

Depression

Kerry J. Ressler, MD PhD and Charles B. Nemeroff, MD PhD

Department of Psychiatry and Behavioral Sciences

Suite 4000, 1639 Pierce Dr.

Emory University School of Medicine

Atlanta, GA 30322

For publication in:

The Molecular and Genetic Basis of Neurologic and Psychiatric Disease,

3rd edition

Edited by: RN Rosenberg MD, SB Prusiner MD, S DiMauro MD,

RL Barchi MD, PhD, and EJ Nestler MD, PhD

Butterworth / Heinemann

Woburn, MA

Introduction

Unipolar Major Depression is a very common syndromal disorder that carries with it extreme morbidity and mortality. Epidemiological and family studies consistently place the lifetime prevalence of the disorder at 5-12% in men and 10-22% in women¹. It is a disorder with considerable morbidity and current estimates suggest that it will soon rank second only to ischemic heart disease as a source of disability worldwide². It is a source of significant mortality, with suicide occurring in 8-15% of patients who had previously been hospitalized for depression. Furthermore, depression is an independent risk factor for the development of coronary artery disease and stroke, and patients with comorbid depression have worse outcomes post-myocardial infarction. In general, medically ill patients with depression suffer significantly more morbidity and mortality than do those without depression.

Clinical Features

Diagnosis of Depressive Disorders

Because psychiatric disorders do not yet have biochemical or genetic markers of high specificity and sensitivity, psychiatric diagnosis in practice remains a purely clinical endeavor based on observation, interview, history, and collateral information. The Diagnostic and Statistical Manual of Mental Disorders, fourth edition (DSM-IV) provides for a more precise and consistent diagnostic framework for psychiatric disorders including information on prevalence, identification of risk factors, determination of optimal treatment modalities, and creation of preventative measures. The DSM-IV Mood Disorders section is composed of three major parts. The first describes the symptom clusters of mood episodes, including major depressive, manic, hypomanic, and mixed episodes. The second part describes the criteria for the syndromes that are defined as Mood Disorders, including Major Depression and Bipolar Disorder, Mood Disorder due to a general medical condition, and Substance-Induced Mood Disorder. The third part includes the specifiers that describe either the most recent mood episode or the course of recurrent episodes.

This chapter focuses on the neurobiology and genetics of the syndrome of Unipolar Depression, also called Major Depression, as contrasted with Bipolar Depression, the depressive phase of manic-depressive bipolar disorder. Major Depressive Disorder is defined by at least one Major Depressive Episode, which is a two week period of decreased functioning in which the patient has either depressed mood and / or anhedonia, in addition to at least four of the following symptoms: i) significant weight change (loss or gain of 5% body weight), ii) insomnia or hypersomnia, iii) psychomotor agitation or retardation, iv) fatigue, v) feelings of worthlessness or guilt, vi) decreased concentration / attention, vii) recurrent thoughts of death or suicidality.

Major Depressive Disorder is classified according to severity, presence of psychosis, and level of remission. Subtypes of major depression, based on symptom clustering or course, include catatonic, psychotic, melancholic, atypical, seasonal pattern, postpartum onset, chronic without remission, and early onset, though the latter is not yet recognized as a separate subtype by DSM. The subtypes that appear to have the most genetic or heritable validity as distinctly separate disorders appear to be i) early onset, ii) melancholic, iii) atypical, iv) seasonal, and v) psychotic. Early onset is typically defined as having the first episode before 25 years of age. Melancholic type indicates a symptom cluster of extreme anhedonia, lack of reactivity to any pleasurable stimuli, worsening morning symptoms, early morning awakening, marked psychomotor agitation or retardation, and significant anorexia or weight loss. Atypical depression refers to a subtype that is almost opposite of melancholic, with significant mood reactivity, appetite increase and weight gain, hypersomnia, leaden paralysis, and significant interpersonal rejection sensitivity. Major Depression with seasonal onset, also known as seasonal affective disorder, describes depression with onset generally in the winter months (during decreased light exposure) that tends to naturally remit during the summer months. Its prevalence is increased in northern climates and there is some evidence that it is responsive to artificial light therapy. Psychotic depression is characterized by the presence of psychosis, usually delusions.

Course

The course of major depression is variable. Symptoms generally develop over a period of days to weeks. A prodromal period including anxiety and mild depressive symptoms may predate the full episode by weeks to months. An untreated episode can last for 6 months or longer, regardless of age of onset. There is generally a complete remission of symptoms over time, but 20-30% of patients do not recover completely for months to years. The majority of patients who experience one Major Depressive Episode, despite attaining a complete remission, will experience subsequent recurrences. The recurrence rate among individuals who have had three or more episodes of major depression is greater than 90%. There is also evidence that two factors, i) increased length of time prior to treatment and ii) increased number of previous episodes, place the patient at risk for more severe and refractory episodes in the future, with less likelihood of achieving complete remission. The chronic subtype of Major Depression occurs in 5-10% of cases and is defined as continuously meeting criteria for Major Depressive Episode for ≥ 2 years without remission.

Depression Syndromes Secondary to Medical and Neurologic Disease

It is important that the clinician be aware that depressive symptoms from moderate to severe can occur in conjunction with numerous systemic medical illnesses (diagnosed as “Mood Disorder with Depressive Features due to a general medical condition”)³. For example, patients with Cushing's disease have up to a 67% lifetime prevalence of depression and high rates of anxiety disorders as well. Furthermore, these symptoms often precede hirsutism, stria, and other physical signs of the disease. Diabetes, both types I and II, are associated with up to a 33% lifetime prevalence. Coronary artery disease (CAD) and congestive heart failure patients have up to a 26% lifetime risk of depression, and there is a marked increase in cardiac morbidity and mortality in patients who have depression compared to matched cardiac patients without depression. Multiple cancers, most notably pancreatic carcinoma, are associated with depression, often preceding the diagnosis of the cancer.

Many neurologic diseases are especially prone to creating secondary Depressive Disorders. Patients with Parkinson's Disease have been found to have a 40-50% lifetime prevalence of depression, with a significant portion having diminished serotonin metabolites in their CSF, and Major Depressive Episode often predates the neurologic symptoms. Huntington's Disease patients exhibit a lifetime prevalence of depression of ~40% and may show depressive symptoms prior to neurologic symptoms. Cerebrovascular disease is a very common cause of late-life depression, with a 30-50% lifetime prevalence of depression. Patients with multiple sclerosis frequently exhibit depression, with the prevalence rates as high as 50%, but they may also experience manic or hypomanic symptoms. Patients with Alzheimer's Disease also have unusually high rates of depression.

Although it is common for clinicians to believe that depression is simply a sequelae of the inability to cope with a debilitating disease in these patients, both biological data and epidemiological data suggest that this is not the primary factor. Instead, it appears that many of the biological mechanisms leading to these systemic and neurologic diseases are also antecedents to the neurobiologic mechanisms of depression (e.g. loss of monoamine neurons in degenerative disorders; impairment to limbic regions of the brain secondary to cerebrovascular accidents; paraneoplastic syndromes; and at times iatrogenic causes -- e.g. glucocorticoid therapy for rheumatoid arthritis or multiple sclerosis).

It is important for the clinician to look for and recognize depression in the medically ill patient, as well as to treat it aggressively. It has been shown repeatedly that depression in the neurologic or medically ill patient is quite responsive to antidepressant medication, and there is increasing evidence that morbidity and mortality are significantly reduced when depression is adequately treated in these patients.

Pathology – Biochemical Alterations in Depression

Neurotransmitter Abnormalities in Depression

There are multiple lines of evidence that the brainstem monoamine systems are dysregulated in depression and anxiety disorders³⁻⁵. A vast literature has documented abnormalities in the norepinephrine (NE) and serotonin (5HT) systems, though there is also burgeoning evidence that dopamine (DA) may have a role in the disorder. The preponderance of evidence suggests that increased NE transmission or receptor supersensitivity occurs in combination with decreased 5HT transmission or receptor hyposensitivity.

It is unlikely, however, that the primary biological “lesion” occurs directly within the NE and 5HT systems. Rather, these neurotransmitters have a role in the modulation of multiple neural systems including those mediating cognition, attention, affect regulation, memory, stress response, endocrine function, and sleep regulation. There is normally precise control of activity within the brainstem nuclei: the locus coeruleus (NE), raphe nucleus (5HT), and ventral tegmental area (DA). Depression appears to be a state in which these systems are dysregulated, resulting in abnormal modulation of the neural circuits that mediate many of the functions outlined above. This dysregulation likely occurs as a common end state of multiple different factors thus creating the heterogeneous syndrome of Major Depression. Antidepressant treatment appears to bring these modulatory systems back to a state of homeostasis, allowing for a return to normal neurotransmitter regulation.

