A Review of Serotonin's Role in Depression and Modern Perspectives

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Abstract

Major depressive disorder (MDD) is a highly prevalent and debilitating illness in the modern world. In the 1960s, the theory that low serotonin (5-HT) was a primary cause of MDD emerged due to the efficacy of 5-HT restoring drugs in treating depression. The 5-HT deficiency hypothesis of depression has since been criticized through studies not being able to directly tie low serotonin to MDD. The discovery of the antidepressant efficacy of the glutamatergic stimulant ketamine led to a reevaluation of depression pathophysiology. Modern perspectives view depression as an issue of disrupted neurocircuitry resulting from stress induced atrophy of certain limbic and cortical brain regions, such as the hippocampus and PFC, and hypertrophy in the fear evaluating amygdala, the reward evaluating nucleus accumbens, and the orbitofrontal cortex. Depression may be treated by potentiating neuroplasticity, that when combined with psychotherapy, helps individuals relearn negative emotional associations and restores dysfunctional neurocircuitry. The functioning of the serotonergic system may be viewed as a vulnerability factor in developing depression due to its involvement in stress, as well as a treatment target which indirectly primes neuroplasticity. Other neurotransmitter systems similarly represent depressive risk factors and antidepressant targets, namely the noradrenergic and dopaminergic systems. Serotonergic antidepressants such as SSRIs see high rates of prescription due to their minimal side effects. They demonstrate slower efficacy than ketamine, whose dissociative side effects and potential for abuse are unideal, demanding further research of its mechanism to find safer and more effective antidepressant targets.

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Introduction

According the the DSM-V, MDD is characterized by having five of the following symptoms during a 2 week period, representing a change from baseline functioning: depressed mood, anhedonia, weight loss or gain, insomnia or hypersomnia, psychomotor agitation or retardation, fatigue, feelings of worthlessness, reduced concentration, and suicidal ideation. At least one of these five symptoms must be either depressed mood or anhedonia. A diagnosis also requires that these symptoms cause significant clinical distress and functional impairment, are not attributable to the effects of a substance or other medical condition, and includes exclusions for other psychotic disorders, including bipolar disorder.[45] Major depressive disorder is a debilitating and chronic illness. With an estimated lifetime occurrence of 16.2% in the USA, and affecting more than 300 million people worldwide, MDD is the second biggest cause of disability today.[1,2] With its potential for lost productivity and the danger of suicide, the prevalence of MDD society has given scientists and medical professionals much reason to find an effective treatment. This has naturally led to research into the biomechanisms behind MDD. One popular explanation is the 5-HT/monoamine deficiency hypothesis of depression, which identifies a deficiency of 5-HT and other monoamine neurotransmitters in the brain as the core pathogenetic factor behind depression.[3]

The monoamine hypothesis has had an influential role in the history of psychology[4]. Much of the evidence supporting the depletion hypothesis comes from the efficacy of serotonin enhancing drugs, as the majority of clincially available antidepressants upregulate 5-HT or norepinephrine (NE), another monoamine neurotransmitter. A summary of drugs currently used to treat depression is shown in Table 1 below.

Table 1: Currently Approved Antidepressant Drugs [43]

Antidepressant Class	**Mechanism**	**Example(s)**
Selective Serotonin Reuptake Inhibitors (SSRIs)	Inhibit the serotonin transporter (SERT), preventing serotonin reuptake into the presynaptic terminal. Currently the first line in treatment of depression due to the relatively minimal side effects.	● Sertraline ● Fluvoxamine ● Fluoxetine ● Paroxetine ● Citalopram ● Escitalopram
Selective Norepinephrine Reuptake Inhibitors (SNRIs)	Inhibit the norepinephrine transporter (NET), and SERT to a smaller degree, preventing both 5-HT and NE reuptake into the presynaptic terminal.	● Venlafaxine ● Desvenlafaxine ● Duloxetine ● Milnacipran ● Levomilnacipran
Atypical Antidepressants	Various effects on the 5-HT, NE, and/or dopamine (DA) systems.	● Bupropion ● Mirtazapine ● Agomelatine
Serotonin Modulators	Inhibit presynaptic 5-HT	● Nefazodone

	reuptake to varying degrees while also acting as 5-HT receptor agonists or antagonists.	• Trazodone • Vilazodone • Vortioxetine
Tricyclic Antidepressants (TCAs)	Inhibit 5-HT and NE reuptake. Also have an affinity for muscarinic M1 receptors and histamine H1 receptors, causing sedation and anticholinergic side effects.	• Amitriptyline • Clomipramine • Doxepin • Imipramine • Trimipramine • Desipramine • Nortriptyline • Protriptyline • Maprotiline • Amoxapine
Monoamine Oxidase Inhibitors (MAOIs)	Inhibit the monoamine oxidase enzyme, which normally breaks down 5-HT, NE, and DA. Not a first line treatment due to adverse drug-drug interactions.	• Selegiline. • Moclobemide • Tranylcypromine • Isocarboxazid • Phenelzine

