The Neurobiology of Depression: Perspectives from Animal and Human Sleep Studies

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This article reviews human and animal studies in the neurobiology of depression. The etiology of the illness, associated neurotransmitter dysregulation, sex steroids, the role of stress, and sleep regulation are discussed. It is suggested that the genesis of depression is related to homeostatic maladaptation that is sexually dimorphic. The authors propose that depressed females are hyperresponsive to stress, whereas depressed males are hyporesponsive to stress. This divergence reflects the exaggeration of naturally occurring differences between males and females, which are most obvious under challenge conditions. The authors conclude that future work in this area should fully evaluate sexual dimorphism, neural plasticity, critical periods, and individual differences in vulnerability. NEUROSCIENTIST 9(1):82–98, 2003. DOI: 10.1177/1073858402239594

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The purpose of this article is to review and update the literature on the neurobiology of depression considering both human and animal studies. This review cannot cover all areas of neurobiology of the illness. Instead, we will provide some key background on the symptoms, epidemiology, and neurotransmitter abnormalities in depression and review the related animal models. A separate section on studies of sleep electrophysiology (EEG) in both those with depression and animal models is included, as this area has provided some of the most compelling data on the neurobiology of depression. Finally, we will outline future directions for an integrated study of the neurobiology of depression. The first step in such an endeavor requires a review of the diagnostic features and symptoms of depression.

Diagnosis

According to the *Diagnostic and Statistical Manual of Mental Disorders* (*DSM-IV*) (APA 1994), major depressive disorder (MDD) is characterized by one or more episodes with five or more of the following symptoms most of the day, nearly every day for at least 2 weeks: 1) depressed mood; 2) markedly diminished interest or pleasure in most activities; 3) significant weight loss or weight gain; 4) insomnia or hypersomnia psychomotor agitation or retardation; 5) fatigue or loss of energy, feelings of worthlessness, diminished ability to think or concentrate; and 6) recurrent thoughts of death. See Table 1 for a summary.

In addition, the symptoms must cause clinically significant occupational or social impairment, cannot be due to a general medical condition (e.g., hypothyroidism) or substance or due to bereavement unless persistent beyond 2 months but cannot be mania. The episode can be further specified as mild, moderate, or severe; with or without psychotic features; in full or partial remission; chronic (at least 2 years in duration); with catatonic, melancholic, or atypical features; or with postpartum onset. Seasonal variation and interepisode recovery may also be specified. To be considered a recurrent illness, two or more episodes separated by at least 2 consecutive months below symptom criteria must be evident.

Epidemiology

With regard to epidemiology, the lifetime prevalence of the illness is 6% to 10% and begins most commonly in the 20s and 30s (Depression Guideline Panel 1993). Risk factors for depression include prior episodes of the illness, family history of MDD, prior suicide attempts, lack of social support, medical comorbidity, stressful life events, current substance abuse, and female gender. Women are at twice the lifetime risk as men, beginning in puberty and continuing to menopause. In addition, the postpartum period increases the risk of first onset of the illness and a recurrence in those already ill (Depression Guideline Panel 1993).

The degree of treatment response is more complicated to estimate, as it depends on the adequacy of the diagnosis, choice, and duration of the treatment. Nevertheless, response rates in a typical 6- to 8-week trial are estimated at 30% to 60%. It appears that response rates to newer antidepressants such as serotonin reuptake inhibitors (SRIs) are on par with older tri-

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cyclic medications, although the side effect profiles of newer agents are more favorable (Depression Guideline Panel 1993). One exception is that those with atypical features (weight gain, hypersomnia, reactive mood) are more likely to respond to monoamine oxidase inhibitors (MAOIs) or SRIs than to tricyclic antidepressants (TCAs). Beyond this, response rates seem to be more determined by dose and length of treatment than by class of antidepressant per se. These data are of particular importance when considering the neurotransmitter abnormalities associated with depression. Both the data on drug response and the symptoms of depression can be defined operationally and modeled in the laboratory. Figure 1 presents a schematic of neurotransmitter abnormalities and associated neurophysiology implicated in depressive symptomatology.

Table 1. Criteria for a Major Depressive Episode (*DSM-IV*)

Five or more of the following symptoms have been present during the same 2-week period and represent a change from previous functioning; at least one of the symptoms is either 1) depressed mood or 2) loss of interest or pleasure.

1. Depressed mood most of the day, nearly every day, as indicated by either subjective report (e.g., feels sad or empty) or observation made by others (e.g., appears tearful). In children and adolescents, it can be irritable mood.
2. Markedly diminished interest or pleasure in all, or almost all, activities most of the day, nearly every day (as indicated by either subjective account or observation made by others).
3. Significant weight loss when not dieting or weight gain (e.g., a change of more than 5% of body weight in a month), or decrease or increase in appetite nearly every day. In children, consider failure to make expected weight gain.
4. Insomnia or hypersomnia nearly every day.
5. Psychomotor agitation or retardation nearly every day (observable by others, not merely subjective feelings of restlessness or being slowed down).
6. Fatigue or loss of energy nearly every day.
7. Feelings of worthlessness or excessive or inappropriate guilt (which may be delusional) nearly every day (not merely self-reproach or guilt about being sick).
8. Diminished ability to think or concentrate, or indecisiveness, nearly every day (either by subjective account or as observed by others).
9. Recurrent thoughts of death (not just fear of dying), recurrent suicidal ideation without a specific plan, or a suicide attempt or a specific plan for committing suicide.

Neurotransmitter Abnormalities

Monoamine Depletion

The observation that pharmacological manipulation of monoamine-influenced depressive symptoms led to the hypothesis that depression results from reduced availability or functional deficiency of serotonin or norepinephrine (Bunney and Davis 1965; Schildkraut 1965; Schildkraut and others 1968). This view was supported by the pharmacological action of both TCAs and MAOIs, namely, the resultant increase in synaptic levels of monoamines. However, studies of cerebrospinal fluid could not confirm decreased monoamine metabolites in those with MDD. Moreover, preclinical studies suggested that the mechanism of action of antidepressant drugs was related to changes in monoamine receptor sensitivity (Charney and others 1981). In a series of more recent studies, Delgado and colleagues manipulated monoaminergic function through the ingestion of a tryptophan-free amino acid drink to deplete serotonin and alpha methyl paratyrosine (AMPT) to deplete catecholamines (Heninger and others 1996). These studies have shown that although depletion of monoamines does not increase depressive symptoms, it does induce relapse in those who have responded to treatment. However, the effects are specific to the type of antidepressant that produced the initial clinical response. Patients who responded to an SRI relapsed with tryptophan depletion. Patients who responded to imipramine relapsed after AMPT but not with tryptophan depletion. These data do support abnormalities in monaminergic *sensitivity* but suggest that antidepressant response involves more than just monoamines.

Increased Cholinergic Sensitivity

Janowsky and colleagues have suggested that the regulation of acetylcholine plays a major role in MDD (Janowsky and others 1972). Cholinergic agonists, cholinesterase inhibitors, and acetylcholine precursors have all been shown to worsen mood in MDD (Janowsky and others 1983; Dube 1993). Moreover, depressed patients show a heightened response to muscarinic cholinergic agonists as evidenced by worsening of mood, anergia, pupillary constriction, sleep (see Section E), and beta-endorphin release (Janowsky and others 1972; Dilsaver and Coffman 1989). Furthermore, abnormalities in levels of cortical choline, an acetylcholine precursor, have been reported in several brain imaging studies (Charles and others 1994; Renshaw and others 1994; Steingard and others 2000). It should be noted, however, that the increased levels of choline may be localized in the frontal cortex with decreased levels of choline evident in other brain regions (Ende and others 1997; Renshaw and others 1997).

