Current PSYCHIATRY

Dissecting melancholia with evidence-based biomarker tools

Insight into the neuroanatomical pathophysiology of depression may shed light on the future of managing this disease

For more than 50 years, depression has been studied, and understood, as a deficiency of specific neurotransmitters in the brain—namely dopamine, norepinephrine, and serotonin. Treatments for depression have been engineered to increase the release, or block the degradation, of these neurotransmitters within the synaptic cleft. Although a large body of evidence supports involvement of dopamine, norepinephrine, and serotonin in the pathophysiology of depression, the observation that pharmacotherapy is able to induce remission only in <50% of patients[1] has prompted researchers to look beyond neurotransmitters for an understanding of depressive disorders (***Table 1, page 42***).

Today, theories of depression focus more on differences in neuron density in various regions of the brain; the effect of stress on neurogenesis and neuronal cell apoptosis; alterations in feedback pathways connecting the pre-frontal cortex to the limbic system; and the role of proinflammatory mediators evoked during the stress response (***Box,***[2,3] ***page 43***). These theories should not be viewed as separate entities because they are highly interconnected. Integrating them provides for a more expansive understanding of the pathophysiology of depression and biomarkers that are involved (***Table 2, page 44***).

In this article, we:

- integrate the large body of evidence supporting the contribution of the above variables to the onset and persistence of depression
- propose a possible risk stratification model
- explore possibilities for treatment.

continued

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Depression

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Chronic stress is believed to be the leading cause of depression

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Table 1

Treatments on the horizon for depression

Stress reduction
Corticotropin-releasing hormone antagonists
11-β- HSD
Dexamethasone
Partial adrenalectomy
Long-term and consistent practice of cognitive-behavioral therapeutic techniques for stress management
Restoration of the appropriate balance between excitatory and inhibitory neurotransmitters
Ketamine and other NMDA antagonists
Benzodiazepines
Anesthetics
Hippocampal neurogenesis and regulation of the HPA axis
Deep brain stimulation
Transcranial magnetic stimulation and other emerging non-invasive neuromodulatory technologies
Exogenous brain-derived neurotrophic factor
Selective serotonin reuptake inhibitors
Serotonin-norepinephrine reuptake inhibitors
Tricyclic antidepressants
Atypical antidepressants
Reduction in inflammation
Adjunctive nonsteroidal anti-inflammatory drug and other anti-inflammatory drugs

The stress response: How does it affect the brain?

Stress initiates a cascade of events in the brain and peripheral systems that enable an organism to cope with, and adapt to, new and challenging situations. That is why physiologic and behavioral responses to stress generally are considered beneficial to survival.

When stress is maintained for a long period, both brain and body are harmed because target cells undergo prolonged exposure to physiologic stress mediators. For example, Woolley and Gould[4] exposed rats to varying durations of glucocorticoids and observed that treating animals with corticosterone injection for 21 days induced neuronal atrophy in the hippocampus and prefrontal cortex and increased release of proinflammatory cytokines from astrocytes within the limbic system. Stressful experiences are believed to be closely associated with development of psychological alterations and, thus, neuropsychiatric disorders.[5] To go further: *Chronic stress is believed to be the leading cause of depression*.

When the brain perceives an external threat, the stress response is called into action. The amygdala, part of the primitive limbic system, is the primary area of the brain responsible for triggering the stress response,[6] signaling the hypothalamus to release corticotropin-releasing hormone (CRH) to the anterior pituitary gland, which, in turn releases adrenocorticotropic hormone to the adrenal glands (***Figure 1, page 45***).[7] The adrenal glands are responsible for releasing glucocorticoids, which, because of their lipophilic nature, can cross the blood-brain barrier and are found in higher levels in the cerebrospinal fluid (CSF) of depressed persons.[7]

Once in the brain, glucocorticoids can be irreversibly degraded in the cytosol by the enzyme 11-β hydroxysteroid dehydrogenase type 2, a potential target for treating depression, or can bind to the glucocorticoid receptor (GR). Results of a research study of the role of cortisol in suppression of proinflammatory cytokine signaling activity in rainbow trout hepatocytes suggest a negative feedback loop for GR gene regulation during stress.[8]

Because this auto-regulation is a crucial step in the physiological stress response, the idea of the GR as an important biomarker in depression has gained popularity. In humans, when the GR binds to glucocorticoids that are released from the adrenal cortex during the stress response, the activated GR-cortisol complex represses expression of proinflammatory proteins in astrocytes and microglial cells and in all cells in the periphery before they are transcribed into proteins.[9] The GR also has been shown to modulate neurogenesis.[8] Repeated stress that persists over a long period leads to GR resistance, thereby reducing inhibition of production of proinflammatory cytokines.

