Brain Mechanisms in Manic Depression

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Manic depressive illness (bipolar disorder) is the mood disorder classically considered to have a strong biological basis. During manic depressive cycles, patients show dramatic fluctuations of mood, energy, activity, information processing, and behaviors. Theories of brain function and mood disorders must deal with the case of bipolar disorder, not simply unipolar depression. Shifts in the nosologic concepts of how manic depression is related to other mood disorders are discussed in this overview, and the renewed adoption of the Kraepelinian “spectrum” concept is recommended. The variable clinical presentations of manic depressive illness are emphasized. New genetic mechanisms that must be considered as candidate factors in relation to this phenotypic heterogeneity are discussed. Finally, the correlation of clinical symptom clusters with brain systems is considered in the context of a three-component model of manic depression.

Indexing Terms: mood disorders/genetics/Tourette syndrome/Creutzfeldt-Jakob disease/fragile X syndrome/heritable disorders

Manic depressive illness is the classic example of a biological mood disorder. Manic depression is closely related to the familial form of recurrent unipolar depression, and it reflects even more strongly all the associations noted between some mood disorders and biological factors. Manic depression is a more homogeneous syndrome than unipolar depression, so it is more informative in biological and pharmacological research studies. Patients experiencing this condition (also termed bipolar disorder) go through cycles of mood and behavior. These cycles have three phases: depressed, or dysthymic; normal, or euthymic; and manic, or hypertymic. The cycles vary in amplitude (severity), and the euthymic intervals between episodes of mania and depression tend to shorten over the years. During the phases of each cycle, patients show dramatic bipolar fluctuations in mood, energy, activity, information processing, psychological functioning, and interpersonal relationships. In either the manic or the depressed phase, psychotic features (delusions, hallucinations) also may appear. Manic depression, therefore, represents the most extreme case of mood instability. As Donald Klein has observed, “...any theory of brain function and affect must deal with this striking phenomenon” (1).

This review is not meant to be an extensive survey of the many studies of biological factors in manic depression. My purpose, rather, is to point out some of the “big facts” about manic depression and to emphasize the problems of accurate nosology that have probably impeded progress to date. The correlation of clinical symptom clusters with the likely brain mechanisms that are dysregulated to produce those symptoms is presented, and I suggest areas where new insights may be expected from current research. For more complete discussions of these areas, readers should consult previous reviews (2, 3) and the comprehensive text of Goodwin and Jamison (4).

Present Concepts of Manic Depression

Variable Presentations

To understand our present concepts of manic depression, it is essential to recognize their origins in the work of Emil Kraepelin. Between 1880 and 1920, Kraepelin first clearly proposed the separation of mood disorders from schizophrenia (dementia praecox). He introduced the term “manic depressive insanity,” which he recognized as a familial condition, and he emphasized the multiple clinical presentations of this disorder, which he regarded as varied expressions of “a single morbid process.” These presentations covered a wide spectrum of severity, from mild, temperamental forms to severe psychotic disorders. Included were cases that today we would call dysthymia, cyclothymia, minor depression, recurrent unipolar depression, bipolar disorder, simple mania, and some psychotic or catatonic states. Kraepelin noted that these various forms of the basic disorder could substitute for each other over time within individual patients and also within affected pedigrees. These observations remain true today, and they are important for current thinking about the genetic components of the “single morbid process.”

Contrary to the original formulation of Kraepelin, however, these varied presentations of a single condition are defined as separate entities in contemporary classifications of mood disorders, such as the third edition of Diagnostic and Statistical Manual of Mental Disorders (DSM III) (5). This deliberately agnostic position about the relatedness of the various mood disorders was adopted mainly for administrative purposes. Family history and longitudinal course, two cardinal validating features of any medical classification, were ignored in DSM III. That position has not been scientifically productive, and the field is likely soon to return to a view more in line with Kraepelin’s. The same point has been made very strongly by Goodwin and Jamison (4). Certainly, the phenomena of patients switching from minor depression to major depression, from unipolar to bipolar disorder, and from nonpsychotic to psychotic presentations are frequently observed, and in genetic studies the most common disorder among relatives of bipolar probands is unipolar depression. The relationship of
these unipolar cases to unipolar depression in nonbipolar pedigrees is not clear at present. What is clear is that unipolar depression and dysthymia, as currently defined by DSM III, are extremely heterogeneous. They include cases within the Kraepelinian spectrum but also cases that may be of quite different etiology (6, 7). That is the essential problem with purely syndromal definitions of clinical disorders.