Norepinephrine Alterations in Depression

The initial catecholamine hypothesis by Schildkraut in 1965 proposed that abnormally low states of NE lead to depressive symptoms, whereas elevated NE states lead to euphoric or manic symptoms. Years of research to further explore these relationships have refuted this simple dichotomy (reviewed in³⁻⁵). Rather there appears to be a complex dysregulation of NE levels and locus coeruleus (LC) firing in states of depression and anxiety, which may lead to increases or decreases in NE release coupled with altered sensitivities of the pre- and post- synaptic receptors.

The principle findings that implicate dysregulation of the noradrenergic system have been comprehensively reviewed⁴⁻⁷. The most consistent data is as follows: i) Increased concentrations of plasma and CSF NE metabolites in patients with major depression or anxiety; ii) Greater variability in the concentration of NE and NE metabolites in patients with depression compared to controls; iii) Altered α_2 receptor binding in depression in postmortem brains; iv) Increased β -adrenergic Receptors in post-mortem tissue; v) Blunted growth hormone (GH) response to clonidine (an α_2 receptor agonist) in depressed patients, especially those who are suicidal; vi) Tyrosine hydroxylase activity (the rate-

limiting enzyme in NE production) is consistently increased in the locus coeruleus of depressed patients studied post-mortem.

In summary, although there is a range of variability regarding findings of NE and its metabolites and pre- and postsynaptic receptor dynamics, the findings consistently show abnormal NE turnover coupled with increased receptor sensitivity. This data suggest that at basal firing conditions, NE levels may indeed be lower than normal, but that more rapid LC firing in response to stress may lead to greater than normal NE transmission in conjunction with supersensitive post-synaptic receptors.

Serotonin Alterations in Depression

The serotonin hypothesis of depression posits a relative deficiency of brain serotonergic activity in depression. As with NE, indirect measures of precursor (tryptophan) availability and metabolite concentrations provided initial evidence for abnormalities in the system. As with the NE system in depression and anxiety, there are also alterations in 5HT receptor populations. Though there has been some variability in this data, overall it has provided a consistent picture of a decrease in serotonergic neural activity during depression.

This data has been reviewed in detail ^{4,5}. In summary the principle consistent findings are i) Increased 5HT₂ and decreased 5HT_{1a} receptor binding in post-mortem brain tissue; ii) Reduced serotonin transporter (SERT) binding in postmortem cerebral cortex and hippocampus; iii) Reduced SERT binding in platelets and in the raphe nucleus of depressed patients, as assessed with functional brain imaging; iv) Diminished prolactin release after fenfluramine and other 5HT secretagogues, suggesting a decreased serotonergic responsiveness; and, v) Decreased serotonin metabolites (5HIAA) in cerebrospinal fluid (CSF), especially in suicidal patients. Finally, selective serotonin reuptake inhibitors (SSRIs) that increase the extracellular fluid concentration of 5HT are effective antidepressants. Overall, this data suggest that impaired serotonergic function is a biochemical trait that underlies the vulnerability for recurrent episodes of depression.

Dopamine Alterations in Depression

An increasingly impressive body of evidence supports a role for a relative DA neuronal deficiency in depression. These findings include i) Reduced concentrations of DOPAC, a major DA metabolite, in postmortem tissue of depressed suicide victims; ii) Evidence from functional brain imaging studies using single proton emission tomography (SPECT) and positron emission tomography (PET) which have measure DA neuronal activity; iii) A markedly blunted GH response to apomorphine, a DA receptor agonist, in depressed patients with a history of suicide attempts; iv) The unusually high

rates of depression in patients with Parkinson's Disease, a disorder associated with DA neuronal cell death; v) The overwhelming evidence for a critical role for DA in mediating reward and pleasure, the absence of which is generally acknowledged as the cardinal symptom of depression, and vi) The efficacy of DA reuptake blockers and DA agonists in the treatment of depression.

Corticotropin Releasing Factor and HPA Axis Alterations in Depression

Hyperactivity of the hypothalamic-pituitary-adrenal (HPA) axis in depressed patients is one of the most consistent findings in the literature on mood disorders (recently reviewed^{4, 8-10}). These data support a preeminent role of hyperactivity of the corticotropin releasing factor (CRF) neural circuits in depression. The most consistent findings are: i) Elevated CSF CRF concentrations in depressed patients; ii) Increased hypothalamic CRF immunoreactivity and CRF mRNA expression and decreased CRF receptor binding in postmortem frontal cortex of suicide victims; iii) Increased adrenocorticotrophic hormone (ACTH) and cortisol during depression; iv) A blunted ACTH (and β -endorphin) response to intravenously administered CRF; v) Glucocorticoid and ACTH non-suppression after dexamethasone administration or the combined dexamethasone/CRF test; and vi) The administration of CRF directly into the CNS of laboratory animals mimics many of the cardinal features of depression, including decreased appetite, disrupted sleep, decreased libido and anhedonia.

The CRF hypersecretion is thought to occur in conjunction with monoamine abnormalities and limbic dysregulation. Activation of the fear-stress response circuitry leads to activation of the central nucleus of the amygdala or the bed nucleus of the stria terminalis (BNST - a similar region of the 'extended amygdala' involved in anxiety). Neurons from these regions release CRF in numerous brain areas in response to stress¹¹. In addition, direct activation of the paraventricular nucleus (PVN) of the hypothalamus leads to CRF release that stimulates the secretion of ACTH from the anterior pituitary gland. In several studies, CRF has been shown to be elevated in CSF of patients with depression and in patients with neurological disorders and comorbid depression. As many as 75% of patients with major depression have overactivity of the HPA axis as characterized by hypercortisolemia. Evidence of significant alterations in CRF neuronal density and increased production suggest that depression involves a state of significantly altered neural circuitry mediating the stress response pathways. Consistent with data discussed below, neuroimaging studies have revealed a correlation between increased amygdala activation and plasma cortisol levels in depression¹². Furthermore, dysregulation of NE and CRF systems occurring in conjunction with stress early in life may contribute to depression and anxiety symptoms in adulthood¹⁰.

Thyrotropin-Releasing Hormone and HPT Axis Alterations in Depression

There have also been consistent findings of abnormalities within the Hypothalamic-Pituitary-Thyroid (HPT) axis in depression⁴: i) Increased CSF thyrotropin-releasing hormone (TRH) concentrations in depressed patients; ii) Decreased nocturnal thyroid-stimulating hormone (TSH) concentrations; iii) A blunted TSH response to intravenously administered TRH administration; and iv) An unusually high rate of autoimmune thyroiditis in depressed patients. Clinically it is recognized that augmentation of antidepressants with one of the thyroid hormones, T₃, is an effective means of converting antidepressant non-responders to responders. Recently a new TRH receptor, TRH-R2, has been discovered that is distributed in thalamic, limbic, and cortical brain regions which is in marked contrast to the TRH-R1 that is limited in distribution to the hypothalamus and anterior pituitary. Additionally, little notice has been paid to the fact that the reticular nucleus of the thalamus expresses as much TRH peptide as the hypothalamus. Growing evidence suggests that this system may well play a significant role in the sleep and attentional abnormalities found in depression. Indeed two-thirds of TRH in the central nervous system is extrahypothalamic. Further understanding of this system will surely prove fascinating, as it may be possible to incorporate the role of this neuropeptide regulatory system with the neurocircuitry information described above.

Pathology – Functional Neurobiology of Depression

Brain Regions Involved in Depression:

Functional imaging experiments with positron emission tomography (PET) and functional magnetic resonance imaging (fMRI) have provided new insights into the brain regions and circuits involved in depression. Numerous studies have found changes in frontal cortical activity in depressed states^{12, 13}. In these studies, there appear to be differential activations of cortex. Dorsal prefrontal cortex (PFC) is generally suppressed in contrast to ventral PFC and orbital cortex which have been found to be more activated in depressed patients compared with controls¹². Antidepressant treatment normalizes these alterations, increasing dorsal PFC activity and decreasing ventral and orbital PFC activity. The amygdala has been found to be consistently activated in depressed patients more than in non-depressed controls, with its imaged neural activity correlated with depression severity¹². As with cortical abnormalities, the altered amygdala activity normalizes with antidepressant response and remission.

Some groups have examined the relationship of normal sadness to depression using emotion provocation paradigms¹³. The dorsal prefrontal areas (Brodmann area 9) are temporarily decreased in activity with transient sadness in healthy controls but remain decreased in activity in depressed patients. Furthermore, they found that ventral prefrontal areas similar to those discussed above (subgenual cingulate, Brodmann area 25) are temporarily increased in normal sadness in healthy volunteers but remain increased in depressed patients. Although other cortical areas have also been found to be altered in depression and sadness, these two regions (dorsal and ventral prefrontal cortex) show the most consistent results. These data suggest that a limbic circuit involving *activation* of ventral prefrontal areas and amygdala in combination with *inhibition* of dorsal prefrontal areas may mediate normal sadness as well as the abnormal mood states of depression. It appears that in major depression, the neural circuits that normally mediate the transient emotions of sadness, dysphoria, and anxiety are unable to return to baseline.

