Dysregulation of adult hippocampal neuroplasticity in major depression: pathogenesis and therapeutic implications

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Abstract

Major depressive disorder (MDD) was previously hypothesized to be a disease of monoamine deficiency in which low levels of monoamines in the synaptic cleft were believed to underlie depressive symptoms. More recently, however, there has been a paradigm shift towards a neuroplasticity hypothesis of depression in which downstream effects of antidepressants, such as increased neurogenesis, contribute to improvements in cognition and mood. This review takes a top-down approach to assess how changes in behavior and hippocampal-dependent circuits may be attributed to abnormalities at the molecular, structural and synaptic level. We conclude with a discussion of how antidepressant treatments share a common effect in modulating neuroplasticity and consider outstanding questions and future perspectives.

Introduction

Major depressive disorder (MDD) is one of the commonest psychiatric conditions in the United States and is the leading cause of disability worldwide¹. Historically, MDD was thought to be a disease of monoamine deficiency characterized by low levels of serotonin, norepinephrine and/or dopamine in the central nervous system²,³. The corollary of this hypothesis was that drug classes that increase the concentration of monoamines...
in the synaptic cleft should have antidepressant properties. Two major problems arose in relation to this antidepressant treatment model. First, although these medications are pharmacologically active within hours, their antidepressant effects are not apparent for weeks after starting treatment. Second, even when the medications are having meaningful pharmacologic effects, many patients do not improve. The most widely accepted response to both questions is to assume that the effects of antidepressants are dependent on downstream processes, such as an increase in neurogenesis, that take time to appear and are only robust in medication responders. Consequently, there has been a paradigm shift from a synaptic effect derived from the monoamine hypothesis to a more complex delayed downstream neuroplasticity hypothesis of antidepressant action that involves correcting a deficiency in neurons, processes and synapses that comprise the pathogenesis of depression.

Neuroplasticity is defined as the brain’s ability to undergo neurobiological changes in response to extrinsic stimuli such as early life adversity and chronic exposure to stress and/or intrinsic stimuli most notably genetic or epigenetic effects. The responses to these changes can be visualized at a structural level (e.g., cell number, dendritic spine density and morphology or synaptic protein levels) and at a functional level (e.g., synchronous firing) that in turn determine the state of networks, stress responses, mood, cognition and behavior. These changes can be adaptive and contribute to resilience in at-risk groups, or be maladaptive, resulting in neuropathology and psychiatric disorders.

The hippocampus is of particular importance in understanding depression pathogenesis. First, the hippocampus plays a critical role in mood regulation, in part, due to its connections with emotion-related brain regions such as amygdala and anterior cingulate cortex (ACC) as well as its feedback role in regulating the hypothalamus-pituitary-adrenal (HPA) axis. Second, the hippocampus is one of the few brain regions thought to be capable of adult neurogenesis. Third, given its role in HPA axis regulation, the high concentrations of hippocampal glucocorticoid receptors make it particularly vulnerable to allostatic load. Allostatic load is elevated in depression, which is associated with prolonged stress response, including elevated levels of cortisol associated with melancholia. As such, hippocampal neuroplasticity has been implicated in MDD etiology and antidepressant action.

**Learning, Memory, and Mood: Network Changes in Depression**

Depression is a heterogenous disease with symptoms spanning multiple domains of emotion and behavior, including but not limited to, changes in mood, anxiety, memory, anhedonia, optimism, sleep, energy, appetite, libido and psychomotor activity. However, in this review, we will focus on the neurobiological basis of two core symptom clusters reported in MDD: cognitive and affective. While affective symptoms are routinely characterized, it has been estimated that cognitive deficits affect 20-90% of MDD patients. Furthermore, deficits in memory, attention and executive functioning have been observed in the absence of a current depressive episode and even in individuals responding well to antidepressant treatment for affective symptoms, suggesting that cognitive deficits are only partly a state-dependent phenotype in MDD. Interestingly, the manifestation of these cognitive deficits is diverse. Some studies find deficits in attention and psychomotor processing...
that correlated with global level of functioning\textsuperscript{24} while others report deficits in executive functioning in conjunction with intact memory, attention and psychomotor performance. These discrepancies may be attributed to differences in cognitive testing methodologies and patient population. More generally, however, MDD is remarkably pleomorphic in terms of mood and vegetative symptoms. Within the same patient, there is no consistency of severity of individual symptoms, symptom components or factors across successive episodes of major depression\textsuperscript{32}. Therefore, different study populations may have different proportions of certain mood or cognitive subgroups of depression, explaining conflicting findings and the wide range in incidence of cognitive deficits.

The pathogenesis of cognitive and affective deficits in untreated MDD is not fully elucidated but likely involves abnormalities across multiple brain regions\textsuperscript{33-35}, and includes but is not limited to changes in functional and/or structural connectivity. The dorsolateral prefrontal cortex (DLPFC) is responsible for attention, working memory and executive function and is positively correlated with working memory load in healthy controls\textsuperscript{36}. Neuroimaging studies have consistently reported DLPFC hypoactivity at rest in unmedicated MDDs\textsuperscript{37, 38} but DLPFC hyperactivity during working memory tasks\textsuperscript{39}. Yet, this hyperactivity is not matched with increased memory performance\textsuperscript{40}. The association between DLPFC activity, memory and MDD has not been consistent, as others have reported DLPFC hypoactivity in conjunction with decreased working memory performance\textsuperscript{41, 42}. Connectivity studies of the middle frontal gyrus (part of the PFC) and hippocampus, report negative correlations between these regions to be associated with illness duration in untreated depressed patients\textsuperscript{33}. Negative correlations indicate that when one brain region is activated the other is deactivated while positive correlations indicate brain synchronicity when regions are activated or inhibited at the same time\textsuperscript{43}. Taken together, these studies suggest inefficient or malfunctioning prefrontal activity and connectivity, which may underlie working memory deficits in a subset of untreated depressed patients.

The PFC plays a role in memory, including working memory, but also is integral in emotion regulation through the cortico-limbic network. Top-down dysregulation of limbic structures may mediate affective symptoms and altered decision-making seen in mood disorders\textsuperscript{44-46}. In healthy controls, when asked to downregulate emotional responses in the presence of an aversive stimuli, the PFC and ACC were hyperactivated and the amygdala was hypoactivated. When participants were asked to upregulate negative emotions in response to aversive stimuli, both the PFC and amygdala were activated\textsuperscript{47}, suggesting a PFC-dependent cognitive component in emotional regulation in healthy individuals. Conversely, when patients with MDD were asked to ignore negative stimuli, they failed to recruit the DLPFC which was correlated with amygdala hyperactivity\textsuperscript{48}. Such examples of altered cognitive control of mood are characteristic of MDD during emotion-related tasks. Inability to focus on external environmental stimuli during periods of rumination can further maintain negative thought content and depressive episodes\textsuperscript{49}. Additionally, focus on negative internal stimuli can result in more strongly encoding negative experiences and sustain negative thoughts and expectations, and underly a biased recall of negative relative to other memories in depressed patients.
In addition to dysfunctional top-down regulation, altered limbic and intra-hippocampal connectivity has been observed in MDD. Connectivity between the amygdala and hippocampus is the link between declarative memory and affect-related memory and is more strongly, positively correlated in MDD patients compared with non-psychiatric controls when participants were retrieving negative emotions. Interestingly, unmedicated adolescents with MDD showed less resting state fMRI (rsfMRI) connectivity between hippocampus and amygdala compared with healthy controls. This lack of connectivity between hippocampus and amygdala correlated with severity of depression. Variations between hippocampal-amygudala connectivity during resting state and emotional and cognitive tasks suggests that this network is context-dependent and modulated by environmental stimuli and individual emotional state.

Abnormal connectivity between individual hippocampal subfields with other brain regions, also contributes to MDD symptoms. Increased connectivity between hippocampal dentate gyrus (DG) (responsible for spatial encoding and memory) and ventrolateral PFC (responsible for regulation of emotions, impulsivity, and memories of anticipated rewards for each action or choice) may contribute to strong negative emotional memories in MDD. Furthermore, in human and rodent studies, changes to hippocampal circuitry have been associated with early life adversity which suggests an epigenetic mechanism for these changes and MDD pathogenesis. Taken together these studies suggest aberrant network organization and functionality may underlie dysregulated emotional perception, elaboration, cognition, and emotion regulation in depressed patients.

A Balancing Act: Cell Death and Survival

Network activity is not only dependent on firing frequency and synchrony, but also relies on the number and type of neurons available in a specific region being recruited for a given activity. As such, hippocampal cell loss and its implications for MDD are complex. The hippocampus comprises the following subregions - Cornu Ammonis (CA) regions 1-4, DG and subiculum (Figure 1). Each subregion has its own unique function, pattern of inputs and outputs, and gene expression profile. In rodents, DG and CA3 contribute primarily to intra-hippocampal connectivity (working to integrate information within the hippocampus), while CA1/CA2 and subiculum are organized into global networks tasked with extrahippocampal communication. Likewise, the hippocampus has a range of functions along its rostral-caudal axis with the anterior/head (ventral in rodents) being responsible for emotional regulation while the posterior/tail (dorsal in rodents) plays a larger role in declarative memories. Differential volume loss within hippocampal subfields (e.g., in CA3 but not CA1) or along the hippocampal axis may underlie different aspects of MDD symptoms and psychopathology.

Although some studies report no volumetric differences between MDD patients and healthy controls, these studies included patients who were either currently on antidepressants or had been on antidepressants at some point in their life. Most studies find that untreated depressed patients have smaller hippocampal volume, neuronal and glial number, and cell size compared with non-psychiatric controls. Moreover, in MDD, the extent of hippocampal gray matter volume loss is related to time spent depressed and smaller...
hippocampal volume is associated with worse depression scores. In addition to MRI, volume estimates have been conducted using unbiased stereology on postmortem human hippocampus. We have shown that DG granule neuron number and DG volume were smaller in anterior and mid, but not posterior hippocampus in unmedicated MDD postmortem. Additionally, we found more granule neurons and a larger DG in resilient subjects who were exposed to childhood adversity but had no lifetime psychiatric diagnosis and died from natural causes. Interestingly, there is disagreement over which regions of the hippocampus are smaller in depression. Some find volumetric sparing of CA1 while others report CA1 volume loss. Some report volume loss selectively in the hippocampal head and others observed volume loss in the hippocampal body. Differences in the study sample may partially explain conflicting results because an array of environmental and internal risk factors may contribute to MDD, and with differing effects on brain regions. For example, MDD patients who reported being sexually or physically abused showed smaller left CA1 volume when compared with MDD patients who were not abused.