Exposure to stress for >21 days leads to overactivity of the HPA axis and GR resistance,[10] which decreases suppression of proinflammatory cytokines. There is evidence that proinflammatory cytokines, tumor necrosis factor-α, and interleukin-6 further induce GR receptor resistance by preventing the cortisol-GR receptor complex from en-

Box

The 'neurotrophic hypothesis' takes hold

Advances in neuroimaging techniques—positron emission tomography, single photon-emission computed tomography, voxel-based morphometry, diffusion tensor imaging, and functional magnetic resonance imaging (fMRI)—have made it possible to examine depression at the level of associated changes in **1)** gray-matter density in the brain and **2)** the integrity of synaptic connections within the neurocircuitry involved in the development and persistence of depression. The idea that the process of neurogenesis and functional differences in neuronal circuitry play an important role in the development of depression has gained popularity, and is today called the "neurotrophic hypothesis."

Change in structure and function. Depression and other mood disorders stem from disturbances in the detection of, response to, and interpretation of emotion. The fronto-limbic circuitry, which includes the prefrontal cortex, hippocampus, amygdala, striatum, and insula, has been shown to be highly involved in the regulation of emotion.[2] These regions display structural and functional alterations on brain imaging studies in patients with depression and other mood disorders. In particular, fMRI and postmortem biopsy consistently show **1)** volumetric and gray-matter reductions in the prefrontal cortex, hippocampus, and striatum and **2)** increased volume and gray matter in the amygdala and insula.[3]

Underlying mediators of neuroapoptosis. Experimental evidence suggests that these changes in structure and function result from a number of direct and indirect factors that mediate neuroapoptosis in the fronto-limbic circuitry that result from exposure to chronic high levels of stress. Those factors include:

- prolonged increase in the systemic level of glucocorticoids
- dysregulation of the HPA axis
- sustained increased in excitatory neurotransmitters, such as glutamate
- chronic glucose deprivation in the prefrontal cortex, hippocampus, and striatum during the stress response
- production of proinflammatory cytokines.

tering cell nuclei and decreasing binding to DNA within the nuclei.[11] Dexamethasone, a GR agonist, has been implicated in research studies for potential re-regulation of the HPA axis in depressed persons.[12]

Nerve cell death in the hippocampus

Studies showing reduced hippocampal volume in unipolar depression and a correlation between the number of episodes and a consequence of untreated depression and studies suggesting that treatment can stop or reduce shrinkage,[13] and recent findings of rapid neurogenesis in hippocampi in response to ketamine, brings our focus to hippocampus in depression.

The greatest density of GRs is found in the hippocampus, which is closely associated with the limbic system.[7] Therefore, the hippocampus is sensitive to increases in glucocorticoids in the brain and plays a crucial role in regulation of the HPA axis.

Evidence shows that in chronic stress exposure (≥21 days), nerve cells in the hippocampus begin to atrophy and can no longer provide negative feedback inhibition to the hypothalamus, causing HPA axis dysregulation and uncontrolled release of glucocorticoids into the bloodstream and CSF.[2] In patients with Cushing syndrome, who produce abnormally high levels of glucocorticoid, the incidence of depression is as high as 50%.[14] Similarly, patients treated with glucocorticoids such as prednisone often experience psychiatric symptoms, the most common being depression. Gould found that partial adrenalectomy increased hippocampal neurogenesis in rat brains, indicating the beneficial effect of stress hormone antagonism.[4] CRH antagonists are being looked at as a promising and less invasive treatment option for depression.