Neural Circuits Mediating Stress & Fear are involved in Depression

The limbic circuitry mediating stress, fear, anger, and other emotions is thought to be critically involved in both depression and anxiety disorders (Figure 1). In normal functioning, the amygdala serves to continuously compare sensory stimuli to previously learned aversive (fear/stress/pain mediating) or appetitive (approach/ motivational/ hedonic mediating) stimuli¹⁴. Recognition of previously associated stimuli activates the appropriate conditioned response pathway. The neural circuits mediating some of the amygdala-dependent behaviors have been clearly demonstrated. For example, the central nucleus of the amygdala (CeA) as well as the bed nucleus of the stria terminalis (BNST) project extensively to the hypothalamic and brainstem circuitry that mediate the stress and fear response (e.g. hypothalamic paraventricular nucleus → HPA axis activation, central gray → freezing behavior, parabrachial nucleus → respiratory distress)¹¹. When the amygdala registers a comparison between current incoming stimuli that have previously been associated with fear or stress, the CeA and BNST are able to rapidly activate a distributed neural system engaging the fight / flight response¹⁵. Prefrontal cortex, with its highly refined information has significant interconnectivity with the amygdala, and it may be required for extinction of aversive memories. This is consistent with the idea that cortical representations are able to modulate limbic associations -- that rational thought should prevail over irrational fear or worry. It has been proposed that the dorsal prefrontal cortex is involved via these connections in regulating affect, providing cognitive control over emotions such as stress, fear,

anger, anxiety, and frustration^{14, 15}. Ventral prefrontal cortex, however, appears to subserve emotional functions itself and its interconnections with the amygdala may be mutually excitatory.

The physiology of the locus coeruleus (LC) is consistent with a nucleus critically involved in attention, vigilance, and orientation^{5, 10, 16}. In awake behaving animals, the LC is most active when orienting to a novel, aversive, or stressful stimulus. NE stimulates potentially stressful memories and fear/stress responses in the amygdala. NE also increases long-term potentiation & contextual conditioning to aversive stimuli in hippocampus. This is consistent with the role of the LC-NE system in vigilance via activation of the fight-flight response. The amygdala and BNST pathways release CRF onto the LC, which activates LC firing and NE release.

NE activation of cortex is complex, with decreased activation at too low or too high levels of release and optimal activation with midrange firing. Thus at high rates of activity, NE may lead to an overactivation of limbic pathways over cortical pathways, as presumably would promote survival if a rapid fight-flight response is needed. Finally, NE activation appears to have an inhibitory role on raphe firing.

In contrast to the LC, the raphe nuclei (RN) show highest firing during internally directed rhythmic movements and behaviors, with diminished firing when orienting to external stimuli¹⁷. 5HT from the RN mediates tolerance to aversive experience in the amygdala, potentially decreasing likelihood of a fight-flight response. 5HT appears to decrease context conditioning in hippocampus with aversive stimuli. These data are consistent with a role of the raphe-5HT system in homeostasis, decreased aggression, and tolerance to aversion. Raphe firing is inhibited both by NE from the LC and by orbital cortex activation. These regions of cortex are activated in correlation with sad or anxious emotion, and are thought to be important in control over amygdala activation¹².

Normal response to stress:

A working model for the role of this neural circuit in normal and pathological responses to stress is as follows⁵: The brainstem monoamine circuits are modulatory systems that exhibit baseline levels of tonic firing and are exquisitely controlled by other neural pathways and complex regulatory loops. During normal functioning, in the presence of a safe environment with internally directed behaviors such as feeding or grooming, the RN are relatively active. Released 5HT acts to inhibit the LC and limbic pathways leading to decreased sensitivity to arousal or stressful/aversive stimuli. During such states, executive cortical areas (dorsal PFC) prevail over limbic control of affect.

When the animal is exposed to stress however, the balance shifts. The recognition of potentially stressful/aversive stimuli by amygdala pathways activates LC firing and the RN is inhibited. LC

activation of amygdala-hippocampal pathways increases the sensitivity to aversive/stressful stimuli further increasing hypothalamic CRF release and subsequently plasma cortisol levels. These combined shifts lead limbic pathways to prevail over prefrontal cortical pathways in the control of affect. The organism is primed in a state of arousal and prepared for initiation of the fight/flight stress response. In the healthy or euthymic condition, the individual returns to a baseline affective state when the stressful/aversive stimulus is gone.

Abnormal regulation during depressed and anxiety states:

In depressed states and in some anxiety states, the aforementioned neural systems are dysregulated. NE transmission is overactive via LC firing, receptor sensitivity, or both. In contrast, 5HT transmission is underactive via inhibited RN firing, decreased receptor sensitivity or both. These neurotransmitter alterations contribute to overactivation of amygdala, BNST, and hippocampal areas activating the stress/fear response. Ventral cortical areas primarily associated with affect and strongly interconnected with the amygdala are also overactivated and may contribute to inhibition of RN firing. Resultant increases in CRF will further activate the LC-NE system promoting vigilance and stress/fear responsiveness, while increases in adrenal glucocorticoids and increased activity of autonomic, visceral, and neural pathways also occur. In this depressed or anxious state the stimulus-response is shifted. A stimulus that might only lead to minimal arousal in the healthy “euthymic” state may now activate significant arousal and continual activation of the fight/flight pathways.

Depression as a Disorder of Decreased Neural Plasticity:

There is considerable data which supports the hypothesis that stress, depression, and anxiety disorders induce degeneration of target neurons, perhaps mediated by cortisol^{18,19}. Hippocampal atrophy has been reported in several studies of depression²⁰, although discordant results have also appeared²¹. Glial cell loss and neuronal abnormalities have been observed in the prefrontal cortex in major depression. Noradrenergic axons have been found with decreased axonal arborization and density in stress models. Serotonergic axon sprouting appears to be dependent on BDNF, which appears to be decreased after stress exposure. Thus it appears that stress and disorders associated with chronic stress may increase neuronal atrophy and perhaps frank neuronal degeneration. Furthermore, hippocampal neurons undergo continuous proliferation well into adulthood. This continued neurogenesis is dependent on the presence of serotonin and inhibited by adrenal steroids¹⁹, both of which are altered in depression. Accumulating evidence shows that antidepressant treatment may reverse the atrophy of

hippocampal neurons, increase cell survival, and increase monoamine axonal sprouting in both rodents and humans¹⁸.

These changes in neuronal populations in the depressed state likely contribute to the dysregulated affective neural circuitry, and may lead to worsening symptoms and resistance to treatment. Decreased neuronal density and atrophy in the hippocampus and prefrontal cortex presumably contribute to decreased activity and responsiveness. Together, these processes likely serve to maintain a state of imbalance in depression by decreasing the ability of cortical and hippocampal areas to inhibit or modulate the stress/fear pathways of the amygdala and interconnected circuitry. The depressed or anxious state is one in which these stress/fear pathways cannot be easily ‘shut off’ or returned to normal, and the individual is left in a chronic state of abnormal affective responsiveness.

Interaction between neurobiology and genetics

Current working models of depression at a neurobiologic level are heavily dependent on the concept of stress as a causal mediator of the depressed state. In fact, the data is most consistent with the hypothesis that depression is a quintessential disorder of gene-environment interaction. As outlined below, numerous family, adoption, and twin studies place the genetic loading at approximately 35-50% for the likelihood of developing depression with an environmental loading of 50-65%. Figure 2 outlines the interacting roles of genes and environment acting through development to influence the phenotype of trait vulnerability, which in combination with ongoing environmental stress may result in depression.

It is increasingly evident that the brain exhibits neural plasticity even into adulthood, and gene products act on neuronal processes to influence initial development as well as ongoing learning and homeostatic responsiveness in adulthood. However, the brain evolved to integrate environmental information and it is biochemically and physically shaped by environment continuously. Therefore, the fact that depression at least is partially environmentally determined should really be no more self-evident or surprising than the findings that congestive heart failure, lung cancer, or type II diabetes are complex genetic disorders that are also partially environmentally determined.

Genetics -- Unipolar depression is a heritable disease

Family association studies

Numerous studies have been performed addressing the question, “Are family members of depressed patients more likely to be depressed than family members of non-depressed patients?” Familial aggregation studies take as the independent variables subjects with major depression and case

controls without depression (controlling for relatively simple variables such as age, sex, and medical history). The dependent variables are the presence of depressive symptomatology in biological relatives (usually first-degree). A recent meta-analysis²² analyzed the extant literature on genetic epidemiological studies of depression and found only five familial association studies that were well designed by the criteria of appropriate controls, diagnostic criteria, systematic recruitment, and direct determination of a diagnosis of major depression vs a bipolar diagnosis.

The studies from this meta-analysis are presented in Table 1. When all studies are analyzed together, there was a very strong association between major depression in the identified patient and first-degree relatives ($p < .00005$). Taken together, these studies indicate that major depression is familial. However, these studies are unable to differentiate genetic influences from familial environmental influences. As discussed above, considerable evidence suggests that the syndrome of depression results from a gene – environment interaction.

