Unipolar depression: Neurobiology

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INTRODUCTION

Unipolar depression is a major public health problem associated with increased functional disability and mortality. The illness likely represents a group of heterogeneous disorders that are phenotypically similar [1]. Efforts to understand the neurobiology of depression, as well as its pathogenesis, are intended to discern these different diseases or subtypes.

This topic reviews the neurobiology of unipolar depression. The pathogenesis, clinical features, assessment, diagnosis, and treatment of unipolar depression are discussed separately:

- (See "Unipolar depression: Pathogenesis".)
- (See "Unipolar depression in adults: Clinical features".)
- (See "Unipolar depression in adults: Assessment and diagnosis".)
- (See "Unipolar major depression in adults: Choosing initial treatment".)
- (See "Unipolar depression in adults: Choosing treatment for resistant depression".)

DEFINITIONS OF DEPRESSION

The term "depression" can be used in multiple ways, which can be confusing; depression may refer to a [2,3]:

- Mood state, as indicated by feelings of sadness, despair, anxiety, emptiness, discouragement, or hopelessness; having no feelings; or appearing tearful. Depressed

(dysphoric) mood may be normal or a symptom of a psychopathological syndrome or a general medical disorder.

- Syndrome, which is a constellation of symptoms and signs that may include depressed mood. Depressive syndromes that are typically encountered include major depression, minor depression, or dysthymia (persistent depressive disorder).

- Mental disorder that identifies a distinct clinical condition. As an example, the syndrome of major depression can occur in several disorders, such as unipolar major depression (also called "major depressive disorder"), bipolar disorder, schizophrenia, substance/medication-induced depressive disorder, and depressive disorder due to another (general) medical condition.

NEUROBIOLOGY

Multiple lines of evidence demonstrate that unipolar depression is associated with altered brain structure and function. However, studies of the neurobiology of depression often use a cross-sectional design, making it unclear whether observed abnormalities represent etiologic causes, sequelae, both, or neither (the depressive syndrome and observed abnormalities may simply coincide with each other) [4].

Hypothalamic-pituitary-adrenal axis — Cortisol responses to stress are greater in patients with acute unipolar major depression, as well as remitted patients, compared with healthy controls [5]. It is thought that in many depressed patients, overproduction of corticotropin-releasing hormone causes excess activity of the hypothalamic-pituitary-adrenal cortex axis [6,7]. Prolonged or excessive secretion of glucocorticoids may lead to suppression of neurogenesis and hippocampal atrophy (figure 1) [8-10].

The hypercortisolemia observed in depressed patients was the basis for studies that evaluated the dexamethasone suppression test as a tool to diagnose major depression [11]. However, the test has poor sensitivity and fair specificity for this purpose. A meta-analysis found that baseline test results prior to treatment had no prognostic value, but that posttreatment nonsuppression of cortisol in patients was significantly associated with poor outcome [12].

Neural networks — A neural network (circuit) consists of interacting brain regions or systems whose activity is highly correlated and distinct from other networks. The neural network model of depression is based upon structural and functional imaging studies and postmortem brain studies [13].

One neural network includes regions of the brain involved in processing emotions (bidirectional projections from the orbital and medial prefrontal cortex and anterior cingulate, to the amygdala and nucleus accumbens), serotonergic projections that modulate this circuit, and the dorsolateral prefrontal cortex (which is critical in the cognitive regulation of emotion) [13-16]. The network is thought to influence autonomic, behavioral, and endocrine aspects of emotion and is impaired during depressive episodes. Exposure to stressors increases activity of serotonergic neurons, which are located in the brainstem (dorsal raphe nucleus) and regulate the prefrontal cortex, amygdala, and other parts of the circuit. In addition, glutamatergic projections from the prefrontal cortex synapse onto GABAergic neurons in the brainstem, which in turn inhibit serotonergic neurons. (See 'Neurotransmitters' below.)

One hypothesis regarding the mechanism of action for antidepressants is that they gradually induce plasticity in neuronal cortical networks, which facilitates recovery of malfunctioning circuits with rehabilitation and psychotherapy [17].