Hippocampal volume loss is not pathognomonic for depression and can occur in the presence of environmental stressors, other psychiatric conditions, and neurodegenerative diseases. Smaller ACC, DLPFC, medial prefrontal cortex (MPFC) and hippocampus were shown in non-depressed individuals with a familial history of depression (first degree relative with MDD diagnosis) exposed to emotional neglect when compared to non-depressed individuals with no familial risk factors but who had been exposed to emotional neglect, suggesting a gene-environment interaction affecting cell viability. Other studies disagree and report an independent environment effect on gray matter volume. For example, in the absence of familial risk, early childhood trauma severity (operationalized via the Childhood Trauma Questionnaire) correlated with amygdala responsiveness and hippocampal volume loss in a group of healthy volunteers, and these associations were not influenced by recent life stress, depression or anxiety scores. Interestingly, other studies suggest volumetric differences may precede environmental trauma and determine the clinical outcome of such adversity. This concept has been demonstrated in an MRI study of PTSD which showed how smaller hippocampal volume predicted risk of PTSD and did not result from the trauma that triggered PTSD.

Currently, reported mechanisms potentially underlying cell loss include, but are not limited to, glutamate/glutamine cycling (see section on Molecular and Cellular Mechanisms of Neuroplasticity), blunted neurogenesis, decreased neurotrophic factor expression and upregulation of pro-apoptotic pathways. One potential process involved in neuronal loss is decreased brain-derived neurotrophic factor (BDNF) via histone modifications to the promoter region associated with downregulation of BDNF transcripts. Given its role in neuronal maturation and differentiation as well as its neuroprotective effects, low brain levels of BDNF may affect neuronal viability in MDD. This is because BDNF can bind to tropomyosin kinase B (TrkB) receptor which activates the mechanistic target of rapamycin (mTOR) signaling pathway which promotes neuronal growth, proliferation and migration. In humans, BDNF polymorphisms were found in adults with young-onset depression. Additionally, BDNF expression was decreased in postmortem hippocampus in untreated MDDs but not in antidepressant-treated depressed individuals. In rodents, BDNF
haploinsufficiency resulted in smaller hippocampal volume and increased anxiety-related behaviors when exposed to chronic stress\textsuperscript{80, 81}.

Upregulation of pro-apoptotic factors such as Bax and downregulation of anti-apoptotic factors like Bcl-2 have been shown in rodent models of depression\textsuperscript{82, 83}. Similarly, upregulation of genes involved in cell death and apoptosis were found in blood and postmortem PFC of patients with MDD\textsuperscript{84, 85}. In rodent models, exposure to a pollutant known to cause cell death or inflammation, caused upregulation of inflammatory markers and mediators of apoptosis in hippocampal neurons and resulted in depressive symptoms\textsuperscript{86, 87}. Elucidating mechanisms that underlie cell death and survival may be critical in harnessing effective therapies for MDD.

A role for adult hippocampal neurogenesis in depression pathology?

A significant contributor to neuroplasticity is adult hippocampal neurogenesis (AHN), the process by which new neurons are generated from adult neural stem cells. This process is regulated through epigenetic modifications of transcription factors, non-coding RNAs and metabolic pathways\textsuperscript{88}. During embryonic development in rodents, primitive dentate progenitors from dentate neuroepithelium migrate along the dentate migratory stream to establish the primitive dentate gyrus\textsuperscript{89, 90}. The majority of dentate granule neurons are generated during the first postnatal week\textsuperscript{90}. Although less is known about embryonic hippocampal neurogenesis in humans, some studies suggest overlap in developmental timing and molecular signatures between the rodent and human brain\textsuperscript{91}. The switch between developmental neurogenesis and AHN is gradual, and some sequencing studies have demonstrated these two processes share highly similar transcriptional trajectories\textsuperscript{91}. Some have demonstrated that neural stem cells in the adult hippocampal subgranular zone (SGZ) niche are remnants of dentate neuroepithelium\textsuperscript{92} and this same population of progenitors exclusively contributes to hippocampal neurogenesis throughout development and into adulthood, shifting out of quiescence at different time points\textsuperscript{93}. Others have argued that these stem cells originated in the ventral hippocampus and migrated dorsally\textsuperscript{94}.

Interestingly, if AHN exists, the extent to which it resembles its embryonic precursor on a morphologic and transcriptomic level remains a critical point of contention. Some groups have reported absent or minimal hippocampal neurogenesis in the mature brain using double immunofluorescence targeting markers expressed by neuronal cells at different maturational stages\textsuperscript{95, 96} and single nucleus transcriptomics\textsuperscript{97}. However, our group and others have shown evidence of neurogenesis throughout adulthood using double immunofluorescence\textsuperscript{98-101}, in situ hybridization\textsuperscript{102} and \textsuperscript{14}C decay-defined neuronal age\textsuperscript{103}. The ability to visualize newborn neurons is heavily dependent on tissue fixation procedures, experimental protocols, and subject selection, as previously described\textsuperscript{102, 104, 105}.

In addition to the histological concerns, skeptics of AHN also raise ideological criticisms. An influential paper from 1985, and a recent review, postulated that evolutionarily advanced brains would favor stability over plasticity, calling into question the evolutionary advantage of integrating new neurons into complex brain circuits\textsuperscript{106, 107}. On the other hand, it has been suggested that AHN provides cognitive adaptability to survive in a variable and ever-
changing environment through the flexible integration of novel information into preexisting representations\textsuperscript{108-110}. A second ideological argument is why the hippocampus would not grow over the lifespan if neurogenesis persists. While $^{14}\text{C}$ decay-defined neuronal age estimates that the human brain adds up to 700 new neurons each day (approx. 0.004\% of total DG neurons), resulting in a 1.7\% cell turnover annually\textsuperscript{103}, in rodents, it has been estimated that up to 30-70\% of newborn neurons die in the first month and that 1300 neurons are eliminated daily from the rodent hippocampus\textsuperscript{111, 112}. Although equivalent studies have not been conducted in humans, it is likely that the rate of cell death offsets neurogenesis thereby preventing expansion of hippocampal volume in adult life.

Although unknown in humans, studies in adult rodents have demonstrated that new born neurons have a critical period (2-4 weeks) of hyperexcitability, when they are preferentially recruited during a wide variety of hippocampal-dependent tasks such as flexible learning\textsuperscript{113, 114}, spatial memory\textsuperscript{115} and most notably pattern separation (the ability to separate similar but different memories or experiences)\textsuperscript{116, 117}. Deficits in AHN may not only explain the learning and memory deficits in MDD, but also play a role in the selective engagement with negative valence memories, mood regulation and antidepressant response\textsuperscript{118-122}. A few studies provide evidence that the absence of neurogenesis elicits depressive like symptoms in rodents\textsuperscript{123, 124}, but most studies find that absent neurogenesis is not sufficient to induce a depressive phenotype\textsuperscript{125} although it is required in mice for the behavioral effects of antidepressants\textsuperscript{118, 126}. In fact, the inability to produce more neurons appears to make the animal vulnerable to the epigenetic effects of chronic stress and subsequently the development of a depressive phenotype\textsuperscript{88}. This may be because newborn neurons confer resilience to stress by inhibiting stress-responsive mature granule neurons during anxiogenic tasks\textsuperscript{127}.

In postmortem human brain, we found fewer neural progenitor cells and mature granular neurons in unmedicated depressed subjects, selectively in anterior DG, compared with non-psychiatric sudden death controls, suggesting that neurogenesis may be blunted in MDD\textsuperscript{62, 63}. Humans receiving chemotherapy, which kills proliferating cells (thus blunting neurogenesis), experience cognitive deficits and are more likely to develop depression than cancer patients treated with other therapies\textsuperscript{128-130}. In rodents, administration of chemotherapy resulted in a loss of hippocampal proliferating cells that correlated with behavioral deficits\textsuperscript{131, 132}. Thus, it is possible that, like in rodents, the role of newborn neurons in humans is predominately for conferring resilience on the hippocampal circuitry, and possibly facilitating circuit rewiring for the antidepressant response.

**Molecular and Cellular Mechanisms of Neuroplasticity**

As previously discussed, patients with depression have disruptions in neurological circuits responsible for mood regulation and cognition, that may underlie MDD symptoms. Long-term potentiation (LTP) and long-term depression (LTD) are two mechanisms that impact cognitive and affective functions impaired in MDD\textsuperscript{133-135}. Increased neuronal firing in the presence of a strong, constant stimulus enhances LTP by subsequently strengthening synapses which mediate learning and memory. LTD, on the other hand, is an activity-dependent reduction in the efficacy and connection of neuronal synapses\textsuperscript{136}.
In the presence of high neuronal stimulus, α-animo-3-hydroxy-5methyla-4-isoxazolepropionic acid (AMPA) receptors and the adjacent N-methyl-D-aspartate (NMDA) receptors remain open, resulting in strong depolarization and calcium influx. Intracellular calcium activates protein kinases responsible for enhancing synaptic communication efficiency through increasing sodium conductance\(^{137, 138}\) (Figure 2). These changes are believed to be responsible for short-term memory, which can last for several hours. The late phase of LTP is dependent on transcription and translation activity for de novo gene expression that mediates structural and enduring functional circuitry changes\(^{139-141}\). One such mechanism that induces these changes is the BDNF-TrkB cellular pathway. The transcription of BDNF is dependent upon activation of the cyclic adenosine monophosphate (cAMP) response element binding protein (CREB) protein which plays a critical role in LTP and synaptic plasticity\(^{142, 143}\). BDNF binding to the TrkB receptor activates several signaling cascades (e.g. MAPK/ERK, PI3K, mTOR)\(^{144}\) responsible for spine enlargement and glutamate sensitivity\(^{145}\) (Figure 3). The role of BDNF-TrkB signaling is most evident in hippocampus through its role in LTP and facilitation of learning and memory\(^{146}\).

LTP in MDD has most frequently been assessed using stress-induced rodent models of depression. These studies have generally observed increases in DG LTP\(^{147}\) and reductions in LTP at Schaffer collaterals-CA1 synapses\(^{148, 149}\) in response to acute and chronic stress. Exposure to stress attenuates LTP in dorsal hippocampus but augments LTP in ventral hippocampus of rodents\(^{150}\), which may explain memory deficits in the presence of strong emotional responses. In humans, LTP is difficult to measure directly. However, proxy measurements such as paired associative stimulation (PAS) using a transcranial magnetic stimulation protocol have shown that PAS-induced increases in motor-evoked potential amplitudes were attenuated during major depressive episodes compared with healthy controls and normalized during remission\(^{151, 152}\). This suggests that LTP attenuation may be a state rather than trait marker in MDD.

