

## Neurobiology Update

### An Update on the Neurobiology of Bipolar Disorder

The recent 26th Biennial Congress of the World Assembly for Mental Health was held from July 22–27, 2001, in Vancouver, Canada. Dr. Robert Post, Editor-in-Chief of the BNN, presented an update of recent findings in the neurobiology of bipolar disorder at this meeting, which are outlined here, along with select summaries of several other presentations.

In addition to the well-established alterations in neuroendocrine function (e.g., multiple studies showing cortisol hypersecretion), and the well-replicated findings of increased intracellular calcium in blood elements of patients with bipolar illness, new findings have emerged with the use of functional brain imaging with positron emission tomography (PET) and with autopsy studies, including those based on new analyses from the Stanley Foundation-sponsored brain bank collection. With PET scans using radioactive 18-fluorodeoxyglucose (FDG) as a marker of regional cerebral metabolism, multiple studies now reveal frontal cortical hypoactivity and relative subcortical hyperactivity, particularly in various parts of the limbic system such as the amygdala and in parts of the basal ganglia. Dr. T. Ketter et al. (2001; *Biol Psychiatry* 49: 97–109) also found evidence of cerebellar hyperactivity which remains even when patients enter the euthymic state. This partially contrasts with the findings in unipolar depression wherein depressed patients show abnormal cerebellar hyperactivity, but with clinical improvement, the hyperactivity normalizes (Fig. 1).

In a principal components analysis of the Beck Depression Inventory, Dr. R. Dunn et al. (2001; *Biol Psychiatry*, in press) found that the factor relating to

anhedonia (lack of pleasure and interest) and psychomotor retardation explained most of the variance in bipolar illness, but in unipolar patients this factor was also supplemented by a major component of negative cognitions (negative automatic thoughts). These negative cognitions in unipolar patients related to frontocortical

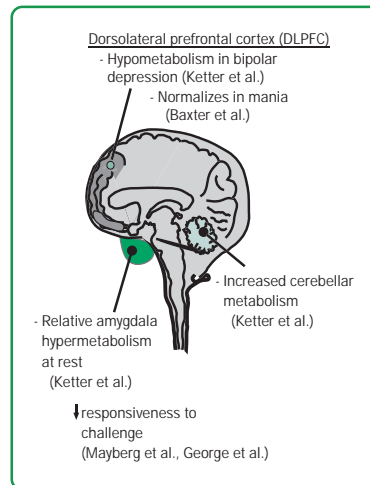


Fig. 1: Functional abnormalities in bipolar illness

hypoactivity, but in both unipolar and bipolar patients, the severity of the factor of anhedonia and psychomotor retardation was inversely correlated with activity in the area of the right insula, temporal lobe, and parts of the adjacent basal ganglia. These findings suggest that psychomotor retardation and anhedonia are crucial elements of the depressive syndrome in bipolar illness and may have a common neural substrate in both unipolar and bipolar disorder, but other components of unipolar illness may be related to alterations in other areas of the brain.



Another striking PET finding in patients with bipolar illness seen by B. Benson and M. Willis at the National Institute of Mental Health (NIMH) is a deficiency in the normal balance of positive and negative correlations of one area of the brain to another typically seen in normal volunteer control subjects. For example, activity in the frontal cortex is highly inversely related to that in cerebellum, such that when activity is low in the frontal cortex, cerebellar activity is high, and vice versa. In contrast, the frontocerebellar relationships in bipolar illness are uniformly positive. Similarly, relationships of the thalamus to other areas of the brain are highly diverse in showing both widespread areas of positive and areas of negative associativity in volunteers, but almost all of the thalamic relationships are exclusively positive in bipolar patients. This suggests that in bipolar illness, the brain has lost some of its normal regulatory balance and that when one area of the brain is active, many other areas of the brain that are normally

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## Neurobiology Update

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deactivated are also activated (Fig. 2). This could account for a failure of adequate modulation of mood and behavior and the excessive and dysregulated mood swings that occur in bipolar illness.

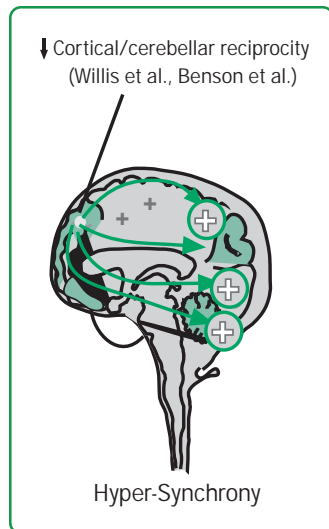


Fig. 2: Associativity abnormalities in bipolar illness

A number of groups studying post-mortem brain specimens of patients who had bipolar illness compared with controls have found evidence of subtle neuronal and glial deficits in the frontal cortex and anterior cingulate gyrus of the bipolar patients (Fig.

3). Consistent with this evidence for glial losses are the findings that glial activity, as marked by measures of both glial fibrillary acidic protein (GFAP) mRNA and the protein itself, are reduced in both bipolar illness and in schizophrenia (Fig. 4, p. 5). Because normal glial function is crucial to adequate neuronal function, such glial alterations could indirectly affect a variety of frontocortical functions that appear to be dysregulated in bipolar illness. Glial cells help take up excess excitatory neurotransmitters such as glutamate and supply a variety of growth factors both for themselves and for neuronal survival. Thus, a deficit in glial cells could account for some of the alterations in neuronal number and function found in bipolar illnesses.

Another finding that has recently emerged from the work of Dr. G. Xing at the NIMH is reduced levels of a critical protein called calcium calmodulin kinase-II (CaMK-II). This enzyme is necessary for normal long-term learning and memory. Mice that have had CaMK-II genetically knocked-out are unable to learn or remember simple mazes. Mice with half the normal level of CaMK-II have deficits in long-term cortically-based memory and have abnormalities in activity and aggression. Dr. Xing has found that patients with bipolar illness have reduced levels of CaMK-II in several areas of their prefrontal cortex (Brodmann's areas 9 and 46) compared with normal controls (Fig. 4, p. 5). Some deficits in CaMK-II have also been observed in patients with unipolar depression but not in those with schizophrenia, suggesting some selectivity of the alterations in affective illness.