Connectivity — Multiple magnetic resonance imaging (MRI) studies indicate that unipolar major depression is associated with dysfunctional connectivity (communication) within different networks:

- A meta-analysis of 25 studies assessed resting-state functional connectivity in 556 patients and 518 healthy controls; approximately 25 percent of the patients were receiving pharmacotherapy at the time of imaging [16]. Major depression was associated with:
  - Hyperconnectivity within the default mode network, which may lead to self-referential thoughts
  - Hypoconnectivity within the frontoparietal network, which may lead to rumination and depressive biases towards internal thoughts
  - Abnormal connectivity between different networks
- A subsequent study enrolled female youth who had no lifetime history of psychopathology, but were at high risk for depression due to their family history [18]. During prospective follow-up lasting approximately six years, 20 subjects developed unipolar major depression, recovered, and then completed resting-state functional MRI scans; another 20 subjects remained depression-free and were also scanned. The results suggested that youth who developed depression had less connectivity in neural networks associated with emotion regulation. Compared with the depression-free group, adolescents who suffered depression manifested less connectivity between the amygdala

and orbitofrontal cortex and between the dorsolateral prefrontal cortex and frontotemporal regions.

One retrospective study used functional MRI to define four separate subtypes ("biotypes") of unipolar major depression, based upon distinct patterns of abnormal resting-state connectivity in frontostriatal and limbic networks [19]. Each subtype was associated with a different symptom profile; in addition, response to repetitive transcranial magnetic stimulation differed among the subtypes, ranging from a low of 23 percent in one subtype to a high of 83 percent in another subtype.

One study of patients with unipolar major depression assessed resting-state connectivity between the subcallosal cingulate cortex and other brain regions, and then randomly assigned the patients to pharmacotherapy or psychotherapy [20]. The pattern of connectivity associated with response to one intervention differed from the pattern of connectivity in patients who remitted with the other intervention.

Anatomic abnormalities — Central nervous system anatomic abnormalities in major depression are generally modest, and neuroimaging studies thus rely upon quantitative assessment (eg, voxel-based morphometry) of gray and white matter changes, rather than visual evaluation [21].

Gray matter volume — The volume of central nervous system gray matter structures is often decreased in unipolar major depression as well as other mental illnesses [22-25]. As an example, a meta-analysis of 193 MRI studies compared the volume of gray matter structures in psychiatric patients (n >7000 patients with unipolar major depression, bipolar disorder, schizophrenia, obsessive-compulsive disorder, substance use disorders, or anxiety disorders) with healthy controls (n >8000) [26]. Gray matter volumes of several brain structures (eg, hippocampus, insula, and anterior cingulate cortex) were smaller in patients than controls. In addition, gray matter volumes were generally comparable across diagnoses, except for a few effects distinguishing depression (and schizophrenia) from other disorders.

Structural neuroimaging in patients with longstanding or untreated depression show [21,27-29]:

- Increased ventricular-brain ratio
- Smaller frontal lobe volumes
- Smaller hippocampal volume

As an example, a meta-analysis of 64 MRI studies showed a number of brain areas were smaller in patients with unipolar major depression (n = 2418), compared with healthy controls (n = 1974)

[30]. The largest effect was in the anterior cingulate cortex. Other areas in the frontal lobe that showed reduced volumes in patients were the orbitofrontal cortex and subgenual prefrontal cortex. In addition, smaller volumes were found in the hippocampus, putamen, and caudate nucleus. Subsequent studies also found that major depression was associated with a smaller volume of the anterior cingulate cortex and orbitofrontal cortex (and the temporal lobes and insula) [24], as well as the hippocampus [23] and putamen [25].

A subsequent meta-analysis restricted itself to 11 studies of 400 medication-free patients with unipolar major depression and 424 healthy controls; the patients manifested smaller gray matter volume in the frontal gyrus, parahippocampal gyrus, and the hippocampus [31].

There is evidence that reduced hippocampal volumes precede the onset of depression in some patients. Volumetric MRI of the hippocampus was conducted in 29 adolescents with major depression, 22 healthy adolescents who had no personal history of a psychiatric illness but were at high risk for developing depression by virtue of at least one biological parent with a history of major depression, and 32 controls with no personal or family psychiatric history [32]. Compared with controls:

- The left hippocampus was smaller in the depressed group by 3.1 percent and the right by 3.0 percent.
- The left hippocampus was smaller in the high-risk group by 4.2 percent and the right by 4.9 percent.