Focus has been diverted to the role of the hippocampus in depression because of its ability to regenerate throughout adulthood, leading potentially to a re-regulation of the HPA axis and subsiding of the stress response, which is universally believed to be the primary precipitating factor in depression onset. Rats require 10 to 21 days of rest to recover from the effects of chronic (21 days) administration of glucocorticoids.[15] If this proves to be a directly proportional relationship, then rats would

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Evidence shows that in conditions of chronic stress exposure, nerve cells in the hippocampus begin to atrophy

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Current depression treatment programs, which average 6 weeks, are not long enough for adequate recovery

Table 2

Proposed biomarkers for depression

Monoamine regulators
Transporters
SERTPR
5-HTTLPR
STin2
Rs25531
SLC6A4
Receptors
5-HT2A
Enzymes
Proinflammatory cytokines (released from astrocytes and glia)
INF-α
Interleukin-2, 4, 6, and 13
Tumor necrosis factor-α
C-reactive protein
Other inflammatory mediators
COX-2
Prostaglandin E2
Glucocorticoid receptor (GR)
Mediators of glutaminergic activity
Ligand-gated channels
N-methyl-D-asparate
GluN2B
GluN2D
α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid
Kainic acid
Metabolic products of the kynurenine pathway
Kynurenic acid
Quinolinic acid
Mediators of GABAergic activity
Receptors
γ-aminobutyric acid-A
α1, α6, and γ subunits
Regulatory enzymes
GAD
GAD67
Regulators of neurogenesis
Brain-derived neurotrophic factor
Vascular endothelial growth factor

need an estimated 120 days to recover from 6 months of constant glucocorticoid exposure. Considering that the same is true for humans, current depression treatment programs, which average 6 weeks, are not long enough for adequate recovery.

Antidepressants such as selective serotonin reuptake inhibitors, serotonin-norepinephrine reuptake inhibitors, and tricyclics stimulate neurogenesis in the hippocampus via increases in brain-derived neurotrophic factor (BDNF), suggesting that these neurotransmitters play an important role depression.[16]

Repetitive transcranial magnetic stimulation (rTMS), a noninvasive neuromodulation therapy approved to treat major depression, delivers brief magnetic pulses to the limbic structures. Treatment facilitates focal stimulation, rapidly applying electrical charges to the cortical neurons. TMS targets prefrontal circuits of the brain that are underactive during depressive episodes. Recent animal studies have suggested that bromodeoxyuridine (BrdU)-positive cells (newborn cells) are increased significantly in the dentate gyrus, in turn suggesting that hippocampal neurogenesis might be involved in the antidepressant effects of chronic rTMS.[17] Although the underlying therapeutic mechanisms of rTMS treatment of depression remain unclear, it appears that hippocampal neurogenesis might be required to produce the effects of antidepressant treatments, including drugs and electroconvulsive therapy.[17]

Selective 'shunting' of energy occurs during the stress response

Hormones released from the adrenal glands during stress divert glucose to exercising muscles and the brain's limbic system, which are involved in the fight-or-flight response.[18] However, metabolic functions and areas of the brain that are not involved in the stress response, such as the cerebral cortex and hippocampus, are deprived of energy as a consequence of this innate selective shunting (***Figure 2, page 46***).[19]

Positron-emission tomography (PET) scanning of the resting brain shows that components of the cerebral cortex (prefrontal cortex, hippocampus, striatum) and areas connecting the cerebral cortex to the limbic system exhibit the most energy consumption in the brain during rest (***Figure 3, page 46***).[20] PET studies also show that neuronal connections within these energy-demanding areas atrophy more rapidly than in any other area of the brain when their energy supply is reduced or cut off.[6]

When the supply of oxygen and glucose to certain areas of the brain is reduced—such as in traumatic brain injury or stroke—the excitatory neurotransmitter glutamate accumulates in extracellular

fluid and causes nerve-cell death.[21] When a conditioned stimulus is presented during fear acquisition, functional magnetic resonance imaging (fMRI) studies of fear-conditioning have consistently reported, in the prefrontal cortex:

- a decrease in the blood oxygen level-dependent signal, below resting baseline
- a reduction in blood flow (***Figure 4, page 47***).[22]

This discovery adds to evidence that demonstrates a decrease in gray-matter density in the frontal lobes as a result of glutaminergic toxicity (***Figure 5, page 47***).