Biological Associations

In addition to the genetic pattern, there are several powerful reasons to propose a biological basis of manic depressive disorder. The pattern of behaviors that accompany the mood shifts is highly suggestive. Patients exhibit altered sleep, appetite, activity level, and psychomotor speed that are sustained for weeks or months and go well beyond simple subjective mood swings. Once precipitated, the episodes appear autonomous and largely unresponsive to environmental influence. Experimental studies reveal that information processing is markedly affected by the manic and depressive phases (8).

The periodicity and seasonal pattern of episodes are striking. Though episodes may occur at any time, for certain patients they cluster into two seasonal peaks. This seasonal pattern is found in 13.5% of recurrent unipolar depressions and in 21.7% of bipolar I patients. The frequency of manic episodes reaches a major peak in the spring and a minor peak in the autumn. For depressive episodes the major peak is in the autumn, with a minor peak in the spring (9). The pattern of recurrences also tends to maintain a periodicity of 12 months or multiples thereof (4). The natural history is one of recurrent episodes with spontaneous remissions, even without treatment. Recent longitudinal data from the National Institute of Mental Health National Collaborative Study reveal that, although manic depressives experience more lifetime episodes overall than unipolar depressives, the excess of episodes is entirely accounted for by the manias: They have the same number of depressive episodes as the unipolar cases (10). This observation may prove important for understanding the fundamental difference between bipolar and unipolar disorders. In other words, manic depressive patients are not just more unstable than unipolar patients in mood regulation in both directions.

The pattern of recurrent episodes suggests an ongoing process with progressive deterioration over time. Kraepelin and others since his time noted a marked tendency for the euthymic intervals to grow shorter with the passage of years. Eventually, a significant number of patients enter a clinically malignant phase of rapid cycling. Apparently, as the brain ages, mood-stabilizing mechanisms that prevent frequent recurrences begin to fail (3). We should further note the occurrence of "secondary" manias and depressions caused by physical disorders (11), especially lesions of the right cerebral hemisphere for mania and of the left hemisphere for depression (3).

Finally, in this listing of biological associations we must note the dramatic effects of somatic treatments on both phases of manic depressive illness. For the most severe, especially psychotic episodes of both depression and mania, electroconvulsive therapy is the most effective and rapid means of terminating the episode. Drug effects also are very clear, both for precipitating as well as treating depressions and manias. For example, depressive episodes may be induced by reserpine or α-methyl DOPA (4). Antidepressant drugs and corticosteroids may precipitate manic episodes. Lithium, carbamazepine, and valproic acid are effective in treating mania, whereas depressive episodes may respond to the classical tricyclic drugs, monoamine oxidase inhibitors, or the selective serotonin-reuptake inhibitors. Recurrences of mania and depression are reduced by lithium in bipolar cases, and by lithium or antidepressants in patients with unipolar depression. Antidepressant drug-induced rapid cycling also is now recognized. Another powerful observation is the reversal of the antidepressant action of tricyclic antidepressants or monoamine oxidase inhibitors in depressed patients by preventing serotonin synthesis with use of p-chlorophenylalanine or with dietary tryptophan restriction (12, 13). In bipolar patients, a switch from mania to depression can also be rapidly induced by the anticholinesterase agent physostigmine (2). In sum, all these "big facts" strongly indicate major biological influences on manic depressive disorder.

Genetics

The familial tendency of manic depressive and related conditions has already been noted. Genetic researchers now increasingly adopt a broad, Kraepelinian "spectrum" approach rather than a narrow, DSM III approach to identifying affected cases within pedigrees, and I have already noted that unipolar depression is the single most common mood disorder among the relatives of bipolar probands. The genetic influence varies among families but, on average, the morbid risk of manic depression and severe recurrent unipolar depression is ~15–20% for first-degree relatives of affected individuals, increasing to ~70% for monozygotic twins; in dizygotic twins, however, the risk is only ~20% (4). The overall population incidence is 1–2%.