Dendritic integration and synaptic strengthening are dependent on neuronal activity since dendritic summation of synaptic inputs are spatially and temporally dependent. Therefore, changes in glutamatergic signaling can increase or decrease excitatory postsynaptic potentials, affecting LTP. In the brain, glutamate is made from glutamine, and after glial reuptake, glutamate is converted back to glutamine. In rodents, acute exposure to stress via restraint or swimming test procedures, increases glutamate production, particularly in hippocampus and prefrontal cortex\(^{153-155}\). However, sustained high levels of glutamate can be toxic to the cell due to dysregulated calcium homeostasis which is essential for maintaining neuronal integrity and long term survival\(^{156}\). Some have reported increased glutamate levels in the plasma of untreated MDD patients\(^{157, 158}\) in line with reports of high CSF glutamate concentrations in severely depressed, hospitalized MDD patients\(^{159}\) and in untreated elderly MDD patients when compared to healthy controls\(^{160}\). In vivo proton magnetic resonance spectroscopy (\(^{1}H\) MRS) detected elevated glutamate levels in ventromedial prefrontal cortex/anterior cingulate cortex in untreated MDD\(^{161}\) consistent with a recent meta-analysis of MRS imaging studies that found higher glutamate/glutamine concentrations in medial frontal cortex of unmedicated MDD but not in antidepressant-treated patients\(^{162}\). As such, lower glutamate may be an antidepressant effect and not part of MDD pathogenesis. It should be noted that most MRS studies assessed Glx levels that are
the sum of glutamate and glutamine, and examined CSF and/or blood which may miss brain region specific abnormalities.

Normal stress responses involve glutamate release which downregulates AMPA and NMDA receptor expression, glutamate clearance by glia, and less dendritic spine and process complexity\textsuperscript{163, 164}. Deficient glutamate clearance, reported in MDD, may be due to downregulation of high affinity glutamate transporters, expressed specifically in glia, but not neurons, in human hippocampus\textsuperscript{165}. Levels of glutamate receptor genes \textit{GLUR1} and \textit{GLUR3} were down-regulated in postmortem DG and CA1 in MDD subjects off medication at time of death but had been previously prescribed antidepressants\textsuperscript{166}. Increased glutamatergic transmission in the presence of stressful situations and lack of glutamate clearance mechanisms may explain strong encoding of negative valence memories in MDD.

Impaired LTP may impact dendritic spine number/density, size, and complexity\textsuperscript{167, 168}. BDNF\textsuperscript{+/−} mice show less dendritic branching as well as dendritic retraction and simplification in CA\textsuperscript{3} and DG\textsuperscript{30} and dysregulation of BDNF/TrkB pathways has been reported in MDD and animal models of depression\textsuperscript{78, 169-171}. Similar reductions have been found in proteins such as CREB and its upstream effectors ERK and PKC\textsuperscript{172-174}. Synaptic strength moderates neural signaling between cells over an extended period\textsuperscript{175, 176}, underlying circuit functionality. Dendritic retraction may be an adaptive way to protect neurons from high glutamate transmission, resulting in less LTP and cognitive decline. Nevertheless, additional studies are needed to determine the extent to which dendritic changes occur in MDD and their regional brain distribution.

**Treatment Induced Neuroplasticity**

While duration or presence of major depression correlates with declines in neuroplasticity, administration of antidepressants may reverse some of the neurobiological changes observed in MDD (Figure 4). As previously discussed, traditional antidepressants target the monoaminergic system to increase levels of monoaminergic neurotransmitters in the synapse. This may upregulate LTP pathways, and downregulate LTD\textsuperscript{177, 178}, having benefits on network activity and consequently cognition and behavior. At a systems level, fMRI studies found that SSRI treatment impacted network functionality in MDD. Studies using rsfMRI detect DLPFC hypoactivity in untreated MDD, and SSRIs increase DLPFC activity to a level comparable with non-psychiatric controls\textsuperscript{179}. Furthermore, modulation of networks can be achieved through deep brain stimulation (DBS)\textsuperscript{180-182}. A double-blinded randomized trial showed enhanced working memory in MDD patients during emotional conditions\textsuperscript{183} after transcranial stimulation of the left DLPFC.

In addition to changes at the circuit level, MRI studies have found that SSRI treatment ameliorated hippocampal volumetric loss over time\textsuperscript{184}. SSRI treatment is associated with normal hippocampal volumes in postmortem human brain while untreated MDD is associated with a smaller hippocampus compared with non MDD sudden death controls\textsuperscript{62}. In line with this, voxel-based morphometry demonstrated increased hippocampal grey matter volume after antidepressant treatment\textsuperscript{185, 186}. Medicated patients experiencing depressive
episodes had smaller gray matter volumes than those in remission\textsuperscript{157} indicating that recovery from a depressive episode may permit brain regrowth.

Changes in brain volume may also be due to decreased neurotoxicity from decreased glutamate concentration. Patients with MDD treated with fluoxetine for 10 days showed a reduction in plasma glutamate levels when compared to baseline\textsuperscript{157}. While this reduction does not lower glutamate levels to the same concentration as healthy controls, it has been shown that antidepressant-treated glutamate levels are positively correlated with Hamilton Depression Rating Scale scores\textsuperscript{187}. Another mechanism that may contribute to restoration of hippocampal volume after antidepressants is increased neurogenesis. We found that antidepressant treatment is associated with more neural progenitor cells and granule neurons in postmortem human DG in MDD compared with non-MDD sudden death controls. This suggests an increase in neurogenesis over normal levels that allows a catchup in mature granule neurons in MDD to regain levels seen in controls\textsuperscript{62, 121}.

Although SSRIs and serotonin-norepinephrine reuptake inhibitor (SNRIs) perform better than placebo at reducing symptoms of depression\textsuperscript{188, 189}, there are weeks-long lag time in attaining full benefit and many patients do not respond. This has increased the need for rapid acting antidepressants. Recent studies have shown that NMDA receptor antagonists like ketamine and 5-HT\textsubscript{2A} receptor agonists like serotonergic psychedelics (the most studied include lysergic acid diethylamide/LSD and psilocybin) induce rapid and sometimes robust antidepressant effects\textsuperscript{190-193}. This makes the mechanism of action of these two types of medication of great interest.

Ketamine is a non-competitive NMDA inhibitor\textsuperscript{194}. At a therapeutic dose, ketamine produces activity-dependent inhibition of less than 50% of NMDA receptors and binds with greater affinity to subunits of NMDA receptors expressed in the synapses of inhibitory interneurons\textsuperscript{195}. The dosage and affinity are important because, to increase LTP, some NMDA receptors must be available. In fact, rodent studies have shown that infusion of ketamine onto hippocampal neurons caused dose-dependent apoptosis, which was rescued by incubation with rapamycin (an inhibitor of mTOR), suggesting context-dependent benefits of ketamine\textsuperscript{196}. Nevertheless, it is hypothesized that when ketamine binds to NMDA receptors, the glutamate in the synapses of excitatory pyramidal neurons in the hippocampus\textsuperscript{197} and PFC\textsuperscript{198, 199} shift transmission to AMPA receptors, and thereby strengthens synaptic connections driving synaptogenesis\textsuperscript{200}. At the same time ketamine can prevent hyperexcitability and subsequent neurotoxicity through antagonism of NMDA receptors. Rodent models of depression show that ketamine administration increases dendritic spine density, length, arborization and morphology in CA1 pyramidal neurons\textsuperscript{201}. This has been hypothesized to be modulated by increases in BDNF/TrkB signaling\textsuperscript{193}. Psychedelic drugs likely work via 5-HT\textsubscript{2A} receptors but require more research to elucidate their antidepressant effects\textsuperscript{202}.

Precision medicine could have an especially powerful impact on diagnosis and treatment of MDD due to the heterogeneity of clinical presentations. Despite our increasing understanding of depression pathophysiology, clinicians are unable to use biomarkers in blood or cerebrospinal fluid, neuroimaging or genomics to diagnose and guide treatment.
for MDD\textsuperscript{203}. Recent studies suggest that blood levels of sertraline, a common first-line antidepressant, can successfully be predicted through analysis of genes involved in sertraline metabolism and thus, giving an indication of drug effectiveness\textsuperscript{204-206}. Similarly, blood testing has identified genes (e.g., NRG1 which is involved in regulation of proliferation, survival, and differentiation of many cell types including neurons and epithelial cells\textsuperscript{207}), proteins (e.g. CD47 which is implicated in neuroinflammatory cascades\textsuperscript{208}), and proinflammatory markers (IL-1\textbeta, IL-6)\textsuperscript{209-211} that are associated with depression. All are candidate screening biomarkers for antidepressant response. Electrophysiological characteristics and neuroanatomy findings indicated that neuroimaging can identify patient-specific targets for DBS and transcranial magnetic stimulation, increasing treatment efficacy\textsuperscript{213, 214}.

**Concluding Remarks and Future Perspectives**

Neuroplasticity is integral to healthy cognitive and affective functioning. Changes in dendritic morphology and density, neurogenesis, growth factor expression and neurotransmitter production all likely contribute to changes in functional connectivity underlying behavioral and cognitive deficits in MDD. These impairments have been targets of antidepressant action and reversal of deficits in neuroplasticity correlated with improvements in symptoms. MDD clinical heterogeneity remains poorly understood, particularly in terms of how it relates to pathogenesis and implications for treatment choices. Although a growing body of research has provided evidence that neuroplasticity is implicated in depression pathogenesis, more research is required to discern disease etiology and how pathological findings can be more specifically reversed. More rigorously characterizing patients with MDD using a combination of symptom-based, genomic, bloodwork, and brain imaging findings may prove useful in detecting depression biologic subtypes related or orthogonal to phenotypes, and better guide treatment planning.

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**References**

1. Friedrich MJ. Depression Is the Leading Cause of Disability Around the World. JAMA 2017; 317(15): 1517.
2. Delgado PL. Depression: the case for a monoamine deficiency. J Clin Psychiatry 2000; 61 Suppl 6: 7–11.
3. Mulinari S. Monoamine theories of depression: historical impact on biomedical research. J Hist Neurosci 2012; 21(4): 366–392. [PubMed: 22947380]
4. Owens MJ. Selectivity of antidepressants: from the monoamine hypothesis of depression to the SSR1 revolution and beyond. J Clin Psychiatry 2004; 65 Suppl 4: 5–10.
5. Dahmen B, Puetz VB, Scharke W, von Polier GG, Herpertz-Dahlmann B, Konrad K. Effects of Early-Life Adversity on Hippocampal Structures and Associated HPA Axis Functions. Dev Neurosci 2018; 40(1): 13–22. [PubMed: 29237154]
6. Mikolas P, Tozzi L, Doolin K, Farrell C, O’Keane V, Frodl T. Effects of early life adversity and FKBP5 genotype on hippocampal subfields volume in major depression. J Affect Disord 2019; 252: 152–159. [PubMed: 30986730]
7. Lambert HK, Peverill M, Sambrook KA, Rosen ML, Sheridan MA, McLaughlin KA. Altered development of hippocampus-dependent associative learning following early-life adversity. Dev Cogn Neurosci 2019; 38: 100666. [PubMed: 31276941]

8. Pacheco A, Aguayo FI, Aliaga E, Muñoz M, García-Rojo G, Olave FA et al. Chronic Stress Triggers Expression of Immediate Early Genes and Differentially Affects the Expression of AMPA and NMDA Subunits in Dorsal and Ventral Hippocampus of Rats. Front Mol Neurosci 2017; 10: 244. [PubMed: 28848384]

9. Sheline YI, Liston C, McEwen BS. Parsing the Hippocampus in Depression: Chronic Stress, Hippocampal Volume, and Major Depressive Disorder. Biol Psychiatry 2019; 85(6): 436–438. [PubMed: 30777168]