Patients with bipolar illness often complain of memory problems, and Dr. Denicoff and associates have found that difficulties with neuropsychiatric function as assessed by a variety of measures tend to be associated with the duration of illness or the number of prior episodes. However, even when patients are assessed when

they are euthymic (without mania or depression), they often have subjective or objective evidence of difficulties in some cognitive domains. In particular, patients with affective disorders have difficulties with facial affect recognition (more so when they are in an episode), but some abnormalities persist into the euthymic well interval. Which type of difficulty in neuropsychiatric function might relate to the observed deficits in brain CaMK-II in bipolar illness remains to be delineated. However, given the evidence presented here that there are pathological neuronal and glial alterations in the prefrontal cortex and specific deficits in chemicals that are critical to the maintenance of long-

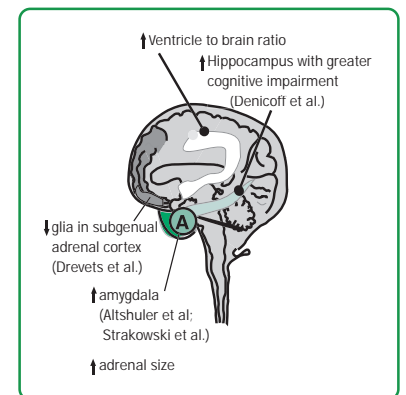


Fig. 3: Structural abnormalities in bipolar illness

term learning and memory, some of the neuropsychological alterations observed in bipolar illness now at least begin to have a plausible neural substrate. Reelin, a critical developmental protein in synapse formation, is also decreased in cortex and hippocampus in patients with bipolar illness and in those with schizophrenia (Guidotti et al. 2000; *Arch Gen Psychiatry* 57: 1061–1069) (Fig. 4, p. 5). The frontal cortex is thought to be involved in a variety of functions that are altered in bipolar disorder. These functions include sociability, planning for the future, decision-making, anticipating untoward consequences of behavior, monitoring both internal states and the affect of significant others, and long-term memory.

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### Bipolar Network News

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The *BNN* is published three times a year by investigators working with patients with bipolar disorder to better understand the long-term course and treatment of the illness. The newsletter is available free of charge to all who request it. Although the editors of the *BNN* have made every effort to report accurate information, much of the work detailed here is in summary or prepublication form, and therefore cannot be taken as verified data. The *BNN* can thus assume no liability for errors of fact, omission, or lack of balance. Patients should consult with their physicians, and physicians with the published literature, before making any treatment decisions based on information given in this issue or in any issue of the *BNN*.

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## Meeting Highlights

Brief meeting notes from the American Psychiatric Association (APA) and Society of Biological Psychiatry (SBP) Meetings

### Society of Biological Psychiatry Meeting Highlights on Bipolar Disorder, May 3–6, 2001:

*Dr. P. Rabins* of Johns Hopkins University School of Medicine compared magnetic resonance imaging (MRI) scans of 14 patients with late-life bipolar disorder with 21 age- and gender-matched controls, and found that patients with bipolar disorder had greater left sylvian fissure and left and right temporal sulcal enlargement, and more bilateral cortical atrophy than controls.

*Dr. M. DelBello* and colleagues at the University of Cincinnati College of Medicine used thin-slice quantitative MRI analysis to study 12 bipolar adolescents and 13 healthy volunteers without psychiatric disorders in whole brain and in regions including prefrontal cortex, third ventricle, lateral ventricles, amygdala and hippocampus. They found that compared with the volunteer group, bipolar adolescents demonstrated smaller prefrontal and larger lateral ventricular volumes, indicating that similar to bipolar adults, bipolar adolescents may have frontal and ventricular abnormalities, and suggesting that these abnormalities may be present early in the course of bipolar illness.

*Dr. S. Kruger* from Gustav-Carus-University, Dresden, Germany, and colleagues induced transient sadness in twenty-one subjects with bipolar disorder; regional changes in cerebral blood flow (CBF) were detected with <sup>15</sup>O-water positron emission tomography (PET). The investigators found that at baseline, bipolar patients showed increases in ventral prefrontal cortex/insula, lateral medial temporal, and globus pallidus/putamen compared to controls. Common increases with sadness in bipolar subjects and controls were seen in premotor cortex, inferior anterior temporal cortex/insula and in cerebellum. Decreased CBF in bipolar disorder at baseline was seen in dorsolateral prefrontal, orbitofrontal and inferior parietal cortical regions. Common regional CBF decreases were seen in dorsolateral prefrontal and inferior parietal cortices and in posterior cingulate. Rostral anterior cingulate CBF was normal at baseline and it increased uniquely in bipolar subjects, and subgenual cingulate increased only in controls. The findings support and expand the existing model of cortical-limbic reciprocity in the regulation of affect.

*Dr. H. Blumberg* and colleagues at Yale University School of Medicine found the presence of an abnormality in func-

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### American Psychiatric Association Meeting Highlights on Bipolar Disorder, May 5–10, 2001:

*Dr. F. Kapczinski* from the Department of Psychiatry, Bioquimica ICBS, Brazil, and colleagues looked at S100B protein serum levels in 20 drug-free bipolar patients in their first manic episode. S100B protein is a calcium-binding protein mostly derived from glial cells that exerts trophic or toxic effects on neural cells depending on its concentration, and which has been used as a marker of brain injury in neuropsychiatric disorders. The investigators found that mean serum concentration of S100B protein was significantly higher in the 20 manic patients compared with matched controls, supporting the hypothesis of glial abnormalities in bipolar disorder.

*Dr. W. Frankle* et al. from Massachusetts General Hospital examined the duration of depressive episodes in bipolar illness and determined the effect of antidepressant treatment on this duration. In 55 patients with bipolar illness with at least one major depressive episode during the study period, Dr. Frankle and his associates found no difference in time to recovery between those on antidepressants at some point during the episode and those not on antidepressants.

In a study of bipolar patients in Taiwan, *Dr. S. Tsai* and colleagues from Taipei Medical College Hospital found that predictors of completed suicide included having a first-degree family history of suicide and having at least one suicide attempt in seven years of illness.

The neurobehavioral outcomes in preschool children who had or had not been exposed to lithium *in utero* were compared by *Dr. A. Viguera* and co-investigators from Massachusetts General Hospital. In 20 children aged 2.5 to six years (10 prenatally exposed to lithium, 10 not exposed) born to mothers with bipolar disorder, the 10 children exposed to lithium *in utero* did not differ in age, sex, or ethnic distribution, and their mean IQ scores were nearly identical. There were also no significant group differences in clinically assessed temperament or distractibility or in risk of parent-reported behavioral or adjustment problems.