Aminergic/Cholinergic Imbalance

The original Janowsky and others (1972) hypothesis did not suggest that the underlying neurotransmitter abnormality was exclusively cholinergic. They suggested instead that an imbalance in cholinergic/noradrenergic

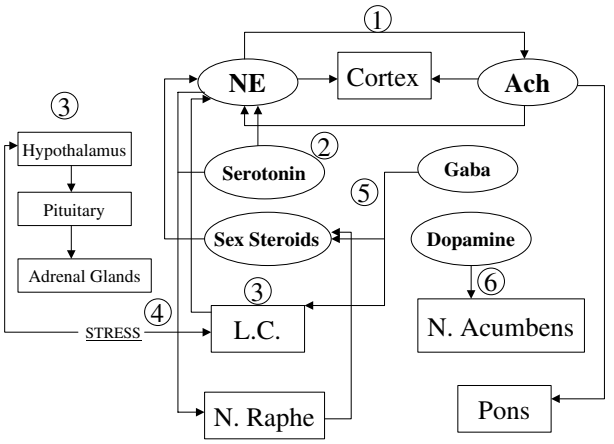

Fig. 1. Putative neurotransmitter abnormalities in depression, implicated brain regions, and neurophysiological action.

1. Reciprocal activity of NE and Ach favors Ach in depression causing short REM latency and negative mood.
2. Low levels of serotonin or lack of sensitivity in serotonin receptors linked to depression.
3. Stress activates locus coereleus and hypothalamic-pituitary-adrenal (HPA) causing release of norepinephrine and ultimately depletion of NE.
4. Serotonin and NE activity modulate activity of the nucleus raphe, which in turn alters release of sex steroids possibly a contributing factor in observed sex differences in depression.
5. Animals developing learned helplessness show in increase in GABA receptors, which may then generate a cascade of noradrenergic activity through the LC.
6. Reduction of dopamine activation of neurons in the nucleus acumbens is related to the appearance of anhedonic behavior.

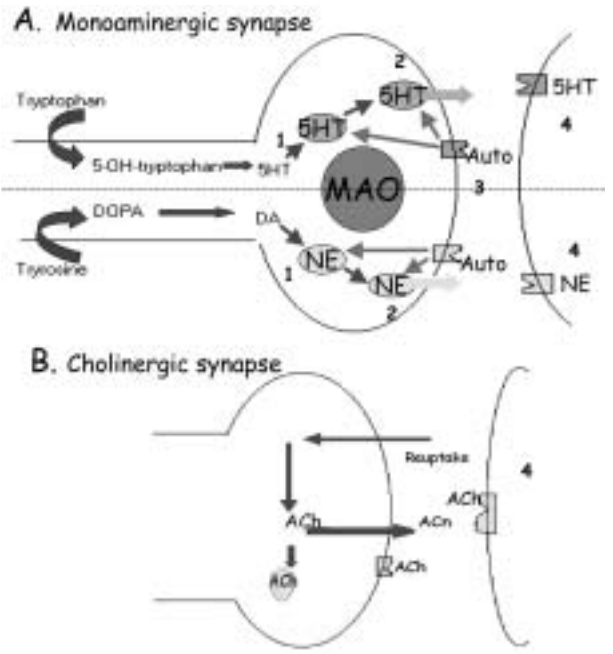

Fig. 2. Schematic representation of (*A*) aminergic and (*B*) cholinergic synaptic mechanisms thought to be involved in antidepressant efficacy.

- **Synthesis (1):** Inhibition of 5-HT synthesis in drug-remitted depressed patients causes relapse.
- **Release (2):** Reduced 5-HT release associated with depressive symptoms. Effects of monoamine oxide inhibitors (MAOIs) on depressive symptoms suggest that excessive degradation of intracellular 5-HT may lead to reduced 5-HT release.
- **Reuptake (3):** Presynaptic mechanisms terminate 5-HT synaptic action. Classic tricyclic antidepressants may have their effects through inhibition of this uptake mechanism.
- **Receptor effects (4):** Postsynaptic receptor sensitivity up-regulation at aminergic sites by tricyclics and electroconvulsive shocks, and putative super-sensitivity at cholinergic synapses implicate these mechanisms in depression.

neurotransmission characterized those with MDD. Inherent in this view is the assumption that no single neurotransmitter abnormality underlies MDD, a position that has become more appealing (Siever and Davis 1985). As will be explicated below, this view of neurotransmitter dysregulation in MDD provides a better fit with physiological, behavioral, and neurobiological data in both humans and animals. Figure 2 presents a schematic of monoaminergic and cholinergic synaptic action as a guideline for reviewing the animal studies. With this information in mind, we will now turn to a review of the animal models of MDD.

Animal Models of MDD

At least 18 distinct animal models of MDD have appeared in the literature (Yadid and others 2000). A problem arises when attempting to validate any of these against MDD. However, Willner (1985) offered an approach for the evaluation of animal models of depression on the basis of how well they satisfy three distinct validity criteria. These criteria are 1) face validity—the degree to which the model exhibits characteristics that parallel the human condition; 2) construct validity—the degree to which derivation of the model parallels our understanding of the etiology of MDD in humans; and 3) predictive validity—the degree to which the response of the animal to antidepressant parallels response in those with MDD. Many studies have been directed at assessing and validating the different models of depression, and this research has been extensively reviewed elsewhere (for example, see Willner 1997; Nemeroff 1998; Yadid and others 2000). The current review focuses on animal models that have reported construct, predictive, *and* face validity. Table 2 presents a summary of key animal models of depression and evidence of validity.

Of the animal models of human depression considered here, most involve a stressor presented at a point in the animal's life that some time later provokes depressive-like behavior in adulthood. This work is a logical extension of the view that depression arises from a traumatic or stressful life event, and thus these models possess both construct and face validity, in addition to predictive validity. The models considered in this section include 1) learned helplessness, 2) chronic mild stress

