; in other words, a non-genetic case of the disorder. The presence of both phenocopies and reduced penetrance indicate that non-genetic factors play a significant role in the cause of bipolar disorder. Furthermore, they make it difficult to determine who does or does not carry the disease allele in families, and thereby complicate both segregation and linkage studies. Another complicating factor is variable expressivity, which occurs when different individuals carrying the same disease gene may express the disorder in different ways. For example, the previously mentioned epidemiologic data suggest that the same genes may predispose to both unipolar and bipolar disorders. Such variability in expression leads to uncertainty regarding how to define "affected." Individuals with bipolar I, bipolar II, recurrent unipolar, single-episode unipolar, and schizoaffective disorder all commonly occur in the same family, not to mention alcoholism and substance abuse. It is unclear which of these family members to consider affected in genetic analyses.

The most difficult confounding factor of all, however, is genetic heterogeneity. In an illness as

common as bipolar disorder, it is highly likely that multiple genes are involved. Different genes can operate and interact in a wide variety of ways to transmit the susceptibility to bipolar disorder. The simplest model is that of a single major locus. In this case, one disease gene alone can predispose someone to bipolar disorder. In a collection of families, however, different single major loci may be operating in different families. Even more complicated, more than one single major locus may be operating in the same family (intrafamilial heterogeneity). Other models assume that multiple genes usually contribute to the predisposition to bipolar disorder in an affected individual. In these polygenic or oligogenic models, each gene may have only a relatively small effect but together combine in an additive or multiplicative fashion to predispose an individual to bipolar disorder.

MOLECULAR GENETIC STUDIES: THE SEARCH FOR GENES

Although epidemiologic data have long supported the role of genetics in bipolar disorder, it has only been recently that molecular genetic methods have made possible the search for specific genes. Genetic linkage, DNA polymorphisms, and the strategy of positional cloning are explained elsewhere in this issue. The application of these methods to bipolar disorder during the past several years has had a manic-depressive course of its own, with highs of discovery and lows of non-replication. The first such high of discovery came in 1987 in studies of the Old Order Amish.

The Old Order Amish

The Old Order Amish are a conservative religious sect living in southeastern Pennsylvania who eschew modern conveniences such as electricity and television and isolate themselves from the world in an agrarian, horse-and-buggy lifestyle. As with other such population isolates, they offer several advantages for studies of genetic disorders. The primary advantage is that of potentially reduced genetic heterogeneity. The current population of 12 000 arose from a group of about 30 original founders who immigrated from Germany nearly 300 years ago. Since then, very little marrying into the Old Order Amish population from the outside has occurred. Therefore, of the multiple genes that likely predispose to bipolar disorder in the general population, perhaps only a few were represented in that original set of founders. Other advantages of studying this population include large sibships, which are very informative for linkage, multiple generations of living family members, and the virtual absence of alcohol and drug abuse, which so often confounds psychiatric diagnoses.

In 1987, Egeland et al[18] reported evidence of genetic linkage between bipolar disorder and two polymorphic DNA markers on chromosome 11 in an extended Amish pedigree. Multi-point analyses of these two markers indicated a lod score of nearly 5, or odds of 100 000:1 in favor of linkage. As the first reported successful application of molecular genetic linkage methods in a psychiatric illness, this finding was very exciting. Unfortunately, numerous other subsequent studies in several other populations failed to replicate the finding.[24-31] Initially, this failure was interpreted as the result of genetic heterogeneity and the presence of a relatively rare gene in the Amish. Later studies in an expanded and updated version of pedigree 110 also failed to replicate the original finding and, in fact, excluded linkage to the 11p15 region with lod scores of less than -10.[32,33] Linkage to these markers was also excluded in a separate extension to pedigree 110.[34] This surprising reversal largely resulted from two factors: new onset of illness in two individuals since the original study and the addition of a new 30-member right extension, which showed strongly negative lods. How is such a dramatic change in results to be interpreted? One possibility is that the first result was simply a false positive. Another is that more than one gene for bipolar disorder is operating in the same Amish family. The changes in diagnosis and expansion of the family may have caused another gene to interfere with detection of the 11p15 locus. The identification of other possible loci in this population, and the application of other statistical methods better suited to the interaction of multiple genes, may be necessary to unravel this puzzle.