*Dr. S. Bouffard* of Massachusetts General Hospital and colleagues administered a self-report survey to 106 women with bipolar disorder to assess information regarding decisions about pregnancy and attempts at

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# APA

### American Psychiatric Association

"The American Psychiatric Association is a medical specialty society recognized worldwide. Its 38,000 U.S. and international member physicians work together to ensure humane care and effective treatment for all persons with mental disorder, including mental retardation and substance-related disorders. It is the voice and conscience of modern psychiatry. Its vision is a society that has available, accessible quality psychiatric diagnosis and treatment."

- APA Website, 2002

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Newspaper of the  
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## SBP

## Society of Biological Psychiatry

"The Society of Biological Psychiatry was founded in 1945 to emphasize the medical and scientific study and treatment of mental disorders. Its continuing purpose is to foster scientific research and education and to raise the level of knowledge and comprehension in the field of psychiatry. Other major aspects of modern psychiatric medicine, the humanitarian emphasis, psychological treatment, and the sociocultural orientation are included in biologic psychiatry. Traditionally, medicine has recognized the importance of psychology, social setting, and emotions in the care of patients. In this sense, biological psychiatry uses the traditional medical model. This comprehensive approach should determine the care and understanding given to people suffering from mental disorders. To achieve its purpose, the Society sponsors an annual meeting, grants awards to distinguished clinical and basic research workers, and publishes the journal, *Biological Psychiatry*."

- SBP Website, 2002

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**Meeting Update: APA and SBP**

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**SBP Meeting Highlights:**

tioning of ventral prefrontal cortex during the Stroop task in 22 patients with bipolar disorder compared with 20 controls. The common dysfunction in this region, across both word generation and selective attention tasks, implicates the involvement of this region in abnormalities in cognitive processing in bipolar disorder.

In six medication-free healthy volunteers and ten mostly euthymic bipolar disorder patients, primarily on gamma-aminobutyric acid (GABA)ergic medications, *Dr. P. Wang* et al. from the Stanford University School of Medicine found that the bipolar patients had 60% increased cerebral GABA, compared with the age and gender-matched controls. These data are consistent with the notion that medication-free depressed bipolar patients have near normal cerebral GABA, which increases with effective treatment.

At the School of Medicine in San Francisco, N-acetylaspartate (NAA; a neuronal/axonal marker) and choline (Cho) were measured by proton magnetic resonance spectroscopic imaging (<sup>1</sup>H MRSI) in the dorsolateral prefrontal cortex (DLPFC), prefrontal white matter (PFWM), thalamus, and cerebellar vermis to determine whether there was evidence for neuronal dysfunction or loss in regions comprising prefrontal-thalamic-cerebellar circuits. *Dr. R. Deicken* and colleagues from the Veterans Affairs Medical Center and the University of California, San Francisco, found that in fifteen medicated euthymic bipolar I disorder patients and 15 control subjects, bipolar I patients demonstrated: bilaterally decreased DLPFC NAA; decreased PFWM NAA bilaterally; increased thalamic NAA bilaterally; decreased cerebellar NAA; bilaterally increased Cho in the DLPFC, but no change in Cho in the other brain regions; and no significant group or lateralized differences in voxel tissue composition for any of the regions. The investigators concluded that the DLPFC reductions in NAA together with increased Cho are consistent with neuronal loss accompanied by increased phospholipid membrane turnover; decreased cerebellar vermis NAA suggests neuronal dysfunction or loss; PFWM NAA reductions are evidence for compromised axonal integrity that may result in functional disconnection of prefrontal-thalamic pathways; increased thalamic NAA may represent neuronal hypertrophy/hyperplasia or abnormal synaptic/dendritic pruning; and that neuronal/axonal pathology of multiple brain regions participates in prefrontal-thalamic-cerebellar pathways in bipolar I disorder.

**APA Meeting Highlights:**

conception. The majority of the sample reported having been discouraged from becoming pregnant by a physician or family member prior to the consultation. Almost half were pregnant either at the time of the consultation or at post-consultation follow-up. Among women who decided not to become pregnant, the most common reasons were concern about risk for relapse before or after giving birth and/or fear of the effects of prenatal exposure to mood stabilizers.

*Dr. G. MacQueen* and associates at McMaster University, Canada, reviewed detailed life chart data from 113 patients with bipolar disorder to examine response and (mood) switch rates in depression. They found that patients who became depressed following a period of euthymia were more likely to respond to treatment (62.5%) than patients who became depressed following a period of mania or hypomania (27.9%). There was also a favorable ratio of response to switching for previously euthymic patients that was particularly high (10:1) for patients treated with antidepressants.

The N-methyl-D-aspartate receptor (NMDAR1) gene was the focus of a study done by *Dr. E. Mundo* and colleagues at the University of Toronto. The glutamate system and the NMDAR1 have been implicated in the pathogenesis of psychoses, and there is good evidence that lithium and valproate act via the NMDAR1. The study sample consisted of 283 patients with a diagnosis of bipolar, bipolar II, or schizoaffective disorders (bipolar type) and their living parents, using a test to compare the number of transmissions and non-transmissions of the alleles possibly associated with the disease from the parents to the affected offspring to detect any deviation from what would be expected by chance. These investigators found a significant association between two polymorphisms of the NMDAR1 and bipolar disorder. ■

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## Neurobiology Update

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To the extent that CaMK-II proves to be definitively altered in the brains of patients with bipolar illness compared with other groups, an obvious question arises as to whether this alteration would be correctable. Although there is promise for gene therapy and enzyme replacement

