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REVIEW

The Neuroanatomy of Depression:
A Review

PETER OAKES, MARIOS LOUKAS, ROD J. OSKOUIAN, AND R. SHANE TUBBS*

Depression is the most common psychiatric disorder, the number one cause of disability and affects up to 15% of the population. The aim of this review is to present a brief synopsis of the various biochemical imbalances thought to contribute to depression, aspects of anatomy possibly implicated in depression, and treatments related to targeting these specific locales. Multiple neurotransmitters and parts of the brain are involved with the disorder of depression. Although an exact etiology for depression has not been found in most cases, various treatments, medicinal, psychiatric and surgical, exist for this disabling disease. An improved knowledge of anatomical sites involved in patients with depression will help in future treatment modalities. Clin. Anat. 30:44–49, 2017.

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INTRODUCTION

Depression, or melancholia, was recognized as a disease state over 2,000 years ago and remains one of the most serious and far-reaching medical problems of our time (Beck, 1967). In the West, it is often defined as "the prolonged presence of either depressed mood or *anhedonia*, a markedly diminished interest or pleasure in response to previously enjoyable activities". Feelings of worthlessness can accompany such changes in mood. It was recently reported that depression is the most common psychiatric disorder and the number one cause of disability in adults under the age of 50. The WHO in 2001 classified it as the leading cause of disability-years (Price and Drevets, 2010). In a recent study, this leading cause of disability was estimated to affect up to 10–15% of the general population (Cleary et al., 2015). Yet another study from earlier in the century found that as many as 16.2% of the general population had experienced an episode of depression within the previous year (Kessler et al., 2003). Even after successful treatment, it is estimated that 20–80% of patients have a depressive episode within five years of symptom alleviation (Sheline et al., 2003). Paradoxically, the etiology of this most prevalent of all mental disorders remains largely unknown. For instance, no single region of the brain or neurotransmitter pathway has been definitively identified yet as a single root cause. In fact, it has been speculated that autonomic imbalances and an increase in cortisol production (often limited to patients with severe depression) can affect other systems of the body and cause increased incidences of cardiac events, coronary heart disease, type II diabetes, and osteoporosis (Price and Drevets, 2010; Hasler, 2010). While it is believed that 30–40% of depression cases are related to genetics, the genes implicated have not been identified (Hasler, 2010). The aim of this review is to present a brief synopsis of the various biochemical imbalances thought to contribute to depression, aspects of anatomy possibly implicated in depression, and treatment related to targeting these specific locales.

While localizing the seat of depression to any given region of the brain remains elusive, several gross morphological differences have been observed between patients with depression and those without. More precise localization remains challenging as different characteristics of the disease (such as age of onset or genetic involvement) can determine which parts of the brain are involved (Price and Drevets, 2010). First, hippocampal volume decreases in depression. The number of days that one has suffered from untreated depression affects hippocampal size

*Correspondence to: R Shane Tubbs; Seattle Science Foundation, Seattle, WA 98122.
E-mail: shanet@seattlesciencefoundation.org

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TABLE 1. Previously mentioned Brain Location, involved with Depression.

Structures of the Brain Found to be Smaller in Depressed Patients
Left Anterior Cingulum[a,b]
Left Amygdala[a]
Left and Right Prefrontal Cortices
Dorsolateral, Dorsomedial, and Ventrolateral Prefrontal Cortices
Superior and Medial Orbitofrontal Cortices
Superior and Medial Frontal Cortices
Temporal Cortices (especially the right temporal and supratemporal lobes)
Fusiform Gyrus
Parahippocampal Gyrus
Cerebellum (slightly more affected on the left)
Cuneus
Lingual Gyrus
Left Precuneus
Superior and Middle Occipital Cortices
Subgenu part of the Prefrontal Cortex Regions of the Infralimbic Cortex (BA 25)
Subgenu part of the Anterior Cingulate Cortex
Frontal Polar or Dorsal Anterolateral Prefrontal Cortex
Temporopolar Cortex
BA 45
Putamen (especially on the right side)
Caudate Nucleus
Posterior Orbital Cortex
Ventral Striatum^
Pars Opercularis
Nucleus Accumbens (Left especially)
Left and Right External Pallidum̂