NMDA Antagonists	Blockades NMDA receptors, which ultimately increases glutamatergic signaling.	• Esketamine

Despite early pharmacological evidence, the monoamine hypothesis has since received criticism due to a lack of strong evidence to indicate a connection between low 5-HT and depression.[5] This, along with issues surrounding the delayed onset of typical monoamine affecting antidepressants presenting danger in cases of suicidal ideation and a meta-analysis that demonstrated SSRIs struggle to outperform placebo[29], has led to the development of alternate hypothesis hoping to develop more effective antidepressants.[4] While there is evidence that 5-HT may play a role in the pathophysiology of depression[6], modern findings suggest the monoamine hypothesis is overly simplistic, and that serotonin should not be viewed as the primary pathogenetic factor behind MDD.[4]

The purpose of this review is to critically evaluate the role 5-HT plays in depression based on modern findings, as well as integrate current ideas about depressive pathophysiology into a central hypothesis about the nature of MDD. The findings presented below also serve the purpose of suggesting directions for future research into antidepressants. Furthermore, I hypothesize that serotonin's involvement in self-control predicts individual resistance to stress, and that a chronic failure of the serotonergic system to maintain goal-directed behavior in the face of adversity is one way depression can develop. I would also like to present the idea that in the case of serotonergic antidepressants such as SSRIs, increases in neuroplastic gene transcription resulting from upregulation of serotonergic signaling is the basis of antidepressant

treatment, with the quality of the environment predicting whether new emotional associations resulting from the increased plasticity are positive, neutral, or negative. This emphasizes the need to pair antidepressant treatment with psychotherapy and supportive care.

Materials and Methods

A systematic review of the role of serotonin in depression was conducted, integrating modern perspectives including reviews of stress, neuroplasticity, genetics, and other monoamines, with the focus to better characterize the pathophysiology of depression and examine avenues of future research in antidepressant therapy. Literature search was conducted primarily using PubMed. Selected papers were qualitatively assessed for their relevance and objectivity before being included. The textbook "*Psychopharmacology.* Sunderland, MA, U.S.A. Sinauer Associates. (2019)" provided broad information and was used to find additional papers it referenced in text. Additional papers were found through manual search of literature reference lists. Overall, findings of 55 papers were included to conduct this review.

Results

Serotonin's Function in the Brain

Discovered over 60 years ago, 5-HT is a neurotransmitter that modulates a wide range of neural activities and psychological processes.[7] 5-HT is mediated by 14 types and subtypes of receptors, that, combined with its role in modulating a large number of physiological and psychological processes, make 5-HT's exact function hard to define.[8] This is compounded by the

sheer extensiveness of serotonergic innervation throughout the central nervous system, as although the cell-bodies of 5-HT-ergic neurons are almost exclusively located in the raphe nuclei of the brain stem, the axons of these neurons spread throughout the entire brain.[8] It can be said that every brain cell is close to a serotonergic fiber, with nearly all behaviors and many other brain functions in some way regulated by serotonin.[7] The primary raphe nuclei are the dorsal raphe (DR) and median raphe, located in the caudal midbrain and rostral pons.[25] Axons from these regions are not uniformly distributed, innervating areas of high dendritic and synaptic density more than white matter tracts.[25] Figure 1 contains a diagram showing serotonergic fiber distributions in the human brain.