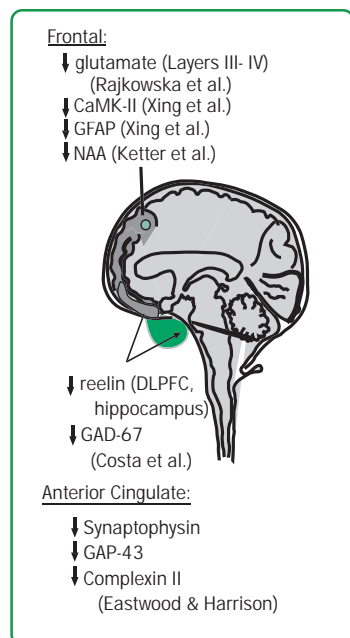


Fig. 4: Biochemical abnormalities in bipolar illness

strategies in the future, it is also possible that some of our current therapeutic agents will be able to compensate for low levels of CaMK-II. Some antidepressants, for example, appear to be able to increase CaMK-II activity, and changing CaMK-II levels or activity may become a new target for therapeutic approaches to the illness. Lithium appears to exert a variety of neuroprotective actions in the central nervous system, and these too could be important to the alterations in prefrontal cortex structure and function noted previously. Lithium could slow, prevent, or reverse some of the abnormalities that are initially there or that may progress over time. Dr. G. Moore et al. have reported that lithium is able to increase

brain N-acetylaspartate (NAA), a marker for neuronal integrity (Moore et al. 2000; *Biol Psychiatry* 48: 1–8), and also increase the amount of gray matter in the brain (Moore et al. 2000; *Lancet* 356: 1241–1242). Because CaMK-II is one of the major elements in neuronal dendrites, it is theoretically possible that lithium or other neuroprotective agents could prevent either further losses in CaMK-II, or begin to ameliorate its deficit.

In summary, new findings in the neurobiology of bipolar illness have given us many new insights into the potential pathophysiology of the illness and new potential approaches to therapeutics.

- Dr. Robert Post

### Related Meeting Presentations

Dr. H. Akiskal of the University of California at San Diego began the plenary session on bipolar illness by reviewing the high incidence of bipolar spectrum disorders (bipolar I, bipolar II, bipolar not otherwise specified, etc.) and noting the findings that a substantial percentage of patients with presumed unipolar depression are actually bipolar when examined more closely for hypomanic symptoms (Allilaire et al. 2001; *Encephale* 27: 149-158).

Dr. T. Young from McMaster University, Ontario, Canada, reviewed work that chronic lithium administration increased glutamate uptake, which could be related to some of its neuroprotective effects, in addition to its ability to decrease cell death factors (such as Bax and p53) and increase cell survival factors (such as brain-derived neurotrophic factor [BDNF], bcl-2 and serine/threonine kinase Akt). Dr. Young reported finding indirect clinical evidence of the effect of antidepressants on BDNF from the Stanley Foundation brain collection; those patients who had been treated with antidepressants at the time of their deaths normalized their cyclic AMP response element binding protein (CREB) levels,

whereas those who had not been treated with antidepressants had decrements in CREB binding compared with controls. CREB is a critical transcription factor in initiating the synthesis of BDNF.

- BDNF is decreased by stress and the protective effects of antidepressants on BDNF may be important to their mechanism of action.

Dr. Young reported evidence of increased neuronal sprouting in the dentate gyrus of the hippocampus (in the supragranular area) in patients with bipolar disorder compared with a variety of other psychiatric groups and controls. Dr. Young also cited preliminary studies suggesting alterations in transforming growth factor beta (TGF $\beta$ ), extracellular signal-regulated protein kinase-6 (ERK-6), and phospholipase-C in patients who died with a diagnosis of bipolar illness compared with controls.

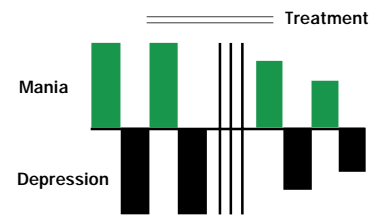
- These data continue to reveal new structural and chemical alterations that may eventually be linked to the manifestations of bipolar illness and thus provide new targets for therapeutics.

Dr. R. Murray from the Institute of Psychiatry, London, in a plenary session on schizophrenia, reported that although there is an important genetic factor in the risk for schizophrenia, a variety of other environmental factors also play a role. These environmental factors and their associated increased risks of developing schizophrenia include: having schizophrenia in a first-degree relative increases the risk by a factor of 10; having obstetrical complications, by a factor of two to three; birth in the springtime, by a factor of one; birth in a city, by a factor of three; having a history of drug abuse, by a factor of 2.7; emigration to a new country, by a factor of three; and significant adverse life events, by a factor of three. Dr. Murray also noted that

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## Life Chart Highlight

Partial response to rTMS in severe depression; switch into hypomania with antidepressants



■ A life chart is a method to systematically track and monitor one's retrospective and prospective course of illness and treatment.

■ With daily entries, a graphic representation of the course of illness and response to treatment is built. It can be easily shared with treatment providers or family members and becomes a continuous and permanent record.

■ Patients rate their mood and functional impairment on a scale, which is converted to a chart. Manic episodes are coded above and depressive episodes below a date line that signifies baseline (or euthymic) mood. Treatments are coded above the manic episode range, and other comorbidities and stressors are noted below the depressive episode range.

■ To obtain a **FREE** life chart, please contact the National Depressive and Manic-Depressive Association (NDMDA) at:

**NDMDA**  
730 N. Franklin St.  
Suite 501  
Chicago, IL 60610  
1-800-826-3632  
www.ndmda.org

### Illness History

The patient whose mood and treatment history are depicted in the life chart at right is a 48-year old bank executive with no history of depression prior to 1999. Shortly after his wife died at the end of 1999, the patient slipped into an increasingly severe depression culminating in extreme agitation, anxiety, a 40-lb. weight loss (on a previously thin frame), insomnia, anorexia, and suicidal thoughts. Following a lack of response to several different serotonin-selective antidepressants (SSRIs), the atypical antipsychotic risperidone (Risperdal®), and mirtazapine (Remeron®) which was also ineffective for both anorexia and insomnia, the patient was referred for electroconvulsive therapy (ECT). However, the patient and his family wanted to avoid this procedure if possible and instead elected to participate in a National Institute of Mental Health (NIMH) clinical research protocol involving repetitive transcranial magnetic stimulation (rTMS) for the potential treatment of his depression.

### Prospective Treatment

The patient was randomized to receive 20 Hz rTMS at 110% of motor threshold for three weeks (5 times/week) which would be followed by a continuation phase of eight weeks with rTMS only. Although clinical improvement rarely reached levels better than moderately severe depression on the life chart, the patient's Hamilton Rating Scale for Depression scores fell from a baseline of 53 pre-rTMS to 33 at the end of three weeks and to 22 after the eight weeks.