Further evidence that reduced hippocampal volume precedes depression was found in a study of 23 daughters of mothers with recurrent episodes of depression during the daughter's lifetime (high risk) and 32 age-matched daughters of mothers with no psychiatric history (low risk) [33]. The daughters were all 9 to 15 years old, and none had any history of psychopathology. MRI found smaller hippocampal volumes in high-risk girls compared with low-risk girls. In particular, the left hippocampus was reduced by 3.5 percent. In addition, a meta-analysis of 193 neuroimaging studies (n >15,000 psychiatric patients) found that gray matter volume in the hippocampus was less in patients with unipolar major depression than patients with other disorders (bipolar disorder, obsessive-compulsive disorder, and anxiety disorders) [26].

Neuroimaging also suggests that age related neurodevelopment (eg, synaptic elimination, dendritic pruning, and myelination) in major depression may be abnormally accelerated:

- An MRI study estimated the difference between neuroanatomic age and chronologic age in the brains of depressed patients (n = 104); neuroanatomic age was based upon images

from healthy controls (n = 800) [34]. In depressed patients, neuroanatomic age was greater than chronologic age (four years), and the gap seemed to be greater among patients with early onset disease compared to patients with late onset.

- Another MRI study, which included 116 patients with unipolar major depression and 116 healthy controls, found that age-related reduction of the putamen was twice as large in the depressed group [25].

Information about the association between depression and increased pruning of cortical gray matter is discussed elsewhere in this topic. (See 'Pruning' below.)

Course of illness — Remission of depression may be associated with an increase in whole brain volume. A prospective observational study of patients who received pharmacotherapy for treatment resistant depression found that patients who remitted for six months (n = 12) manifested an increase in whole brain volume, including gray matter volume [35]. By contrast, patients who failed to remit for 12 months manifested decreased white matter volume.

Recurrence of depression may be associated with loss of gray matter [36]. A retrospective study included patients hospitalized for unipolar major depression and assessed with structural MRIs at baseline and approximately two years later [37]. Among patients who recovered from the index episode and then suffered at least one recurrent episode (n = 37), cortical gray matter volumes decreased in the dorsolateral prefrontal cortex and insula. Among patients without a recurrence, gray matter volumes in these areas remained stable. Use of psychotropic medication and depression severity were not associated with gray matter volumes.

White matter integrity — Unipolar depression is associated with microstructural deficits in central nervous system white matter tracts [21]. White matter deficits may underlie dysfunction of fronto/corticolimbic neural circuits implicated in the pathogenesis of depression, including circuits involved in emotion regulation. (See 'Neural networks' above.)

Diffusion tensor MRI studies in patients with unipolar major depression have identified deficits in white matter tracts traversing multiple areas, including the corpus callosum and superior longitudinal fasciculus [38]:

- A meta-analysis of 23 studies assessed white matter integrity in 736 patients and 668 controls; 29 percent of the patients were receiving pharmacotherapy at the time of imaging [39]. Major depression was associated with white matter abnormalities in the corpus callosum.

- Another meta-analysis included 15 studies with 434 patients and 429 controls, and avoided the confounding effect of medications by including only those studies with medication-free patients [40]. Major depression was characterized by white matter deficits in the corpus callosum, cerebellum, superior longitudinal fasciculus, and the arcuate network.

- A subsequent study enrolled 577 patients and 1867 controls; white matter integrity was disrupted in the superior longitudinal fasciculus, superior thalamic radiation, and forceps major [41].

Disruption of white matter tracts is also seen in pediatric depression. Two diffusion tensor MRI studies of unmedicated adolescents with depression (n = 52 and 25) and healthy controls (n = 42 and 21) both found microstructure abnormalities in the uncinate fasciculus, which connects the amygdala and hippocampus with the prefrontal cortex [42,43].