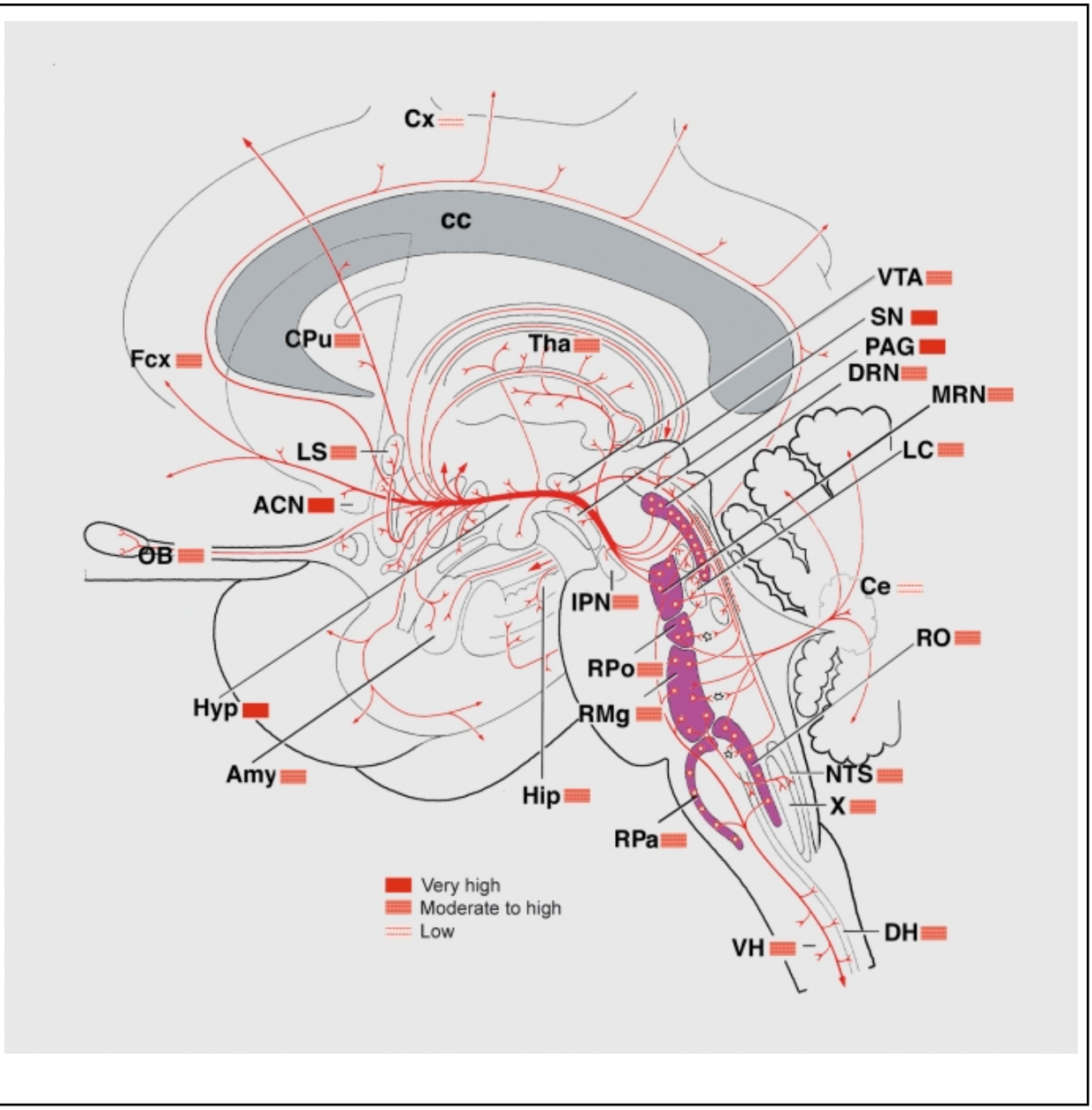

Figure 1. A sagittal view of human serotonergic neurocircuitry. The raphe nuclei are shown in purple, with their axonal projections shown in red. The densities of fiber distribution are shown by the colored boxes, according to the key. "X, dorsal motor n of the vagus nerve; ACN, accumbens n; Amy, amygdala; cc, corpus callosum; Ce, cerebellum; CPu, caudate-putamen; Cx, cortex; DH, dorsal horn spinal cord; DRN, dorsal raphe n; Fcx, frontal cortex; Hip, hippocampus; Hyp, hypothalamus; IPN, interpeduncular n; LC, locus coeruleus; LS, lateral septum; MRN, median raphe n; n, nucleus; NTS, n of the solitary tract; OB, olfactory bulb; PAG, periaqueductal gray; RMg, raphe magnus n; RO, raphe obscurus n; Rpa, raphe pallidus; RPo, raphe pontis n; SN, substantia nigra; Tha, thalamus; VH, ventral horn; VTA, ventral tegmental area." Figure adapted from Charnay et al.[46]