Why do most affected members of a pedigree manifest unipolar depression or some milder variant within the affective disorders spectrum, while others manifest the manic depressive syndrome? A good example is the family tree of Virginia Woolf. In this example, displayed in Jamison's recent text (14), there are 10 affected individuals, only 2 of whom are definitely bipolar. The others have unipolar depressions, cyclothymia, or unspecified psychosis.

Relationship of Unipolar to Bipolar Depression

To answer the question just stated, one must clarify the relationship of recurrent unipolar depression to bipolar disorder. Goodwin and Jamison (4) argue for the Kraepelinian spectrum view. The longitudinal data mentioned above (10) tend to support the proposal that bipolar subjects have a second genetic vulnerability for
manias superimposed on their general genetic loading for recurrent depressions. This suggestion is strengthened by the finding that the risk factors for manias differ from those for depressions (10). Though the two-genome model for manic depression has not been prominent recently, we must also note that no single-gene models involving chromosome 11 or chromosome X have been replicated in recent linkage studies (15, 16). The sex ratios of unipolar and bipolar disorders also are intriguing. For unipolar depression, the female: male ratio is 2–3:1, whereas this ratio is 1:1 for bipolar disorder. This difference again suggests that manias and depressions are caused by separate factors.

New Genetic Mechanisms

Despite the clear familial inheritance patterns, the yield of genetic linkage studies in unipolar and manic depressions over the past 30 years has been disappointing. For that reason, newly identified genetic mechanisms in neurological disorders are being closely studied for their applicability to psychiatric conditions such as the mood disorders.

A first example is Gilles de la Tourette’s disease. In this condition, characterized by motor tics and coprolalia, recent studies of large pedigrees strongly support the disease spectrum concept (17). Three disorders previously thought to be quite separate according to conventional classifications were identified as alternative expressions of the genotype. These three were classical Tourette disease, simple motor tics (without the vocal tics), and, most surprisingly, obsessive compulsive disorder. A gender effect was noted as well, with Tourette disease predominating among males and obsessive compulsive disorder among females. All three conditions are now known to be associated with dysfunction of the basal ganglia (18). This example well illustrates the potential power of genetic studies to force revisions of standard disease classifications that are based solely on clinical features.

A completely new genetic mechanism of pleomorphic disease expression was described in 1992 (19). In this example, two phenotypically distinct disorders have been associated with an identical point mutation in codon 178 of the prion protein gene located on the short arm of chromosome 20. The two disorders are a type of familial Creutzfeldt–Jakob disease and fatal familial insomnia. The first condition is a diffuse spongiform encephalopathy that presents with a subacute dementia, whereas the clinical features of fatal familial insomnia are subacute intractable insomnia, dysautonomia, and selective destruction of thalamic nuclei. Whether familial Creutzfeldt–Jakob or fatal familial insomnia is expressed depends on a common allelic polymorphism at codon 129 of the same gene. The frequencies of the methionine and valine alleles at this position are 0.62 and 0.38, respectively. Familial Creutzfeldt–Jakob disease occurs when the valine allele is present; fatal familial insomnia is associated with the methionine allele. Furthermore, patients homozygous for the respective alleles at codon 129 had more severe disease and earlier onset. Thus, a common allelic polymorphism separate from the major mutation can radically alter the clinical expression of the major mutation.

Another recently recognized exception to the classical Mendelian patterns of inheritance is the trinucleotide repeat type of mutation now identified in several conditions to date, including Huntington disease, myotonic dystrophy, and fragile X syndrome. These triplet repeats direct the synthesis of repeating units of single amino acids (20) and they show great variation in length of expansion. In the case of fragile X syndrome, for example, the length of the trinucleotide repeat at Xq27.3 is highly polymorphic in the normal population (from 6 to ~42 triplets); asymptomatic carriers have from ~50 to 200 copies, whereas affected cases have expansions as great as 2000 or more copies. In other words, the mutation is not the same for each member of the pedigree. The reasons for this variability are not known. However, such a mechanism can explain the clinical facts of these disorders such as incomplete penetrance and variability of symptoms from one individual to another. Patients with the longer repeat segments presumably have more severe symptoms than those with shorter ones. These aspects and others, such as “anticipation,” are discussed by Ross et al. (20). (“Anticipation” refers to the tendency of a genetic disorder to be more severe and to present with an earlier age of onset in succeeding generations. Ross et al. (20) summarize the evidence for anticipation in manic depressive pedigrees.) The potential applicability of all these new genetic concepts to manic depression and to the Kraepelinian spectrum of mood disorders is obvious.