10. Ruiz NAL, Del Ángel DS, Olguín HJ, Silva ML. Neuroprogression: the hidden mechanism of depression. Neuropsychiatr Dis Treat 2018; 14: 2837–2845. [PubMed: 30464468]

11. Kvichansky AA, Tret'yakova LV, Volobueva MN, Manolova AO, Stepanichev MY, Onufriev MV et al. Neonatal Proinflammatory Stress and Expression of Neuroinflammation-Associated Genes in the Rat Hippocampus. Biochemistry (Mosc) 2021; 86(6): 693–703. [PubMed: 34225592]

12. Bienkowski MS, Bowman I, Song MY, Gou L, Ard T, Cotter K et al. Integration of gene expression and brain-wide connectivity reveals the multiscale organization of mouse hippocampal networks. Nat Neurosci 2018; 21(11): 1628–1643. [PubMed: 30297807]

13. Alaerts K, Bernaerts S, Vanaudenaerde B, Daniels N, Wenderoth N. Amygdala-Hippocampal Connectivity Is Associated With Endogenous Levels of Oxytocin and Can Be Altered by Exogenously Administered Oxytocin in Adults With Autism. Biol Psychiatry Cogn Neurosci Neuroimaging 2019; 4(7): 655–663. [PubMed: 30846366]

14. Liu B, Liu J, Wang M, Zhang Y, Li L. From Serotonin to Neuroplasticity: Evolvement of Theories for Major Depressive Disorder. Front Cell Neurosci 2017; 11: 305. [PubMed: 29033793]

15. Price RB, Duman R. Neuroplasticity in cognitive and psychological mechanisms of depression: an integrative model. Mol Psychiatry 2020; 25(3): 530–543. [PubMed: 31801966]

16. Sanchez-Mendoza EH, Cambor-Perujo S, Martins Nascentes-Melo L, Dzyubenko E, Fleischer M, Silva de Carvalho T et al. Compromised Hippocampal Neuroplasticity in the Interferon-α and Toll-like Receptor-3 Activation-Induced Mouse Depression Model. Mol Neurobiol 2020; 57(7): 3171–3182. [PubMed: 32504419]

17. Ruiz S, Buyukturkoglu K, Rana M, Birbaumer N, Sitaram R. Real-time fMRI brain computer interfaces: self-regulation of single brain regions to networks. Biol Psychol 2014; 95: 4–20. [PubMed: 23643926]

18. Schumacher A, Villaruel FR, Ussling A, Riaz S, Lee ACH, Ito R. Ventral Hippocampal CA1 and CA3 Differentially Mediate Learned Approach-Avoidance Conflict Processing. Curr Biol 2018; 28(8): 1318–1324.e1314. [PubMed: 29606418]

19. Eriksson PS, Perfilieva E, Björk-Eriksson T, Alborn AM, Nordborg C, Peterson DA et al. Neurogenesis in the adult human hippocampus. Nat Med 1998; 4(11): 1313–1317. [PubMed: 9809557]

20. Boldrini M, Fulmore CA, Tartt AN, Simeon LR, Pavlova I, Poposka V et al. Human Hippocampal Neurogenesis Persists throughout Aging. Cell Stem Cell 2018; 22(4): 589–599 e585. [PubMed: 29625071]

21. Wang Q, Van Heerikhuize J, Aronica E, Kawata M, Seress L, Joels M et al. Glucocorticoid receptor protein expression in human hippocampus; stability with age. Neurobiol Aging 2013; 34(6): 1662–1673. [PubMed: 23290588]

22. McIntyre RS, Cha DS, Soczynska JK, Woldeyohannes HO, Gallagher LA, Kadlow P et al. Cognitive deficits and functional outcomes in major depressive disorder: determinants, substrates, and treatment interventions. Depress Anxiety 2013; 30(6): 515–527. [PubMed: 23468126]

23. Conradi HJ, Ormel J, de Jonge P. Presence of individual (residual) symptoms during depressive episodes and periods of remission: a 3-year prospective study. Psychol Med 2011; 41(6): 1165–1174. [PubMed: 20932356]

24. Jaeger J, B erns S, Uzelac S, Davis-Conway S. Neurocognitive deficits and disability in major depressive disorder. Psychiatry Res 2006; 145(1): 39–48. [PubMed: 17045658]
25. Kaser M, Zaman R, Sahakian BJ. Cognition as a treatment target in depression. Psychol Med 2017; 47(6): 987–989. [PubMed: 27938430]

26. Siddarth P, Funes CM, Laird KT, Ercoli L, Lavretsky H. Predictors of Cognitive Improvement Following Treatment for Late-Life Depression. J Geriatr Psychiatry Neurol 2021; 34(2): 162–168. [PubMed: 32208884]

27. McAllister-Williams RH, Bones K, Goodwin GM, Harrison J, Katona C, Rasmussen J et al. Analysing UK clinicians’ understanding of cognitive symptoms in major depression: A survey of primary care physicians and psychiatrists. J Affect Disord 2017; 207: 346–352. [PubMed: 27743537]

28. Pu S, Noda T, Setoyama S, Nakagome K. Empirical evidence for discrete neurocognitive subgroups in patients with non-psychotic major depressive disorder: clinical implications. Psychol Med 2018; 48(16): 2717–2729. [PubMed: 29679991]

29. Hammar A, Sorensen L, Ardal G, Oedegaard KJ, Kroken R, Roness A et al. Enduring cognitive dysfunction in unipolar major depression: a test-retest study using the Stroop paradigm. Scand J Psychol 2010; 51(4): 304–308. [PubMed: 20042028]

30. Semkovska M, Quinlivan L, O'Grady T, Johnson R, Collins A, O'Connor J et al. Cognitive function following a major depressive episode: a systematic review and meta-analysis. Lancet Psychiatry 2019; 6(10): 851–861. [PubMed: 31422920]

31. Perini G, Cotta Ramusino M, Sinforiani E, Bernini S, Petrachi R, Costa A. Cognitive impairment in depression: recent advances and novel treatments. Neuropsychiatr Dis Treat 2019; 15: 1249–1258. [PubMed: 31190831]

32. Oquendo MA, Barrera A, Ellis SP, Li S, Burke AK, Grunebaum M et al. Instability of symptoms in recurrent major depression: a prospective study. Am J Psychiatry 2004; 161(2): 255–261. [PubMed: 14754774]

33. Cao X, Liu Z, Xu C, Li J, Gao Q, Sun N et al. Disrupted resting-state functional connectivity of the hippocampus in medication-naïve patients with major depressive disorder. J Affect Disord 2012; 141(2-3): 194–203. [PubMed: 22460056]

34. de Kwaasteniet B, Ruhe E, Caan M, Rive M, Olabarriaga S, Groefsema M et al. Relation between structural and functional connectivity in major depressive disorder. Biol Psychiatry 2013; 74(1): 40–47. [PubMed: 23399372]

35. Hao ZY, Zhong Y, Ma ZJ, Xu HZ, Kong JY, Wu Z et al. Abnormal resting-state functional connectivity of hippocampal subfields in patients with major depressive disorder. BMC Psychiatry 2020; 20(1): 71. [PubMed: 32066415]

36. Braver TS, Cohen JD, Nystrom LE, Jonides J, Smith EE, Noll DC. A parametric study of prefrontal cortex involvement in human working memory. Neuroimage 1997; 5(1): 49–62. [PubMed: 9038284]

37. Baxter LR, Schwartz JM, Phelps ME, Mazzotti CA, Guze BH, Selin CE et al. Reduction of prefrontal cortex glucose metabolism common to three types of depression. Arch Gen Psychiatry 1989; 46(3): 243–250. [PubMed: 2784046]

38. Soares JC, Mann JJ. The functional neuroanatomy of mood disorders. J Psychiatr Res 1997; 31(4): 393–432. [PubMed: 9352470]

39. Harvey PO, Fossati P, Pochon JB, Levy R, Lebaster G, Lehericy S et al. Cognitive control and brain resources in major depression: an fMRI study using the n-back task. Neuroimage 2005; 26(3): 860–869. [PubMed: 15955496]

40. Matsuo K, Glahn DC, Peluso MA, Hatch JP, Monkul ES, Najt P et al. Prefrontal hyperactivation during working memory task in untreated individuals with major depressive disorder. Mol Psychiatry 2007; 12(2): 158–166. [PubMed: 16983390]

41. Elliott R, Baker SC, Rogers RD, O'Leary DA, Paykel ES, Frith CD et al. Prefrontal dysfunction in depressed patients performing a complex planning task: a study using positron emission tomography. Psychol Med 1997; 27(4): 931–942. [PubMed: 9234470]

42. Okada G, Okamoto Y, Morinobu S, Yamawaki S, Yokota N. Attenuated left prefrontal activation during a verbal fluency task in patients with depression. Neuropsychobiology 2003; 47(1): 21–26. [PubMed: 12606841]
43. Fox MD, Snyder AZ, Vincent JL, Corbetta M, Van Essen DC, Raichle ME. The human brain is intrinsically organized into dynamic, anticorrelated functional networks. Proc Natl Acad Sci U S A 2005; 102(27): 9673–9678. [PubMed: 15976020]

44. Zetsche U, D’Avanzato C, Joormann J. Depression and rumination: relation to components of inhibition. Cogn Emot 2012; 26(4): 758–767. [PubMed: 21970297]

45. Joormann J, Levens SM, Gotlib IH. Sticky thoughts: depression and rumination are associated with difficulties manipulating emotional material in working memory. Psychol Sci 2011; 22(8): 979–983. [PubMed: 21742932]

46. Lewis EJ, Blanco I, Raila H, Joormann J. Does repetitive negative thinking affect attention? Differential effects of worry and rumination on attention to emotional stimuli. Emotion 2019; 19(8): 1450–1462. [PubMed: 30714778]

47. Ochsner KN, Ray RD, Cooper JC, Robertson ER, Chopra S, Gabrieli JD et al. For better or for worse: neural systems supporting the cognitive down- and up-regulation of negative emotion. Neuroimage 2004; 23(2): 483–499. [PubMed: 15488398]

48. Fales CL, Barch DM, Rundle MM, Mintun MA, Snyder AZ, Cohen JD et al. Altered emotional interference processing in affective and cognitive-control brain circuitry in major depression. Biol Psychiatry 2008; 63(4): 377–384. [PubMed: 17719567]

49. Nolen-Hoeksema S, Morrow J, Fredrickson BL. Response styles and the duration of episodes of depressed mood. J Abnorm Psychol 1993; 102(1): 20–28. [PubMed: 8436695]

50. Disner SG, Beevers CG, Haigh EA, Beck AT. Neural mechanisms of the cognitive model of depression. Nat Rev Neurosci 2011; 12(8): 467–477. [PubMed: 21731066]

51. Hamilton JP, Gotlib IH. Neural substrates of increased memory sensitivity for positive stimuli in major depression. Biol Psychiatry 2008; 63(12): 1155–1162. [PubMed: 18281017]