Table 2. Summary of Key Animal Models of Depression and Evidence of Validity

Model	Features of Construct Validity	Face Validity (MDD-like Attributes)	Predictive Validity	References
Chronic mild stress	A variety of stressors over an extended period of time leading to reduced hedonia A variation on learned helplessness	Reduced consumption sweetened solution: anhedonia, ↓ locomotor activity, disrupted sleep. Reversed by several days antidepressants	Nearly all clinically effective antidepressants tested reverse the anhedonia	Willner (1997), Willner and others (1987, 1992), Monleon and others (1995)
Social defeat	Reduced social status, loss of rank, stressors that are thought to lead to depressive behavior	Reduced activity in open field, classic stress response	Reversed by sleep deprivation	Meerlow, De Boer, and others (1996); Meerlo, Overkamp, Benning, and others (1996); Meerlo, Overkamp, Daan, and others (1996); Meerlo, Overkamp, and others (1997); Meerlo, Pragt, and others (1997); Meerlo, Van den Hoofdakker, and others (1997)
Maternal separation	Early-life maternal bond affects development of later emotional life	Heightened fear and aggression, inability to cope with stress, novelty-induced fearfulness, ↑ hypothalamic-pituitary-adrenal (HPA) response to stressors	Several different classes of anti depressant drugs attenuate or reverse behavioral and endocrinological effects of maternal separation	Chamove and others (1973), Heim and others (1997), Ladd and others (1996, 2000), Liu and others (1997)
Early REMS deprivation: drugs	Early-life stressor leading to depressive-like behavior	Sexual response, aggression in males, reward-seeking, increased REMS, increased activity in outer areas of open field	Behavioral abnormalities respond positively to imipramine treatment	Corner and others (1980), Mirmiran (1986); Mirmiran and others (1981, 1983); Vogel and others (1980); Vogel, Neill, Hagler, and others (1990), Vogel, Neill, Kors, and others (1990)
Early REMS deprivation: instrumental techniques	Early-life stressor leading to depressive-like behavior	Anhedonia, reduced intake of sweetened solution	?	See this review
Flinders sensitive line of rats	Genetic predisposition for supersensitivity to cholinergic agonists	Supersensitive to cholinergic agonists, increased REMS, appetite, and weight, reduced activity (especially in forced swim test)	Chronic treatment with TCAs, SRIs (but not other drugs), reverse immobility in forced swim test	Overstreet (1986, 1993), Overstreet and others (1994, 1995), Overstreet and Russell (1982), Russell and others (1982), Yadid and others (2000)

model, 3) social defeat, and 4) maternal separation. Models related to sleep deprivation and regulation are reviewed later. The first three models can be considered variants on an adult model of uncontrollable stress, such

as an aversive or stressful environmental variable, that evokes a relatively prolonged reactive "depressive" response and elicits behaviors consistent with those observed in patients with MDD. The maternal separation model crosses over two views of depression that early traumatic events produce "depressive" behaviors in adulthood and that there are critical periods in social and brain development in which the animal (or human) is particularly vulnerable to long-term consequences of trauma and stress.

Learned Helplessness

The learned helplessness model of MDD rests on the premise that animals exposed to uncontrolled or unpredictably aversive events for a sufficient period of time will develop long-lasting deficits in escape performance (Miller and Seligman 1975). Early work on learned helplessness suggested that during inescapable shock the animal could not respond behaviorally and thus the only available response was an alteration in neurotransmitter activity that in turn produced the depressive behavior (Anisman and Zacharko 1982). Furthermore, the behavioral responses parallel some of the symptoms of depression in humans (lack of self-efficacy, hopelessness) (Willner 1984, 1997). Learned helpless animals also exhibit loss of appetite and weight (Seligman and others 1980), have decreased locomotor activity (Wagner and others 1977), and perform poorly in appetitively and aversively motivated tasks (Rosellini and others 1982, 1984) and in uncontrollable stress paradigms (Willner 1984). Additionally, TCAs, MAOIs, and electroconvulsive shock effectively reduce the behavioral and physiological effects of shock exposure, providing evidence of the face validity of the model (Willner 1984).

Naruo and others (1993) used an unpredictable shock situation combined with variable ratio response testing to induce depressive behavior in a set of rats. Animals exposed to the unpredictable shocks showed a reduction in the number of successful escapes and were then treated with either imipramine or chlordiazepoxide. The animals treated with imipramine showed increases in the number of successful escapes during testing, whereas the animals receiving chlordiazepoxide increased their responding, but not successful responding.

Edwards and others (1992) used the learned helplessness model to evaluate changes in 5-HT. Rats were exposed to uncontrollable shock and then retrained in a shock escape task. They found elevated levels of 5-HT in hippocampal slices of the learned helpless rats but not in controls, who performed poorly. No group differences were found in acetylcholine, dopamine, or noradrenaline. These data suggest that the development of depression in this animal model is dependent upon increased levels of 5-HT, but depression in humans has been associated with lowered levels of 5-HT that is treated with SRIs. Petty and others (1994) found similar changes in 5-HT in the medial frontal cortex, using a learned helplessness paradigm. They found that 5-HT release after stress showed a significant increase with helpless behavior.

Work by Wu and others (1999) also examined the role of serotonin in learned helplessness. No differences were evident in 5-HT1A receptor density. Moreover, 5-HT2A receptor density was reduced in the dorsal hippocampus in the nonhelpless animals. By contrast, 5-HT2A receptor density was reduced in the amygdala in both helpless and nonhelpless animals. Such results underscore the complexity in the physiology of learned helplessness. To further explore the role of 5-HT in learned helplessness, Papolos and others (1996) antagonized 5-HT2A receptors with an antisense oligonucleotide. This procedure has the effect of down-regulating activity at these receptors. When compared with controls in a shock avoidance procedure, the experimental animals behaved as if they had developed learned helplessness, supporting a reduction in 5-HT2A activity.

Weiss and Simpson (1988) looked specifically at norepinephrine (NE) changes in the locus coeruleus (LC) associated with "stress induced depression." Initially they found a large depletion of NE in that area following the induction of stress. Because of this depletion of NE, it was suggested that this would also reduce activity in alpha-2 receptors, which normally inhibit firing in LC neurons. Pharmacological blockade of these neurons increases the firing of LC neurons to excitatory stimuli. When the stressed animals were tested with excitatory stimuli, they also showed an elevation of LC activity, suggesting diminished activation of alpha-2 receptors. The overall effect of this transformation in LC would be to disinhibit LC neurons, resulting in a depletion of NE in the stressed animals. This is consistent with clinical findings that drugs that augment NE activity (e.g., MAOIs, TCAs) have a beneficial effect on depressed mood patients. However, Brannan and others (1995) did not obtain changes in beta adrenergic receptor density using tail shock stress and shuttle avoidance, indicating that the development of learned helplessness is dependent upon the specific experimental procedures.

Extending beyond the influence of noradrenergic transmitter changes, Kram and others (2000) examined $GABA_A$ and $GABA_B$ receptor changes in a learned helplessness paradigm. They found that helpless animals had an increase in density of $GABA_A$ receptors, whereas animals that did not develop helplessness showed lower levels of $GABA_B$ receptors.

Chronic Mild Stress

Willner (Willner 1997; Willner and others 1987) developed an animal model to parallel the anhedonia that is also characteristic of MDD. In rats that have experienced a varying array of chronic mild stressors (CMS) for a 2-week period, intake of sweetened solution is reduced compared to nontreated animals. In this model, rats are compared on their responses when presented with a two-bottle choice of either normal tap water or a sweetened water solution of either sucrose or saccharine as an objective measure of hedonic tone. Utilization of sac-

charine as the sweetening agent eliminates calorific intake as a confounding factor. Additionally, rats exposed to the CMS paradigm exhibit other behavioral changes that parallel those in human depressives, including decreased locomotor activity (Willner 1997) and disrupted sleep (Cheeta and others 1997). The effects of CMS can persist for several weeks after the CMS session.

Nearly all clinically effective antidepressants tested in this model reversed the induced reduction in consumption of sweetened solution (Wilner and others 1992; Monleon and others 1995). Moreover, sucrose preference returned to baseline levels only after a 3- to 5-week delay, paralleling response time to antidepressant medications in those with MDD. Chronic, but not acute, antidepressant administration also reversed the observed increase in 5-HT2A and beta-adrenergic receptors in the cortex of CMS rats (Papp and others 1994a). Furthermore, dopamine receptors were decreased in CMS rats and this decrease was reversed by chronic imipramine (Papp and others 1994b). Willner (1997) reported that dopamine release is reduced in vivo in CMS rats. Furthermore, dopamine antagonists reversed the increase in sucrose preference elicited with antidepressants (Sampson and others 1991). Subsequent neurophysiological analyses suggested that these effects are mediated by dopaminergic cells in the nucleus acumbens (Willner and others 1991).