Clinical Symptoms and Brain Mechanisms

Whatever the genetic locus eventually identified for the familial mood disorders, we still need to consider the brain systems involved in the expression of clinical symptoms. Only then may the steps between the gene mutation and the clinical disorder be clarified. In the case of Huntington disease, for example, we already know from correlative neuroanatomy and neuropathology that the primary affected site is the caudate nucleus. For the familial mood disorders, we can likewise examine the symptoms in reference to the brain mechanisms through which they are expressed. Several models have been proposed over the years to correlate mood symptoms with brain mechanisms (see refs. 3, 4). A recent formulation of one such neurobiological model (3) is outlined below.

The signs and symptoms of depression and mania are at first confusing because not all patients express exactly the same features, and because psychological symptoms are so prominent in addition to behavioral and physiological changes. Current diagnostic criteria such as DSM III (5) do not clarify matters by simply giving a catalog of the possible features without any attempt to consider how they are linked through underlying constructs. It is possible, however, to view the manifold signs and symptoms of manic depression as related to dysregulation of three major neurobiological systems: those that involve...
reinforcement–reward functions, central pain mechanisms, and psychomotor activity.

**Reinforcement–Reward Dysregulation**

An essential feature of the depressed phase of manic depression is anhedonia, the inability to obtain pleasure or satisfaction from sources that previously did give pleasure. These sources are both external stimuli and internal stimuli (cognitions). The experience of pleasure in response to stimuli is an evolved function of the brain termed consummatory reward. In animal studies the hedonic experience is inferred from stimulus-seeking behavior (termed incentive reward). Humans can report the hedonic experience directly. The classical animal paradigms to study hedonic functions are intracranial self-stimulation, self-administration of drugs, and food or place preferences.

In the depressed phase of manic depression, the reward system of the brain may be viewed as inhibited. The patient is unable to experience the normal reinforcing properties of stimuli. On this basis, the patient reports lack of pleasure in relationships and activities that previously were engaging, such as social settings, work, and avocations. Loss of enjoyment of basic drives such as sex and food intake are viewed in the same light. Cognitions or internally derived stimuli also lose their rewarding property. On this basis, the depressed patient's self-image changes from competent and valued to incompetent and devalued. Cognitions of the future change from the expectation of pleasure and success to anticipation of emptiness and failure. The important point here is that some of the specifically human, psychological aspects of depressive anhedonia can be understood in the same way as the more simple anhedonic symptoms and behaviors.

In the manic phase, the reward system is viewed as disinhibited, i.e., dysregulated in the opposite direction. Manic patients over-attend to stimuli with excessive eagerness. From being anhedonic and withdrawn, they switch to exaggerated seeking of social contact and sensory stimulation. Their mood switches from boredom and disinterest to pathological satisfaction and intrusive overinterest, with marked distractibility as new stimuli present to them, either from their environment or in the form of cognitions from within. The self-image is grandiose and omnipotent rather than devalued and incompetent, and the manic's perception of the future is unrealistically optimistic rather than pessimistic. In summary, the affective information processing of the positive (reinforcing, rewarding) properties of both internal cognitions and external stimuli is dysregulated in the manic depressive patient. The salient fact to keep in mind when contemplating these switches of hedonic capacity is that it is the same person, with the same developmental history and a constant environment, who cycles between, e.g., incompetent vs omnipotent self-perceptions. The critical factor, then, is the ability of the reinforcement–reward system to detect the positive qualities of self-cognitions, no less than of external stimuli or of cognitions about the future.