[a]Denotes an accompanying decrease in oligodendrocytes.
[b]Denotes conflicting study results, with some showing enlargement of the region or no change.
Frodl et al., 2008**;** Price and Drevets, 2010**;** Bowen et al., 1989; Baumann et al., 1999.

directly, in contrast to patients who have undergone pharmacological treatment for the condition (Sheline et al., 2003). This decrease in hippocampus size has been further studied, revealing that the left hippocampus may be more affected than the right (Frodl et al., 2008). Some have reported this hippocampal shrinkage as reaching 8–19% (Price and Drevets, 2010; Stockmeier et al., 2004). Some authors report that it is accompanied by a decrease in gray matter density (Frodl et al., 2008) while others have found an increase in neuronal and glial cell density (Sheline et al., 2003). A similar size disparity was found between patients who had achieved remission and those who had not (Frodl et al., 2008). In rats, repeated stress results in atrophy of dendrites and a decreased glial cell count in the hippocampus (Price and Drevets, 2010). It has been speculated that this hippocampal shrinkage is due to a reduction of neuropil, which occurs in Major Depressive Disorder (MDD), and to a change in water content and brain plasticity (Stockmeier et al., 2004; Hercher et al., 2009). Many other portions of the brain have been associated with lower gray matter density in MDD patients than in healthy controls or remitted patients (Table 1). Specifically, lesions of the subgenu part of the anterior cingulate cortex, left perigenulate anterior cingulate cortex, and left subgenu part of the cingulate cortex are closely associated with familial MDD (Price and Drevets, 2010; Hasler, 2010). Several prominent studies have claimed that the most prominent volumetric abnormalities are a reduction in gray matter of the left anterior and left subgenu part of the cingulate cortex (Price and Drevets, 2010; Hasler, 2010). Lesions of the striatum, degenerative basal ganglia disease, and the orbital and medial prefrontal cortices have also been associated with episodes of MDD (Price and Drevets, 2010).

Within these atrophied structures of the brain, several neurocircuits are also aberrant. One such circuit is formed by the orbital and medial prefrontal cortex and the associated areas of the thalamus, temporal cortex, striatum, and limbic system (Price and Drevets, 2010). Another, the abnormality of which could contribute to the symptoms of depression as well as some of the associated autonomic and neuroendocrine disturbances, is the medial network and its related limbic structures (Price and Drevets, 2010). It is believed that deficits that alter synaptic transmission in these pathways could ultimately be responsible for the mood alteration seen in MDD (Price and Drevets, 2010). One specific example of this altered pathway can be revealed by experiment. Depressed patients often process stimuli in a more negative manner, causing them to have increased negative recall on memory tests, a quicker response to sad words on an affective attention shifting task, an increased reaction to sad as opposed to happy or neutral faces on face dot-probe tasks, and a more negative interpretation of ambiguous phrases or situations (Price and Drevets, 2010). Another neural model that relates the neuroendocrine autonomic neurotransmitter pathway to these disparities proposes that impairment of the medial prefontal network and basolateral amygdala unbridles efferent signaling from the central amygdaloid nucleus and bed nucleus of the stria terminalis to the brainstem and hypothalamus (Price and Drevets, 2010). While the amygdala mediates the release of corticotropin releasing factor (CRF), any subsequent effect is inhibited by stimulation of the glucocorticoid receptors of the ventral anterior cingulate cortex (Price and Drevets, 2010). Thus, lesions in this part of the brain in rodents result in higher concentrations of adrenocorticotropic hormone during stress (Price and Drevets, 2010). Such oversecretion was seen in severe depression, along with pituitary and adrenal gland growth and increased levels of CRF in the cerebrospinal fluid (Price and Drevets, 2010). Invoked stress levels are believed to contribute to the abnormal enlargement of the HPA-axis seen in response to stress and depression, believed to be secondary to increasingly high levels of CRF and ACTH (Price and Drevets, 2010). Depressed patients exhibit a dampened response of ACTH release relative to CRF levels because the CRF receptor density in the PFC is reduced, indicating chronic activation of the system (Price and Drevets, 2010). Unfortunately, treatment targeting this system has proved unfruitful to date (Hasler, 2010).