Another study found evidence that patients with current melancholic major depression were distinguished from patients with current nonmelancholic major depression and from controls with no history of depression by white matter abnormalities in the right anterior limb of the internal capsule, which connects the thalamus to the cingulate and frontal cortices [44].

Cellular alterations — The number, density, and size of neurons and glial cells in patients with major depression are abnormal.

Postmortem studies found that the density of certain gamma-aminobutyric acid (GABA) neurons in the occipital cortex was reduced by 28 percent in patients with major depression compared with psychiatrically healthy controls, and by 50 percent in the prefrontal cortex [45,46]. These changes are consistent with findings that levels of GABA are altered in depression. (See 'Neurotransmitters' below.)

The size of neurons in the prefrontal cortex was decreased by 18 to 20 percent in postmortem brain specimens from patients with major depression compared with healthy controls and by 23 percent in the anterior cingulate cortex [46-48].

A review found that the density and number of glial cells was reduced in major depression [49]. This included decreases in the prefrontal cortex, especially the orbital prefrontal cortex, dorsolateral prefrontal cortex, amygdala, and anterior cingulate cortex. In addition, impaired glial cell functions (glutamate metabolism, production of neurotrophic factors, and myelination) probably contribute to the pathophysiology of depression.

Pruning — Depression may be associated with increased pruning of cortical gray matter. Selective elimination of gray matter normally occurs during adolescence, resulting in volume loss and thinning. One study using prospective and retrospective data included children (n = 193) who underwent MRI multiple times; the children were three to six years of age at study enrollment and were followed for up to 11 years [50]. After controlling for potential confounding factors (eg, age, sex, ratio of income to needs, use of psychotropic medications, and psychiatric comorbidity), the analyses found that gray matter volume loss and thinning were greater in children with unipolar major depression than nondepressed children. Cortical gray matter volume decreased more rapidly in children with more depressive symptoms, such that reduction in volume was nearly two times faster in children with five symptoms, compared with children with no depressive symptoms. By contrast, family history of depression and traumatic experiences were not associated with alterations in the trajectory of gray matter maturation. The investigators speculated that the cortical changes associated with childhood depression may be related to experience-dependent neuroplasticity, rather than other genetic or psychosocial processes.

Vascular function — Multiple studies suggest that late-life depression is associated with peripheral and cerebral vascular dysfunction:

- A series of meta-analyses pooled data from 48 studies with more than 43,000 participants (mean age 66 years), including more than 9000 individuals with depression [51]. Most of the studies were cross-sectional. The investigators found that:
  - Higher levels of the plasma endothelial biomarker soluble intercellular adhesion molecule-1 occurred more often in depressed individuals than nondepressed individuals (odds ratio 1.6, 95% CI 1.3-2.0). Increased levels of the marker indicate dysfunction.
  - Increased severity of white matter hyperintensities, indicating cerebral small vessel disease, occurred more often in individuals with depression than those without depression (odds ratio 1.3, 95% CI 1.2-1.4).
  - Pooled results from prospective studies of individuals without depression at baseline, who were followed for an average of four years, found that new onset of depressive syndromes was more likely to occur in individuals with more severe white matter hyperintensities, compared to individuals with less severe lesions (odds ratio 1.2, 95% CI 1.1-1.3).

In addition, depression during late life, especially depression with first onset in late life (eg, age 60 years or greater), is accompanied by more diffuse cerebrovascular dysfunction than early

onset depression. In a meta-analysis of five cross-sectional MRI studies (n = 220 patients with late-life depression), periventricular white matter abnormalities were detected five times more often in patients with late-onset compared with early-onset depression (odds ratio 5, 95% CI 2-9); in addition, deep white matter hyperintensities (nine studies, 542 patients) were detected four times more often in patients with late-onset depression (odds ratio 4, 95% CI 3-7) [52]. This suggests that the structural abnormalities represented by white matter hyperintensities may be part of the etiology of late-onset depression. The investigators reasoned that if the reverse were true (ie, if depression or its treatment caused white matter hyperintensities), one would expect to find these lesions more often in patients with early-onset depression because of their longer duration of illness. Nevertheless, other explanations may account for the study results, such as an underlying pathologic process that predisposes older individuals to concurrently develop both depression and white matter lesions.