Study	Risk - Subject's Relatives	Risk - Control's Relatives	Odds Ratio
Tsuang et al., Br J Psych 1980; 137:497	15.2	7.5	2.2
Gershon et al., Arch Gen Psych 1982; 39:1157	16.6	5.8	3.2
Weissman et al., Arch Gen Psych 1984; 41:13	17.6	5.9	3.4
Maier et al., Arch Gen Psych 1993; 50:871	21.6	10.6	2.3
Weissman et al., Arch Gen Psych 1993; 50:767	21.0	5.5	4.6

Table 1 Risk of Major Depression in First Degree Relatives from Family Association Studies (Data compiled from Sullivan et al., 2000²²)

Adoption studies

When compared with other psychiatric disorders, there are far fewer studies of adoption involving probands with unipolar depression compared to bipolar disorder or schizophrenia. Table 2 lists the three studies that are considered the most well controlled. They clearly have their pitfalls -- primarily in that the ability to gain diagnostic data on the biological parent is very limited. Nonetheless, 2 of the 3 studies provide suggestive evidence that the risk of developing major depression is significantly higher if the biological parent suffered depression, regardless of the adoptive environment. This strongly suggests that a significant component of the relative risk for depression must be genetic. Nonetheless, these studies have limited statistical power and remain of relatively limited utility for determining heritable risk.

Study	Population	Relative risk if Biological Parents had Depression
Von Knorring et al., Arch Gen Psych 1983; 40: 943	56 adoptees, 115 controls	0.71 NS
Cadore et al., J Affective Disord 1985; 9: 155	48 depressed, 395 non-depressed	2.54 $p = .05$ *
Wender et al., Arch Gen Psych 1986; 43: 923	71 adoptees, 75 controls	7.24 $p = .03$

Table 2 Relative Risk of Major Depression in Adopted Offspring

* = study initially did not meet $p=.05$ level when gender separately examined, when Sullivan et al, 2000 reanalyzed data combining gender, significance was found²².

Twin Studies

As with other disorders, twin studies have proved to be the most powerful tool to determine the relative contribution of heritability. Furthermore the comparison of monozygotic twins to dizygotic twins allows for the critical variables of genes vs. environment to be finely separated. This analysis and interpretation is based on the assumption that monozygotic and dizygotic twins receive similar environmental inputs. There is evidence that monozygotic twins are treated much more similarly than are dizygotic twins by their family members -- especially early in development -- therefore some of the differences between these two groups that were assumed to be genetic might in fact be due to environmental factors. This argument and the data supporting this assumption are discussed in detail in Kendler (1993)²³. This same group performed a meta-analysis of the extant twin studies (Table 3) and determined that the best model to fit the entirety of the data was one in which genetic liability accounted for 37% of the risk of major depression.

This concatenation of data suggests that unipolar or major depression is clearly genetically heritable. These studies likely underestimate the genetic liability, because measurement error, in terms of under- or mis-diagnosis lead to higher specific environment predictions and lower the genetic variance prediction. Another recent study by Kendler and colleagues examined a longitudinal sample of twins in which repeated clinical assessments decreased measurement error. Indeed, this longitudinal study found genetic liability of major depression to be 66%. This level approaches the heritability estimates found in bipolar disorder and schizophrenia.

Study (Patient Pop.)	Patient Population	Country	Sex	Concord.		Genetic Liability	Shared Env. Liability	Specific Env. Liability
				MZ	DZ			
Kendler et al., Behav Genet 1995; 25: 217	Clinical	Sweden	M	.50	.33	49%	21%	30%
			F	.32	.20	17%	0%	83%
McGuffin et al., Arch Gen Psych 1996; 53:129	Clinical	UK	M	.46	.15	58%	0%	42%
			F	.46	.22	38%	0%	62%
Lyons et al., Arch Gen Psych 1998; 55:468	Community	US	M	.23	.14	36%	0%	64%
Bierut et al., Arch Gen Psych 1999; 56:557	Community	Australia	M	.34	.30	24%	0%	76%
			F	.50	.37	44%	0%	56%
Kendler and Prescott Arch Gen Psych 1999; 56:39	Community	US	M	.41	.34	31%	0%	69%
			F	.47	.43	38%	0%	62%

Table 3 Summary of Twin Studies and Hereditary Liability Estimates
(Data compiled from Sullivan et al., 2000²²)

Genetic Studies – The Search for Quantitative Traits

Although the available data are incontrovertible concerning a genetic contribution to major depression, it appears likely that this syndrome arises from numerous genetic and environmental insults

and may comprise a heterogeneous set of diseases. Given this heterogeneity, how can the susceptibility genes for depression be identified? An increasingly important approach to this problem is the search for quantitative traits that may underlie depression (reviewed elsewhere²⁴). This approach is derived from an increasing recognition that the heritable component of depression do not arise from single genes that are necessary and sufficient to cause a disorder. Rather, such quantitatively inheritable traits likely arise from the interactions of multiple genes with the environment. A number of studies have now approached the problem of identifying the quantitative traits that underlie the heritable component of depression.

Kendler and colleagues examined the clinical characteristics of major depression as predictive variables of risk of depression in relatives²⁵. Using the Virginia Twin Registry, they examined 3786 twin pairs, 1765 of whom had a lifetime history of the disorder, of whom 639 (36.2%) had affected co-twins. Their best-fit model suggested that number of episodes, duration of longest episode, and recurrent suicidal thoughts were the clinical features most predictive of risk for major depression in the co-twin. Surprisingly, age of onset and number of depressive symptoms did not predict twin relative risk. In fact, the only two symptoms of the 14 symptom criteria from DSM-IV for major depression significantly correlated with increased co-twin risk, i.e. 1) suicidal thoughts (risk 1.4, $p < .001$) providing additional evidence for the genetic contribution to suicidality, and 2) feelings of guilt had some predictive validity (risk 1.21, $p = .03$). These findings are consistent with the view that depression a syndromal definition, and cannot be broken down into symptoms as quantitative markers for determining genetic causality. Nevertheless, it is quite likely that subtypes of depression characterized by greater severity, e.g. psychotic depression, may be more heritable.

In fact, an attempt to focus on defining subtypes of major depression that may be more heritable for association or linkage studies has been undertaken. A recent study examined a subtype of depression based on age of onset, early-onset recurrent major depressive disorder (RE-MDD)²⁶, which some evidence suggest is the most familial form of the disorder. The population was defined as having a first episode prior to 25 years of age, and having had at least two episodes of nonpsychotic, unipolar major depression. Eighty-one families having probands with RE-MDD were ascertained, and familial association studies were performed. The associations in these families were compared to population prevalence rates for RE-MDD. This study supported a sex-independent, Mendelian dominant mode of inheritance for RE-MDD. This and other similar evidence suggest that a major locus contributes to the expression of RE-MDD, and possibly other mood disorders. However, the methods used do not allow the determination of whether the same major locus is segregating across families or whether multiple major loci are involved (genetic heterogeneity).

DSM-IV described subtypes of Major Depression (Melancholic, Atypical, Post-partum, and Seasonal) are based on symptomatic clustering from validated epidemiologic prevalence studies. Unfortunately, there is little evidence that these subtypes delineate separate qualitative diseases that can be genetically separable. Melancholic depression is the oldest recognized variant of depression and recent well-controlled twin studies have examined its heritability²⁷. In this study there was increased risk of the co-twin having major depression if the proband had major depression, melancholic subtype. However, the genetic contribution of melancholic and non-melancholic depression seemed largely to reflect depression severity, per se, and not melancholia.

A different approach to understanding the genetic basis of depression takes the view that the 50-60% variance of depression accounted for by stressful life events may be mainly due to an interaction with genetic traits. For example, different personality traits may lead a person to engage in more risk-taking behavior, while other traits may lead to poorer coping skills. These traits might be primarily genetically determined, thus placing the person at an increased likelihood of depression in response to environmental stressors.

To examine these questions, McGuffin and colleagues examined sibling pairs of depressed probands and healthy controls in the Cardiff Depression Study²⁸. They sought to determine whether there might be a common familial factor influencing vulnerability to depression and the experiencing of life events. They used a sib-pair design of familial association with 108 probands with major depression and their siblings compared with 105 healthy controls and siblings. Outcomes were based on diagnostic interviews, and data was collected concerning adverse life events. Lifetime relative risk of unipolar depression in siblings of depressed subjects compared to control siblings was 9.74. However, there was no significant difference in life events measures in proband siblings compared to controls. Thus, there appeared to be no evidence for a common factor contributing to both depression and life events in this study. Therefore, they conclude that the >60% variance in depression accounted for by life events / environment was not likely genetically determined. A similar study by the same group looked specifically at risk-taking or sensation seeking behavior. Surprisingly, they found that sensation seeking correlated negatively with depression, though sensation-seeking itself seemed to be an independent familial trait. It appeared that although sensation seeking correlated positively with life events, these were not the more severe events that are typically associated with precipitating depressive episodes. Thus, it does not appear that sensation seeking is a risk factor for depression and may in fact even be slightly protective.