The nucleus acumbens is thought to be a critical neural substrate for more general reward and motivational state, appetitive behaviors, and social interaction (Wise 1998; Koob and LeMoal 2001; Nestler and others 2002). In addition, overexpression of the transcription factor CREB (cAMP response element binding protein) in the nucleus acumbens is activated by stress and elicits depressive behaviors (Pliakas and others 2001; Nestler and others 2002). Note, however, that up-regulation of CREB in other brain regions, most notably the hippocampus, has opposite effects on depressive behavior (Duman and others 1997).

Social Defeat

Stressful life events are important factors in the etiology of depression. Losing a confrontation to a perceived superior leads to low self-esteem in humans and loss of social rank in animals and has been termed *social defeat* (Marrow and others 1999). Social defeat has been proposed as a natural stressor in humans (Bjorkqvist 2001), rats (Bohus and others 1991), and mice (Koolhaas and others 1997; Keeney and Hogg 1999). In addition to the stress response induced by confrontational social interactions, loss of rank has been associated with increased risk of depression (Brown and others 1986). Similarly, it is argued that in species that develop hierarchical social structures, loss of position in these animal groups could be considered a model of human loss of rank (Marrow and others 1999), a situation that has been proposed as an animal model of human depression (Willner 1995). Social defeat in rats has been shown to induce a classic stress response including cardiovascular and neuroendocrine activation, hyperthermia, and behavioral reactions, such as reduced exploration in an open field test (Meerlo, De Boer, and others 1996; Meerlo, Overkamp, Benning, and others 1996; Meerlo, Overkamp, Daan, and others 1996; Meerlo, Overkamp, and others 1997; Meerlo, Pragt, and others 1997; Meerlo, Van den Hoofdakker, and others 1997). In the Meerlo studies (Meerlo, De Boer, and others 1996; Meerlo, Overkamp, Benning, and others 1996; Meerlo, Overkamp, Daan, and others 1996), the effect of the social defeat persisted over several weeks and was reversed by total sleep deprivation, consistent with sleep deprivation effects in those with MDD (Gillin 1983; Wu and Bunney 1990) (see Section E). The social defeat model, it has been argued, has good construct, face, and predictive validity (Meerlo, De Boer, and others 1996). However, more recent studies have questioned this model on several aspects regarding its validity (Marrow and others 1999).

The models discussed above share the common attribute of an acute stressor producing long-term behavioral effects in adult animals that resemble the symptoms and behavior seen in patients with MDD. However, there are other paradigms that have stronger construct validity as animal models of MDD, namely, those than focus on long-term effects of early exposure and neural plasticity. The models considered in the sections below are based on the observation that stressful events in early childhood predispose one to depression later in life (Nemeroff 1998).

Maternal Separation

Since Freud (1966) and Bowlby (1977a, 1977b), it has been understood that the bond between mother and her offspring has a central hold on the development of the offspring's emotional life. Harlow's pioneering work with the maternally deprived rhesus monkey repeated this tenet (Chamove and others 1973; Ruppenthal and others 1976). Maternally separated rhesus monkeys not only exhibited heightened fear and aggression, and an inability to cope with stressors, they also revealed profound neuroanatomical changes (Martin and others 1991). Given these early observations and the additional evidence that maternal separation in rats is capable of affecting both behavioral responses and the hypothalamic-pituitary-adrenal (HPA) axis response, Nemeroff's group (e.g., Ladd and others 1996; Heim and others 1997) has pursued the hypothesis that early maternal separation in rats might serve as a suitable paradigm for the effects of aversive early experience on behavioral responsiveness to stress later in life, as an animal model of behavioral responses associated with mood disorders in human depressives. These workers have proposed a stress diathesis model that postulates an interaction between a genetic vulnerability or predisposition and stressful life events in the genesis of human depression (construct validity) (Ladd and others 2000). Starting with the demonstration that maternal separation increased adrenal responsiveness and increased novelty-

induced fearfulness in rats, these researchers postulated that the simple separation from the primary caregiver could have such far-reaching effects because of two interlinked processes—the underlying plasticity of the developing nervous system and consequent alterations in the regulation of the stress response (Ladd and others 2000). In support of their hypothesis, Nemeroff's group has demonstrated an inverse correlation between time spent by the dam engaged in maternal behavior and subsequent stress responsiveness of the offspring after reaching adulthood (Liu and others 1997). These researchers have also shown that several classes of antidepressant drugs attenuate or reverse the behavioral and endocrinological effects of maternal separation (predictive validity) (Ladd and others 1996). In addition, this group had demonstrated that after normalization of the behavioral and endocrine responses in the adult maternal-separation-rat by antidepressant treatment, withdrawal of the antidepressant drug treatment reverses the positive effects of the drug, much as is seen in human depressives after stopping their medications. This suggests that the neurochemical cascade associated with drug withdrawal is similar to the initiating events of the primary affective episode (face validity). To test this hypothesis, their current investigations are focused on these behavioral and endocrinological events after withdrawal of antidepressant drugs from adult maternal separation rats as a model for the underlying pathophysiology of affective disorders (Ladd and others 2000).

Matthews and others (1996) used repeated separation of rat pups from their mother during early neonatal development. This has the effect of reducing hedonic responsiveness as measured by the animals' interest in consuming sweet solutions, similar to early work using CMS to induce anhedonia in animals.

In a paradigm that integrates maternal separation and learned helplessness, Edwards and others (1999) attempted to selectively breed animals susceptible to learned helplessness and to evaluate the effect of early stress on activity in the HPA axis. Groups of animals were interbred for 33 generations and were subjected to two types of stress, exposure to cold and maternal separation. HPA activity was monitored by measuring plasma corticosterone levels. As expected, corticosterone levels increased as pups grew from day 7 to day 21 in response to stress. The levels of corticosterone were lower in the learned helpless group. Unstressed animals all had similar corticosterone levels. Nevertheless, a genetic susceptibility to developing learned helplessness was associated with differences in the development of HPA activity induced by stress.

Another alternative procedure for inducing depression in animals is social isolation. Ehlers and others (1993) used social separation to induce depressive behaviors and found concomitant EEG activity, ACTH, and CRF. Furthermore, these changes were different in male and female animals, with a greater reduction in CRF receptor density in males. Social isolation was also used by Fone and others (1996) to look at physiological and behavioral changes induced by this procedure in combination with mCPP (m-chlorophenylpiperazine), a serotonin agonist. Administration of mCPP caused a greater elevation in plasma corticosterone in animals that had been reared in isolation than in group-housed controls. Also, mCPP lowered levels of hippocampal 5-HT2C for animals reared in isolation when compared to stressed animals not receiving mCPP. The earlier results suggest a contribution of 5-HT2C in the development of alterations generated by social isolation and suggest that these animals may show an amplified down-regulation of 5-HT2C receptors following an agonist challenge. Jaffe (1998) looked at Ca2+ and the effects of social isolation on release of DA and 5-HT and found that extracellular Ca2+ induced release of 5-HT and DA was increased in stressed animals.