The function of the dorsal raphe tract has been widely studied in cat brains. While awake, the dorsal raphe fires tonically at a constant, slow rate.[25] It also can fire in phasic bursts, facilitating motor output while suppressing sensory processing.[25] Phasic firing must be triggered by excitatory inputs to the DR, such as through glutamatergic pathways from the PFC, lateral habenula, hypothalamus, and various brainstem areas.[25] The DR also receives cholinergic input from the laterodorsal and pedunculopontine nuclei, located in the pons, and inhibitory GABA inputs from different areas like the hypothalamus, the substantia nigra, the ventral tegmental area (VTA), the periaqueductal gray, and GABAergic interneurons in the DR itself.[25] Finally, other neuronal systems are integrated in regulating 5-HT activity, such as dopaminergic activity in the VTA and noradrenergic activity in the locus coeruleus.[25] During slow wave sleep, DR firing becomes slower and irregular, and effectively ceases firing during REM sleep.[25]

5-HT's effects on behavior are varied, modulating a range of processes also affected by depression, such as mood, appetite, sleep, activity, suicide, sexual behavior, and cognition, including learning and memory.[8] In addition, an alteration of 5-HT function has been observed in a plethora of clinical conditions, including anxiety, OCD, eating disorders, aggression, suicide, impulse disorders, alcohol abuse, and premenstrual syndrome.[8] Serotonergic tracts have been robustly connected to aggression and impulse control.[25] For example, tryptophan hydroxylase 2 KO mice, which are effectively prevented from synthesizing 5-HT in the brain, demonstrate a large increase in aggressive behavior in resident-intruder tests.[25] These mice are also seen to become more compulsive and impulsive, but less anxious.[25] They show poorer social communication and insufficient maternal care, highlighting 5-HTs involvement in mood and behavior.[25] In addition, 5-HT has been shown to be involved in pain analgesia[25] and locomotion[53] in the spinal cord, as well as gut motility in the peripheral nervous system.[25]

The 14 serotonin receptors are grouped as follows: 5-HT_{1A}, 5-HT_{1B}, 5-HT_{1D}, 5-HT_{1E}, 5-HT_{1F}, 5-HT_{2A}, 5-HT_{2B}, 5-HT_{2C}, 5-HT_3, 5-HT_4, 5-HT_{5A}, 5-HT_{5B}, 5-HT_6, and 5-HT_7.[44] Besides 5-HT_3, serotonin receptors are metabotropic G-protein coupled receptors.[44] A brief summary of each of their functions is shown in Table 2 below. Of the 5-HTRs, 5-HT_{1A} and 5-HT_{2A} have been studied the most for their role in depression, due to their high expression in limbic and cortical regions respectively[44], which will be elaborated more in later sections.

Table 2: The Functions of the 5-HT Receptors[25, 44]

5-HT Receptor	**Type**	**Mechanism**	**Effect**	**Notes**
5-HT_{1A}	$G_{i/o}$ coupled	Decrease cellular cAMP	Inhibitory	Presynaptic raphe cell 5-HT autoreceptor, highly expressed postsynaptically in limbic regions.
5-HT_{1B}	$G_{i/o}$ coupled	Decrease cellular cAMP	Inhibitory	Terminal raphe cell 5-HT autoreceptor.
5-HT_{1D}	$G_{i/o}$ coupled	Decrease cellular cAMP	Inhibitory	Terminal raphe cell 5-HT

				autoreceptor.
5-HT_{1E}	$G_{i/o}$ coupled	Decrease cellular cAMP	Inhibitory	Expressed cortically, not expressed in mice.
5-HT_{1F}	$G_{i/o}$ coupled	Decrease cellular cAMP	Inhibitory	Expressed primarily in motor regions, antimigraine target.
5-HT_{2A}	$G_{q/11}$ coupled	Increase cellular IP3 and DAG	Excitatory	High cortical expression, primary serotonergic hallucinogenic target (LSD, Psilocin, DOI), activates genes mediating neuroplasticity.
5-HT_{2B}	$G_{q/11}$ coupled	Increase cellular	Excitatory	Important for