With this substantial partial, but clinically insufficient, degree of response to rTMS, the patient was started on venlafaxine (Effexor®) and gabapentin (Neurontin®) for his re-

sidual depression and anxiety, respectively, as augmented by lorazepam (Ativan®) initially and then folic acid and triiodothyronine (T<sub>3</sub>, Cytomel®). On a dose of 300 mg of venlafaxine and 900 mg/day of gabapentin, the patient's mood switched into a hypomanic episode in May of 2001 (characterized by increased energy, jocularity, and inappropriate behavior toward other patients and staff) which was only partially responsive to the addition of lithium. This hypomanic episode was followed by another period of moderately severe depression (June, 2001) which appeared to improve with increasing doses of venlafaxine and the initiation of lamotrigine (Lamictal®). Another rapid mood switch occurred in July of 2001 despite increasing doses of divalproex sodium (Depakote®). Following the addition of the atypical antipsychotic olanzapine (Zyprexa®), the patient finally entered a period of euthymia in August of 2001 (no depressive or hypomanic symptoms).

### Treatment Observations

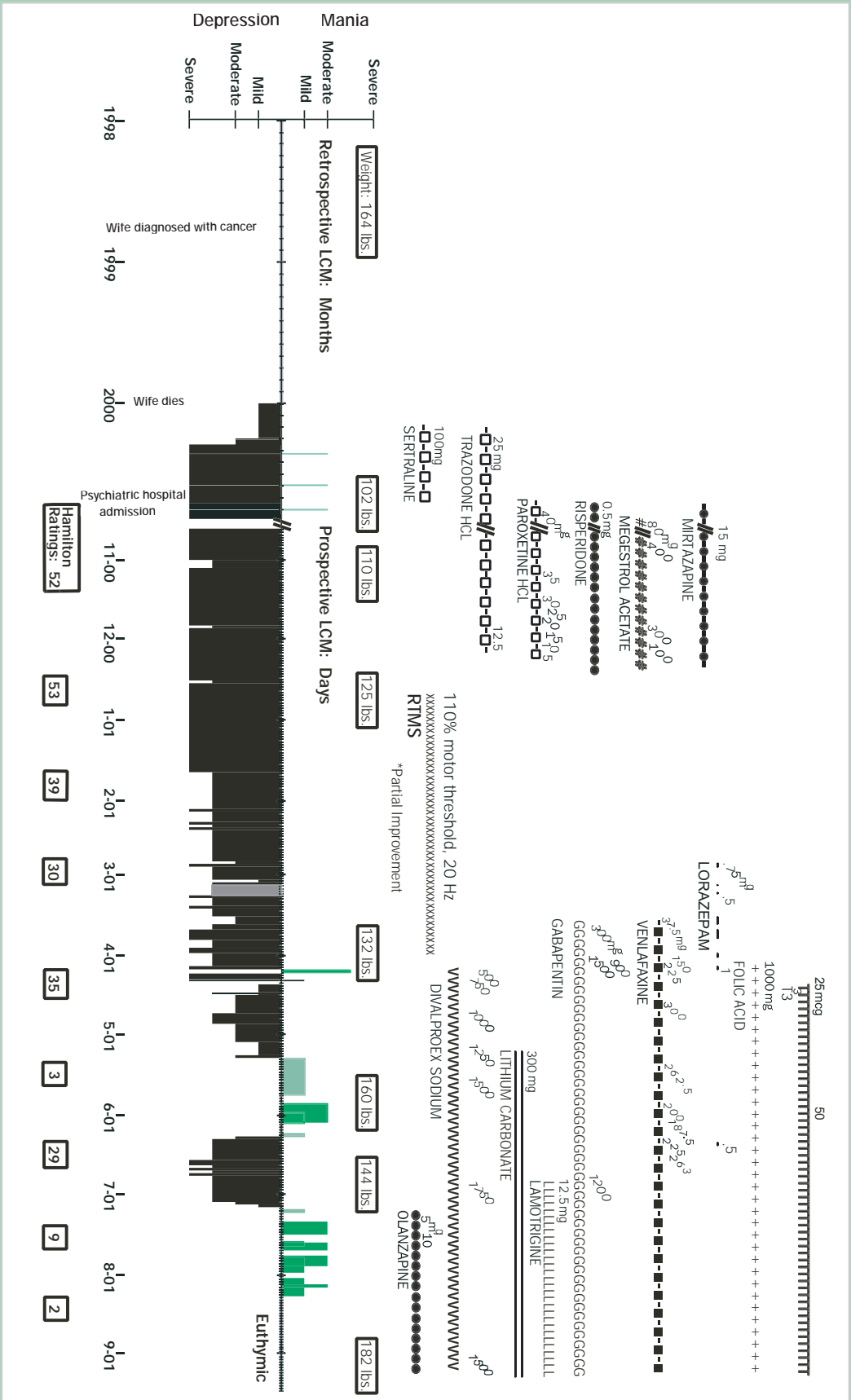
This patient's life chart illustrates a number of points of clinical interest. As noted by Dr. Kraepelin (1921) and many others over the past century, the illness often begins with a severe psychosocial stressor, such as the loss or the death of others. This patient's profound depression and cachexia (severe weight loss) following his wife's death was only partially responsive to rTMS, in this case administered at 20 Hz at 110% of motor threshold. We had observed previous moderate effects of rTMS at these frequencies utilizing 80% of motor threshold (George et al. 1997; *Am J Psychiatry* 154: 1752–1756) and 100% of motor threshold (Kimbrell et al. 1999; *Biol Psychiatry* 46: 1603–1613) and hoped that by increasing the length of the clinical trial (from two

to three weeks) and the intensity of the rTMS (from 100% to 110% of motor threshold) we would observe more robust and clinically meaningful effects. However, our initial experience with these parameters in treatment-refractory patients at the NIMH has not been notably more successful than our previous studies at the lower intensities for only two weeks. This parallels the mixed results of some rTMS studies in the scientific literature, but is different from a number of others, as noted below.