Additional information about cerebrovascular disease and depression is discussed separately. (See "Complications of stroke: An overview", section on 'Depression' and "Diagnosis and management of late-life unipolar depression".)

Brain activity — Functional neuroimaging shows that unipolar major depression is associated with increased or decreased activity in several brain areas, including those that may be involved in emotion regulation and reward processing [21]. In addition, changes in activity occur after treatment. Although metabolic studies have been used to diagnose depression and predict treatment response, functional neuroimaging for these purposes is not standard practice.

Imaging studies of brain activity differ in their methods, including whether subjects are performing a cognitive task during data acquisition or resting quietly, as well as the type of neuroimaging that is used. These differences may be related to varying or inconsistent results across studies:

- A meta-analysis of 14 functional MRI studies included youth aged 4 to 24 years who were diagnosed with unipolar major depression (n = 246) and healthy controls matched on age (n = 274); the studies examined central nervous system activity during tasks involving affective processing and executive functioning (eg, planning) [53]. The analyses found consistent patterns of abnormal activation in the depressed group, including:
  - Diminished activation in the cuneus and insula as well as heightened activity in the dorsolateral prefrontal cortex and superior temporal cortex, which may be related to negative affect and anhedonia.
  - Overactivity in the anterior cingulate cortex and thalamus, which may explain hypervigilance toward emotional stimuli.

- A subsequent meta-analysis of eight studies examined regional cerebral blood flow in 198 medication-free patients and 227 healthy controls; both groups rested quietly during neuroimaging, which consisted of single photon emission computed tomography, positron emission tomography, or MRI [54]. Compared with controls, cerebral blood flow in the patients was:

  - Increased in the caudate nucleus, insula, precuneus, hippocampus, and posterior cingulate cortex

  - Decreased in the frontal gyrus and anterior cingulate cortex

Reward networks — Multiple imaging studies have found that major depression is associated with abnormal activity within brain circuits (eg, the ventral tegmental area and nucleus accumbens network) that are thought to be involved in reward processing [55]. As an example, functional MRIs assessed brain activity in 30 patients with unipolar major depression and in 31 healthy controls during a task related to monetary gain (reward processing) [56]. Compared with controls, patients demonstrated weaker responses to monetary gains in the nucleus accumbens and caudate.

In addition, prospective studies in healthy individuals indicate that decreased striatal activity at baseline predicts subsequent depressive syndromes [57,58]. A study performed functional MRIs in healthy subjects (n >1000) during a task involving monetary incentives and assessed the subjects two years later for depression [59]. Decreased activation of the ventral striatum at baseline was associated with an increased risk of depressive syndromes at follow-up. In addition, a dose-response effect was observed, such that baseline striatal activation was lowest in subjects who developed probable major depression, highest in subjects who remained healthy, and intermediary in those who developed minor depression.

Association with treatment — Regional cerebral metabolic activity patterns may change with treatment of depression. One observational study using both prospective and retrospective data found that after depressed patients were successfully treated, metabolic changes occurred in different brain regions, depending upon whether patients received pharmacotherapy or psychotherapy [60].

In addition, regional cerebral metabolic activity may be associated with treatment outcomes. A prospective observational study enrolled 61 patients with unipolar major depression who had not been treated with antidepressants and obtained arterial spin-labelling MRIs before commencing antidepressants [61]. In patients who responded poorly to at least two adequate antidepressant trials, baseline cerebral perfusion was lower in limbic-striatal areas, compared with patients who responded to treatment.

Sleep and circadian rhythms — Changes in sleep architecture during depression include decreased [62,63]:

- Rapid eye movement latency
- Slow-wave sleep

Depression is also associated with alterations in central circadian rhythms that are related to diurnal variation in symptoms. Blunted circadian rhythms involve body temperature, blood pressure, pulse, plasma cortisol, norepinephrine, thyroid stimulating hormone, and melatonin [64]. The abnormal rhythms return to normal with antidepressant treatment and probably underlie the therapeutic benefits of circadian rhythm phase-shifting via light therapy or sleep deprivation [65].