		IP3 and DAG		heart and brain development, knockout is lethal, involvement in certain cardiac pathologies.
$5\text{-}HT_{2C}$	$G_{q/11}$ coupled	Increase cellular IP3 and DAG	Excitatory	Inhibits dopaminergic neurotransmission, high expression in amygdala, associated with anxiety when activated.
$5\text{-}HT_{3}$	Cation channel	Depolarize cell	Excitatory	The only ionotropic 5-HT receptor, located on peripheral terminals of vagus nerve,

				antagonists are anti-nausea and anxiolytic.
5-HT_4	G_s coupled	Increase cellular cAMP	Excitatory	High expression in hippocampus and motor regions, appear to mediate LTD in hippocampus, high expression in gastric periphery, promotes gut motility.
5-HT_{5A}	$G_{i/o}$ coupled	Decrease Cellular cAMP	Inhibitory	Possibly important in cerebellar functioning.
5-HT_{5B}	$G_{i/o}$ coupled	Decrease Cellular cAMP	Inhibitory	Not expressed in humans.
5-HT_6	G_s coupled	Increase cellular	Excitatory	Highly

		cAMP		expressed in striatum and cortex, blockade enhances cholinergic neurotransmission and promotes learning/memory.
5-HT_7	G_s coupled	Increase cellular cAMP	Excitatory	Expressed in the suprachiasmatic nucleus of hypothalamus, appears to regulate circadian processes, high gut and spinal cord expression.

Origins of the 5-HT/Monoamine Hypothesis

The 5-HT hypothesis of depression can be traced to clinical observations in the 1950s, where Iproniazid, a drug for Tuberculosis, unexpectedly displayed an antidepressant effect in tuberculosis patients. This was coupled with the drug's ability to inhibit monoamine oxidase (MAO) A and B, the enzymes responsible for metabolizing 5-HT and NE, and thereby increased brain monoamine levels.[3] These findings served as early evidence in 1965, when Joseph Schildkraut presented the hypothesis that depression could be tied to a deficiency of norepinephrine and other catecholamines, but also emphasized the likely involvement of serotonin.[9] His formulation heavily relied on drug-based evidence and recognized the theory was likely an oversimplification of a complex biological state.[10] While Schildkraut focused primarily on the relationship between NE and depression, in 1967, Alec Coppen identified a connection between 5-HT and MDD, citing pharmacological evidence that depletion of monoamines in the brain could induce depression in a subset patients receiving reserpine for hypertension, that increasing the effectivity of monoamines with monoamine oxidase inhibitors (MAOI) could alleviate depression, and that there was evidence of disturbances in amine metabolism in MDD.[11] The identification of 5-HT being an important factor was shown by the fact that tryptophan, the amino acid precursor of 5-HT, potentiated the antidepressant action of MAOIs in depressed patients.[11] Today, the theory remains influential in the pharmaceutical industry, and Selective Serotonin Reuptake Inhibitors (SSRI) antidepressants are now among the best-selling drugs in medical practice.[9] This highlights the need of further research into the neuropathophysiology behind depression, as modern findings and counterevidence to the 5-HT hypothesis suggest there could be superior alternative treatments, which will be further explained in the section below.

Expanding Upon the 5-HT Deficiency Hypothesis

Although pharmacological evidence is the basis of the 5-HT deficiency hypothesis, it has also opened up alternative explanations. Both MAOIs and TCAs increase other monoamines in addition to 5-HT, suggesting NE and dopamine (DA) may also play an important role in depression.[6] 5-HT activates excitatory 5-HT_{2A} receptors on GABA neurons that dampen NE neuron activity, and inhibits DA activity in the VTA, potentially explaining the lack of therapeutic benefit of SSRIs in some patients[6], as a lack of dopaminergic signaling is believed to contribute to anhedonia.[33] The role of other monoamines in depression is further evidenced by the fact that treatments involving SSRIs combined with drugs that reverse this dampening action (i.e. NE reuptake inhibitors or DA agonists) have led to effective augmentation strategies against MDD in patients resistant to SSRI treatment.[6] The involvement of these other monoamine systems makes it hard to narrow down 5-HT as the primary cause of depression.