52. Cullen KR, Westlund MK, Klimes-Dougan B, Mueller BA, Houri A, Eberly LE et al. Abnormal amygdala resting-state functional connectivity in adolescent depression. JAMA Psychiatry 2014; 71(10): 1138–1147. [PubMed: 25133665]

53. Turecki G, Meaney MJ. Effects of the Social Environment and Stress on Glucocorticoid Receptor Gene Methylation: A Systematic Review. Biol Psychiatry 2016; 79(2): 87–96. [PubMed: 25687413]

54. Smith KE, Pollak SD. Early life stress and development: potential mechanisms for adverse outcomes. J Neurodev Disord 2020; 12(1): 34. [PubMed: 33327939]

55. Rusch BD, Abercrombie HC, Oakes TR, Schaefer SM, Davidson RJ. Hippocampal morphometry in depressed patients and control subjects: relations to anxiety symptoms. Biol Psychiatry 2001; 50(12): 960–964. [PubMed: 11750892]

56. Vakili K, Pillay SS, Lafer B, Fava M, Renshaw PF, Bonello-Cintron CM et al. Hippocampal volume in primary unipolar major depression: a magnetic resonance imaging study. Biol Psychiatry 2000; 47(12): 1087–1090. [PubMed: 10862809]

57. Ashutari M, Greenwald BS, Kramer-Ginsberg E, Hu J, Wu H, Patel M et al. Hippocampal/amygdala volumes in geriatric depression. Psychol Med 1999; 29(3): 629–638. [PubMed: 10405084]

58. Sheline YI, Wang PW, Gado MH, Csernansky JG, Vannier MW. Hippocampal atrophy in recurrent major depression. Proc Natl Acad Sci U S A 1996; 93(9): 3908–3913. [PubMed: 8632988]

59. Luo Y, Cao Z, Wang D, Wu L, Li Y, Sun W et al. Dynamic study of the hippocampal volume by structural MRI in a rat model of depression. Neurol Sci 2014; 35(11): 1777–1783. [PubMed: 24929958]

60. Czéh B, Simon M, Schmelting B, Hiemke C, Fuchs E. Astroglial plasticity in the hippocampus is affected by chronic psychosocial stress and concomitant fluoxetine treatment. Neuropsychopharmacology 2006; 31(8): 1616–1626. [PubMed: 16395301]

61. Roddy DW, Farrell C, Doolin K, Roman E, Tozzi L, Frodl T et al. The Hippocampus in Depression: More Than the Sum of Its Parts? Advanced Hippocampal Substructure Segmentation in Depression. Biol Psychiatry 2019; 85(6): 487–497. [PubMed: 30528746]

62. Boldrini M, Santiago AN, Hen R, Dwork AJ, Rosoklija GB, Tamir H et al. Hippocampal granule neuron number and dentate gyrus volume in antidepressant-treated and untreated major depression. Neuropsychopharmacology 2013; 38(6): 1068–1077. [PubMed: 23303074]
63. Boldrini M, Galfalvy H, Dwork AJ, Rosoklija GB, Trencesvka-Ivanovska I, Pavlovski G et al. Resilience Is Associated With Larger Dentate Gyrus, While Suicide Decedents With Major Depressive Disorder Have Fewer Granule Neurons. Biol Psychiatry 2019; 85(10): 850–862. [PubMed: 30819514]

64. Liu MN, Pantouw JG, Yang KC, Hu LY, Liou YJ, Lirng JF et al. Sub-regional hippocampal volumes in first-episode drug-naïve major depressive disorder. Neurosci Lett 2021; 763: 136178. [PubMed: 34416346]

65. Frodl T, Carballedo A, Frey EM, O’Keane V, Skokauskas N, Morris D et al. Expression of glucocorticoid inducible genes is associated with reductions in cornu ammonis and dentate gyrus volumes in patients with major depressive disorder. Dev Psychopathol 2014; 26(4 Pt 2): 1209–1217. [PubMed: 25422956]

66. Huang Y, Coupland NJ, Lebel RM, Carter R, Seres P, Wilman AH et al. Structural changes in hippocampal subfields in major depressive disorder: a high-field magnetic resonance imaging study. Biol Psychiatry 2013; 74(1): 62–68. [PubMed: 23419546]

67. Travis S, Coupland NJ, Silversone PH, Huang Y, Fujiwara E, Carter R et al. Dentate gyrus volume and memory performance in major depressive disorder. J Affect Disord 2015; 172: 159–164. [PubMed: 25451411]

68. Yuan M, Rubin-Falcone H, Lin X, Rizk MM, Miller JM, Sublette ME et al. Smaller left hippocampal subfield CA1 volume is associated with reported childhood physical and/or sexual abuse in major depression: A pilot study. J Affect Disord 2020; 272: 348–354. [PubMed: 32553377]

69. Carballedo A, Lisiecka D, Fagan A, Saleh K, Ferguson Y, Connolly G et al. Early life adversity is associated with brain changes in subjects at family risk for depression. World J Biol Psychiatry 2012; 13(8): 569–578. [PubMed: 22515408]

70. Dannlowski U, Stuhmann A, Beutelmann V, Zwanzger P, Lenzen T, Grotegerd D et al. Limbic scars: long-term consequences of childhood maltreatment revealed by functional and structural magnetic resonance imaging. Biol Psychiatry 2012; 71(4): 286–293. [PubMed: 22112927]

71. Xie H, Claycomb Erwin M, Elhai JD, Wall JT, Tamburrino MB, Brickman KR et al. Relationship of Hippocampal Volumes and Posttraumatic Stress Disorder Symptoms Over Early Posttrauma Periods. Biol Psychiatry Cogn Neurosci Neuroimaging 2018; 3(11): 968–975. [PubMed: 30409391]

72. Banasr M, Dwyer JM, Duman RS. Cell atrophy and loss in depression: reversal by antidepressant treatment. Curr Opin Cell Biol 2011; 23(6): 730–737. [PubMed: 21996102]

73. Lopez JP, Mamdani F, Labonte B, Beaulieu MM, Yang JP, Berlim MT et al. Epigenetic regulation of BDNF expression according to antidepressant response. Mol Psychiatry 2013; 18(4): 398–399. [PubMed: 22547115]

74. Tsankova NM, Berton O, Renthal W, Kumar A, Neve RL, Nestler EJ. Sustained hippocampal chromatin regulation in a mouse model of depression and antidepressant action. Nat Neurosci 2006; 9(4): 519–525. [PubMed: 16501568]

75. Waterhouse EG, An JJ, Orefice LL, Baydyuk M, Liao GY, Zheng K et al. BDNF promotes differentiation and maturation of adult-born neurons through GABAergic transmission. J Neurosci 2012; 32(41): 14318–14330. [PubMed: 23055503]

76. Li H, Lin LY, Zhang Y, Lim Y, Rahman M, Beck A et al. Pro-BDNF Knockout Causes Abnormal Motor Behaviours and Early Death in Mice. Neuroscience 2020; 438: 145–157. [PubMed: 32413397]

77. Takei N, Nawa H. mTOR signaling and its roles in normal and abnormal brain development. Front Mol Neurosci 2014; 7: 28. [PubMed: 24795562]

78. Strauss J, Barr CL, George CJ, Ryan CM, King N, Shaikh S et al. BDNF and COMT polymorphisms: relation to memory phenotypes in young adults with childhood-onset mood disorder. Neuromolecular Med 2004; 5(3): 181–192. [PubMed: 15626819]

79. Chen B, Dowlatshahi D, MacQueen GM, Wang JF, Young LT. Increased hippocampal BDNF immunoreactivity in subjects treated with antidepressant medication. Biol Psychiatry 2001; 50(4): 260–265. [PubMed: 11522260]
80. Chen ZY, Jing D, Bath KG, Ieraci A, Khan T, Siao CJ et al. Genetic variant BDNF (Val66Met) polymorphism alters anxiety-related behavior. Science 2006; 314(5796): 140–143. [PubMed: 17023662]

81. Magariños AM, Li CJ, Gal Toth J, Bath KG, Jing D, Lee FS et al. Effect of brain-derived neurotrophic factor haploinsufficiency on stress-induced remodeling of hippocampal neurons. Hippocampus 2011; 21(3): 253–264. [PubMed: 20095008]

82. Kosten TA, Galloway MP, Duman RS, Russell DS, D'Sa C. Repeated unpredictable stress and antidepressants differentially regulate expression of the bcl-2 family of apoptotic genes in rat cortical, hippocampal, and limbic brain structures. Neuropsychopharmacology 2008; 33(7): 1545–1558. [PubMed: 17700647]

83. Luo C, Xu H, Li XM. Post-stress changes in BDNF and Bcl-2 immunoreactivities in hippocampal neurons: effect of chronic administration of olanzapine. Brain Res 2004; 1025(1-2): 194–202. [PubMed: 15464760]

84. Zeng D, He S, Ma C, Wen Y, Song W, Xu Q et al. Network-based approach to identify molecular signatures in the brains of depressed suicides. Psychiatry Res 2020; 294: 113513. [PubMed: 33137553]

85. Amidfar M, Kim YK, Scaini G, Quevedo J. Evidence for additionally increased apoptosis in the peripheral blood mononuclear cells of major depressive patients with a high risk for suicide. Am J Med Genet B Neuropsychiatr Genet 2018; 177(4): 388–396. [PubMed: 29633502]

86. Zhang H, Wei M, Lu X, Sun Q, Wang C, Zhang J et al. Aluminum trichloride caused hippocampal neural cells death and subsequent depression-like behavior in rats via the activation of IL-1β/JNK signaling pathway. Sci Total Environ 2020; 715: 136942. [PubMed: 32007895]

87. Moxon LN, Rose SE, Haseler LJ, Galloway GJ, Brereton IM, Bore P et al. The visibility of the 1H NMR signal of ethanol in the dog brain. Magn Reson Med 1991; 19(2): 340–348. [PubMed: 1881324]

88. Niklison-Chirou MV, Agostini M, Melino I, Melino G. Regulation of Adult Neurogenesis in Mammalian Brain. Int J Mol Sci 2020; 21(14).