The brain system that mediates reinforcement–reward is known from animal studies of intracranial self-stimulation. Although stimulation of electrodes implanted in most areas of the brain does not induce self-stimulation, in certain areas it is highly rewarding. These areas include noradrenergic and dopaminergic cell bodies in the brain stem, and their limbic forebrain projection areas such as hypothalamus and septal nuclei. In recent years there has been increasing recognition that the basal ganglia are involved in hedonic behaviors, especially incentive reward functions that involve foresight and motivated planning of activity to obtain consummatory rewards. Reports of profound anhedonia and disinterest without dysphoria after localized lesions of the basal ganglia are especially instructive (see ref. 3). Acetylcholine is regarded as an inhibitory neurotransmitter in this system. Neuropeptides such as enkephalins and Substance P also modulate self-stimulation.

Thus, one distinct group of classical symptoms in manic depression can be viewed as mediated by this particular neurobiological system. It is also clear that more than one neurobiological system may be involved in the expression of those symptoms through this system.

**Central Pain Dysregulation**

Another group of signs and symptoms in manic depression is viewed as being mediated by dysregulation of a separate brain system, for which the term "central pain mechanism" is used (1–3). In the depressed phase this system is seen as disinhibited, whereas in mania it is inhibited. The essential distinction between central pain and anhedonia is that between bad (or aversive) and not-good (or nonrewarding).

In the depressed phase, stimuli that previously were nonaversive are experienced as distressing. Again, these stimuli are both external and internal (cognitive). On this basis, the depressed patient perceives neutral events as catastrophic. For example, one patient whose spouse was 30 min late visiting him in the hospital became convinced she had been killed in a road accident en route, and proceeded agitatedly to call the police to confirm this belief. Changes in self-image due to central pain dysregulation go beyond feelings of incompetence and devaluation. The depressed patient perceives himself as bad, unworthy, and guilty.

When manic, however, the same person displays a cognitive blindness to the aversive or negative properties of stimuli. Hence the characteristic denial of illness and the disregard of the manic for the painful consequences of his own behavior. That is why manic patients will behave out of character in such ways as reckless driving, foolish investments, spending sprees, embarrassing sexual indiscretions, and risk-taking of all kinds. The self-image of the manic shifts from painful self-deprecation to euphoric self-esteem.

The brain system that interprets the negative emotional significance of cognitions and external stimuli comprises the central pain pathways, in which intracranial self-stimulation is aversive rather than reinforcing or neutral. The sites thus identified include the mid-
brain tegmentum, the periaqueductal gray area of the midbrain, and periventricular areas of the thalamus more rostrally. The classical sensory projection systems involving intralaminar thalamic relay nuclei, primary sensory neocortex, and cortical association areas have descending connections to the subcortical pain areas mentioned above. The amygdala, in particular, occupies a central position in appraising stimulus input to yield a “value transformation…that encodes the adaptive value or affective significance of the stimulus” (21). There is also experimental evidence linking the basal ganglia to pain perception and regulation (see ref. 3). An emerging concept is that the basal ganglia exert a sensory gating function in the process of stimulus appraisal by modulating the thalamus, which up to now has been regarded as the major site of selective attention to sensory input and its affective significance.

Of the classical neurotransmitters, serotonin and acetylcholine are known to be important in the perception of pain. Reduction of serotonergic activity, as with p-chlorophenylalanine, increases responses to aversive stimuli; increasing cholinergic activity has a similar effect. Brain enkephalins and other neuropeptides also are involved in mediating pain responding. Thus, this second fundamental brain system is viewed in contemporary models as responsible for the expression of a distinct set of signs and symptoms characteristic of manic depression. These clinical features are different from those mediated by the reinforcement–reward system.

Psychomotor Regulation

The clinical changes seen in manic depression include a third group of signs and symptoms termed “psychomotor function.” Included here are speed of thought process, cognitive associations, speech volume, speech latency, speech quantity, nonverbal communicative gestures, and physical energy. Overall, psychomotor function is accelerated during mania and decelerated during depression. In extreme forms, the psychomotor dysregulation can progress to depressive stupor on the one hand, and to manic frenzy on the other.