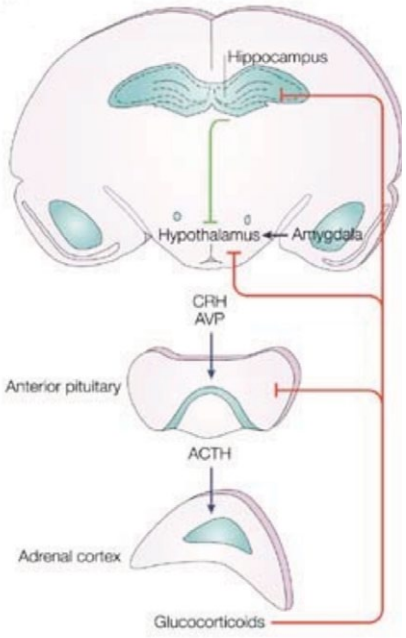
Activation of L-glutamate, believed to play a significant role in depression and other neuropsychiatric disorders, triggers calcium-dependent intracellular responses that "excite cells to death," so to speak—thereby causing nerve-cell apoptosis and a reduction in synaptic connections between different areas of the brain responsible for learning and memory.[23] Malfunction of these synaptic connections is thought to be partially responsible for depression and other psychiatric disorders.

Excessive activation of *N*-methyl-D-asparate (NMDA) receptors is thought to be the underlying mechanism that leads to neuronal cell death in glutaminergic toxicity. Therefore, NMDA receptor proteins have become a target in treating neurodegenerative psychiatric illnesses. There is more than one type of NMDA receptor; some of them are excitatory, others are inhibitory. Four compounds have presented as therapeutic candidates for inhibition of NMDA receptor functioning and treatment of depression: those that inhibit glutamate binding, those that block the ion channel, and those that inhibit receptor binding to the terminal regulatory domain.[24]

Regrettably, these chemical compounds are not receptor-selective, but small structural modifications of these NMDA receptors have been found and lead to significant changes in potency and selectivity. This should serve as a unique starting point for developing highly specific NMDA receptor modulator agents for a variety of neuropsychiatric and neurological conditions. GLYX-13, a derivative of ketamine (an NMDA receptor antagonist), has been implicated for use in treating depression. It has been tested on 2 large phase-II study groups.[25]

Figure 1

The HPA axis



During the stress response, the amygdala prompts the hypothalamus to release corticotropin-releasing hormone (CRH) to the anterior pituitary gland, which releases adrenocorticotropic hormone (ACTH) to the adrenal glands. In turn, the adrenal glands release glucocorticoids. The sequence is known as the HPA axis. The hippocampus plays an important role in regulating the HPA axis.

Source: Reference 7

Neuronal circuitry of depression is altered by prolonged stress

Symptoms of depression can be explained by the anatomical circuit shown in ***Figure 6*** (***page 48***).[15,20] Impaired concentration, diminished ability to process new information, and decline in memory function are associated with decreased nerve density in the hippocampus, which plays a key role in learning, memory, and encoding of emotionally relevant data into memory.[26] The hippocampus interacts with the amygdala to provide input about the context in which stimuli occur.

Depressed people often demonstrate impulsivity and have difficulty controlling

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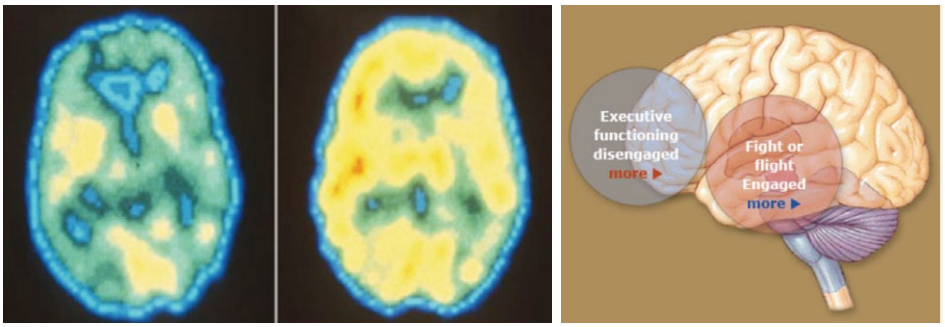
NMDA receptor proteins have become a target in treating neurodegenerative psychiatric illnesses

Depression

Figure 2

Energy supply in a stressed brain

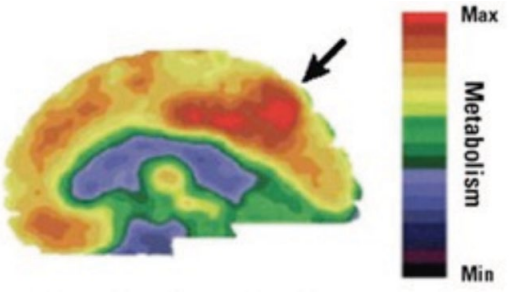


Left: A PET scan allows comparison of glucose uptake in a non-stressed brain (*left*) and a stressed brain (*right*). In the stressed brain, energy supply is significantly reduced in the cerebral cortex and increased in the limbic regions and occiput. *Right*: A depiction of the energy shift that occurs during the stress response.