It should come to no surprise that rearrangement of the neurocircuitry of the brain in depression is accompanied by microscopic changes in brain anatomy. Postmortems on patients who experienced severe depression have shown synaptic reorganization in the hippocampus (Sheline et al., 2003). Cell plasticity is also altered in the fronto-limbic regions (Hercher et al., 2009). The densities of oligodendrocytes (speculated to be secondary to elevated glucocorticoid secretion and glutamatergic transmission), astrocytes, and microglia are reduced (Hercher et al., 2009; Price and Drevets, 2010). The subcortex has been implicated in a change in neuronal density (Hercher et al., 2009). Specifically, there are changes in cortical thickness, neuronal size and density, and glial density, in layers II-IV of the rostra orbitofrontal region (Rajkowska et al., 1999). Lower cortical layers in the caudal orbitofrontal cortex in MDD patients have decreased glial densities and lesser changes in neuronal size (Rajkowska et al., 1999). There are similar alterations in the dorsolateral prefrontal cortex's supra- and infragranular layers (Rajkowska et al., 1999). Patients suffering from depression also have lower glial cell counts than healthy patients in the following structures: the pregenual anterior cingulate cortex, the dorsal anterolateral, dorsal, orbital, and subgenual prefrontal cortices, and the amygdala (Price and Drevets, 2010; Hasler, 2010). These patients also showed a decreased average neuron size in the dorsal anterolateral prefrontal cortex (Price and Drevets, 2010). In MDD patients, the expression of several genes coding axonal growth and synaptic communication in the middle temporal cortex are reduced (Price and Drevets, 2010). Indeed, there is some decrease in myelination in many regions, including the middle temporal gyrus, the frontal polar cortex, and the dorsolateral prefrontal cortex, and a decrease in white matter in the genu and splenial regions of the corpus callosum, all of which supports the notion that myelination is decreased in MDD (Price and Drevets, 2010). Other genes also appeared to be missing in these patients, including some of those encoding cell communication and signal transduction (Aston et al. 2005). Such a combination of structural changes is believed to result in deficient synaptic communication in the above regions of the brain, with even signal transduction pathways implicated as faulty in some genetic variants (Aston et al., 2005). Other cytological differences in the brains of MDD patients include the increased density of granule cells and glia in the following structures: dentate gyrus, pyramidal neurons, and all cornu ammonis/hippocampal subfields (Stockmeier et al., 2004). Average soma size in pyramidal neurons, on the other hand, is greatly diminished in these patients (Stockmeier et al., 2004).

Perhaps one of the most intensely studied fields in relation to depression is the physiological adjustments that cause the disease; elucidation of such pathways would allow the disorder to receive more specific, targeted pharmacological treatments. Among the several functional changes in the brain, changes in blood flow during certain activities can be quite telling. Patients resistant to pharmacological treatment of depression exhibit increased blood flow to the subgenu part of the cingulate gyrus, and patients suffering from an episode of depression have increased activation of the middle occipital gyrus, cuneus, middle temporal gyrus, left frontal gyrus, left inferior parietal lobule, medial frontal gyrus, parahippocampal gyrus, cerebellum, right parahippocampal gyrus, and culmen (Cerullo et al., 2014). Similar areas show increased blood flow in patients suffering from bipolar disorder I (Cerullo et al., 2014). Alternatively, patients with depression have decreased cerebral blood flow in selected parts of the cerebellum, basal ganglia, prefrontal, premotor, temporal, and frontal cortices, dorsal anterior cingulated gyrus, and anterior insula (Fitzgerald et al., 2008). During a verbal fluency task, MDD patients exhibited lesser changes in hemodynamics in the prefrontal and temporal regions than healthy controls (Pu et al., 2015). Specifically in patients with suicidal ideations, there was a similar deficit in blood flow in the right dorsolateral prefrontal cortex, orbitofrontal cortex, and right frontopolar cortex (Pu et al., 2015). Blood flow is increased to the subgenu part of the anterior cingulate cortex when feelings of sadness are evoked experimentally (Price and Drevets, 2010). Tellingly, imaging has shown that treatments for depression via pharmacology, vagus nerve stimulation, or deep brain stimulation cause some parts of the brain that have gone awry to adjust their metabolism and blood flow appropriately following treatment (Price and Drevets, 2010). Another study compared the effect of external emotional stimulation on the pregenual anterior cingulate cortex, ventromedial prefrontal cortex, and dorsal posterior cingulate cortex in MDD patients and controls: those with MDD had lower negative blood oxygenation level-dependent (BOLD) responses (Grimm et al., 2009). Such activity of the blood in these areas correlates with "depression severity and feelings of hopelessness" (Grimm et al., 2009). Such results suggest that reduced negative BOLD responses in cortical midline regions are inexorably linked to abnormal negative emotional processing in the disease (Grimm et al., 2009).