One limitation of most of the human and animal studies discussed thus far is the short duration recording periods, particularly in those studies examining neurotransmitter regulation. Implicit in this work is the assumption that brain organization and mood response is static. There is ample evidence of diurnal variations and rhythmic changes in mood and brain regulation. Studies of brain regulation during sleep provide additional insight into the role of adrenergic and cholinergic neurotransmitters in MDD. To evaluate the animal models of MDD that utilize sleep EEG paradigms, we will first consider the findings in depressed patients.

Sleep in MDD

The study of sleep EEG abnormalities in MDD has a 40-year history, with more than 1300 published studies in the past 20 years alone (Armitage and Hoffmann 1997), including several seminal review articles (Reynolds and Kupfer 1987; Knowles and MacLean 1990; Berger and Riemann 1993). The majority of studies on macroarchitecture, based on visual stage scoring of the polysomnogram, have reported abnormalities in the timing and/or distribution of rapid eye movement (REM) and non-rapid eye movement (NREM) sleep stages as primary characteristics of those with MDD. Healthy adults typically show the first REM sleep period about 90 minutes after sleep onset. There are usually three to five REM periods in a given night that progressively lengthen from a few minutes to over an hour in length. Short REM latency (65 minutes), increased REM time, and increased eye movement density, an index of phasic activation, have all been reported in MDD. In addition, decreased slow-wave sleep (stages 3 and 4 of NREM); increased awake time; early, middle, or late insomnia; and increase light stage 1 sleep have also been reported as characteristic of MDD (Reynolds and Kupfer 1987; Knowles and MacLean 1990; Berger and Riemann 1993; Armitage and Hoffmann 1997). Moreover, studies of the EEG frequencies underlying REM and NREM sleep stages, or so-called microarchitecture, have identified additional abnormalities in those with MDD. Increased fast-frequency beta activity and elevated alpha has been reported in patients compared with healthy adults (Borbély and others 1984; Armitage and others

1992, 1993, 1995; Armitage 1995; Armitage and Hoffmann 1997). By contrast, delta activity within NREM sleep, also known as slow-wave activity (SWA), is reduced in MDD (Borbély and others 1984; Kupfer and others 1984a, 1984b, 1986, 1989). Despite clear evidence that more than REM sleep is disturbed in MDD, the majority of studies (including animal work) have focused on REM.

McCarley (1982) postulated that sleep disturbances in MDD were largely due to increased cholinergic activation that resulted in the early onset of REM sleep. This model, based on animal studies (Hobson and others 1975; McCarley and Hobson 1975), assumes that because cholinergic neurons in the pontine reticular formation of the brain stem are activated during REM sleep whereas noradrenergic/serotonergic neurons in the locus coeruleus and dorsal raphe are deactivated, the neurotransmitter systems involved in REM sleep control are reciprocal and responsible, in part, for subsequent REM/NREM sleep cycle oscillations. He reasoned that an early onset of REM sleep in MDD (i.e., short REM latency) reflects an imbalance in normal cholinergic/aminergic neurotransmission that produces disinhibition of REM sleep (McCarley 1982; Massaquoi and McCarley 1992; McCarley and Massaquoi 1992). There has been fairly strong support that the administration of cholinergic agonists indeed triggers an earlier onset of REM in both animal and human studies (cf. Riemann and Berger 1992; Riemann and others 1992; Riemann, Hohagen, Krieger, and others 1994; Riemann, Hohagen, Bahro, and Berger 1994; Riemann, Hohagen, Bahro, Lis, and others 1994), although the response has not always been largest in those with MDD (Berger and others 1989; Gillin and others 1991). Nevertheless, most studies have shown a shorter mean REM latency or inter-REM-interval in response to cholinergic challenge in those with MDD, compared with healthy controls, including very recent work on orally administered aricept (Perlis and others 2002).

Antidepressant Effects on REM Sleep

Most antidepressants suppress REM sleep, either increasing the latency to the first REM sleep period or decreasing total REM sleep time (for a review, see Vogel, Buffenstein, and others 1990; Sharpley and Cowen 1995; Thase 1998; Armitage 2000). MAOIs are the most potent REM suppressors, even eliminating REM sleep in some patients, although this may not be the case with newer reversible MAOIs (Monti 1989; Minot and others 1993). With the exception of iprindole and trimipramine, TCAs are also potent REM suppressors, with the largest effects observed for clomipramine and desipramine (Dunleavy and others 1972; Kupfer and others 1989, 1991). Moreover, clinical response to some TCAs (clomipramine and amitriptyline) appears tied to the degree of REM sleep suppression (Kupfer and others 1976; Gillin and others 1978; Hochli and others 1986). These findings were also consistent with the clinical response obtained with behavioral REM sleep deprivation, achieved by awakening patients every time they showed electrophysiological characteristics of REM sleep (Vogel and others 1968). This, coupled with the view that REM sleep was increased in patients with depression, led Vogel and colleagues to postulate that the antidepressant response to pharmacological agents was due to the REM suppressing effects (Vogel, Buffenstein, and others 1990). However, more recent studies have demonstrated that improvement in depressive symptoms on SRIs is not correlated with the induced REM sleep changes (van Bemmel, Beersma, and others 1993; van Bemmel, Van den Hoofdakker, and others 1993; Staner and others 1995; Rush and others 1998). Moreover, there are a number of antidepressant agents that are clinically efficacious but do not suppress REM sleep, including nefazodone (Armitage and others 1997; Rush and others 1998), bupropion (Nofzinger and others 1995), and mianserin (Mendlewicz and others 1985). Nevertheless, the suggestion that REM sleep plays a unique role in depressive symptomatology and behavior has persisted and has strongly influenced animal models of MDD.

Animal Models of REM Sleep Abnormalities in MDD

REM Deprivation and Antidepressants in Neonatal Rats

In the early 1980s, Mirmiran, Corner, and their coworkers (Corner and others 1980; Mirmiran and others 1983; Mirmiran 1986) began testing the hypothesis, originally proposed by Roffwarg and others (1966), that the abundance of REM sleep observed in developing organisms serves an active and necessary function in the normal development of the CNS. Mirmiran and others (Corner and others 1980; Mirmiran and others 1981, 1983; Mirmiran 1986) adopted a lesion paradigm to test this hypothesis and eliminated REM sleep in neonatal rats by daily injections of an antidepressant drug, which suppresses REM sleep. Daily clomipramine (CMI) injections or saline injections were continued from 8 days to 21 days postnatal. As adults, the two treatment groups were tested on sexual response, aggression, open field behavior, and several measures of brain development as well as a number of standard sleep stage indices. Compared with controls, CMI-treated males exhibited maturational deficiencies on the behavioral measures, REM sleep alterations, and reduced sizes of specific anatomical brain measures. Mirmiran was equivocal with regard to attributing these deficiencies to increased 5-HT2 or reduced neural activation (Mirmiran 1986). Soon after, however, Vogel (Vogel and others 1980) observed that the behavioral abnormalities exhibited by Mirmiran and others's REM sleep-deprived rats closely paralleled certain features of behavior of some of his human MDD patients. He subsequently initiated studies assessing this model as a pharmacologically induced model of MDD (Vogel, Neill, Kors, and others 1990; Yavari and others 1993). The rats' open field and sexual