Source: Reference 19

Figure 3

Glucose and the cerebral cortex



This PET scan shows that areas of the cerebral cortex regulating control of emotions require the highest amount of glucose and are particularly sensitive to the energy deprivation that occurs during the stress response.

Source: Reference 20

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Deep brain stimulation has proved effective at increasing synaptic connections between the prefrontal cortex and the limbic system

expression of emotions—traits that are attributed to increased neuronal density in the amygdala and insula, which has been illustrated in PET scans and voxel-based morphometry in depressed patients.[27] These brain areas are implicated in subjective emotional experience, processing of emotional reactions, and impulsive decision-making. The amygdala is normally highly regulated by the prefrontal cortex, which uses rational judgment to interpret stimuli and regulate the expression of emotion.

A study involving a facial expression processing task demonstrated reduced connectivity between the amygdala and prefrontal cortex and increased functional connectivity among the amygdala, hippocampus, and caudate-putamen in depressed patients.[24] And in a study that measured white matter conduction in various brain areas in depressed patients, the greatest reduction was found in areas connecting the limbic system to the prefrontal cortex and hippocampus—believed to be caused by stress response-induced ischemic glutaminergic neuroapoptosis.[21] Such neuroapoptosis might lead to irrational interpretation of stimuli, unchecked expression of emotion, and impulsive thoughts and behavior that are often present in depression and other mood disorders.

Deep brain stimulation (DBS), in which electrodes are implanted in the brain, has proved effective at increasing synaptic connections between the prefrontal cortex and the limbic system when electrodes are placed appropriately.[28] Patients with refractory depression who are treated with DBS show increased gray-matter density and functional activity in the prefrontal cortex, hippocampus, and fronto-limbic connections.[29] DBS also increases neurotransmission of dopamine, serotonin, and norepinephrine within the fronto-limbic circuitry.[30]

Identifying risk factors for depression

Genetic risk factors. Forty percent of patients with depression have a first-degree relative with depression, suggesting a strong genetic component.[10] Inherited differences in hippocampal volume, synaptic connections between the prefrontal cortex and amygdala, γ-aminobutyric acid (GABA)/glutamate balance, BDNF neurotransmitter receptors, and anatomic positioning of the limbic system in relation to other brain structures might account for the heritability of psychiatric disorders such as depression.

Evidence has been consistent that hippocampal volume is diminished in the brain of depressed persons. However, there is no prospective cohort study to determine whether people who have lower gray-matter hippocampal density or volume, or both, before depression onset develop symptoms later in life. There also is no study to determine the percentage of people who have lower-than-average hippocampal gray-matter density or volume and who have a first-degree relative with depression. Such studies would yield valuable information about anatomic variables that increase the risk of depression.

It has been proposed that low GABA function is an inherited biomarker for depression. Bjork and coworkers found a lower plasma level of GABA in depressed subjects and in their first-degree relatives, confirming that GABAergic tone might be under genetic control.[11] Genetic loci studies in mice have linked depressive-like behavior to GABAergic loci on chromosomes 8 and 11, encoding alpha 1, alpha 6, and gamma subunits of $GABA_A$ receptors.[23]

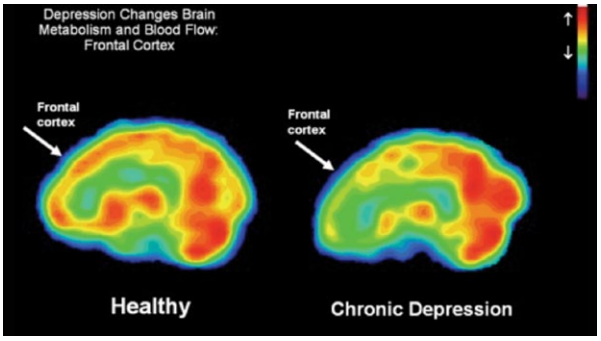
A recent study in humans showed that severe, treatment-resistant depression with anxiety was linked to a mutation in the B1 subunit of the $GABA_A$ receptor. Positive genetic associations were found between polymorphism in human $GABA_A$ receptor subunit genes.[11]