Information about circadian rhythms and seasonal affective disorder is discussed separately. (See "Seasonal affective disorder: Epidemiology, clinical features, assessment, and diagnosis", section on 'Pathogenesis'.)

Inflammation — Multiple psychiatric disorders are associated with inflammation, and several studies have established that unipolar major depression is associated with higher mean serum concentrations of peripheral inflammatory markers, including the cytokines tumor necrosis factor and interleukin-6 (IL-6) and the acute phase reactant C-reactive protein (CRP) [66-71]. As an example:

- In a cross-sectional population study (n = 852 adults) that controlled for potential confounding factors (eg, age, sex, and smoking), serum biomarkers of low-grade inflammation such as CRP and tumor necrosis factor were associated with the presence of major depression and minor depression (odds ratio 1.6, 95% CI 1.2-2.1) [70].

- A prospective observational study measured serum concentrations of IL-6 at age nine years and then assessed the subjects for depression at age 18 years (approximately 4500 subjects). After adjusting for sociodemographic and clinical variables (eg, past mental health problems), subjects in the top third of IL-6 values compared with the bottom third at age nine years were more likely to be depressed at age 18 years (odds ratio 1.6, 95% CI 1.1-2.1) [71].

Furthermore, markers of inflammation are hypothesized to define a subpopulation of depressed individuals most likely to benefit from anti-inflammatory treatment. This theory is supported by data from a pooled analysis of 15 prospective studies including 56,351 individuals with depressive symptoms demonstrating that systemic inflammation is primarily associated with physical symptoms [72]. Elevated CRP or IL-6 was associated with changes in appetite,

feeling as if everything is a great effort, loss of energy, sleep difficulties, and concentration difficulties. In contrast, there was no association between the inflammatory markers and specific emotional symptoms such as fearfulness, hopelessness, feeling "bothered" by things, and feeling as if life has been a failure.

However, it is not clear that increased peripheral inflammation reflects increased central nervous system inflammation [73].

Inflammation may also be related to treatment resistant depression [73,74]:

- A study enrolled unmedicated outpatients with current major depression (n = 98), measured immune markers, and retrospectively assessed the number of prior antidepressant trials during the current episode [75]. A greater number of failed trials was associated with increased serum levels of tumor necrosis factor, IL-6, and soluble tumor necrosis factor receptor 2. In addition, patients with three or more failed trials had higher levels of each marker than patients with zero or one failed trial.

- Studies have found that among patients with depression, increased levels of acute phase reactants or cytokines prior to treatment were associated with a decreased response [76]. In addition, serum concentrations of inflammatory markers are elevated in patients with a history of nonresponse to antidepressants, compared with treatment responsive patients.

The hypothesis that inflammation may be associated with depression is supported by positive results from randomized trials of anti-inflammatory agents in depressed patients [77].

In addition, randomized trials that evaluated cytokine modulators in patients with chronic inflammatory disorders (eg, psoriasis or rheumatoid arthritis) found that these anti-inflammatory drugs improved comorbid depression [78].

Inflammation in major depression may be related to changes in connectivity (communication) between different areas of the brain. Resting-state MRIs in 48 medication-free patients with major depression found that increased serum levels of CRP were associated with decreased connectivity between the [79]:

- Ventral striatum and the prefrontal cortex, which in turn correlated with increased anhedonia

- Dorsal striatum and the prefrontal cortex, which in turn correlated with increased psychomotor slowing

In addition, increased serum levels of other inflammatory cytokines (IL-6, interleukin-1 beta, and interleukin-1 receptor antagonist) were associated with decreased connectivity between the striatum and prefrontal cortex.

Additional information about major depression and connectivity is discussed elsewhere in this topic. (See 'Connectivity' above.)

Telomere length — Depression is associated with abnormally short telomeres; this association is thought to represent accelerated cellular aging [80]. Telomeres are nucleotide sequences that are found at both ends of chromosomes and are thought to protect the chromosome from damage. The length of telomeres normally decrease over time in a progressive fashion, and this process is viewed as a marker of cellular age.

Studies that suggest depression is associated with short telomeres include the following:

- A meta-analysis of 11 studies (n >5000 depressed patients and healthy controls) found that telomere length was shorter in the depressed group than the controls, and the difference was moderately large [81]. However, heterogeneity across studies was substantial.