The anatomic substrate of these functions is viewed as the “distributed processing system,” which includes frontal cortex, basal ganglia, cerebellum, and thalamus (22). For the executive control of motor programming by this system, Shepherd (22) has emphasized the central programming role played by the subcortical striatal system, as opposed to the primacy previously accorded to the motor and premotor cortex. Nauta (23) stresses the equivalent functions of the ventral striatum (nucleus accumbens) and ventral pallidum, with their corresponding connections to ventral tegmental dopamine nuclei (A9 area), dorsomedial thalamus, and limbic cortex, including amygdala, in the executive control of cognitive processes and emotional expression. Of the classical neurotransmitters, dopamine has a facilitatory (accelerating) role, and acetylcholine has the opposite effect. In the depressed phase of manic depression, the psychomotor deceleration resembles the bradyphrenia seen in Parkinson disease, at times separately from bradykinesia. In agreement with this emphasis on the striatum in psychomotor function are reports of “pure psychic akinesia” after bilateral lesions of the basal ganglia (24).

Clinical Illustrations

The three neurobiological systems described above in association with specific groups of signs and symptoms in manic depression display bipolar dysregulation according to the phase of illness. They are also to some extent independent or orthogonal components of manic depression because change can be seen at times in one system independent of changes in the others. Several clinical examples illustrate this point.

The occurrence of mixed states is the primary example. About 30% of manic episodes are of this type, where dysphoric (central pain) features coexist with psychomotor acceleration and increased incentive drive. This state is not the same as agitated depression (3, 25), a point on which today we disagree with Kraepelin. Another mixed state well described by Kraepelin is manic stupor, in which the patient has grandiose thoughts and elated mood but diminished psychomotor drive. These instances tell us clearly that the three dimensions of manic depression can be dissociated at times.

As a depressive episode develops, a prodromal change in the reinforcement–reward system frequently appears before psychomotor slowing, and central pain symptoms may be the last to appear. The patient will become quiet, withdrawn, and anergic for days or weeks before dysphoric symptoms develop. Family members often are aware of the developing episode of depression before the patient is.

In the early phase of response to a tricyclic antidepressant drug such as imipramine, improvement is seen in psychomotor and hedonic function before the dysphoric symptoms begin to abate. Ward staff will report that the patient is spending more time out of his room, seeking social contact, eating better, and is less psychomotor-retarded, though at this transitional time the patient reports feeling unchanged in his dysphoric thoughts. For these reasons, this early response to a tricyclic is recognized clinically as a time of increased risk of suicide attempt.

In the treatment of mania, use of a neuroleptic drug such as haloperidol will control the dopamine-driven psychomotor acceleration and incentive drive but does not modify the inhibited central pain features. Thus, manic patients continue to express grandiose thoughts and convulsions of special powers despite the psychomotor slowing produced by the drug. Basically, use of a neuroleptic drug by itself in treating a manic episode simply provides behavioral control of the patient until the mania resolves of its own course.

As a final example, the acetylcholinesterase inhibitor physostigmine will rapidly produce dramatic change in a manic subject. Within 10 min of starting an infusion of physostigmine, the patient will display psychomotor slowing, decreased hedonic activity, and reduced incentive drive. Only later will dysphoric symptoms appear.
in the form of depressed mood, tearfulness, pathological guilt, and suicidal ideation. As the drug is eliminated over the next 2 h, the patient will return to his previous manic state.

In each of these clinical examples, the neurotransmitter basis of the specific shifts can be inferred (see ref. 2). Other examples also could be given. The importance of these clinical illustrations is to emphasize that analysis of the signs and symptoms in terms of specific brain systems is possible. The challenge for the future will be to understand more completely the anatomic and neurotransmitter connections among these three brain systems in manic depression. The basal ganglia are likely to assume a prominent place in these connections (3).

From this review, one can see that single-neurotransmitter theories of the disorder are not likely to account for the wide array of observed signs and symptoms. The nature of the switch mechanism into mania or depression is still speculative, as is our understanding of how lithium protects against both manic and depressive switches. There is no longer any doubt, however, of the genetic influence in manic depression or of the major importance of biological factors in the etiology and treatment of this disorder.

This work was supported by NIH grant MH40159, CRC/PE for the study of depression in late life.

References