GABA metabolizing enzymes also can be considered biological modifiers of depression. For example:

- GABA uptake and metabolism is controlled by the **enzyme glutamic acid decarboxylase** (GAD); depression has been

Figure 4

Blood flow to the cerebral cortex is reduced in depression

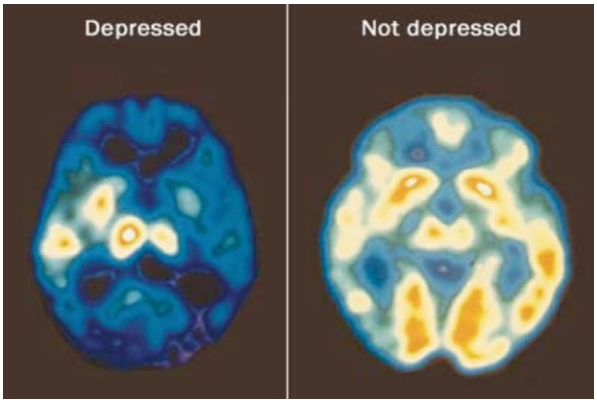


Reduced flow is a result of stress response-induced energy shunting.

Source: Reference 22

Figure 5

Glutamate exposure during stress affects the frontal cortex



Both activity and grey matter density are reduced in the frontal cortex and hippocampus in the depressed brain, compared with the non-depressed brain. These reductions are likely mediated by increased glutamate exposure during stress.

Source: Mayo Clinic Foundation for Medical Education and Research. Reproduced with permission

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Both activity and grey matter density are reduced in the frontal cortex and hippocampus in the depressed brain

Depression

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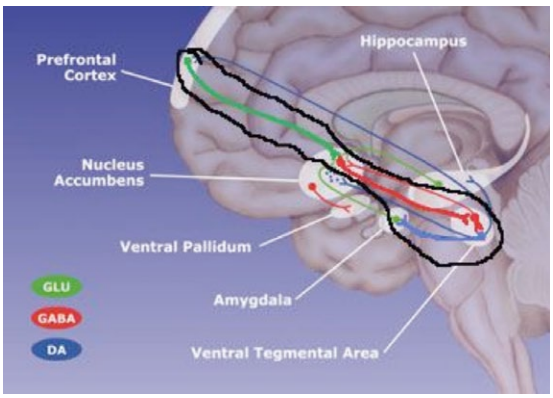
Early life experiences play an important role informing synaptic connections between the frontal cortex and the limbic system

Figure 6

Neurocircuitry involved in the pathogenesis of depression



The amygdala—responsible for determining the emotional significance of a stimulus and generating the learned response to that emotion by sending signals to the temporal lobes, sensory, and motor cortices—is activated when dopamine is released from the ventral tegmental area. When the prefrontal cortex determines that an emotion is "inappropriate," the hippocampus and the prefrontal cortex stimulate the nucleus accumbens to inhibit the release of dopamine from the ventral tegmental area to the amygdala. (The target area of activation is circled in black.)

Source: References 15,20

found to be associated with a polymorphism in the GAD67 gene encoding an isoform of GAD.[11]

- **GABA transaminase** (GABA-T) is another key enzyme in GABA turnover.[31] It catabolizes GABA.

We can conclude that, to a high degree, depression depends on GABA production and metabolism.

A variant in the human BDNF gene, in which valine is substituted for methionine in position 66 of the pro-domain of the BDNF protein, is associated with

- a decrease in the production of BDNF
- increased susceptibility to neuropsychiatric disorders, including depression, anxiety disorder, and bipolar disorder (*Figure 7, page 57*).[32]

People with the MM allele have been found to have a small hippocampal neuronal density and poor hippocampus-dependent memory function in neuroimaging studies.[23] They also displayed diminished ventromedial prefrontal cortex volume and presented with aversive memory extinction deficit (ie, "holding grudges").