In a similar way, patients suffering from depression differed from non-depressed controls in their mean oxy-Hb changes during certain activities, notably in the right frontal temporal region, suggesting decreased activity in this portion of the brain (Noda et al., 2012; Akashi et al., 2015). During verbal fluency tasks, patients with depression exhibited lower mean oxy-Hb changes than controls (Akashi et al., 2015). Patients suffering from bipolar disorder differed from healthy patients in a similar way in the frontotemporal cortical and the left temporal regions, the latter being correlated with symptom severity (Mikawa et al., 2015). One study correlated these lower blood flows to Hamilton Rating Scale for Depression results (Liu et al., 2014): decreases in blood flow to the lateral and lower prefrontal cortex, and specifically low oxy-Hb concentrations in both prefrontal and anteromedial prefrontal cortices, were correlated with MDD (Liu et al., 2014).

Numerous neuromodulatory systems in the brain have also been implicated in depression, including the GABAergic pathway **(**Hercher et al., 2009). Some studies have shown a decrease in cerebral GABA

levels (notably in the dorsomedial/dorsal anterolateral prefrontal cortex and occipital cortex) in depressed patients, and a reduction in the "Glx" peak, which represents the concentrations of glutamate and glutamine (particularly in the dorsomedial/dorsal anterolateral and ventromedial prefrontal cortices) (Price and Drevets, 2010). GABA neurotransmission was also altered in the occipital cortex in MDD patients (Cerullo et al., 2014). Even a single dose of the glutamate N-methyl-D-aspartate (NMDA) receptor antagonist ketamine rapidly alleviated the symptoms in these patients (Hasler, 2010).

Glucose metabolism also differs between the brains of patients with depression and those without (Price and Drevets, 2010). It is more rapid in depressed patients than in patients in remission in parts of the brain that are abnormal in either structure or blood flow (and in the left and right lateral orbital cortices and posterior cingulate cortex). It is believed to be correlated with glutamatergic transmission (suggesting altered excitatory amino acid transmission due to hypermetabolism) (Price and Drevets, 2010). More succinctly, metabolic abnormalities in the limbic and paralimbic structures of the mesiotemporal and prefrontal cortices are associated with MDD (Drevets et al., 2002). Interestingly, there is evidence that such symptoms can occur before depression is clinically manifest, as evidenced by cancer patients who developed depression versus those who did not (Price and Drevets, 2010). Metabolism is decreased in many of these structures during symptom remission after treatment with either antidepressants, electroconvulsive therapy, or deep brain stimulation (Nahas et al., 2007; Price and Drevets, 2010).

A recent meta-analysis revealed that the most consistent finding in MDD patients was decreased brain activity at rest in the lateral frontal and temporal cortices, insula, and cerebellum, which increased again after successful treatment, and increased activity in the ventromedial frontal areas and striatum (Hasler, 2010). Furthermore, numerous publications have correlated severity of MDD symptoms with metabolism levels in the subgenual anterior cingulate cortex and the accumbens/ventral internal capsule (Drevets et al., 2002; Price and Drevets, 2010).

The best-known neurotransmitter to be targeted pharmacologically in depression is serotonin (Hasler, 2010). Low levels have been associated with tryptophan depletion and symptoms of depression (Hasler, 2010). Tryptophan deficiency could be induced in MDD patients in remission and led to increased cerebral glucose utilization in certain areas, causing depressive symptoms (Neumeister et al., 2004). Similar effects were seen in MDD patients in whom catecholamine depletion was induced, specifically in the limbic-cortical-striatal-pallidal-thalamic circuitry (Hasler et al., 2008). In particular, abnormalities of certain serotonin receptors (such as serotonin-1A receptor) have been linked with depression (Hasler, 2010).

Depression also seems to be negatively correlated with dopamine release, as secretion is decreased when monetary rewards are introduced (Price and Drevets, 2010). In patients with depression, dopamine metabolite levels are low in CSF and jugular vein plasma (Hasler, 2010). Low levels in the nucleus accumbens have also been linked to anhedonic symptoms (Hasler, 2010).