- In a meta-analysis of 38 studies (n >34,000 depressed patients and controls), telomere length was shorter in the depressed group than the nondepressed group [82]. However, the difference in telomere length between the two groups was small and there was evidence of publication bias.

- A subsequent study examined telomere length in patients with depressive and/or anxiety disorders (n >1500) and in healthy controls (n >600); after adjusting for potential confounding factors (eg, age, sex, and chronic diseases), the analyses showed that telomere length was shorter in patients than controls [83]. In addition, patients with the most severe depressive/anxiety symptoms had the shortest telomeres [84].

Race and ethnicity may mediate the relationship between depression and telomere length. A study of more than 2700 individuals found that telomere length was shorter in White Americans with depression than nondepressed White Americans, whereas in Black Americans or Hispanics, depression was not associated with telomere length [85].

Most of the studies examining depression and telomere length have been cross-sectional studies. Although the direction of the association is unclear, it appears that depression is associated with short telomeres, but that short telomeres are not associated with depression:

- A meta-analysis of 25 studies (n >21,000 depressed patients and controls) found that telomere length was shorter in the depressed group than the controls [86]. In the five

longitudinal studies, there was no relationship between depression and telomere length, whereas in the cross-sectional studies, depression was associated with telomere length.

- In a subsequent study that measured telomere length at study entry, mean telomere length was shorter in individuals (n = 370) who were previously hospitalized for depression (before study entry), compared to individuals (n >53,000) with no such prior history [87]. Following study entry, individuals with no past history of depression were followed prospectively for an average of eight years; short telomeres at baseline were not associated with an increased risk of depression.

These results are consistent with the hypothesis that depression causes physiologic changes that shorten telomeres [86].

Neurotransmitters — Depression involves abnormal functioning of several neurotransmitters, including:

- Monoamines (serotonin, norepinephrine, and dopamine)
- GABA
- Glutamate

Early theoretical models postulated that depression is due to diminished neurotransmission of monoamines, particularly serotonin and norepinephrine. It now appears that more complex dynamics, including intracellular cascades triggered by the monoamines, are involved in the onset of depression and the response to antidepressant medications [88].

The role of the serotonergic system has been repeatedly demonstrated in an experimental model that rapidly depletes tryptophan, the precursor amino acid required for central synthesis of serotonin. Patients in remission from major depression with selective serotonin reuptake inhibitors often exhibit a severe, rapid relapse after acute tryptophan depletion [89,90]. In addition, a meta-analysis of nine observational studies showed that serum concentrations of tryptophan were significantly lower in unmedicated patients with major depression (n = 156) than controls (n = 203), and the clinical difference was large [91].

The role of catecholamine system (norepinephrine and dopamine) has also been examined using a depletion paradigm with alpha-methyl-para-tyrosine, which rapidly depletes catecholamines by inhibiting their synthesis. A study found that patients treated with desipramine, a norepinephrine reuptake inhibitor, suffered a rapid increase in depression rating scale scores after taking alpha-methyl-para-tyrosine but not after taking placebo [92].

Decreased dopamine transmission has been associated with depression in genetic, neurochemical, neuroimaging, postmortem, and animal studies [93]. These studies support the hypothesis that some patients have a subtype of depression that is dopamine-sensitive and resistant to treatment with antidepressants that act initially on the serotonin and norepinephrine pathways.

Numerous studies implicate changes in GABA and glutamate in the pathophysiology of depression [94]. Magnetic resonance spectroscopy studies in medication-free subjects with major depression observed elevated levels of glutamate and lower levels of GABA in the occipital cortex [95], and found that increased basal ganglia glutamate was associated with increased anhedonia and increased psychomotor slowing [96]. In addition, abnormal reductions in glutamate/glutamine and GABA concentrations were found in the prefrontal cortex of unmedicated depressed patients [97]. These findings suggest that the changes in glutamate and GABA may vary by brain region. A gene expression study in the cingulate and prefrontal cortex of depressed suicides found significant alterations in glutamate recycling (glutamine synthase and GLUL), glutamate receptors (GRIA1, GRIA3, GRIK1, GRM3), and GABA receptors (GABARB3, GABRD, GABARG2) in depressed suicides versus controls [98].