89. Urbán N, Guillemot F. Neurogenesis in the embryonic and adult brain: same regulators, different roles. Front Cell Neurosci 2014; 8: 396. [PubMed: 25505873]

90. Bayer SA, Altman J. Hippocampal development in the rat: cytogenesis and morphogenesis examined with autoradiography and low-level X-irradiation. J Comp Neurol 1974; 158(1): 55–79. [PubMed: 4430737]

91. Hochgerner H, Zeisel A, Löörrerberg P, Linnersson S. Conserved properties of dentate gyrus neurogenesis across postnatal development revealed by single-cell RNA sequencing. Nat Neurosci 2018; 21(2): 290–299. [PubMed: 29335606]

92. Seki T, Sato T, Toda K, Osumi N, Imura T, Shioda S. Distinctive population of Gfap-expressing neural progenitors arising around the dentate notch migrate and form the granule cell layer in the developing hippocampus. J Comp Neurol 2014; 522(2): 261–283. [PubMed: 23983092]

93. Berg DA, Su Y, Jimenez-Cyrus D, Patel A, Huang N, Morizet D et al. A Common Embryonic Origin of Stem Cells Drives Developmental and Adult Neurogenesis. Cell 2019; 177(3): 654–668.e615. [PubMed: 30929900]

94. Li G, Fang L, Fernández G, Pleasure SJ. The ventral hippocampus is the embryonic origin for adult neural stem cells in the dentate gyrus. Neuron 2013; 78(4): 658–672. [PubMed: 23643936]

95. Sorrells SF, Paredes MF, Cebrían-Silla A, Sandoval K, Qi D, Kelley KW et al. Human hippocampal neurogenesis drops sharply in children to undetectable levels in adults. Nature 2018; 555(7696): 377–381. [PubMed: 29513649]

96. Cipriani S, Ferrer I, Aronica E, Kovacs GG, Verney C, Nardelli J et al. Hippocampal Radial Glial Subtypes and Their Neurogenic Potential in Human Fetuses and Healthy and Alzheimer’s Disease Adults. Cereb Cortex 2018; 28(7): 2458–2478. [PubMed: 29722804]

97. Franjic D, Skarica M, Ma S, Arellano JJ, Tebbenkamp ATN, Choi J et al. Transcriptomic taxonomy and neurogenic trajectories of adult human, macaque, and pig hippocampal and entorhinal cells. Neuron 2021.
98. Boldrini M, Fulmore CA, Tartt AN, Simeon LR, Pavlova I, Poposka V et al. Human Hippocampal Neurogenesis Persists throughout Aging. Cell Stem Cell 2018; 22(4): 589–599.e585. [PubMed: 29625071]

99. Moreno-Jiménez EP, Flor-García M, Terreros-Roncal J, Rábano A, Cafini F, Pallas-Bazarru N et al. Adult hippocampal neurogenesis is abundant in neurologically healthy subjects and drops sharply in patients with Alzheimer’s disease. Nat Med 2019; 25(4): 554–560. [PubMed: 30911133]

100. Terreros-Roncal J, Moreno-Jiménez EP, Flor-García M, Rodríguez-Moreno CB, Trinchero MF, Cafini F et al. Impact of neurodegenerative diseases on human adult hippocampal neurogenesis. Science 2021; 374(6571): 1106–1113. [PubMed: 34672693]

101. Tobin MK, Musaraca K, Disouky A, Shetti A, Bheri A, Honer WG et al. Human Hippocampal Neurogenesis Persists in Aged Adults and Alzheimer’s Disease Patients. Cell Stem Cell 2019; 24(6): 974–982.e973. [PubMed: 31130513]

102. Tartt AN, Fulmore CA, Liu Y, Rosoklija GB, Dwork AJ, Arango V et al. Considerations for Assessing the Extent of Hippocampal Neurogenesis in the Adult and Aging Human Brain. Cell Stem Cell 2018; 23(6): 782–783. [PubMed: 30526880]

103. Spalding KL, Bergmann O, Alkass K, Bernard S, Salehpour M, Huttner HB et al. Dynamics of hippocampal neurogenesis in adult humans. Cell 2013; 153(6): 1219–1227. [PubMed: 23746839]

104. Moreno-Jiménez EP, Terreros-Roncal J, Flor-García M, Ávila J, Rábano A, Llorens-Martín M. Evidences for Adult Hippocampal Neurogenesis in Humans. J Neurosci 2021; 41(12): 2541–2553. [PubMed: 33762406]

105. Flor-García M, Terreros-Roncal J, Moreno-Jiménez EP, Ávila J, Rábano A, Llorens-Martín M. Unraveling human adult hippocampal neurogenesis. Nat Protoc 2020; 15(2): 668–693. [PubMed: 31915385]

106. Duque A, Arellano JI, Rakic P. An assessment of the existence of adult neurogenesis in humans and value of its rodent models for neuropsychiatric diseases. Mol Psychiatry 2021.

107. Rakic P Limits of neurogenesis in primates. Science 1985; 227(4690): 1054–1056. [PubMed: 3975601]

108. Garthe A, Behr J, Kempermann G. Adult-generated hippocampal neurons allow the flexible use of spatially precise learning strategies. PLoS One 2009; 4(5): e5464. [PubMed: 19421325]

109. Kempermann G New neurons for ‘survival of the fittest’. Nat Rev Neurosci 2012; 13(10): 727–736. [PubMed: 22948073]

110. Kempermann G Adult Neurogenesis: An Evolutionary Perspective. Cold Spring Harb Perspect Biol 2015; 8(2): a018986. [PubMed: 26684183]

111. Sun W, Winseck A, Vinsant S, Park OH, Kim H, Oppenheim RW. Programmed cell death of adult-generated hippocampal neurons is mediated by the proapoptotic gene Bax. J Neurosci 2004; 24(49): 11205–11213. [PubMed: 15590937]

112. Dayer AG, Ford AA, Cleaver KM, Yassaee M, Cameron HA. Short-term and long-term survival of new neurons in the rat dentate gyrus. J Comp Neurol 2003; 460(4): 563–572. [PubMed: 12717714]

113. Shors TJ, Townsend DA, Zhao M, Kozorovitskiy Y, Gould E. Neurogenesis may relate to some but not all types of hippocampal-dependent learning. Hippocampus 2002; 12(5): 578–584. [PubMed: 12440573]

114. Burghardt NS, Park EH, Hen R, Fenton AA. Adult-born hippocampal neurons promote cognitive flexibility in mice. Hippocampus 2012; 22(9): 1795–1808. [PubMed: 22431384]

115. Snyder JS, Hong NS, McDonald RJ, Wojtowicz JM. A role for adult neurogenesis in spatial long-term memory. Neuroscience 2005; 130(4): 843–852. [PubMed: 15652983]

116. Clelland CD, Choi M, Romberg C, Clemenson GD, Fragnieri A, Tyers P et al. A functional role for adult hippocampal neurogenesis in spatial pattern separation. Science 2009; 325(5937): 210–213. [PubMed: 19590004]

117. Sahay A, Wilson DA, Hen R. Pattern separation: a common function for new neurons in hippocampus and olfactory bulb. Neuron 2011; 70(4): 582–588. [PubMed: 21609817]

118. Santarelli L, Saxe M, Gross C, Surget A, Battaglia F, Dulawa S et al. Requirement of hippocampal neurogenesis for the behavioral effects of antidepressants. Science 2003; 301(5634): 805–809. [PubMed: 12907793]
119. David DJ, Samuels BA, Rainer Q, Wang JW, Marsteller D, Mendez I et al. Neurogenesis-dependent and -independent effects of fluoxetine in an animal model of anxiety/depression. Neuron 2009; 62(4): 479–493. [PubMed: 19477151]

120. Malberg JE, Eisch AJ, Nestler EJ, Duman RS. Chronic antidepressant treatment increases neurogenesis in adult rat hippocampus. J Neurosci 2000; 20(24): 9104–9110. [PubMed: 11124987]

121. Boldrini M, Underwood MD, Hen R, Rosoklija GB, Dwork AJ, John Mann J et al. Antidepressants increase neural progenitor cells in the human hippocampus. Neuropsychopharmacology 2009; 34(11): 2376–2389. [PubMed: 19606083]

122. Duman RS, Nakagawa S, Malberg J. Regulation of adult neurogenesis by antidepressant treatment. Neuropsychopharmacology 2001; 25(6): 836–844. [PubMed: 11750177]

123. Wang H, Warner-Schmidt J, Varela S, Enikolopov G, Greengard P, Flajolet M. Norbin ablation results in defective adult hippocampal neurogenesis and depressive-like behavior in mice. Proc Natl Acad Sci U S A 2015; 112(31): 9745–9750. [PubMed: 26195764]

124. Revest JM, Dupret D, Koehl M, Funk-Reiter C, Grosjean N, Piazza PV et al. Adult hippocampal neurogenesis is involved in anxiety-related behaviors. Mol Psychiatry 2009; 14(10): 959–967. [PubMed: 19255582]

125. Petrik D, Lagace DC, Eisch AJ. The neurogenesis hypothesis of affective and anxiety disorders: are we mistaking the scaffolding for the building? Neuropsychopharmacology 2012; 62(1): 21–34. [PubMed: 21945290]

126. Hill AS, Sahay A, Hen R. Increasing Adult Hippocampal Neurogenesis is Sufficient to Reduce Anxiety and Depression-Like Behaviors. Neuropsychopharmacology 2015; 40(10): 2368–2378. [PubMed: 25833129]

127. Anacker C, Luna VM, Stevens GS, Millette A, Shores R, Jimenez JC et al. Hippocampal neurogenesis confers stress resilience by inhibiting the ventral dentate gyrus. Nature 2018; 559(7712): 98–102. [PubMed: 29950730]

128. Pereira Dias G, Hollywood R, Bevilacqua MC, da Luz AC, Hindges R, Nardi AE et al. Consequences of cancer treatments on adult hippocampal neurogenesis: implications for cognitive function and depressive symptoms. Neuro Oncol 2014; 16(4): 476–492. [PubMed: 24470543]

129. Wen S, Xiao H, Yang Y. The risk factors for depression in cancer patients undergoing chemotherapy: a systematic review. Support Care Cancer 2019; 27(1): 57–67. [PubMed: 30225571]

130. Wigmore P. The effect of systemic chemotherapy on neurogenesis, plasticity and memory. Curr Top Behav Neurosci 2013; 15: 211–240. [PubMed: 23239468]

131. Christie LA, Acharya MM, Parihar VK, Nguyen A, Martirosian V, Limoli CL. Impaired cognitive function and hippocampal neurogenesis following cancer chemotherapy. Clin Cancer Res 2012; 18(7): 1954–1965. [PubMed: 22338017]

132. Egeland M, Guinaudie C, Du Preez A, Musaelyan K, Zunszain PA, Fernandes C et al. Depletion of adult neurogenesis using the chemotherapy drug temozolomide in mice induces behavioural and biological changes relevant to depression. Transl Psychiatry 2017; 7(4): e1101. [PubMed: 28440814]

133. Bear MF, Malenka RC. Synaptic plasticity: LTP and LTD. Curr Opin Neurobiol 1994; 4(3): 389–399. [PubMed: 7919934]

134. Kaminska M, Harris J, Gijsbers K, Dubrovsky B. Dehydroepiandrosterone sulfate (DHEAS) counteracts decremental effects of corticosterone on dentate gyrus LTP. Implications for depression. Brain Res Bull 2000; 52(3): 229–234. [PubMed: 10822166]

135. Jay TM, Rocher C, Hotte M, Naudon L, Gurden H, Spedding M. Plasticity at hippocampal to prefrontal cortex synapses is impaired by loss of dopamine and stress: importance for psychiatric diseases. Neurotox Res 2004; 6(3): 233–244. [PubMed: 15325962]

136. Huganir RL, Nicoll RA. AMPARs and synaptic plasticity: the last 25 years. Neuron 2013; 80(3): 704–717. [PubMed: 24183021]