Another aspect of personality that has been extensively studied as a vulnerability factor to depression is the trait of neuroticism. Although neurosis, a term last used in DSMII, is an imprecise

term encompassing many aspects of personality, neuroticism, per se, has been objectively measured. In the last decade, a five-factor model of personality has emerged, with personality being considered a result of five dimensions: extroversion, agreeableness, conscientiousness, neuroticism, and openness²⁹,³⁰. These factors have been found to have considerable heritability and may be akin to genetically determined temperaments (see below). Neuroticism, defined by a collection of anxiety traits and negative emotionality, has been repeatedly shown to be an independent risk factor for depression (Table 4). Although a rigorous understanding of personality is far from complete and other approaches define neuroticism as made up of temperamental traits such as high harm avoidance and character traits such as low self-directedness³¹, it remains a useful measure of trait vulnerability.

Study	Measure	Results of Neuroticism Traits
Weissman et al., Am J Psych 1978; 135 (7): 797	Neuroticism Scale (Maudsley Personality Inv.) 8-48 mos prospective	Most important predictor of long-term outcome after treatment
Charney et al., Am J Psych 1981; 138 (12): 1601	DSM-III diagnosis of personality disorder Inpatients Chart-Review	Related to earlier onset and worse outcome (p<.001)
Black et al., J Affect Disord 1988; 14: 115	DSM-III diagnosis of personality disorder Case-controlled	Poorer response to medication and poorer recovery (p<.025)
Duggan et al., J Affect Disord 1995; 35: 139	Neuroticism score of Eysenck Personality Inv. Family association study	Increased risk of depression in probands and relatives
O'Leary and Costello, J Affect Disord 2001; 63: 67	Neuroticism Scale (Maudsley Personality Inv.) 18 month prospective study	Higher neuroticism scores correlate with longer time to remission (p<.01)

Table 4 Neuroticism is a Contributing Trait for Major Depression

Similarly, behavioral temperament is thought to be largely genetically inherited. Such temperamental differences in individuals likely then lead to differential responses to environmental experience. In a well-designed series of studies, Kagan and colleagues have shown that about 20% of healthy children are born with a temperament that predisposes them to be highly reactive to novel events and fearful of unfamiliar people and environments³². They termed this trait behavioral inhibition. Furthermore, this trait appears to be heritable and is present in infancy. Through prospective studies, these temperamental influences have been shown to place 'reactive' infants and behaviorally inhibited children at higher risk for anxiety and affective disorders as adolescents.

Both the neuroticism trait in adults and the behavioral inhibition temperament in children seem to rely more on symptomatology that is associated with anxiety than depression, per se. However, it is increasingly clear that anxiety and depression are likely quantitative spectrum disorders with remarkable comorbidity of both syndromes and symptoms, and are not, in fact, easily separable. There is now evidence that anxiety and depression have common genetic origins. Furthermore the phenotypic differences between anxiety and depression appear to be dependent upon the environment. Thus

vulnerability, as indexed by the personality scale of neuroticism, overlaps genetically to a substantial extent with both anxiety and depression³³.

Kendler's group has scrutinized the role of gene-environment interaction by evaluating the role of stressful life events in depression in women from twin pairs. Their data suggest that a genetic vulnerability to major depression might be expressed only if an individual is exposed to stressful life events. Thus, major depression is a disorder in which vulnerability may occur through multiple different genetic pathways. It is clearly the interaction between genetic vulnerability and environmental experience that determines the vulnerability to major depression.

Molecular Genetics

Although there are currently linkage studies underway using genome screens that may well be informative in bipolar disorder and schizophrenia, there are no published data available from such studies examining major depression. However, numerous candidate gene linkage studies have been conducted using polymorphisms of genes that encode proteins thought to be involved in the biochemical pathways underlying depression or in the treatment of depression. The majority of these studies have revealed either no significant linkage or have shown statistically that the polymorphism shows no linkage (LOD < -2) to depression (Table 5).

Gene or Loci	Illness	Study	size	Result	Reference
NET	Major Dep. (MD)	Assoc	329	NS	Zill et al., 2002 Neuropsychopharm 26(4):489
Golf	MD	Assoc	321	NS	Zill et al., 2002 Psychiatr Genet 12(1): 17
Alpha2 adr	MD	Linkage	17 families	LOD < -2	Wang et al., 1992 J Affect Disord 25(3): 191
Esterase-D 13q14	MD	Linkage	8 families	NS	Wesner et al., 1991 J Stud Alcohol 52(6): 609
DopaBH 9q34	MD + BP	Linkage	5 families	NS	Sherrington et al., 1994 Biol Psych 36(7): 434
HLA	MD + BP	Linkage	10 families	NS	Suarez and Croughan, 1982 Psychiatr Res 7(1): 19
HLA linkage Chr 6	MD + BP	Linkage	19 families	NS	Suarez and Reich, 1984 Arch Gen Psych 41(1): 22
MAOA	MD + BP	Assoc	403	NS	Syagailo et al., 2001 Am J Med Genet 105(2): 168
Tryp Hyd, 5HT2A, 5HT2C, 5-HTTLR, DRD4, DAT1, COMT	MDD	Assoc	274	NS	Frisch et al., 1999 Mol Psychiatry 4(4): 389
D2,D3, TH	MD + BP	Linkage	23 families	NS	Serretti et al., 2000 J Affect Disord 58(1): 51
38 SSTRPs (linked to 12 candidate genes)	MD, recurrent	Linkage	34 families	NS	Neiswanger et al., 1998 Am J Med Genet 81(5): 443
Chr16, 18, 21, 4	MD, recurrent	Linkage	5 families	NS	Balciuniene et al., 1998 Mol Psychiatry 3(2): 162
30 markers (linked to multiple candidate genes)	Depressive spectrum	Linkage	27 families	NS, (except 9q LOD=1.7)	Wilson et al., 1989 Biol Psychiatry 26(2): 163

**Table 5 Candidate Gene Linkage Studies in Unipolar Depressive Disorders --
Negative Findings**

In contrast, studies of the serotonin reuptake transporter (SERT) and, to a lesser extent 5HT receptors, have been recently fruitful (Table 6). In multiple studies by different groups, a polymorphism within the promoter of the serotonin transporter (5HT transporter linked promoter region - 5HTTLPR) has been repeatedly linked to depression, anxiety, and neuroticism traits. This polymorphism exists about 1000 base pairs upstream of the transcription initiation site for SERT within the promoter region. It has been shown that the short allele variant is associated with reduced SERT gene expression, reduced SERT binding, and reduced 5HT uptake³⁴. These data suggest that decreased expression of the SERT gene is associated with increased neuroticism traits and increased risk for depressive or anxiety disorders. These studies are consistent with the biochemical data that serotonin-containing neurons in the brain may contribute to personality traits and play a role in the risk for depression. Another polymorphism within the SERT gene with a variable number of tandem repeats (VNTR) has been reported to be associated with major depression, although other studies have not yet replicated this finding. While it does not explain all of the genetic variance contributing to major depression, SERT appears to be a gene that, when not optimally expressed, places the individual at increased risk for neuroticism and depression.

Recently, an unexpected and exciting finding has appeared in a related area. Gratacos and colleagues have identified a duplication on human chromosome 15 as a significant susceptibility factor for panic and phobic disorders³⁵. One of the candidate genes in this region is a neurotrophic factor receptor (NTK3) that is abundantly expressed in the locus coeruleus, the primary site for norepinephrine production. Given the high degree of comorbidity and shared symptomatology of anxiety disorders and depression, it will be interesting to see if this duplication increases the risk for some types of depression. This finding will likely rejuvenate the cytogenetic approach to examining familial forms of depression.