X-LINKAGE

A similar story of inconsistent results and non-replication has unfolded in studies of the X chromosome. Indirect evidence of X-linked genes has long been reported for affective disorder. In families of bipolar probands, women have been reported to be at a twofold greater risk for unipolar disorder than men.[35-37] A decreased frequency of male-to-male transmissions has also been reported and supports an X-linked gene.[38,39] These results have not been uniformly replicated in other studies, however.[40,41] Evidence for linkage has been reported for several classic markers on the X chromosome, including color blindness, the Xg blood group,[42] glucose-6-phosphate dehydrogenase deficiency (G6PD),[43] and factor IX.[44] The large distance between Xg and the other reported loci argues against linkage to that marker.[45] The strongest such evidence to date was reported by Baron et al[46] in a study of color blindness and G6PD deficiency in several large Israeli pedigrees. Multi-point analyses indicated lod scores higher than 9 to these two Xq28 markers. In a frustrating repeat of the Amish study, however, these results could not be replicated in several other studies of North American families using RFLP markers.[25,28,47,48] Again, genetic heterogeneity was blamed until subse-

TABLE 3
A Summary of Loci Potentially Linked to Bipolar Disorder

Locus	Chromosome	Reference	Result
Insulin, HRAS	11p15	Egeland et al[16]; Kelsoe et al[32]	excluded?
Tyrosine Hydroxylase	11p15	Leboyer et al[62]	positive association
		Lim et al[63]	lod 1.9
		Gurling et al[61]	lod 3.58—two locus analysis with D21S171
Color-blindness; G6PD	Xq28	Baron et al[45,49]	diminished evidence, lod 2.09
DXS994	Xq26	Pekkarinen[52]	lod 3.1
D18S40	18p	Berrettini et al[50]	lod 2.6, positive APM & ASP*
D18S41	18q	Stine et al[53]	lod 3.51, in paternal pedigrees
D18S554	18q22-q23	Freimer et al[54]	lod 3.7
D18S43	18q23	Coon et al[55]	lod 2.22
D18S43	18q23	De Bruyn[56]	lod 1.18
PFKL	21	Straub et al[60]	lod 3.4, positive APM & ASP*
D21S171	21	Gurling et al[61]	lod 3.58—two locus analysis with TH
D4S394	4p	Blackwood et al[64]	lod 4.1
D7S78	7	Detera-Wadleigh et al[65]	lod 3.87
D16S510	16p13	Ewald et al[66]	lod 2.65, multipoint
D20S66	20	Detera-Wadleigh et al[64]	lod 2.54
Dopamine Transporter	5p	Kelsoe et al[66]	lod 2.38
D1S103	1	Gejman et al[68]	lod 2.34
D22S29	22	Gerhard[69]	lod 2.0
D22S303	22q	Lachman et al[67]	lod 2.5
Darier's disease	12q	Dawson et al[70]	lod 1.6
D5S62	5q	Coon et al[96]	lod 1.1
D6S7	6	Ginns et al[97]	lod 2.46
D13S1	13	Ginns et al[97]	lod 1.6
D15S45	15	Ginns et al[97]	lod 1.7

*APM=affected pedigree member method; ASP=affected sib-pair method.

quent studies in extended and updated versions of the same families with more informative DNA markers substantially reduced the evidence for linkage.[49]

CURRENT STATUS OF LINKAGE STUDIES

Table 3 is a partial summary of some recently reported loci with positive evidence of linkage. For several of these loci, the evidence for linkage is strongly suggestive and supported by similar results from other independent studies. A lod score of 3 or its equivalent is the conventional threshold for statistical significance. However, it is currently being debated whether this or a higher standard is most appropriate. Therefore, there is no clear consensus as to which of these results are significant. The evidence for other loci is more modest. More data will be necessary in order to determine, in a definitive fashion, which of these are real loci and which are false positives.