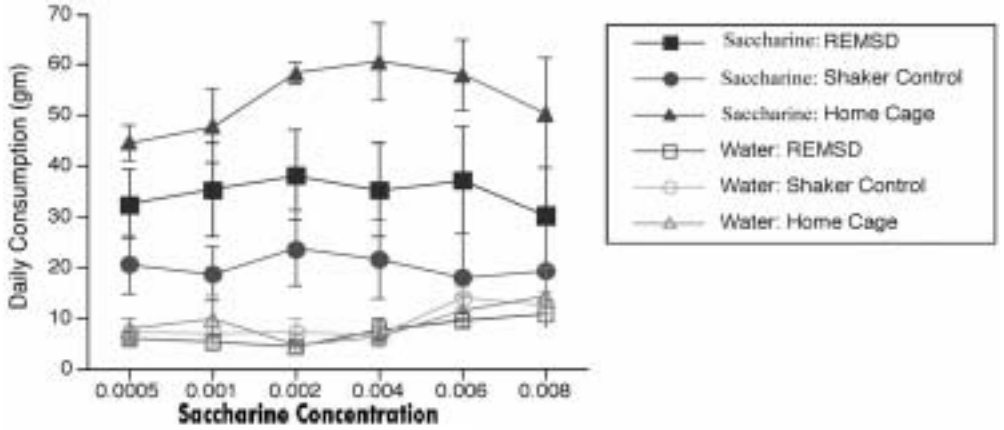

Fig. 3. Rats between the ages of P21 and P28 are REM sleep-deprived (REMSD) by a mechanism that shook their cages whenever the computer detected an entrance to the REM sleep state on the digitized electrophysiology. Littermate controls were stimulated on a regular "make-up" schedule that delivered the same number of shakes as its "yoked" REMSD rat had received in the preceding half hour. Thus, both groups received the same number of shakes, but the control rats received most of their shakes while awake only. After this phase and prior to the behavioral testing, which began at P90, REMS deprived and control animals are kept in standard multianimal housing and on standard lighting schedules (12L/12D). During the saccharine test, the rats are kept in standard housing but are deprived of fluids for 23 hours. At the end of each 23-hour period, animals are removed to individual cages that have two water bottles, which are randomized on a day-to-day basis for position. One bottle is tap water and the other is a variable concentration tap water and saccharine solution. Animals are given free access to choose between either tap water or a varying concentration saccharine solution for one hour daily. Tested as adults, REMSD rats consumed similar amounts of water to either the yoked shaker control animals or the controls reared in their home cage. The latter consumed more saccharine solution than either REMSD or shaker control animals. Although the REMSD animals consumed less saccharine solution than the home cage controls, it is of interest that the yoked shaker control animals showed a larger experimental effect on saccharine consumption. It is conceivable that the cage-shaking stimulation may be a stronger stressor to the shaker control group by virtue of its presentation in wakefulness compared with that used to eliminate REMS in the REMSD group.

behavior is "depressed" compared with normals. They show decreased sexual, aggressive, reduced reward-seeking in the form of intracranial self-stimulation activity, and hyperactivity in the outer areas of the open field tests (face validity). Even more convincing perhaps was Vogel's finding that CMI-treated rats have disordered REM sleep patterns as adults that resemble those found in some patients with MDD (Vogel, Neill, Kors, and others 1990), for example, increased REM sleep amounts, an increased number of sleep-onset REM periods, and decreased REM sleep latency. Furthermore, Vogel, Neill, Hagler, and others (1990) reported that some of the negative behavioral effects of early CMI treatment can be improved in these animals by administration of imipramine (predictive validity).

The interpretation of these observations, however, is less than straightforward. In particular, the construct validity of the use of systemic CMI injections remains uncertain. Neonatal treatment of rats with systemic injections of this powerful monoamine reuptake blocker, which is relatively selective for serotonin (5-HT), may have nonspecific effects in the developing CNS aside from those directly affecting the brain regions thought to mediate MDD. This would be particularly true for a compound like CMI, which so strongly affects the whole of the monoaminergic system that is diversely and widely represented in the brain and most active during waking. Accordingly, the systemic injections utilized in the Vogel/Mirmiran model may affect CNS development in ways that are unrelated to the effect on the role REM sleep plays in brain maturation, normal or otherwise. It is perhaps procedurally more defensible to specifically eliminate REM sleep during development by instrumentally removing REM sleep without drugs. By making more circumscribed "lesions" with such instrumental means to cause behavioral and REM-sleep alterations in adult rats, which accurately parallel the human condition, it is possible to produce a model of MDD with stronger construct validity.

REM Deprivation in Neonatal Rats Utilizing Instrumental Techniques

As mentioned above, consumption of saccharine solution has been utilized in rats as a test of hedonic tone (Willner 1997). Preliminary studies in rats that were REM deprived (or not) when young, utilizing instrumental methods (Hogan and others 2001), demonstrated differences in preference for saccharine water over tap water when the rats were adults > 60 days postnatal. The animals presented in Figure 3 were at least 60 days postnatal when tested and were REM deprived between days 21 and 28 postnatal.

The rats were REM-deprived by a mechanism that shook their cage whenever the computer detected an entrance to the REM sleep based on amplitude criteria applied to the digitized ECoG and EMG signals (Hogan and others 2001). Littermate controls were stimulated on a regular "make-up" schedule that delivered the same number of shakes as its "yoked" REM-deprived rat had received in the preceding half hour. Thus, both groups received the same number of shakes, but the control rats

received most of their shakes while awake only. After this phase and prior to the behavioral testing at > 60 days postnatal, REM-deprived and control animals were kept in standard multi-animal housing and on standard lighting schedules (12L/12D). Tested as adults, the REM-deprived rats consumed similar amounts of water to either the yoked control animals on the shakers or the home cage–reared controls. The latter consumed more saccharine solution than either REM-deprived or shaker control animals. Although the REM-deprived animals consumed less saccharine solution than the home cage controls, it is of interest that the yoked shaker control animals showed a larger effect of treatment on saccharine consumption. It is conceivable that the cage-shaking stimulation may be a stronger stressor for the control animals than that used for the REM-deprived experimental group, as the controls receive the stimulation in wakefulness rather than during REM sleep. It has been argued that all forms of sleep deprivation are stressful (Rampin and others 1991); however, the stimulation of the shaker control group, given the present results, suggests that this condition is similar to the Willner (1997) condition of chronic mild stress. Presentation of the stressor early in life during the neonatal plasticity period may allow for the effectiveness of the treatment over the relatively short period of these experiments.

These results have ramifications for the present consideration of animal models of MDD. It could be argued that both varieties of this REM deprivation model possess some face validity. Both reduce hedonic tone in adult animals after a stressful treatment during the neonatal plasticity phase. Likewise, both models have some construct validity, and though it remains to be confirmed for the instrumental REM deprivation version, if it too follows the Vogel data, both versions could also have predictive validity. The instrumental REM deprivation model might be particularly useful for comparisons with chronic mild stress models, given they are produced in the same species at different points in the animal's life: in early development with the former and in the adult with the latter.