This patient does not represent the vast majority of patients with unipolar depression, who do not switch into mania or hypomania upon treatment with antidepressants. The risk of this occurrence in unipolar patients is estimated to be approximately 1–2%. However, antidepressant-related switches into mania or hypomania are substantially higher in patients with known bipolar disorder. It is worth noting that this patient had three prior brief periods of hypomania during antidepressant treatment in 2000, none of which lasted longer than 24 hours. Once engendered, this patient's recurrent, more sustained hypomanias in May and July were not readily responsive to mood stabilizers such as lithium carbonate and divalproex sodium, or the putative mood stabilizer lamotrigine. The addition of an atypical antipsychotic (olanzapine) was needed to achieve euthymia.

This patient thus represents an atypical individual not only because of his antidepressant-induced recurrent hypomanias, but also because his hypomanic and recurrent depressive episodes required very complex combination treatment in order for euthymia to be reached. The patient

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**Life Chart Highlight:** Partial response to repetitive transcranial magnetic stimulation (rTMS) in a patient with severe, treatment-refractory depression triggered by his wife's death. The retrospective life chart method (LCM) continues until October 2000 and then is followed by daily prospective ratings by the nursing staff of the NIMH 3-West clinical research unit (who were blind to the rTMS parameters). Dr A. Speer of the Biological Psychiatry Branch, NIMH, conducted the rTMS study. Complex combination treatment was eventually required to achieve an illness remission.

## Life Chart Highlights

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was discharged on a number of different types of psychotropic drugs (including antidepressants, mood stabilizers, and atypical antipsychotics) for his now recurrent affective disorder, which would be classified according to DSM-IV as bipolar disorder-not otherwise specified (BP-NOS), because his hypomania emerged in association with antidepressant treatment, i.e., a substance-induced bipolar illness.

One could argue that following clinical remission, the patient should be weaned from several of these agents. However, in the absence of serious side effects, we and the patient chose to proceed with continuation therapy, especially in light of earlier attempts to reduce doses of the antidepressant venlafaxine in June which appeared to be associated with the re-emergence of a severe depression. Our research at NIMH (Frye et al. 2000; *J Clin Psychiatry* 61: 9-15) and that of many others has similarly observed the need for increasingly complex combination therapy for patients with both unipolar and bipolar mood disorders in order to achieve substantial improvement or remission.

### rTMS Update

Although our experience and that of a number of other investigative groups with rTMS has generally not been associated with striking degrees of clinical improvement, three studies have directly compared the efficacy of rTMS and ECT.

- Grunhaus et al. (2000; *Biol Psychiatry* 47: 314-324) reported that rTMS was equal in efficacy to ECT in patients with non-psychotic depression, but was clearly inferior to ECT in those patients with psychotic depression. The parameters used for rTMS were 10 Hz at 90% of motor threshold. ECT in this study was right unilateral, and it should be noted that this study may not

have been an adequate comparison because: 1) bilateral ECT is often more clinically effective than unilateral ECT; and 2) only 9.6 ECT treatments were used compared with 20 rTMS treatments. There was an 80% response rate to ECT in the entire group of patients with a range of depressive severities, including those with psychotic depression (16 of 20 patients responded). In contrast, only nine (45%) of 20 responded to rTMS in this entire cohort of more severely ill patients.

- Pridmore et al. (2000; *Int J Neuropsychopharmacol* 3: 129-134) also found that in 32 patients suffering a major depressive episode, an average of 12.2 rTMS treatments (20 Hz at 100% of motor threshold) was not significantly different from an average of 6.2 right unilateral ECT treatments.

- Similarly, Janicak and colleagues (2000) have reported that rTMS treatments (10 Hz rTMS at 110% of motor threshold) in 14 patients with either bipolar disorder or major depressive disorder achieved a degree of efficacy not significantly different from that administered with bilateral ECT using bitemporal electrode placements. In this study there was a nonsignificant trend for rTMS to be less effective than ECT; if there were a larger number of subjects, this trend might have emerged as statistically significant.

In two different studies at the NIMH, Kimbrell et al. (1999; *Biol Psychiatry* 46: 1603-1613) and Speer et al. (2000; *Biol Psychiatry* 48: 1133-1141) have found that some patients respond to 1 Hz and not 20 Hz, and vice versa, such that the degree of improvement on one frequency was inversely correlated with the degree of improvement on the other.

Thus, it is of interest that two of the three studies comparing rTMS to ECT used the intermediate frequency of 10 Hz, rather than low (1 Hz) or high (20 Hz) frequencies as in our studies at the NIMH, and excellent results (clinical remissions) were observed in substantial numbers of patients. This raises the prospect that driving neural activity with either low or high rTMS is not optimal and that an intermediate frequency of 10 Hz (cycles/second), much like that which occurs spontaneously in the alpha frequency on the electroencephalogram (EEG), might be preferable. However, one study (Pridmore et al., 2000) used 20 Hz at 100% of motor threshold and still saw substantial degrees of improvement. This raises the question of differences in patient populations and, in particular, differences in treatment refractoriness.

### Conclusions

The patient illustrated in this life chart highlight failed to respond to two SSRIs, a risperidone/trazodone augmentation, and then a trial of augmentation with mirtazapine. Yet, he would not have had a very high treatment-refractory index score compared with many other patients. Most of our patients studied at the NIMH present with depressions that are much more resistant to many more treatment options than this particular patient. This degree of treatment resistance appears to be of some prognostic relevance even for ECT. Sackeim and associates (Prudic et al. 1996; *Am J Psychiatry* 153: 985-992) have observed much higher response rates to ECT in patients whose depression has not demonstrated a prior failure to respond to antidepressants compared with those who have failed prior antidepressant treatments. It is likely that the degree of treatment resistance will be an important factor in response to rTMS as well.

(Continued on page 9)



## Meeting Update: APA and SBP

(Continued from page 4)

### SBP Meeting Highlights:

*Dr. M. Frye* and co-investigators from the UCLA School of Medicine assessed and compared the degree of hippocampal gliosis in postmortem hippocampal slices from patients who had bipolar disorder with and without alcohol comorbidity. Activated or reactive gliosis was defined as the hypertrophy and proliferation of astrocytes and microglial cells and has been identified as evidence of ongoing neuronal degeneration. Fixed postmortem hippocampal specimens were obtained from the Stanley Foundation Neuropathology Consortium, and clinical information including diagnosis, alcohol use (past/present), and autopsy information was reviewed from individuals with bipolar disorder, schizophrenia, unipolar depression, and normal controls. They found no significant difference in total gliosis, white matter gliosis, or gray matter gliosis between diagnostic groups. However they did find a difference in total gliosis and gray matter gliosis as a function of age, and between diagnostic groups in the alveus, CA2 (higher in bipolar patients), and subiculum hippocampal subfields. This study was similar to the majority of negative gliosis studies in schizophrenia.