Berrettini et al[50] reported evidence of possible linkage to several loci on chromosome 18 as part of a systematic survey of the genome in 22 families. Although the maximum lod within their dataset is only 2.38, their data stands out because several families have positive lods at several different markers in the 18 centromeric region. Their data is also strongly positive using two nonparametric methods, the affected pedigree member (APM)[61] method ($P<0.0001$) and the affected sib-pair (ASP)[62] method ($P<0.0004$). By testing only for allele sharing among affected members, these methods avoid assumptions regarding mode of transmission and, hence, are more robust to non-mendelian transmission. It is of interest that in their data using parametric methods, some families have positive lods under dominant models and some under recessive. This finding would be consistent with different mutations at the same disease locus and a heterogeneous mode of transmission. The most important evidence for this region comes from several recent reports that independently support this finding.[53-56] Such independent support is the most critical test for a linkage and makes chromosome 18 the strongest linkage finding in bipolar disorder to date. However, other studies have provided only limited or no support for this region.[57,58] Two interesting features stand out about this data. First, the region involved is quite large, with at least three different areas of chromosome 18 implicated. If the finding is real, this raises the question of whether there is more than one bipolar locus on the chromosome. Secondly, two reports indicate that the linkage may be seen preferentially in

families in which primarily paternal transmission occurs.[58,59] This raises the possibility of a "parent of origin" effect in which the differences in male and female meiosis may affect the expression of the disease. Although the implicated region is rather large, two possible candidate genes stand out: a G protein, $G_{\alpha s}$, which mediates signal transduction from some dopamine receptors, and the receptor for ACTH.

Straub et al[60] recently reported evidence for linkage to loci on chromosome 21. In a systematic genome survey of 47 families, they identified one family with a maximum lod score of 3.4 at the marker PFKL on 21q22.3. Fourteen other markers in this region also showed positive lods, as did five of the other 46 families. A combined lod score analysis of the entire family set did not support linkage, although APM analyses were very positive ($P<0.0003$). Support for this finding also comes from a recent report in which a lod score of 3.58 was obtained in an analysis that assumed two loci for bipolar disorder, one on chromosome 21 and the other at tyrosine hydroxylase on chromosome 11p15.[61] Such analyses, which take genetic heterogeneity into account, may have great power to identify disease loci, and will likely be increasingly employed in studies of psychiatric illnesses.

Despite the failure in 1989 to replicate the linkage to 11p15 in the Amish, several subsequent studies continue to provide suggestive support for this region. Most notable of these studies is the previously mentioned study implicating both chromosome 21 and tyrosine hydroxylase on 11p15. This region is also implicated by one study demonstrating genetic association[62] and one positive linkage study.[63] Furthermore, in the 1989 follow-up study in Amish pedigree 110, although the lod scores dropped substantially from the original report, a lod score of 2.88 was still obtained in the updated core pedigree. Although these data are not convincing, the possibility of a bipolar locus on 11p15 must still be considered.

In a similar fashion, despite the history of non-replication of linkage to the X chromosome, Pekkarinen et al[62] recently reported evidence of linkage to Xq26, a region that is different but near Xq28 and that was previously reported to be linked.

Several other positive results from Table 3 warrant mention. In a study of a large Scottish kindred, Blackwood et al[64] recently reported a lod score of 4.1, one of the highest lod scores reported to date, to a region on chromosome 4p. Another high lod score of 3.87 has also been reported by Detera-Wadleigh et al[65] on chromosome 7. Kelsoe et al[66] have reported suggestive evidence of linkage to the dopamine transporter locus on chromosome 5p. As the site of action of amphetamine and cocaine, this is a very appealing candidate gene. Two studies have provided suggestive evidence of linkage to loci on chromosome 22.[67,68] Chromosomal deletions in this general region produce a congenital dysmorphism syndrome called velo-cardio-facial syndrome (VCFS). About one third of adolescents with VCFS develop psychosis and a variety of other psychiatric symptoms. This region has also been implicated in linkage studies of schizophrenia.[69] The cosegregation of a genetic skin disease, Darier's disease, with bipolar disorder in a Welsh family led Dawson et al[25] to investigate the region containing the Darier's disease locus on chromosome 12q. In a series of families with bipolar disorder but without Darier's disease, they found suggestive evidence of linkage to several markers on 12q. Lastly, Ginns et al[27] reported suggestive evidence of linkage to three regions on chromosomes 6, 13, and 15 as part of their systematic genome survey of the Amish.