137. Collingridge GL, Isaac JT, Wang YT. Receptor trafficking and synaptic plasticity. Nat Rev Neurosci 2004; 5(12): 952–962. [PubMed: 15550950]
138. Citri A, Malenka RC. Synaptic plasticity: multiple forms, functions, and mechanisms. Neuropsychopharmacology 2008; 33(1): 18–41. [PubMed: 17728696]
139. Costa-Mattioli M, Sossin WS, Klann E, Sonenberg N. Translational control of long-lasting synaptic plasticity and memory. Neuron 2009; 61(1): 10–26. [PubMed: 19146809]
140. Malenka RC, Bear MF. LTP and LTD: an embarrassment of riches. Neuron 2004; 44(1): 5–21. [PubMed: 15450156]
141. Mayford M, Siegelbaum SA, Kandel ER. Synapses and memory storage. Cold Spring Harb Perspect Biol 2012; 4(6).
142. Bourtchuladze R, Frenguelli B, Blendy J, Cioffi D, Schutz G, Silva AJ. Deficient long-term memory in mice with a targeted mutation of the cAMP-responsive element-binding protein. Cell 1994; 79(1): 59–68. [PubMed: 7923378]
143. Won J, Silva AJ. Molecular and cellular mechanisms of memory allocation in neuronetworks. Neurobiol Learn Mem 2008; 89(3): 285–292. [PubMed: 17962049]
144. Tejeda GS, Díaz-Guerra M. Integral Characterization of Defective BDNF/TrkB Signalling in Neurological and Psychiatric Disorders Leads the Way to New Therapies. Int J Mol Sci 2017; 18(2).
145. Tanaka J, Horiike Y, Matsuzaki M, Miyazaki T, Ellis-Davies GC, Kasai H. Protein synthesis and neurotrophin-dependent structural plasticity of single dendritic spines. Science 2008; 319(5870): 1683–1687. [PubMed: 18309046]
146. Lu B, Nagappan G, Lu Y. BDNF and synaptic plasticity, cognitive function, and dysfunction. Handb Exp Pharmacol 2014; 220: 223–250. [PubMed: 24668475]
147. Huang CC, Chu CY, Yeh CM, Hsu KS. Acute hypernatremia dampens stress-induced enhancement of long-term potentiation in the dentate gyrus of rat hippocampus. Psychoneuroendocrinology 2014; 46: 129–140. [PubMed: 24882165]
148. Alfarez DN, Joëls M, Krugers HJ. Chronic unpredictable stress impairs long-term potentiation in rat hippocampal CA1 area and dentate gyrus in vitro. Eur J Neurosci 2003; 17(9): 1928–1934. [PubMed: 12752792]
149. Chaouloff F, Hémar A, Manzoni O. Acute stress facilitates hippocampal CA1 metabotropic glutamate receptor-dependent long-term depression. J Neurosci 2007; 27(27): 7130–7135. [PubMed: 17611266]
150. Maggio N, Segal M. Striking variations in corticosteroid modulation of long-term potentiation along the septotemporal axis of the hippocampus. J Neurosci 2007; 27(21): 5757–5765. [PubMed: 17522319]
151. Kuhn M, Mainberger F, Feige B, Maier JG, Mall V, Jung NH et al. State-Dependent Partial Occlusion of Cortical LTP-Like Plasticity in Major Depression. Neuropsychopharmacology 2016; 41(11): 2794. [PubMed: 27609501]
152. Player MJ, Taylor JL, Weickert CS, Alonzo A, Sachdev P, Martin D et al. Neuroplasticity in depressed individuals compared with healthy controls. Neuropsychopharmacology 2013; 38(11): 2101–2108. [PubMed: 23676792]
153. Moghaddam B, Bolinno ML, Stein-Behrens B, Sapolsky R. Glucocorticoids mediate the stress-induced extracellular accumulation of glutamate. Brain Res 1994; 655(1-2): 251–254. [PubMed: 7812782]
154. Moghaddam B Stress preferentially increases extraneuronal levels of excitatory amino acids in the prefrontal cortex: comparison to hippocampus and basal ganglia. J Neurochem 1993; 60(5): 1650–1657. [PubMed: 8097232]
155. John CS, Smith KL, Van’t Veer A, Gompf HS, Carlezon WA, Cohen BM et al. Blockade of astrocytic glutamate uptake in the prefrontal cortex induces anhedonia. Neuropsychopharmacology 2012; 37(11): 2467–2475. [PubMed: 22739467]
156. Gleichmann M, Mattson MP. Neuronal calcium homeostasis and dysregulation. Antioxid Redox Signal 2011; 14(7): 1261–1273. [PubMed: 20626318]
157. Küçükibrahimoğlu E, Saygin MZ, Calişkan M, Kaplan OK, Unsal C, Gören MZ. The change in plasma GABA, glutamine and glutamate levels in fluoxetine- or S-citalopram-treated female patients with major depression. Eur J Clin Pharmacol 2009; 65(6): 571–577. [PubMed: 19373461]
158. Altamura CA, Mauri MC, Ferrara A, Moro AR, D’Andrea G, Zamberlan F. Plasma and platelet excitatory amino acids in psychiatric disorders. Am J Psychiatry 1993; 150(11): 1731–1733. [PubMed: 8214185]

159. Levine J, Panchalingam K, Rapoport A, Gershon S, McClure RJ, Pettegrew JW. Increased cerebrospinal fluid glutamine levels in depressed patients. Biol Psychiatry 2000; 47(7): 586–593. [PubMed: 10745048]

160. Hashimoto K, Bruno D, Nierenberg J, Marmar CR, Zetterberg H, Blennow K et al. Abnormality in glutamine-glutamate cycle in the cerebrospinal fluid of cognitively intact elderly individuals with major depressive disorder: a 3-year follow-up study. Transl Psychiatry 2016; 6: e744. [PubMed: 26926880]

161. Kantrowitz JT, Dong Z, Milak MS, Rashid R, Kegeles LS, Javitt DC et al. Ventromedial prefrontal cortex/anterior cingulate cortex Glx, glutamate, and GABA levels in medication-free major depressive disorder. Transl Psychiatry 2021; 11(1): 419. [PubMed: 34354048]

162. Moriguchi S, Takamiya A, Noda Y, Horita N, Wada M, Tsugawa S et al. Glutamatergic neurometabolite levels in major depressive disorder: a systematic review and meta-analysis of proton magnetic resonance spectroscopy studies. Mol Psychiatry 2019; 24(7): 952–964. [PubMed: 30315224]

163. Yuen EY, Wei J, Liu W, Zhong P, Li X, Yan Z. Repeated stress causes cognitive impairment by suppressing glutamate receptor expression and function in prefrontal cortex. Neurosci 2012; 73(5): 962–977. [PubMed: 22405206]

164. Floriou-Servou A, von Ziegler L, Waag R, Schläppi C, Germain PL, Bohacek J. The Acute Stress Response in the Multiomic Era. Biol Psychiatry 2021; 89(12): 1116–1126. [PubMed: 33722387]

165. Bernard R, Kerman IA, Thompson RC, Jones EG, Bunney WE, Barchas JD et al. Altered expression of glutamate signaling, growth factor, and glia genes in the locus coeruleus of patients with major depression. Mol Psychiatry 2011; 16(6): 634–646. [PubMed: 20386568]

166. Duric V, Banasr M, Stockmeier CA, Simen AA, Newton SS, Overholser JC et al. Altered expression of synapse and glutamate related genes in post-mortem hippocampus of depressed subjects. Int J Neuropsychopharmacol 2013; 16(1): 69–82. [PubMed: 22339950]

167. Lisman J, Raghavachari S. A unified model of the presynaptic and postsynaptic changes during LTP at CA1 synapses. Sci STKE 2006; 2006(356): re11. [PubMed: 17033044]

168. Bourne JN, Harris KM. Balancing structure and function at hippocampal dendritic spines. Annu Rev Neurosci 2008; 31: 47–67. [PubMed: 18284372]

169. Balu DT, Hoshaw BA, Malberg JE, Rosenzweig-Lipson S, Schechter LE, Lucki I. Differential regulation of central BDNF protein levels by antidepressant and non-antidepressant drug treatments. Brain Res 2008; 1212(1): 37–43. [PubMed: 18433734]

170. Martinowich K, Lu B. Interaction between BDNF and serotonin: role in mood disorders. Neuropsychopharmacology 2008; 33(1): 73–83. [PubMed: 17882234]

171. Kim YK, Lee HP, Won SD, Park EY, Lee HY, Lee BH et al. Low plasma BDNF is associated with suicidal behavior in major depression. Prog Neuropsychopharmacol Biol Psychiatry 2007; 31(1): 78–85. [PubMed: 16904252]

172. Xu Y, Ku B, Tie L, Yao H, Jiang W, Ma X et al. Curcumin reverses the effects of chronic stress on behavior, the HPA axis, BDNF expression and phosphorylation of CREB. Brain Res 2006; 1122(1): 56–64. [PubMed: 17022948]

173. Laifenfeld D, Karry R, Grauer E, Klein E, Ben-Shachar D. Antidepressants and prolonged stress in rats modulate CAM-L1, laminin, and pCREB, implicated in neuronal plasticity. Neurobiology of disease 2005; 20(2): 432–441. [PubMed: 15905095]

174. Grønli J, Bramham C, Murison R, Kanhema T, Fiske E, Bjorvatn B et al. Chronic mild stress inhibits BDNF protein expression and CREB activation in the dentate gyrus but not in the hippocampus proper. Pharmacol Biochem Behav 2006; 85(4): 842–849. [PubMed: 17204313]

175. Price JL, Drevets WC. Neurocircuitry of mood disorders. Neuropsychopharmacology 2010; 35(1): 192–216. [PubMed: 19693001]

176. Ho VM, Lee JA, Martin KC. The cell biology of synaptic plasticity. Science 2011; 334(6056): 623–628. [PubMed: 22053042]
177. Harmer CJ, Duman RS, Cowen PJ. How do antidepressants work? New perspectives for refining future treatment approaches. Lancet Psychiatry 2017; 4(5): 409–418. [PubMed: 28153641]

178. Kraus C, Castrén E, Kasper S, Lanzenberger R. Serotonin and neuroplasticity - Links between molecular, functional and structural pathophysiology in depression. Neurosci Biobehav Rev 2017; 77: 317–326. [PubMed: 28342763]

179. Fales CL, Barch DM, Rundle MM, Mintun MA, Mathews J, Snyder AZ et al. Antidepressant treatment normalizes hypoactivity in dorsolateral prefrontal cortex during emotional interference processing in major depression. J Affect Disord 2009; 112(1-3): 206–211. [PubMed: 18559283]

180. Sullivan CRP, Olsen S, Widge AS. Deep brain stimulation for psychiatric disorders: From focal brain targets to cognitive networks. Neuroimage 2021; 225: 117515. [PubMed: 33137473]