Investigators from the University of Pittsburgh School of Medicine and from other international research centers in Brazil and Italy examined potential abnormalities in pituitary volume in bipolar patients and in a comparison group of unipolar disorder subjects. Led by *Dr. R. Sassi*, and using T1-weighted coronal MRI images, the group found significantly smaller pituitary volumes in 23 bipolar patients compared with 34 healthy controls and 13 unipolar patients, with no significant effects of medication, duration of illness, or familial history of affective disorders on pituitary volume. No significant differences were found between unipolar patients and healthy controls.

Corpus callosum abnormalities in bipolar disorder patients were studied by *Dr. P. Brambilla* and associates at the University of Pittsburgh Medical Center. Twenty-four bipolar patients and 36 healthy controls were studied using 3D gradient echo imaging. Bipolar patients had a significantly smaller total callosal, isthmus, and anterior splenium areas compared with healthy controls. The investigators concluded that brain interhemispheric communication in bipolar disorder may be altered, and that callosal anatomical abnormalities may be involved in the pathophysiology and cognitive impairment of bipolar disorder.

*Dr. H. Strasser* and colleagues from Johns Hopkins School of Medicine conducted a pilot study comparing third and lateral ventricular volumes of nine schizophrenic subjects, nine bipolar subjects, and 18 normal adults matched for age and sex. The nine bipolar subjects completed neuropsychological tests of working memory, free recall learning, and delayed recall for words and designs. Subjects with bipolar disorder had larger ventricular volumes than normal controls. Among subjects with bipolar disorder, ventricular volumes correlated inversely with working memory and free recall learning for both verbal and visual material, but not with delayed recall. These initial findings confirm previously reported differences in ventricular volumes among schizophrenic and bipolar subjects compared to controls (Fig. 3, p. 2). ■

## Life Chart Highlights

(Continued from page 8)

In summary, intervening in the affective disorders with rTMS continues to hold promise, although the degree of efficacy with a given set of parameters in different patient populations is still highly variable and unpredictable across studies. Further continued exploration of different rTMS parameters appears indicated before rTMS becomes widely accepted or clinically available in the United States. ■

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## Neurobiology Update

(Continued from page 5)

although the search continues for genetic risk factors for schizophrenia, it is evident from his work and the work of others that there are no primary genes (those with large effect); instead there appear to be many genes with small effects that contribute to the development of schizophrenia.

- This is also likely to be true in bipolar disorders and the other major psychiatric illnesses as well, in contrast to neurological disorders with single-gene defects, such as Huntington's disease. Complex disorders like hypertension are associated with alterations in 75 genes, whereas lung cancer involves 215 genes at a very high level of significance. ■

## Meeting Highlights

American College of Neuropsychopharmacology (ACNP) Meeting, December 9–13, 2001

# ACNP

■ "The principal function of the American College of Neuropsychopharmacology (ACNP) is to further research and education in neuropsychopharmacology and related fields by: a) promoting the interaction of a broad range of scientific disciplines of brain and behavior in order to advance the understanding of prevention and treatment of diseases of the nervous system including psychiatric, neurological, behavioral and addictive disorders; b) encouraging scientists to enter research careers in fields related to these disorders and their treatment; and c) ensuring the dissemination of relevant scientific advances in these disorders."

- ACNP Website, 2002

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■ **Newsletter:**  
ACNP Bulletin,  
www.acnp.org/  
bulletin.php

*As in recent ACNP annual meetings, panels and symposia on bipolar illness this year were again greatly under-represented compared with those focusing on other major mental disorders, such as schizophrenia. However, there were a number of interesting findings presented in the poster sessions, which will be selectively and briefly noted here:*

Dr. V. Kafantaris of Hillside Hospital, New York, and colleagues completed a double-blind, placebo-controlled discontinuation study in 40 of 108 subjects with adolescent-onset mania who responded to four weeks of lithium monotherapy. These responders were randomly assigned to a switch to placebo or continuation on lithium. Although more patients relapsed after the switch to placebo (13/21, or 61.9%) compared with those who continued on lithium (10/19, or 52.6%), the difference was not statistically significant. However, all four of the patients who required hospitalization were in the placebo group.

- *One important point of this study is that there is a substantial rate of breakthrough symptoms even in those who remain on lithium treatment during the continuation phase treatment for adolescent mania.*

Dr. M. Bauer and colleagues at the UCLA Neuropsychiatric Institute and Hospital examined the clinical and cerebral metabolic effects of high-dose L-thyroxine ( $T_4$ , Synthroid®) treatment in nine euthyroid women (without thyroid problems) with bipolar depression. High-dose  $T_4$  treatment (mean dose, 320 mcg/d, range 300–400 mcg) was associated with statistically significant improvement in depression on both the Hamilton Rating Scale for Depression and the Beck Depression Inventory. Five women were full responders and

four were partial responders. In the first six study completers, the mood changes occurred in parallel with increases in left middle frontal gyrus metabolism on positron emission tomography (PET) scan and a decrease in left hippocampal and amygdala metabolism.

- *High or supraphysiological doses of  $T_4$  continue to hold promise in patients with refractory bipolar depression and cycling. Whether the changes in metabolism on PET studies relate either to the direct effects of  $T_4$  or indirectly to the observed improvement in mood nonspecifically remains to be further investigated.*

Dr. R. Sassi and coworkers from the University of Pittsburgh Medical Center performed a proton spectroscopy (1H-MRS) study of the dorsolateral prefrontal cortex in adolescents with bipolar disorder (n=7) and in healthy controls (n=9). These investigators found a significant decrease in levels of N-acetylaspartate (NAA), a putative marker of neuronal integrity. They also found a significant decrease in levels of creatine, and a trend toward decreased levels of myo-inositol.