SOME TENTATIVE CONCLUSIONS AND HOPE FOR THE FUTURE

The search continues for bipolar genes. The experience with chromosomes 11 and X have been sobering on investigators, yet the faith remains strong that the overall approach will ultimately be successful. Several tentative conclusions can be reached regarding this search based on results to date and the complexities of bipolar genetics already described. First, lod scores must be interpreted with caution. High lods found in only one population or family set must be viewed with caution, and independent replication must be the only gold standard. As the search for genes has continued and many groups have screened substantial portions of the genome, it has become apparent that high lods will not be a common occurrence. False negatives and missing real linkages are also a great danger. Therefore, mildly positive lods should not be too readily dismissed. Second, a variety of statistical methods should be employed, including those more robust to non-mendelian transmission and genetic heterogeneity. The ASP method,[62] the APM method,[61] non-parametric multipoint methods and associated methods may be particularly useful in this regard. The recent development of methods employing models of several interacting genes also shows great promise.[66] Third, a large sample size requiring collaboration between investigators will likely be required. The recent NIMH genetics initiative has funded several centers for family collection, and their goal of 200 families with bipolar disorder should soon be achieved. This collection will be an invaluable resource for collaborative studies.

Finally, recent success in mapping genes for two other complex disorders provides encouragement. Alzheimer's disease shares many of the complexities likely to be present in bipolar disorder, yet at least three loci have been identified.[67] Although investigators of this illness had the advantage of a pathognomonic brain abnormality, success also came from a large international collaboration and the use of a variety of statistical strategies. More recently, a number of genes for diabetes have been

mapped by a systematic genome survey of a large collection of affected sib-pairs.[68] Several of these loci, which have now been convincingly replicated, had previously shown only inconsistent results by lod score and association methods. The course of progress in these complex disorders echo the recent history of gene mapping efforts for bipolar disorder and thereby provide both hope and direction.

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302.89 Frotteurism

The paraphiliac focus of Frotteurism involves touching and rubbing against a nonconsenting person. The behavior usually occurs in crowded places from which the individual can more easily escape arrest (e.g., on busy sidewalks or in public transportation vehicles). He rubs his genitals against the victim's thighs and buttocks or fondles her genitalia or breasts with his hands. While doing this he usually fantasizes an exclusive, caring relationship with the victim. However, he recognizes that to avoid possible prosecution, he must escape detection after touching his victim. Usually the paraphilia begins by adolescence. Most acts of frottage occur when the person is ages 15–25 years, after which there is a gradual decline in frequency.

Diagnostic criteria for 302.89 Frotteurism

A. Over a period of at least 6 months, recurrent, intense sexually arousing fantasies, sexual urges, or behaviors involving touching and rubbing against a nonconsenting person.

B. The fantasies, sexual urges, or behaviors cause clinically significant distress or impairment in social, occupational, or other important areas of functioning.

302.2 Pedophilia

The paraphiliac focus of Pedophilia involves sexual activity with a prepubescent child (generally age 13 years or younger). The individual with Pedophilia must be age 16 years or older and at least 5 years older than the child. For individuals in late adolescence with Pedophilia, no precise age difference is specified, and clinical judgment must be used; both the sexual maturity of the child and the age difference must be taken into account. Individuals with Pedophilia generally report an attraction to children of a particular age range. Some individuals prefer males, others females, and some are aroused by both males and females. Those attracted to females usually prefer 8- to 10-year-olds, whereas those attracted to males usually prefer slightly older children. Pedophilia involving female victims is reported more often than Pedophilia involving male victims. Some individuals with Pedophilia are sexually attracted only to children (Exclusive Type), whereas others are sometimes attracted to adults (Nonexclusive Type). Individuals with Pedophilia who act on their urges with children may limit their activity to undressing the child and looking, exposing themselves, masturbating in the presence of the child, or gentle touching and fondling of the child. Others, however, perform fellatio or cunnilingus on the child or penetrate the child's vagina, mouth, or anus with their fingers, foreign objects, or penis and use varying degrees of force to do so. These activities are commonly explained with excuses or rationalizations that they have "educational value" for the child, that the child derives "sexual pleasure" from them, or

that the child was "sexually provocative"—themes that are also common in pedophiliac pornography.