The Flinders Sensitive Line of Rats

Depressive disorders in humans are well known to have a genetic component. However, only relatively recently have models been put forth that have a genetic basis. The Flinders Sensitive Line (FSL) of rats (so called because the line was first bred at the University of Flinders, Australia) is one of the earliest (Overstreet and Russell 1982; Russell and others 1982; Overstreet 1986) and best studied line of animals specifically bred as a genetic animal model of depression (for a review, see Overstreet 1993; Overstreet and others 1995; Yadid and others 2000). Based on the observation that human depressives are supersensitive to cholinergic agonists (Janowsky and others 1980), the original FSL rats were developed by selective breeding for high and low sensitivity (Flinders Resistive Line [FRL]) to the anticholinesterase, diisopropyl fluorophosphate. After determining that the differences between the FSL and FRL rats were not due to bred-in changes in acetylcholinesterase, the line was eventually standardized to the animal's hypothermic response to a specific dose of the muscarinic agonist, oxotremorine (Overstreet and Russell 1982; Russell and others 1982). In addition to the indicated construct validity, there are many behavioral similarities between the FSL rats and their depressed human counterparts (Overstreet 1993; Overstreet and others 1995; Yadid and others 2000). Besides being more sensitive to cholinergic agonists, the FSL rats have elevated REM sleep (Shiromani and others 1988), appetite and weight changes (Overstreet 1993), reduced activity (Overstreet and Russell 1982; Russell and others 1982), an increased anhedonia after exposure to CMS (Pucilowski and others 1993), and exaggerated immobility in the Porsolt forced swim test (Overstreet and others 1994; Overstreet 1986). Several physiological similarities between human depressives and FSL rats add to the face validity of the model. Patients with MDD have been shown to have HPA axis dysfunction, abnormalities in both slow-wave and REM sleep, and immune dysfunctions. All these are reflected in the physiology of their FSL counterpart (Overstreet 1993). In terms of REM sleep, FSL rats have a greater amount of REM and a shorter interval between REM sleep periods. FSL rats do not exhibit the large decreases in slow-wave sleep that have been reported in depressed humans, leading to the suggestion that sleep alterations are related to circadian rhythm abnormalities in FSL rats. This notion is not inconsistent with a phase advance of a circadian oscillator hypothesized as a characteristic of MDD (Czeisler and others 1987). To date, however, the evidence in those with MDD does not support an advance in circadian phase (Monk and others 1994). Although the FSL do not entirely mimic the HPA abnormalities seen in depressed humans, on many measures, the model does have high construct and face validity.

A large body of data addresses the predictive validity of the FSL based on the effects of a variety of antidepressant treatments. The predictive validity of the FSL model of depression has been most often demonstrated using the Porsolt (Porsolt and others 1978) forced swim test, utilizing the length of time spent floating immobile in a cylinder of water as the dependent measure. Typically applied in normal rats as a screen for antidepressant activity of candidate drugs, in this case the rat is subacutely administered the antidepressant between two sessions in the swim tank spaced 24 hours apart. Because FSL rats are more immobile than normals, the preliminary session in the swim tank was eliminated and the putative antidepressant was given chronically for 14 days prior to the test in the swim tank. Data indicate that the FSL rats exhibited positive, antidepressant-like responses in the swim test when treated chronically with classical tricyclics, imipramine and desipramine, or the newer generation antidepressants, SRIs, like sertraline and paroxetine (Overstreet 1993; Yadid and others 2000). Because chronic treatment with accepted antidepressants, but not with a variety of other agents, reduces

the immobility of FSL rats, the model has a high degree of predictive validity (Pucilowski and Overstreet 1993; Overstreet and others 1995; Yadid and others 2000). It has been proposed that the pattern of drug effects in this model indicates the possibility of serotonergic mechanisms controlling the exaggeration of the immobility of the FSL rats and argues against a direct role for cholinergic mechanisms in the exaggerated immobility (Overstreet and others 1995). Recent data have broadened the applicability of the FSL model from the traditional monoaminergic models to include neuromodulators, such as beta-endorphin (Yadid and others 2000) and other neurotransmitters/neuromodulators, for example, GABA, several neuropeptides, and growth factors that broaden the perspective well beyond REM sleep (Nestler 1998). From our viewpoint, NREM sleep abnormalities are of equivalent importance in understanding the neurobiology of MDD.

NREM Sleep in MDD

Rather than increased REM activation or REM sleep disinhibition, Borbély and colleagues suggested that NREM sleep regulation and homeostasis are impaired in those with MDD (Borbély and Wirz-Justice 1982). This hypothesis is based on a two-process model of sleep regulation (Borbély 1982a, 1982b), where the amount of SWA in NREM sleep is determined by the amount of prior wakefulness, the level of sleep propensity during the day, and depth of sleep at night (Process S). Process S accumulates during waking hours and slow-wave sleep propensity rises and dissipates over the night as the SWA declines. Measuring the temporal SWA evolution during NREM sleep is presumed to approximate Process S, and thus there is an exponential decline in SWA across successive NREM sleep periods. The second process (Process C) reflects the circadian control of sleep propensity that is highest at 3 to 5 a.m., when it is very difficult to overcome the need to sleep, and is lowest at 4 p.m., when sleep propensity is minimal. Process C is presumed to reflect internal clock control of circadian rhythms, the threshold for maintaining wakefulness and REM sleep control, and is unaffected by the amount of prior wakefulness. It is assumed that in a healthy brain, the propensity for REM sleep increases as SWA dissipates, thus explaining the short-duration first REM period when SWA pressure is high, and the increase in REM as SWA dissipates across the night (Borbély 1982a, 1982b). Thus, the *time course* of SWA approximates Process S, not the total amount of SWA.

With regard to MDD, Borbély and Wirz-Justice (1982) proposed that the reduction in slow-wave sleep reported in some patients with MDD resulted from an impairment in Process S, with diminished accumulation of sleep pressure during the daytime and reduced dissipation of SWA at night. Thus, both slow-wave sleep time and SWA are reduced in the initial NREM sleep period, allowing an earlier onset of the first REM period with a longer duration. In a later review article, Wirz-Justice (1995) further postulated that extending prior wakefulness or sleep deprivation would normalize SWA regulation and Process S in MDD. Note, however, that the only evidence cited in support of the proposed Process S deficiency in MDD were the antidepressant effects of sleep deprivation and relapse after recovery sleep and reduced slow-wave sleep time coupled with short REM (Borbély and Wirz-Justice 1982).

As mentioned above, reduced SWA has also been reported as a characteristic of MDD (Borbély and others 1984; Armitage and others 1992, 1993, 1995; Armitage 1995; Armitage and Hoffmann 1997). Moreover, Kupfer's group reported on the abnormal distribution of SWA in those with MDD (Kupfer and others 1990). Our own work has shown that the time course of SWA is abnormal in those with MDD (Armitage, Hoffmann, Fitch, and others 2000; Armitage, Hoffmann, Trivedi, and others 2000) but adds the caveat that it appears to be sex dependent. Men with MDD had a significantly slower rate of decay with lower initial accumulation of SWA than all other groups. These SWA abnormalities appear to be specific to MDD and were not evident in men with schizophrenia (Hoffmann and others 2000). It should be noted that a definitive study of homeostatic abnormalities in MDD requires a direct manipulation of SWA through sleep deprivation. Nevertheless, these data provide strong evidence of sex differences in sleep EEG in those with MDD. Moreover, women with MDD are more likely to show dysregulation and loss of synchronized ultradian sleep EEG rhythms (cf. Armitage and others 1999; Armitage and Hoffmann 2001). Although both men and women are vulnerable to the disease, it appears that females are inherently at greater risk for MDD. Sex steroids no doubt play a major role. Coupled with reports of sex differences in the symptoms of MDD (Shaw and others 1995) response to antidepressant treatment (Thase and others 2000) and lifetime risk for MDD (Kessler 2000), these findings suggest that the underlying pathophysiology of MDD is also gender dependent.