181. Schlaepfer TE, Bewernick BH, Kaiser S, Hurlemann R, Coenen VA. Deep brain stimulation of the human reward system for major depression—rationale, outcomes and outlook. Neuropsychopharmacology 2014; 39(6): 1303–1314. [PubMed: 24513970]

182. McIntyre CC, Hahn PJ. Network perspectives on the mechanisms of deep brain stimulation. Neurobiol Dis 2010; 38(3): 329–337. [PubMed: 19804831]

183. Wolkenstein L, Plewnia C. Amelioration of cognitive control in depression by transcranial direct current stimulation. Biol Psychiatry 2013; 73(7): 646–651. [PubMed: 23219367]

184. Smith R, Chen K, Baxter L, Fort C, Lane RD. Antidepressant effects of sertraline associated with volume increases in dorsolateral prefrontal cortex. J Affect Disord 2013; 146(3): 414–419. [PubMed: 23017544]

185. Arnone D, McKie S, Elliott R, Juhasz G, Thomas EJ, Downey D et al. State-dependent changes in hippocampal grey matter in depression. Mol Psychiatry 2013; 18(12): 1265–1272. [PubMed: 23128153]

186. Samann PG, Hohn D, Chechko N, Kloiber S, Lucae S, Ising M et al. Prediction of antidepressant treatment response from gray matter volume across diagnostic categories. European neuropsychopharmacology : the journal of the European College of Neuropsychopharmacology 2013; 23(11): 1503–1515. [PubMed: 23920122]

187. Mitani H, Shirayama Y, Yamada T, Maeda K, Ashby CR, Kawahara R. Correlation between plasma levels of glutamate, alanine and serine with severity of depression. Prog Neuropsychopharmacol Biol Psychiatry 2006; 30(6): 1155–1158. [PubMed: 16707201]

188. Locher C, Koechlin H, Zion SR, Werner C, Pine DS, Kirsch I et al. Efficacy and Safety of Selective Serotonin Reuptake Inhibitors, Serotonin-Norepinephrine Reuptake Inhibitors, and Placebo for Common Psychiatric Disorders Among Children and Adolescents: A Systematic Review and Meta-analysis. JAMA Psychiatry 2017; 74(10): 1011–1020. [PubMed: 28854296]

189. Zhang G, Stackman RW. The role of serotonin 5-HT2A receptors in memory and cognition. Front Pharmacol 2015; 6: 225. [PubMed: 26500553]

190. Bouso JC, Dos Santos RG, Alcázar-Córcoles M, Hallak JEC. Serotonergic psychedelics and personality: A systematic review of contemporary research. Neurosci Biobehav Rev 2018; 87: 118–132. [PubMed: 29452127]

191. Zanos P, Gould TD. Mechanisms of ketamine action as an antidepressant. Mol Psychiatry 2018; 23(4): 801–811. [PubMed: 29532791]

192. Kadriu B, Greenwald M, Henter ID, Gilbert JR, Kraus C, Park LT et al. Ketamine and Serotonergic Psychedelics: Common Mechanisms Underlying the Effects of Rapid-Acting Antidepressants. Int J Neuropsychopharmacol 2021; 24(1): 8–21. [PubMed: 33252694]

193. Anis NA, Berry SC, Burton NR, Lodge D. The dissociative anaesthetics, ketamine and phencyclidine, selectively reduce excitation of central mammalian neurones by N-methyl-aspartate. Br J Pharmacol 1983; 79(2): 565–575. [PubMed: 6317114]

194. Dravid SM, Erreger K, Yuan H, Nicholson K, Le P, Lyuboslavsky P et al. Subunit-specific mechanisms and proton sensitivity of NMDA receptor channel block. J Physiol 2007; 581(Pt 1): 107–128. [PubMed: 17303642]
196. Liu FF, Zhao S, Liu P, Huo SP. Influence of mTOR signaling pathway on ketamine-induced injuries in the hippocampal neurons of rats. Neurol Res 2019; 41(1): 77–86. [PubMed: 30373500]

197. Zorumski CF, Izumi Y, Mennerick S. Ketamine: NMDA Receptors and Beyond. J Neurosci 2016; 36(44): 11158–11164. [PubMed: 27807158]

198. Sattar Y, Wilson J, Khan AM, Adnan M, Azzopardi Larios D, Shrestha S et al. A Review of the Mechanism of Antagonism of N-methyl-D-aspartate Receptor by Ketamine in Treatment-resistant Depression. Cureus 2018; 10(5): e2652. [PubMed: 30034974]

199. Aleksandrova LR, Phillips AG, Wang YT. Antidepressant effects of ketamine and the roles of AMPA glutamate receptors and other mechanisms beyond NMDA receptor antagonism. J Psychiatry Neurosci 2017; 42(4): 222–229. [PubMed: 28234212]

200. Duman RS, Aghajanian GK. Synaptic dysfunction in depression: potential therapeutic targets. Science 2012; 338(6103): 68–72. [PubMed: 23042884]

201. Treccani G, Ardalan M, Chen F, Musazzi L, Popoli M, Wegener G et al. S-Ketamine Reverses Hippocampal Dendritic Spine Deficits in Flinders Sensitive Line Rats Within 1 h of Administration. Mol Neurobiol 2019; 56(11): 7368–7379. [PubMed: 31037646]

202. Artin H, Zisook S, Ramanathan D. How do serotonergic psychedelics treat depression: The potential role of neuroplasticity. World J Psychiatry 2021; 11(6): 201–214. [PubMed: 34168967]

203. Lenze EJ, Nicol GE, Barbour DL, Kannampallil T, Wong AWK, Piccirillo J et al. Precision clinical trials: a framework for getting to precision medicine for neurobehavioural disorders. J Psychiatry Neurosci 2021; 46(1): E97–E110. [PubMed: 33206039]

204. Shelton RC, Parikh SV, Law RA, Rothschild AJ, Thase ME, Dunlop BW et al. Combinatorial Pharmacogenomic Algorithm is Predictive of Citalopram and Escitalopram Metabolism in Patients with Major Depressive Disorder. Psychiatry Res 2020; 290: 113017. [PubMed: 32485484]

205. Islam F, Gorbovskaya I, Müller DJ. Pharmacogenetic/Pharmacogenomic Tests for Treatment Prediction in Depression. Adv Exp Med Biol 2021; 1305: 231–255. [PubMed: 33834403]

206. Claudio-Campos K, Padrón A, Jenkins G, Nainaparampil J, Nelson R, Martin A et al. Accepetability, Feasibility, and Utility of Integrating Pharmacogenetic Testing into a Child Psychiatry Clinic. Clin Transl Sci 2021; 14(2): 589–598. [PubMed: 33166056]

207. Barrenschee M, Lange C, Cossais F, Egberts JH, Becker T, Wedel T et al. Expression and function of Neuregulin 1 and its signaling system ERBB2/3 in the enteric nervous system. Front Cell Neurosci 2015; 9: 360. [PubMed: 26441531]

208. Gheibihayat SM, Cabezas R, Nikiforov NG, Jamialahmadi T, Johnston TP, Sahebkar A. CD47 in the Brain and Neurodegeneration: An Update on the Role in Neuroinflammatory Pathways. Molecules 2021; 26(13).

209. Roman M, Irwin MR. Novel neuroimmunologic therapeutics in depression: A clinical perspective on what we know so far. Brain Behav Immun 2020; 83: 7–21. [PubMed: 31550500]

210. Howren MB, Lamkin DM, Suls J. Associations of depression with C-reactive protein, IL-1, and IL-6: a meta-analysis. Psychosom Med 2009; 71(2): 171–186. [PubMed: 19188531]

211. Zunszain PA, Anacker C, Cattaneo A, Choudhury S, Musaelyan K, Myint AM et al. Interleukin-1β: a new regulator of the kynurenine pathway affecting human hippocampal neurogenesis. Neuropsychopharmacology 2012; 37(4): 939–949. [PubMed: 22071871]

212. Le-Niculescu H, Roseberry K, Gill SS, Levey DF, Phalen PL, Mullen J et al. Precision medicine for mood disorders: objective assessment, risk prediction, pharmacogenomics, and repurposed drugs. Mol Psychiatry 2021; 26(7): 2776–2804. [PubMed: 33828235]

213. Scangos KW, Makhoul GS, Sugrue LP, Chang EF, Krystal AD. State-dependent responses to intracranial brain stimulation in a patient with depression. Nat Med 2021; 27(2): 229–231. [PubMed: 33462446]

214. Modak A, Fitzgerald PB. Personalising transcranial magnetic stimulation for depression using neuroimaging: A systematic review. World J Biol Psychiatry 2021; 22(9): 647–669. [PubMed: 33779486]
Figure 1: Hippocampus Anatomy.
The hippocampus is divided into multiple subregions including the dentate gyrus (DG), Cornu Ammonis (CA) regions 1-4, and subiculum (not shown). The entorhinal cortex (EC) acts as the gateway into the hippocampus via the perforant path which projects onto the DG (1). The DG sends fibers to CA3 through the mossy fiber pathway (2). CA3 pyramidal cells receive inputs from the associated/commissural fibers (not shown) and send their projections to CA1 via Schaffer collaterals (3). Lastly, neurons in CA1 project back into the entorhinal cortex and into subiculum (4).
Figure 2: Mechanisms of Synaptic Plasticity.

Left: Under basal conditions, glutamate is released from the pre-synaptic neuron. Once in the synaptic cleft, glutamate stimulates AMPA receptors on the post-synaptic neuron, triggering depolarization noted by the influx of sodium ions. With a weak stimulus, influx of sodium into the pre-synaptic neuron is minimal and infrequent, resulting in infrequent and low amplitude excitatory postsynaptic potentials (EPSPs).

Right: Under high levels of stimulation, more glutamate is released from the pre-synaptic neuron resulting in stronger depolarizations on the post-synaptic neuron. Stronger depolarization increases the amount of calcium in the cell and removes magnesium from NMDA receptors, allowing more sodium to enter. High intracellular calcium levels activate kinases like Protein Kinase C (PKC) and Calcium/Calmodulin dependent protein kinase II (CaMKII) which phosphorylates AMPA receptors thereby increasing their conductance. In both scenarios, glial cells present at the synaptic cleft aid in glutamate reuptake.
Figure 3. Molecular Regulators of Neuroplasticity.

Brain-derived neurotrophic factor (BDNF) attaches to a Tropomyosin receptor kinase B (TrkB) receptor on the post-synaptic neuron. BDNF signaling causes expression of phosphoinositol 3-kinase (PI3K) which is responsible for cell proliferation and survival. PI3K activates Protein Kinase B (Akt) and Mitogen-activated protein kinase (MEK) pathways which lead to expression of cAMP response element binding protein (CREB) and mammalian target of rapamycin (mTOR), respectively. High intracellular Ca^{2+} concentrations from AMPA and NMDA activation activate CAMKII which also stimulates CREB production. CREB is a key element needed for neurite outgrowth, neurogenesis and synaptic plasticity.
Figure 4. Before and After Treatment.
Table shows cognitive/behavioral, network/circuit, neuron structure and number, synapse function and signaling pathways alterations in untreated and treated depression.