Most neurons that utilize serotonin, noradrenaline, and dopamine in intercellular transmission are located in the midbrain and brainstem nuclei and send communications to other parts of the brain, indicating the importance of monoamines in regulating mood, reward processing, sleep, and other brain activities; a possible crossroads, deficiency in which could help explain the effects of depression (Hasler, 2010). With this belief in mind, some have remarked that almost every drug that increases monoamine concentrations has antidepressant benefits (Hasler, 2010). Another possibility is disruption of the circadian rhythm: certain symptoms of depression such as daytime fatigue and sleep disturbances point to this (Hasler, 2010). Overall, however, very few if any of these patterns of physiological differences apply to all depressed patients—a reminder of the complexity of the task that faces us (Hasler, 2010).

NONPHARMACOLOGICAL APPROACHES

Although the main current treatments for depression are pharmacological and psychotherapeutic, between ten and thirty percent of patients do not respond to either option (Cleary et al., 2015). Several alternative treatments have emerged because of this high rate of unresponsiveness, the most promising being deep brain stimulation (DBS). Hyperacute responses occur in many patients, who experience "sudden calmness or lightness," or "disappearance of the void". Such a dramatic response is believed to be due to deactivation of the hyperactive Cg25 region, which regulates negative emotions. The most common site for placing the DBS electrode is in the subgenual cingulate white matter (Cg25WM), targeted bilaterally. In one trial, five of the six patients met the predetermined parameters for response to therapy by the two month mark, and four of them continued to respond past the six month mark. While moderate spells of depression persisted in the patients over several weeks, the greater symptoms of "painful emptiness" had been relieved hyperacutely following treatment. After three months of stimulation, Cg25 and BA11 exhibited decreased blood flow. In the long-term responders, blood flow also decreased in the hypothalamus, anterior insula, medial frontal cortex, dorsolateral prefrontal, dorsal anterior, and posterior cingulate, premotor and parietal regions. Metabolism as a whole decreased in the accumbens area/ventral internal capsule following DBS treatment (Price and Drevets, 2010). These patients also experienced improved sleeping habits, energy levels, and motivation. Other studies have reported comparable success rates of around 50% (Jiménez et al., 2013; Luigjes et al., 2013). Additional suggested targets for DBS include: the lateral habenula, subcallosal cingulate, and the ventral capsule/ventral striatum (Cleary et al., 2015). The only reported side effects included lightheadedness and psychomotor slowing when a high enough treatment level was reached, and local infection at the level of the chest or scalp.

An alternative to DBS is vagus nerve stimulation. Following treatment, BOLD responses on fMRI were decreased in the right medial prefrontal cortex, anterior cingulate, and left anterior temporal pole, and over time in the right somatosensory cortex and right insula (the last being most strongly associated with depressive symptoms, an interesting fact considering its importance in vicero-autonomic, limbic, and somatic pain functions) (Nahas et al., 2007). Initially, vagus nerve stimulation caused an increase in limbic activity, but deactivation superseded this around Week 30, which was also when symptoms were alleviated (Nahas et al., 2007). Response to the BOLD-fMRI increased in the right superior temporal gyrus (Nahas et al., 2007). After ~6 months of treatment, vagus nerve stimulation caused increases in the CSF concentration of homovanillic acid, a metabolite of dopamine (Nahas et al., 2007).

Other alternative approaches to treating resistant depression include electroconvulsive therapy and transcranial magnetic stimulation. In electroconvulsive therapy, cerebral blood flow quadruples and the metabolic rate triples post-ictally, and there is immediate prefrontal and medial frontal deactivation (Nahas et al., 2007). This treatment decreases the broader limbic-thalamo-cortical circuitry's activity (Price and Drevets, 2010). Transcranial magnetic stimulation localized to the prefrontal cortex causes local and transynaptic modulation of subcortical regions, including the anterior cingulate cortex and amygdala, and in this respect it is similar to other treatments for depression.

CONCLUSIONS

Major depression remains one of the most serious medical problems plaguing the world, and to date no universal explanation has been established in terms of anatomy or pharmacology or neurocircuitry. Many techniques have been developed in attempts to locate the seat of disease within the brain, but much work remains to be done in this field.

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