Gender, Sex Steroids, and MDD

Several lines of evidence suggest that the sex differences in prevalence and pathophysiology of MDD relate to sex steroids and hormonal regulation. First, women are at twice the lifetime risk for MDD during the reproductive years from puberty to menopause (Kessler 2000). Postpartum (Garvey and Tollefson 1984) and premenstrual periods (Rausch and Parry 1993) and the use of high-progesterone oral contraceptives (Cullberg 1972) all increase the risk of dysphoria and mood disturbance (Janowsky and others 1996; Parry 2000). As suggested by the animal studies reviewed above, serotonin, catecholamines, GABA, and acetylcholine all play a role in depressive behaviors. Serotonin is also implicated in the regulation of gonadotropin release, particularly in neurons in the dorsal raphe and neurons in the preoptic area that release luteinizing hormones (Tanaka and others 1993; Tillet and others 1993). Sensitivity to tryptophan and resultant behavior effects of depletion may also be sex dependent in rats and mice and in humans (Matsuda

and others 1991; Marsh and others 2002). Moreover, gonadectomy and chronic steroid exposure alter monoaminergic metabolism (Bitar and others 1991). Estrogen or estradiol also has direct effects on serotonin receptor availability, and tryptophan levels have been shown to be associated with postpartum depression (Rausch and Parry 1993). Ovarian steroids probably also influence the synthesis release and metabolism of catecholamines, as reviewed by Janowsky and others (1971). Estrogen also alters alpha 2 adrenergic binding in platelets, depending on the phase of the menstrual cycle in humans (Best and others 1992). Both $GABA_A$ and $GABA_B$ receptor complexes are directly influenced by sex steroids, although the effects are region specific and opposite for estrogen and progesterone (Schumacher and others 1989).

Perhaps most striking, the expression of the regulation of progesterone and estrogen is sex dependent. Thus, sex differences are even evident on the molecular levels (Pfaff and Severino 1996). There is overwhelming evidence of sexual dimorphism in brain structure and function, most notably cerebral-evoked potentials, cerebral glucose metabolism and blood flow, overall metabolic rates, and hypothalamic pituitary adrenal axis response to challenge (Gur and Gur 1990; Allen and others 1991; Gur and others 1995; Manber and Armitage 1999; Rhodes and Rubin 1999). This, coupled with the impact of ovarian steroids on brain regulation, is suggestive of greater adaptive response or neural plasticity in females. Indeed, there is evidence from sleep studies to support this view. Healthy young females appear to show a greater SWA response to sleep deprivation than healthy young males (Armitage and others 2001). Such findings not only indicate a greater response to challenge in general, but specifically to a homeostatic challenge and may well reflect greater neuronal plasticity.

We have argued that the sex differences in brain organization give rise to sex-specific vulnerabilities to brain dysregulation under conditions of extreme challenge. Thus, greater plasticity should produce hyperresponsivity, whereas more static brain organization would be more likely to move toward inertia.

Recent preliminary data have shown that women with MDD show an even greater SWA response to homeostatic challenge than healthy control women. By contrast, men with MDD show little SWA response to sleep deprivation. Thus, the women with MDD appear hyperresponsive, whereas the men with MDD are hyporesponsive (Fig. 4).

The view that homeostatic abnormalities contribute to MDD is also supported by the work of Duman and colleagues (Duman 1999). Their view is that receptor regulation and adaptation to changes in monoamine levels serves to maintain homeostasis. They also suggest that stress exposure results in neural atrophy or damage. The mechanisms generating SWA and sleep regulation may be of critical importance to understanding sex differences in MDD. Neurotrophic factors, atrophy, and cell damage could reduce SWA and impair homeostatic regulation. Neuronal damage could then lead to increased

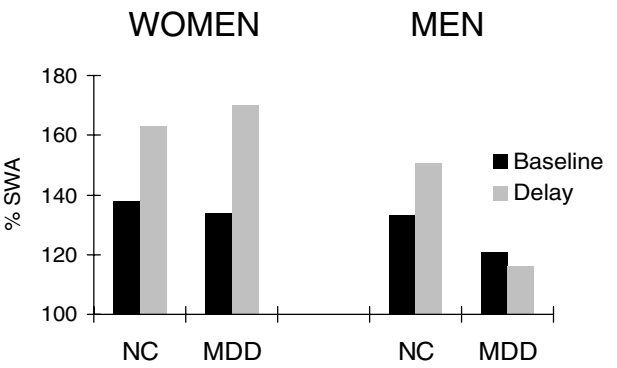

Fig. 4. The Effects of a 2-hour sleep delay on the accumulation of slow-wave activity (SWA) by group and sex: SWA is derived from power spectral analysis in the 0.5-4 Hz frequency band (left central electrode) in the first non-rapid eye movement (NREM) (stages 2, 3, and 4) period, expressed relative to average SWA in all NREM sleep time in major depressive disorder (MDD) women (MDDW) and MDD men (MDDM) compared with age-matched healthy normal control women (NCW) and men (NCM). SWA data are shown for baseline sleep and after a 2-hour delay of habitual bedtime. Prior wakefulness is held constant within and across groups. Note the lower accumulation of SWA in the depressed men, both at baseline and after the delay, evidence of homeostatic hyporesponse. All other groups showed higher percentage SWA in response to delay, with the largest response in MDD women, evidence of homeostatic hyperresponse. Also note that the magnitude of the sex difference is twice as large in the group with MDD as evidenced by a significant group-by-sex interaction ($P < 0.03$). Armitage and others (2002).

sensitivity to stress and impair HPA regulation and feedback to other brain areas (Duman 1999). Postmortem studies of suicide victims are consistent with this view (Mann and Arango 1999). The neurotrophic hypothesis of MDD is consistent with our data in men but requires some revision to account for the findings in women. This is also true for the animal studies reviewed.

Remarkably, sex differences in sleep homeostasis are even evident in *Drosophila* lacking the circadian cycle (cyc^{01}) gene. Shaw and colleagues (2002) reported a 3 times greater recovery from sleep deprivation in cyc^{01} females than males. These data provide strong support for sexual dimorphism in fundamental brain regulation and circadian rhythm homeostasis under high-stress conditions and lay credence to our suggestion that this sexual dimorphism contributes to genesis of depression.

The idea of greater neural plasticity in females has relevance well beyond depression. Studies of neural degeneration, Alzheimer's disease, recovery from stroke, and normal aging all indicate more plastic brain organization in females. Moreover, there are numerous instinctive behaviors necessary for survival that are sexually dimorphic, reproductive behavior in particular. We speculate that most if not all appetitive behaviors, sleep regulation included, are sexually dimorphic. We suggest that the genesis of MDD is related to homeostatic maladaptation that is sex specific.

If our speculations are correct, similar sex differences should also be evident in animal models of MDD. We

predict that maternal separation, sleep deprivation, and chronic stress should all produce larger effects in female animals. Alternatively, greater neural plasticity and adaptive response in females may result in a faster recovery or may depend on the timing of exposure. Establishing potential sex differences in critical periods of brain development and vulnerability to environmental stressors is essential to understanding the neurobiology of MDD and relative risk for this disease.

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