Individuals may limit their activities to their own children, stepchildren, or relatives or may victimize children outside their families. Some individuals with Pedophilia threaten the child to prevent disclosure. Others, particularly those who frequently victimize children, develop complicated techniques for obtaining access to children, which may include winning the trust of a child's mother, marrying a woman with an attractive child, trading children with other individuals with Pedophilia, or, in rare instances, taking in foster children from nonindustrialized countries or abducting children from strangers. Except in cases in which the disorder is associated with Sexual Sadism, the person may be attentive to the child's needs in order to gain the child's affection, interest, and loyalty and to prevent the child from reporting the sexual activity. The disorder usually begins in adolescence, although some individuals with Pedophilia report that they did not become aroused by children until middle age. The frequency of pedophiliac behavior often fluctuates with psychosocial stress. The course is usually chronic, especially in those attracted to males. The recidivism rate for individuals with Pedophilia involving a preference for males is roughly twice that for those who prefer females.

Diagnostic criteria for 302.2 Pedophilia

A. Over a period of at least 6 months, recurrent, intense sexually arousing fantasies, sexual urges, or behaviors involving sexual activity with a prepubescent child or children (generally age 13 years or younger).

B. The fantasies, sexual urges, or behaviors cause clinically significant distress or impairment in social, occupational, or other important areas of functioning.

C. The person is at least age 16 years and at least 5 years older than the child or children in Criterion A.

Note: Do not include an individual in late adolescence involved in an ongoing sexual relationship with a 12- or 13-year-old.

Specify if:

Sexually Attracted to Males
Sexually Attracted to Females
Sexually Attracted to Both

Specify if:

Limited to Incest

Specify type:

Exclusive Type (attracted only to children)
Nonexclusive Type

6(c)

WAYNE A. STILLINGS, M.D.
KARE & THERAPY, INC.

680 Craig Road, Suite 210
St. Louis, MO 63141-7120
Tel.: (314) 994-0100
Fax: (314) 994-9139

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AND NEUROLOGY

October 31, 2011

Mr. William Lake
Chief Media Bureau
Federal Communications Commission
Washington, D.C. 20554

RE: Mike Rice

Dear Sir(s):

By way of introduction, I have been in private practice of neuropsychiatry and forensic psychiatry for 32 years. I am an Associate Clinical Professor of Psychiatry at the Washington School of Medicine in St. Louis, Missouri.

Mr. Rice has been under my psychiatric treatment for 20 years, including a six-month psychiatric hospitalization at Barnes Hospital in St. Louis. I have been treating Mr. Rice for bipolar disorder, mixed; dissociative disorder, NOS; dysthymia; and alcohol abuse with a combination of psychotropic medications and psychotherapy.

Mr. Rice is fully recovered and rehabilitated from his psychiatric condition created by the aforementioned four psychiatric diseases. His recovery is complete and impressive. He remains on one psychotropic medication, generic Wellbutrin 300mg per day, for his affective disorder. He has been fully compliant with psychiatric treatment and rehabilitation. There is no evidence that he will relapse. He is receiving only monitoring and maintenance psychiatric treatment.

He is a very productive member of his community. He has served on his neighborhood board of directors twice during the past five years and has amply demonstrated good character since his legal problem.

It is my opinion to a reasonable degree of medical and psychiatric certainty that Mr. Rice is qualified for FCC licensure.

For further information in support of the above, please refer to my declaration dated 05/17/2001.