Gene (Polymorphism)	Population	Study size	OR or LOD	Reference
SERT (5HTTLPR short allele)	Neuroticism	Assoc 397	P<.01 association with Neuroticism	Greenberg et al., 2000 Am J Med Gen 96(2): 202
SERT (5HTTLPR short allele)	Neuroticism & Anxiety	Assoc 505	7-9% inheritance of anxiety p<.01	Lesch et al., 1996 Science 274(5292): 1527
SERT (VNTR)	Major Depression	Assoc 276	OR= 6.95	Ogilvie et al., 1996 Lancet 347(9003): 731
SERT (5HTTLPR)	MD - Melancholia	Assoc 158	P=.007 small +assoc	Gutierrez et al., 1998 Human Gen 103(3): 319
SERT pro (5HTTLPR)	MD or BP	Assoc 1024	P=.02, OR=1.53	Collier et al., 1996 Mol Psychiatry 1(6): 453
5HT2C (c23s)	Major Depression	Assoc 2063	P=.006 small +assoc	Lerer et al., 2001 Mol Psychiatry 6(5): 579
5HT2A	Fibromyalgia	Assoc 283	P=.008 + assoc	Bondy et al., 1999 Neurobiol Dis 6(5): 433
5HT2A (102 T/C polym)	MD (SAD)	Assoc 323	OR=7.57 P=.002	Arias et al., 2001 Mol Psychiatry 6(2): 239
TH (HUMTH01)	Insulin Resistance Depression	Assoc 465	P<.0001 Insulin Resist. assoc with TH	Chiba et al., 2000 Metabolism 49(9): 1145

Table 6 Candidate Gene Linkage Studies in Unipolar Depressive Disorders – Positive Findings

Animal Models

There have been number of animal models developed to study depression. Virtually all of these have focused on either developmental or environmental stress to produce a depressed phenotype^{3,4}. More recent genetic animal models have been created through the use of mice with transgenic DNA insertion or homologous recombination (knockouts). One of the most impressive models to date is arguably the 5HT_{1A} receptor knockout³⁶. Mice lacking this receptor have been shown to exhibit anxiety and fear behavior in several behavioral paradigms. The same group has recently used elegant molecular biology techniques to ‘rescue’ the phenotype of these knockout animals by replacing the 5HT_{1A} receptor with transgenesis. Using a tissue specific promoter that has limited expression, the 5HT_{1A} gene is replaced within neurons of the hippocampus, amygdala, and forebrain, but specifically not the raphe nuclei³⁷. This limited expression is sufficient to rescue the behavioral phenotype of 5HT_{1A} knockout mice, suggesting that it is the 5HT_{1A} gene in these target areas that contributes to anxiety-like behavior, and not its role in autodeedback within the raphe. Finally, using a conditional gene that can be replaced for limited periods of time, they showed that the replacement is only necessary during development. If the 5HT_{1A} gene is replaced only during the first months of life, but is absent again in adulthood, the animal shows normal levels of anxiety-like behavior as an adult. However, if it is replaced only in adulthood and not earlier during development, the behavioral phenotype is not restored. These data elegantly reveal how a specific interaction between a gene, environment, and development can lead to establishing normal and abnormal adult anxiety-like behavior.

Interestingly though other 5HT receptors and the 5HT transporter have also been studied by this knock-out method, such manipulations have not resulted in specific increases in anxiety-like or depressive behavior. A different approach has been taken to create a neuron-specific knockout of the glucocorticoid (GR) and mineralocorticoid (MR) receptors³⁸. It appears that in the GR knockout, feedback inhibition of hypothalamic CRF secretion is blocked, but amygdala expression of CRF is unaltered. These GR deficient animals have diminished anxiety responses in the dark / light box and elevated O-maze, spending more time in open, lighted regions than controls. In contrast, MR knockout animals have greatly increased CRF levels and exhibit an increase in HPA axis activity. These MR deficient animals also exhibit significant increases in anxiety-like behavior. These studies are in their early phases and need to be considered in the context of the complexity (including possible memory loss) of these animals. Nonetheless, they are consistent with the hypothesis that corticosteroid responsiveness in the brain is a critical mediator of stress and likely contributes to the environmental stress – gene interaction.

Interestingly, CRF knockout mice displayed no significant alterations in anxiety or depression. This may be due to redundant functions of CRF with the recently discovered CRF homologue urocortin. Nonetheless, when CRF is overproduced via a transgenic approach, animals show increased anxiety-like behavior. Additionally, the CRFR₁ and CRFR₂ receptor knockouts both show significant alterations in anxiety-like behavior³⁹. CRFR₁ mutant mice have impaired stress responses and display *decreased* anxiety-like behavior. In contrast, CRFR₂ mutant animals are hypersensitive to stress and display *increased* anxiety-like behavior. When a double mutant animal is made, both sexes display *increased* anxiety-like behavior, though the males show significantly more. Furthermore the CRFR₂ genotype of the mother affects the anxiety-like behavior of the male pups, such that a pup born to a heterozygous or homozygous mutant mother displays more anxiety-like behavior, regardless of pup genotype. This seems to be due to the anxiety / stress state of the mother during pup development. These results implicate the known CRF receptors as well as the role of environment – gene interaction in the development of anxiety or depressive behavior.

In summary, animal models using targeted mutagenesis of candidate genes have been used with success to model anxiety-like and some depression-like phenotypes. As more candidate genes are discovered via genome screens for quantitative trait markers, molecular biology will allow the scrutiny of the function of those genes within relevant neural circuits.

Treatment of Depression

In experimental studies, there are rapid effects of antidepressants on the firing rate of certain neurons and associated increase in the release of neurotransmitter. However, there is often a 3-5 week lag between the initiation of antidepressant action and clinical efficacy in both depression and anxiety disorders. Thus the alterations in these systems after chronic, not acute, antidepressant treatment is key to understanding their mechanism(s) of action. The selective serotonin reuptake inhibitors (SSRIs), the combined serotonin / norepinephrine reuptake inhibitors (SNRIs), and the tricyclic antidepressants (TCAs) all appear to act, at least in part, by inhibiting the reuptake of 5HT and / or NE neurotransmitters at the synaptic cleft. Thereby they create an initial increase in neurotransmitter availability (Table 7). The changes that occur after chronic antidepressant treatment are quite complicated, however, and likely result from the homeostatic mechanisms of autoreceptors and feedback projections that regulate this neural circuitry.

The data for changes in NE neurotransmission following chronic antidepressant treatment have been relatively consistent. They are: i) the concentrations of NE and its metabolites are decreased in CSF after chronic administration of both noradrenergic and serotonergic antidepressants; ii) a decrease in locus coeruleus firing rate occurs with chronic antidepressant treatment; iii) down regulation of the β -adrenergic receptors occurs after chronic antidepressant treatment and electroconvulsive therapy (ECT); and, iv) there is a decrease in tyrosine hydroxylase activity within the locus coeruleus after chronic antidepressant treatment and ECT. Thus it has become increasingly accepted that long-term antidepressant treatment is associated with, and may depend upon, decreasing transmission of the locus coeruleus - NE system^{4, 5, 7, 10}.

As opposed to NE, the raphe 5HT system appears to exhibit increased activity with chronic antidepressant treatment⁴⁻⁶. Evidence for this includes: i) increased 5HT concentrations in forebrain and raphe demonstrated by microdialysis after chronic antidepressant treatment; ii) increased prolactin responsiveness to tryptophan or fenfluramine challenge occur with chronic antidepressant treatment, suggesting enhanced 5HT responsiveness; iii) increased density and sensitivity of the postsynaptic 5HT_{1A} receptors occurs with antidepressant treatment and ECT; and, iv) decreased serotonin transporter density has been reported with chronic antidepressant treatment, suggesting increased synaptic concentrations of 5HT. Together these data convincingly demonstrate that long-term antidepressant treatment is associated with, and may depend upon, increasing transmission of the raphe nuclei serotonin system^{4-7, 10}.

Mechanism	Antidepressant
Primarily Serotonin reuptake inhibition	Clomipramine Fluoxetine Citalopram
Primarily Norepinephrine	Nortriptyline

reuptake inhibition	Reboxetine
Mixed Norepinephrine / Serotonin reuptake inhibition	Amitriptyline Paroxetine Imipramine Duloxetine Venlafaxine Milnacipram
Mixed Serotonin / Dopamine reuptake inhibition	Sertraline
Serotonin Reuptake Inhibitor + 5HT ₂ Receptor Antagonist	Nefazodone Trazodone
Serotonin 5HT _{2R} & 5HT _{3R} antagonist + Norepinephrine α 2 R antagonist	Mirtazapine
Monoamine Oxidase Inhibitors (inhibit breakdown of 5HT/NE/DA)	Phenylzine Isocarboxazid Tranylcypromine

Table 7 Mechanism of Action of Currently Available Antidepressants

Mechanism of Antidepressant Drug Action

It may be counterintuitive that the alterations in overall NE and 5HT activity would shift in opposite directions with antidepressant treatment. These changes appear to occur in both systems whether the treatment is 5HT reuptake specific, NE reuptake specific, or ECT. This suggests that there are systemic changes that occur in the treatment of depression that serve to alter both NE and 5HT neuromodulatory systems. It appears that the combination of 5HT_{1A} autoreceptor desensitization, α 2 autoreceptor sensitization, and β AR desensitization all result in an increase in 5HT_{1A} post-synaptic transmission and a decrease in β AR transmission⁶. Through such alterations in receptor regulation and interactions between the excitatory NE and inhibitory 5HT system, antidepressants appear to work through correcting dysregulated NE transmission and increasing 5HT transmission.

Despite the apparent similarity of NE or 5HT acting antidepressants on the NE and 5HT systems, it has been reproducibly shown that serotonergic-specific or noradrenergic-specific antidepressants depend on the availability of 5HT and NE, respectively, for their antidepressant efficacy⁷. Rapid depletion of 5HT, but not NE, induces rapid relapse in depressed patients during SSRI-induced remission. Similarly rapid depletion of NE, but not 5HT, induces rapid relapse in depressed patients who have achieved remission with noradrenergic antidepressants. However, healthy volunteers and patients in remission no longer on antidepressants do not appear to be sensitive to monoamine depletion. These results suggest that monoamines play a critical role in modulating other neurobiologic systems involved in recovery from depression, rather than representing the primary pathophysiological cause of depression.