Another neurotrophic factor, vascular endothelial growth factor (VEGF), is a survival factor for endothelial cells and neurons and a modulator of synaptic transmission. Understanding the molecular and cellular specificity of antidepressant-induced VEGF will be critical to determine its potential as a therapeutic target in depression.[33] Delineating the relationship between VEGF and depression has, ultimately, the potential to shed light on the still elusive neural mechanisms that underlie the pathophysiology of depression and the mechanisms by which antidepressants exert their effects.[34]

Genetic polymorphisms in monoamine receptors (5-HT2A), transporters (SERTPR, 5-HTTLPR, STin2, rs25531, SLC6A4), and regulatory enzymes should not be overlooked.[35] There is reproducible evidence that variability in these polymorphisms are associated with variability in:

- vulnerability to depression
- the response to treatment with existing antidepressant medications.[1]

Most studies that look at changes in neuronal circuitry focus on the integrity of synaptic connections between the frontal cortex and limbic system; few of them have closely examined the importance of the anatomic proximity of the 2 regions. It might be that having an amygdala that is relatively closer to the frontal cortex and the hippocampus reduces a person's risk of depression, and vice versa. This association needs to be investigated further with imaging studies.

Environmental risk factors. The brain is thought to be plastic until age 30.[5] Plasticity diminishes with age after age 7—except for the hippocampus, which can regenerate throughout life.[36] Early life experiences play an important role in forming synaptic connections between the frontal cortex and the limbic system, through a process known as fear conditioning.

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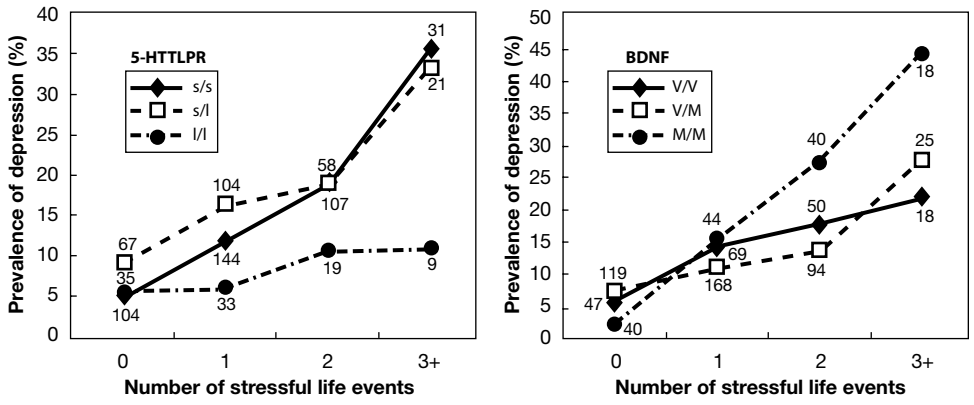
Figure 7

Number of stressful life events correlates with prevalence of depression



The graphs show the correlation between the number of stressful life events by age group and the prevalence of depression. Each graph represents a distinct variant of each gene (5-HTTLPR and BDNF—the val66met polymorphism). These findings suggest that **1)** stressful life events interact with the 5-HTTLPR and BDNF genotypes and **2)** the environmental risk of depression is modified by at least 2 genes. These gene–environment interactions are found into old age.

Source: Reference 32

Children learn early in life which stimuli are to be perceived as threatening or aversive and how to respond to best preserves their safety and internal sense of well-being. Those who grow up in a hostile environment learn to perceive more stimuli as threatening than children who grow up in a nurturing environment.[32] It is possible that the amygdala is larger in children who grow up in less-than-ideal circumstances because this region is constantly being recruited—at the expense of the more rational frontal cortex.

Evidence suggests that these conditions reduce hippocampal neurogenesis[37]:

- increasing age
- substance abuse (opiates and methamphetamines)
- inadequate housing
- minimal physical activity
- little opportunity for social stimulation
- minimal learning experience.

continued on page 66

Related Resources

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Bottom Line

Depression has been understood as a neurotransmitter deficiency in the brain; treatments were engineered to increase release, or block degradation, of those neurotransmitters. Novel theories—all interconnected—of the neuroanatomical pathophysiology of depression focus more on differences in neuron density in the brain; effects of stress on neurogenesis and neuronal cell apoptosis; alterations in feedback pathways connecting the pre-frontal cortex to the limbic system; and the role of pro-inflammatory mediators evoked during the stress response.

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Having an amygdala that is relatively closer to the frontal cortex and the hippocampus might reduce a person's risk of depression

Depression continued from page 57

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