Very truly yours,

Wayne A. Stillings, M.D.
Assistant Professor of Clinical Psychiatry
Washington University School of Medicine

WAS/mlt

The Society of Broadcast Engineers

Washington, D. C.

In accordance with the provisions of the
SBE Program of Certification and for
professional experience in broadcast engineering

Mike S. Rice

is hereby certified as a

Professional Broadcast Engineer

In testimony whereof witness the signatures of the President and Secretary
under the seal of this society this 1st day of July, 1990

Brad Dick
President

Paul Zenty
Secretary

No. 389 Expires 7-1-95

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SBE

PROGRAM OF CERTIFICATION

SOCIETY OF BROADCAST ENGINEERS, INC.
8445 Keystone Crossing Ste. 140 • Indianapolis, IN 46240
Telephone: 317/253-1640 • FAX: 317/253-0418
Web Site: http://www.SBE.org

CHAIRMAN
TERRENCE M. BAUN, CPBE
Criterion Broadcast Services
5300 W. Garfield Ave.
Milwaukee, WI 53208-1018
tbaun@sbe.org

COMMITTEE
JAMES T. BERNER, JR., CSTE
WGNX/WGNX-DT
1810 Briarcliff Road NE
Atlanta, GA 30329
jberner@sbe.org

DAVID CARR, CPBE
7 Dunlin Meadow Court
The Woodlands, TX 77381
dncarr46@hotmail.com

DANE E. ERICKSEN, PE, CSRTE
Hammett & Edison, Inc.
Box 280068
San Francisco, CA 94128
deriksen@h-e.com

RICHARD A. FARQUHAR, CPBE
RAF Associates, Inc.
4620 Timothy Lane
Canal Winchester, OH 43110
rick@rafassociates.com

DOUGLAS W. GARLINGER, CPBE
LeSEA Broadcasting
P.O. Box 394
Westfield, IN 46074-0394
dgarlinger@prodigy.net

RALPH HOGAN, CPBE
Washington State University
P.O. Box 642530
Pullman, WA 99164-2530
rhogan@wsu.edu

TROY D. PENNINGTON, CSRE
WZZK-AM/FM, WODL-FM
301 Beacon Parkway W, Ste 200
Birmingham, AL 35209
troy.pennington@cox.com

RICHARD A. RYAN, CPBE
Reactor Wisconsin
3820 S. Sunny Ridge Lane
New Berlin, WI 53151-6030
ryan@exxopc.com

HRISTOPHER H. SCHERER, CSRE
BE Radio Magazine
9800 Metcalf Ave.
Overland Park, KS 66212-2216
cscherer@sbe.org

ROY TRUMBULL, CSTE
KRON
P.O. Box 3412
San Francisco, CA 94119
roymbull@kron.com

CHAIRMAN EMERITUS
JAMES C. WULLIMAN, CPBE
721 W. Calle Del Regalo
Green Valley, AZ 85614-2803
jcwulliman@juno.com

CERTIFICATION DEPARTMENT
Linda Godby-Emerick
Certification Director
SBE Office
Indianapolis, IN
lgodby@sbe.org

Kathleen Moran
Certification Assistant
kmoran@sbe.org

July 12, 2000

Mr. Mike Rice, CPBE
Contemporary Broadcasting
216 Rio Vista Drive
St. Charles, MO 63303

Dear Mr. Rice:

Thank you for your support of the Certification Program. Enclosed is your wallet certification card stating you are "Life" certified. Also enclosed is a Life Certification gold seal for your certificate and your life designation for your certificate. Please notify the Certification Secretary of any change of address you should have in the future so our records can be kept current.

If at anytime you would like to support the continuing education of the broadcast engineering profession, please consider making a donation to the Ennes Educational Foundation Trust Scholarship program.

On behalf of the National Certification Committee we congratulate you on your well-deserved "Life" certification and wish you well in your future endeavors. It's been a pleasure to work with you.

Sincerely,

Linda Emerick

Linda Godby-Emerick
Certification Director

Enclosures

Mike S. Rice

is hereby certified as a

PROFESSIONAL BROADCAST ENGINEER

Number 589 Expires [illegible]

Certification Secretary