Through these mechanisms, serotonergic, noradrenergic, and dual-acting antidepressants appear to reset the dysregulated neural systems, perhaps in similar ways. In general, 5HT and NE neurotransmission is increased and decreased, respectively. These changes are thought to decrease amygdala and ventral prefrontal hyperactivity, thus increasing tolerance to aversion and increasing

dorsal prefrontal control over affective response. ECT appears to exert similar chronic effects on these symptoms. Although the mechanism(s) of action of ECT remain obscure, one that has been hypothesized is via strengthening of prefrontal cortex connectivity with limbic structures secondary to seizure activity. Psychotherapy might produce similar effects on these systems, via increasing cognitive and cortical control over limbic pathways. Shifting the balance of NE and 5HT activity would also result in decreased adrenal glucocorticoid levels and increased neurotrophic factor activity, slowly increasing neuronal density and axonal growth¹⁸. The slow time course of antidepressant response may reflect the combined time courses of the relatively early adaptation of monoamine transmission and receptor sensitivity, the later increases in strength of cortical modulation of limbic circuitry, and the delayed increases in neurotrophic factor-mediated neuronal growth and arborization.

Conclusion and Future Directions:

Unipolar major depressive disorder is a disorder of significant prevalence and morbidity. It is clearly a heritable disorder, and genetic influences appear to account for 30-50% of the vulnerability for this disorder. Despite this evident genetic role, the underlying pathophysiology is clearly heterogeneous. It appears that abnormalities in multiple different gene pathways may lead to a similar endpoint. The interaction between neural development, genes and environment render major depression one of the quintessential disorders of shared interaction between gene and environment. A combination of genetic predisposition and environmental stress appear to lead to similar alterations in the CNS systems that underlie affective responsiveness. Candidate gene studies to date suggest a potentially preeminent role of polymorphisms within the serotonin reuptake transporter. These polymorphisms may increase the risk of personality traits that increase vulnerability to depression and suicide to environmental insults. Animal models support a role for abnormalities of both the 5HT system and the CRF system in increasing risk of anxiety and depressive symptomatology. Through animal models and human imaging, the neural circuitry involving dorsal and ventral prefrontal cortical interactions with limbic subcortical structures is being elucidated. Furthermore, a model of how brainstem monoamine neuronal circuitry may modulate these systems is beginning to be clarified.

To date, the only linkage and association studies that have been published investigating genetic loci for major depression have used a relatively small number of candidate genes. Future hypothesis-neutral linkage studies performed with genome-wide scans will allow for identification of novel genetic loci that underlie the genetic variance of depression. A better understanding of the quantitative traits that increase vulnerability to depression will be critical for progress in such linkage studies. More advanced imaging techniques are currently being undertaken that utilize specific positron emission

tomography (PET) ligands in humans with depression. Additionally, advancing micro-PET applications in transgenic rodents will soon allow for gene-circuit interactions to be visualized. Thus it will soon be possible to approach the genetic mechanisms of vulnerability to depression, the role of these genes in transgenic models, and the roles of these genes in the neural circuits that underlie affective response. These types of studies will further the understanding of depressive symptomatology and the pathophysiology of major depression, as well as enhance treatment options for these debilitating disorders.

Selected References:

1. Kessler, R.C., S. Zhao, D.G. Blazer, and M. Swartz, Prevalence, correlates, and course of minor depression and major depression in the National Comorbidity Survey. *J Affect Disord*, 1997. 45(1-2): p. 19-30.
2. Murray, C.J. and A.D. Lopez, Global mortality, disability, and the contribution of risk factors: Global Burden of Disease Study. *Lancet*, 1997. 349(9063): p. 1436-42.
3. Kaplan, H. and B. Sadock, eds. *Comprehensive Textbook of Psychiatry, 6th edition*. 1995, Williams & Wilkins: Baltimore.
4. Schatzberg, A. and C. Nemeroff, eds. *Textbook of Psychopharmacology*. 1998, American Psychiatric Press: Washington, DC.
5. Ressler, K.J. and C.B. Nemeroff, Role of serotonergic and noradrenergic systems in the pathophysiology of depression and anxiety disorders. *Depress Anxiety*, 2000. 12(Suppl 1): p. 2-19.
6. Blier, P., Crosstalk between the norepinephrine and serotonin systems and its role in the antidepressant response. *J Psychiatry Neurosci*, 2001. 26(Suppl): p. S3-10.
7. Delgado, P.L., Depression: the case for a monoamine deficiency. *J Clin Psychiatry*, 2000. 61(Suppl 6): p. 7-11.
8. Ladd, C.O., R.L. Huot, K.V. Thirivikraman, C.B. Nemeroff, M.J. Meaney, and P.M. Plotsky, Long-term behavioral and neuroendocrine adaptations to adverse early experience. *Prog Brain Res*, 2000. 122: p. 81-103.
9. Holsboer, F., Stress, hypercortisolism and corticosteroid receptors in depression: implications for therapy. *J Affect Disord*, 2001. 62(1-2): p. 77-91.
10. Koob, G.F., Corticotropin-releasing factor, norepinephrine, and stress. *Biol Psychiatry*, 1999. 46(9): p. 1167-80.
11. Davis, M., The role of the amygdala in conditioned and unconditioned fear and anxiety., in *The Amygdala, 2nd edition: A Functional Analysis.*, J. Aggleton, Editor. 2000, Oxford University Press: New York. p. 213-288.
12. Drevets, W.C., Neuroimaging studies of mood disorders. *Biol Psychiatry*, 2000. 48(8): p. 813-29.
13. Mayberg, H.S., M. Liotti, S.K. Brannan, S. McGinnis, R.K. Mahurin, P.A. Jerabek, J.A. Silva, J.L. Tekell, C.C. Martin, J.L. Lancaster, and P.T. Fox, Reciprocal limbic-cortical function and negative mood: converging PET findings in depression and normal sadness. *Am J Psychiatry*, 1999. 156(5): p. 675-82.
14. Lang, P.J., M. Davis, and A. Ohman, Fear and anxiety: animal models and human cognitive psychophysiology. *J Affect Disord*, 2000. 61(3): p. 137-59.
15. LeDoux, J., *The Emotional Brain: The Mysterious Underpinnings of Emotional Life*. 1996, New York, NY: Simon & Schuster.
16. Robbins, T. and B. Everitt, Central Norepinephrine Neurons and Behavior, in *Psychopharmacology: The Fourth Generation of Progress*, F. Bloom and D. Kupfer, Editors. 1995, Raven Press, Ltd: NYC. p. 363-372.
17. Jacobs, B. and C. Fornal, Activity of Serotonergic Neurons in Behaving Animals. *Neuropsychopharmacology*, 1999. 21(2S): p. 9S-15S.
18. Duman, R., J. Malberg, and J. Thome, Neural Plasticity to Stress and Antidepressant Treatment. *Biol Psychiatry*, 1999. 46: p. 1181-1191.
19. Gould, E., Serotonin and hippocampal neurogenesis. *Neuropsychopharmacology*, 1999. 21(2 Suppl): p. 46S-51S.
20. Bremner, J., M. Narayan, E. Andersen, H. Miller, and D. Charney, Hippocampal volume reduction in major depression. *Am J Psychiatry*, 2000. 157(1): p. 115-118.