Glutamate antagonists may thus be beneficial in treating major depression. (See "Ketamine and esketamine for treating unipolar depression in adults: Administration, efficacy, and adverse effects".)

Other neurotransmitters and neuromodulators may play a role in depression. These include endocannabinoids and the CB1 receptor, brain-derived neurotrophic factor (BDNF), acetylcholine, protein p11, and substance P [99-102]:

- Blockade of the cannabinoid CB1 receptor by the weight loss and smoking cessation medication rimonabant was associated with onset of depression symptoms to the extent that further drug development was suspended [102]. Circulating endocannabinoid ligands are reduced in patients with depression.

- BDNF appears to be involved in depression by linking stress, neurogenesis, and hippocampal atrophy [103,104]. However, BDNF may be a component of a wide range of psychopathology beyond depression.

Acetyl-L-carnitine — Serum levels of acetyl-L-carnitine, an endogenously produced molecule, may be decreased in unipolar depression. In one study of patients with acute unipolar major depression (n = 71) and age- and sex-matched healthy controls (n = 45), mean acetyl-L-carnitine levels were lower in patients than controls and the clinical difference was large [105]. In addition, the levels were lower in male patients than male controls, and in female patients than

female controls. Other analyses found that higher scores on the depression rating scale and an earlier age of onset were each associated with lower serum concentrations of acetyl-L-carnitine.

These results suggest that acetyl-L-carnitine may be a biomarker that can help diagnose unipolar major depression. In addition, it may be possible to treat patients with exogenous acetyl-L-carnitine [106].

PATHOGENESIS

Unipolar depression likely represents a group of heterogeneous disorders that are phenotypically similar. Depression can thus be considered the final common pathway of different disease processes that occur across a biopsychosocial continuum. (See "Unipolar depression: Pathogenesis".)

SOCIETY GUIDELINE LINKS

Links to society and government-sponsored guidelines from selected countries and regions around the world are provided separately. (See "Society guideline links: Depressive disorders".)

SUMMARY

- Cortisol responses to stress are elevated in patients with acute unipolar major depression, as well as remitted patients. (See 'Hypothalamic-pituitary-adrenal axis' above.)
- A neural network (circuit) consists of interacting brain regions or systems whose activity is highly correlated and distinct from other networks. Unipolar major depression is associated with dysfunctional connectivity (communication) within different networks. (See 'Neural networks' above.)
- Central nervous system anatomic abnormalities in unipolar major depression, which are generally modest, include decreased volume of gray matter structures. As an example, the hippocampus is smaller in depressed patients, and it appears that this reduced volume precedes onset of depression in at least some patients. In addition, depression is associated with microstructural deficits in white matter tracts. (See 'Anatomic abnormalities' above.)
- The number, density, and size of neurons and glial cells in patients with major depression are abnormal. (See 'Cellular alterations' above.)

- Late-life depression is associated with peripheral and cerebral vascular dysfunction. (See 'Vascular function' above.)

- Unipolar major depression is associated with altered activity in several brain areas, including those that may be involved in emotion regulation and reward processing. (See 'Brain activity' above.)

- Unipolar major depression is also associated with higher mean serum concentrations of peripheral inflammatory markers, including the cytokines tumor necrosis factor and interleukin-6 and the acute phase reactant C-reactive protein. (See 'Inflammation' above.)

- Depression is associated with abnormally short telomeres; this association is thought to represent accelerated cellular aging. Telomeres are nucleotide sequences that are found at both ends of chromosomes and are thought to protect the chromosome from damage. (See 'Telomere length' above.)

- Depression involves abnormal functioning of several neurotransmitters, including serotonin, norepinephrine, dopamine, gamma-aminobutyric acid, and glutamate. (See 'Neurotransmitters' above.)

- Unipolar depression likely represents a group of heterogeneous disorders that are phenotypically similar. Depression can thus be considered the final common pathway of different disease processes that occur across a biopsychosocial continuum. (See "Unipolar depression: Pathogenesis".)

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