- *These data replicate those of Winsberg et al. (2000; Biol Psychiatry 47: 475–481) in adults (Fig. 4, p. 5), continuing to indicate altered structure and function in the prefrontal cortex of patients with bipolar illness. Moreover, this study suggests that these changes may be evident early in the course of illness and could theoretically even precede the onset of illness.*

Dr M. Kramer of Merck Research Laboratories replicated an earlier finding of the effectiveness of a substance P antagonist in depression. A new substance P antagonist (Compound A) showed similar antidepressant effi-

cacy in this 6-week, double-blind, placebo-controlled study of patients with major depression.

- *We look forward to further studies of this potential novel approach to therapeutics of depression and their possible extension to patients with bipolar depression as well, particularly because there was excellent tolerability and few side effects from these substance P antagonists.*

In a preliminary report from their ongoing study, Dr. G. Arnell and colleagues from Gothenburg, Sweden, reported that the combination of olanzapine (Zyprexa®) and fluoxetine (Prozac®) was more effective in treatment-resistant major depression than venlafaxine (Effexor®) after four weeks of treatment in 20 patients. Thirty percent (30%) of the venlafaxine group responded, whereas 70% of the combination group responded. However, a quality of life measurement showed little change, even in the combination group.

Dr. B. Nemets of Beersheva Mental Health Center in Israel reported that an omega-3 fatty acid, specifically the ethyl ester of eicosapentaenoic acid (E-EPA), was significantly more effective than placebo in 20 patients with breakthrough depressive symptoms during four weeks of adjunctive antidepressant therapy.

- *This is the third positive study of omega-3 fatty acids in depression (Stoll et al. 1999, Arch Gen Psychiatry 56: 407–412; Horrobin and Peet, 2001, Biol Psychiatry 49: 37S). The Stanley Foundation Bipolar Network has recently completed recruiting and entering 60 patients with cycling bipolar disorder into a*

*(Continued on page 11)*

## Meeting Highlights: ACNP

(Continued from page 10)

randomized trial of 6 grams of EPA versus placebo for four months, and will soon complete recruitment for another 60 randomized for treatment of acute bipolar depression. As soon as these results are available, they will be noted here and in the literature.

Dr. C. Adler and co-investigators from the University of Cincinnati College of Medicine used functional magnetic resonance imaging (fMRI) to find that the number of affective episodes (particularly depression) in patients with bipolar disorder was associated with decreased performance in a working memory task and that the degree of left amygdala and hippocampal activation during this task was positively correlated with the prior number of depressive episodes.

- *These data add to the growing body of literature suggesting that the number of episodes, and particularly depressive episodes, may be associated with altered biochemistry and neurocognitive performance. To the extent that this and related studies prove replicable, this viewpoint emphasizes the importance of instituting pharmacoprophylaxis early in the course of illness in an attempt to prevent as many major affective episodes as possible.*

Smaller hippocampal volumes have been associated with posttraumatic stress disorder (PTSD) in a number of studies, but not all. Dr. M. Gilbertson of the Veterans Administration Medical Center in Manchester, New Hampshire, and colleagues tried to sort out the cause and effect relationships in the association of hippocampal volume and PTSD. They studied twin pairs who were discordant for combat exposure during the Vietnam War (one twin exposed, the other not exposed), and found that reduced hippocampal volume was associated with PTSD, but the non-combat-exposed twin without PTSD also had a smaller hippocampal vol-

ume, suggesting that smaller hippocampi constitute a preexisting vulnerability factor for the development of PTSD in those who were exposed to trauma, as opposed to the more commonly held view that small hippocampi are caused by the PTSD.

- *Some of these very same questions are pertinent to some of the neurobiological illness associations being revealed in bipolar illness and reported here. Are they pre-existing vulnerability factors or secondary effects of the illness itself?*

Dr. G. Rajkowska of the University of Mississippi Medical Center found a marked reduction in overall density of glial cells in the orbitofrontal cortex of patients with both bipolar disorder and schizophrenia. Previously, this investigator has reported different patterns of glial pathology in the dorsolateral prefrontal cortex in schizophrenia and bipolar illness (Fig. 4, p. 5), suggesting that there are regional specificities and commonalities in glial number in these two illnesses.

- *As previously noted in the BNN, a variety of other data suggest glial abnormalities including reduction in glial fibrillary acidic protein (GFAP) and mRNA in frontal cortex of patients with bipolar illness and schizophrenia (Fig. 4, p. 5). GFAP is a measure of glial activation and these findings, together with the glial reductions reported by Rajkowska, suggest converging clues for abnormalities in these two major psychiatric illnesses.*

The prevalence of bipolar spectrum disorders (which includes bipolar I, bipolar II, and bipolar not otherwise specified) in adults in the United States was surveyed by Dr. R. Hirschfeld from the University of Texas Medical Branch and other colleagues around the country, through the use of a mood disorder questionnaire. Of the 67% of people who responded, 3.8% of the men and 3.0% of the women were determined to have a bipolar spectrum disorder. The

prevalence of bipolar spectrum disorder was highest among respondents aged 18-24 years, those living in the Southeast, those living in rural areas and small cities, and among those with an income of less than \$20,000. This overall prevalence rate (3.7%) is nearly twice that previously reported in the United States. ■

### //www: bipolar

Websites re: bipolar illness that may be helpful to you:

www.nami.org  
National Alliance for the Mentally Ill  
www.ndmda.org  
National Depressive and Manic-Depressive Association  
www.narsad.org  
National Alliance for Research on Schizophrenia and Depression  
www.bpkids.org  
The Child and Adolescent Bipolar Foundation  
www.bpsos.org  
Bipolar Significant Others  
www.nimh.nih.gov/publicat/childmenu.cfm  
NIMH Child and Adolescent Mental Health  
www.clinicaltrials.gov  
NIMH Clinical Trial Database  
www.stepbd.org  
Systematic Treatment Enhancement Program for Bipolar Disorder  
www.edc.gsph.pitt.edu/stard  
Sequenced Treatment Alternatives to Relieve Depression  
www.ncbi.nlm.nih.gov/entrez/query.fcgi  
PubMed (National Library of Medicine)  
www.nih.gov  
National Institutes of Health  
www.bipolarnetwork.org  
Stanley Foundation Bipolar Network

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**In This Issue:**

Update on the Neurobiology of Bipolar Illness  
Meeting Highlights: APA, SBP, ACNP  
Life Chart Highlight: rTMS, Antidepressant-Induced Switching

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**Bipolar Network News**

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