21. Muller, M., P. Lucassen, A. Tassouridis, W. Hoogendijk, F. Holsboer, and D. Swaab, Neither major depression nor glucocorticoid treatment affects the cellular integrity of the human hippocampus. *Eur J Neurosci*, 2001. 14(10): p. 1603-12.
22. Sullivan, P.F., M.C. Neale, and K.S. Kendler, Genetic epidemiology of major depression: review and meta-analysis. *Am J Psychiatry*, 2000. 157(10): p. 1552-62.
23. Kendler, K.S., Twin studies of psychiatric illness. Current status and future directions. *Arch Gen Psychiatry*, 1993. 50(11): p. 905-15.
24. Eley, T.C. and R. Plomin, Genetic analyses of emotionality. *Curr Opin Neurobiol*, 1997. 7(2): p. 279-84.
25. Kendler, K.S., C.O. Gardner, and C.A. Prescott, Clinical characteristics of major depression that predict risk of depression in relatives. *Arch Gen Psychiatry*, 1999. 56(4): p. 322-7.
26. Maher, B.S., M.L. Marazita, W.N. Zubenko, D.G. Spiker, D.E. Giles, B.B. Kaplan, and G.S. Zubenko, Genetic segregation analysis of recurrent, early-onset major depression: Evidence for single major locus transmission. *Am J Med Genet*, 2002. 114(2): p. 214-21.
27. Kendler, K.S., The diagnostic validity of melancholic major depression in a population-based sample of female twins. *Arch Gen Psychiatry*, 1997. 54(4): p. 299-304.
28. Farmer, A., T. Harris, K. Redman, S. Sadler, A. Mahmood, and P. McGuffin, Cardiff depression study. A sib-pair study of life events and familiarity in major depression. *Br J Psychiatry*, 2000. 176: p. 150-5.
29. Briggs, S., Assessing the five-factor model of personality description. *J Personality*, 1992. 60(2): p. 253-293.
30. Petersen, T., K. Bottanari, J. Alpert, M. Fava, and A. Nierenberg, Use of the five-factor inventory in characterizing patients with major depressive disorder. *Compr Psychiatry*, 2001. 42(6): p. 488-493.
31. Cloninger, R., Temperament and Personality. *Curr Opin Neurobiol*, 1994. 4: p. 266-273.
32. Kagan, J. and N. Snidman, Early childhood predictors of adult anxiety disorders. *Biol Psychiatry*, 1999. 46(11): p. 1536-41.
33. Kendler, K.S., E.E. Walters, M.C. Neale, R.C. Kessler, A.C. Heath, and L.J. Eaves, The structure of the genetic and environmental risk factors for six major psychiatric disorders in women. Phobia, generalized anxiety disorder, panic disorder, bulimia, major depression, and alcoholism. *Arch Gen Psychiatry*, 1995. 52(5): p. 374-83.
34. Lesch, K.P., D. Bengel, A. Heils, S.Z. Sabol, B.D. Greenberg, S. Petri, J. Benjamin, C.R. Muller, D.H. Hamer, and D.L. Murphy, Association of anxiety-related traits with a polymorphism in the serotonin transporter gene regulatory region. *Science*, 1996. 274(5292): p. 1527-31.
35. Gratacos, M., M. Nadal, R. Nartin-Santos, M. Pujana, J. Gago, B. Peral, L. Armengol, I. Ponsa, R. Miro, A. Bulbena, and X. Estivill, A Polymorphic Genomic Duplication on Human Chromosome 15 is a Susceptibility Factor for Panic and Phobic Disorders. *Cell*, 2001. 106: p. 367-379.
36. Gingrich, J.A. and R. Hen, Dissecting the role of the serotonin system in neuropsychiatric disorders using knockout mice. *Psychopharmacology (Berl)*, 2001. 155(1): p. 1-10.
37. Gross, C., X. Zhuang, K. Stark, S. Ramboz, R. Oosting, L. Kirby, L. Santarelli, S. Beck, and R. Hen, Serotonin1A receptor acts during development to establish normal anxiety-like behaviour in the adult. *Nature*, 2002. 416(6879): p. 396-400.
38. Gass, P., H.M. Reichardt, T. Strekalova, F. Henn, and F. Tronche, Mice with targeted mutations of glucocorticoid and mineralocorticoid receptors: models for depression and anxiety? *Physiol Behav*, 2001. 73(5): p. 811-25.
39. Bale, T.L., R. Picetti, A. Contarino, G.F. Koob, W.W. Vale, and K.F. Lee, Mice deficient for both corticotropin-releasing factor receptor 1 (CRFR1) and CRFR2 have an impaired stress response and display sexually dichotomous anxiety-like behavior. *J Neurosci*, 2002. 22(1): p. 193-9.

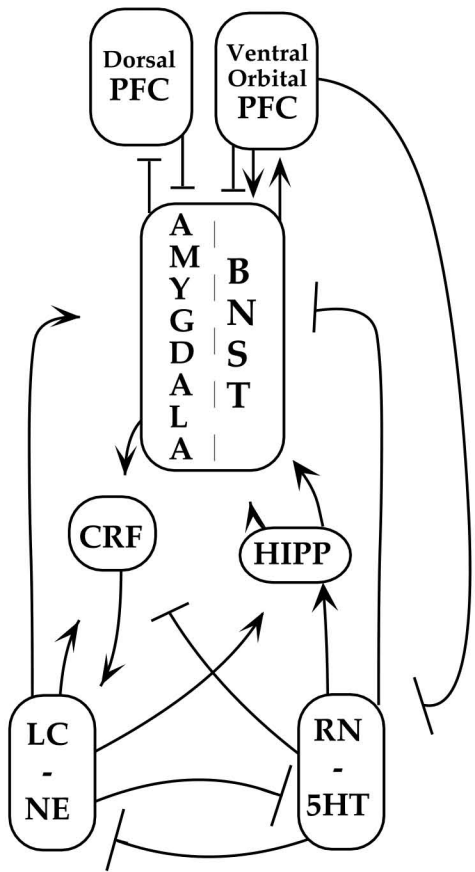
Figure 1 Neurotransmitter Modulation of Affective Circuitry Involved in Depression

The brainstem modulatory nuclei, Locus Coeruleus with Norepinephrine (LC-NE) and Raphe Nuclei with Serotonin (RN-5HT), are shown with their primary excitatory (->) and inhibitory (-|) effects on limbic circuitry. During the euthymic state, stressful or fearful stimuli initially activate the LC-NE system via release of corticotrophin releasing factor (CRF) from the amygdala and from the paraventricular nucleus of the hypothalamus. This release is opposed by 5HT release that promotes aversion tolerance and decreases the stress response mediated by the amygdala / bed nucleus of the stria terminalis (BNST). There are reciprocal connections between amygdala and prefrontal cortical (PFC) areas. These areas are critical for the extinction of fearful memories and aversion tolerance, however the ventral prefrontal areas may also serve to activate amygdala and inhibit RN activity. Multiple genetic and environmental determinants lead to alterations in these systems resulting in a dysregulated state of functioning in depression (shown above: thick lines and hash lines represent increased and decreased activity, respectively). In this state, the LC-NE system is hyperresponsive to stress or fear stimuli, and the RN-5HT system is hyporesponsive with decreased inhibition of stress reactivity. The cortical modulation of limbic reactivity is dysregulated and likely contributes to the altered NE/5HT functioning.

Figure 2 Genetic and Environmental Interactions Mediate the Onset of Depression

This schematic diagram summarizes the combined roles of genes (contributing 35-50% of the variance) and environment (50-65% of the variance) in the development of major depression. It is thought that early environmental experience (including pre- and perinatal insults as well as early familial interactions) during development interact with different genes leading to distinct traits or temperaments. Combinations of personality traits likely provide both protection and vulnerability to environmental insults (life events) during adolescence and adulthood.

Euthymic



Normal Stress / Fear Response
Normal Aversion Tolerance

Genetic Vulnerability
Environmental Vulnerability
Stress



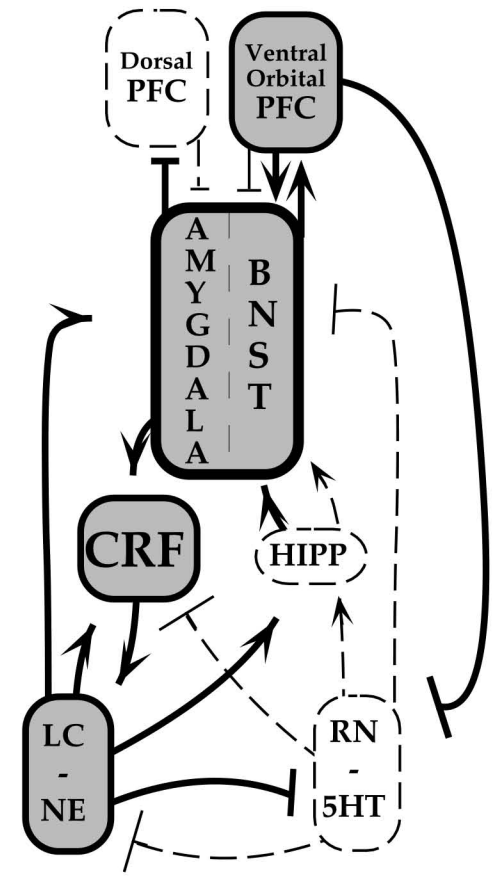
- ↑ NE turnover
- ↑ B-AR sensitivity
- ↓ 5HT turnover
- ↓ 5HT1a sensitivity
- ↑ CRF / Glucocorticoids
- ↓ Neurotrophins / Neurogenesis
- ↑ Cell Death / Atrophy

Antidepressant Treatment
Electroconvulsive Therapy



- ↓ NE turnover
- ↓ B-AR sensitivity
- ↑ 5HT turnover
- ↑ 5HT1a sensitivity
- ↓ CRF / Glucocorticoids
- ↑ Neurotrophins / Neurogenesis
- ↓ Cell Death / Atrophy

Depression



Hypersensitive Stress / Fear Response
Diminished Aversion Tolerance

Genetic Predisposition

Environmental Experience
(pre- and post-natal)

Development

Trait Vulnerability

trauma
ongoing stress
illness

social support
coping skills

Depression