More of the evidence classically supporting the 5-HT theory of depression has been found to be inconclusive at best under scrutiny. The use of pharmacological evidence citing SSRI efficacy is questionable, as only 50% of patients respond to SSRIs, and effective remission only occurs less than 30% of the time.[13] Although controversial, the pooled results of FDA clinical trials of SSRIs showed placebo was able to duplicate the antidepressant response of SSRI by 80%[7], and it demonstrated that SSRIs exactly demonstrate superiority to placebo in severe depression only.[3] Another review found long-term antidepressant therapy with drugs such as SSRIs to be generally innefective.[55] Furthermore, the delayed onset of SSRI efficacy despite its immediate increase of 5-HT in the synaptic cleft shows that simply raising 5-HT levels does not treat MDD.[4] Additionally, while tryptophan depletion can cause a recurrence of symptoms in certain recovering MDD patients, such as those responding to the atypical antidepressant

mirtazapine, it has been shown to have little to no effect in otherwise healthy controls.[6] As stated by Lacasse et al., "The fact that there is no peer-reviewed article that can be accurately cited to support claims of 5-HT deficiency in any mental disorder while there being many that present counterevidence"[9], has led to research efforts to expand pathophysiological models of depression in order to better understand the disorder and improve treatment options. In the following sections, I will first explain the role of 5-HT in MDD, especially concerning the involvement of its receptors and neurocircuitry, before providing accounts of modern antidepressant research into stress pathways, genetics, neuroplasticity, and other monoamine systems. Finally, I will explain how these systems are integrated in the onset and maintenance of MDD.

Role of 5-HT Dysregulation in MDD

As detailed above, much of the basis for the 5-HT hypothesis of depression comes from the efficacy of serotonin enhancing drugs. As demonstrated by Iproniazid, MAOIs are an effective treatment for MDD; they inhibit the oxidation of monoamines, increasing extracellular levels of 5-HT, NE, and dopamine. Another class of drugs, tricyclics, were also found to be moderately effective antidepressants, acting by blocking 5-HT and NE reuptake. SSRIs are a more pharmacologically specific antidepressant that act by inhibiting 5-HT reuptake into raphe nuclei neurons, leading to increased 5-HT levels throughout the brain after chronic treatment,[2] and serving as a first line treatment for depression.[43]

In addition to evidence from drug treatments, several interesting observations serve to support the idea that serotonin plays at least some role in MDD. Tryptophan depletion, which effectively lowers brain 5-HT levels, can cause a recurrence of depressive symptoms in recovering MDD patients who were responsive to certain serotonergic antidepressants.[3]

Additionally, low 5-HT was found to have a robust correlation with suicide patients, although its correlation to MDD has been shakier.[3]

While the above findings serve to evidence the depletion hypothesis, studies into serotonin receptors and genetic polymorphisms served to demonstrate mood disorders modulated by serotonin had more to do with a general dysfunction of serotonergic circuitry, which could result from either hyper- or hypo- function of serotonin pathways depending on the brain region, stage of neurodevelopment, an receptors involved. For example, increased 5-HT_{2A}R cortical receptors, ante- and post-mortem, have been repeatedly associated with depression and depressive personality traits, with a link between it and suicidality.[3] This receptor is correspondingly seen to be reduced after successful antidepressant treatment, coinciding with the onset of clinical efficacy.[22]

Studies into 5-HT_{2A}R have found its signaling to be associated with anxiogenesis, as 5-HT_{2A} KO mice demonstrate reduced anxiety, with restoration of the receptor in the PFC normalizing anxiety-like behavior.[22] This effect may be a result of serotonergic signaling onto the PFC being responsible for modulating downstream signaling in the amygdala (AMG), with serotonin's demonstrated modulation of anxiety being one way it is involved in the intersection of stress and depression.[22] Indeed, potentiation of this receptor with the hormone CRH, which regulates the stress response along with other roles, led to increased anxiety-like behavior in mice in response to the 5-HT_{2A} agonist DOI.[22] Finally, frontolimbic receptor density of 5-HT_{2A} in humans is correlated both with anxiety and the ability to cope with stress, with prefrontal 5-HT_{2A} receptors on descending fibers that control the DR being involved in stress responses.[22] In clinical studies, downregulation of these receptors after treatment with various antidepressants

was found to coincide with the onset of antidepressant efficacy in patients with major depression.[22]

It must be noted that a general upregulation in 5-HT receptors does not occur in depression, as shown by the apparent decrease of hippocampal 5-HT_{1A}Rs in chronically depressed patients.[3] This corresponds with an observation of postsynaptic 5-HT_{1A}Rs mediating anxiolytic effects[47]. It has been theorized the postsynaptic 5-HT_{1A}R receptor is also involved impulse control, such as by increasing patience and anti-aggression.[47]It must be mentioned that postsynaptic 5-HT_{1A}Rs have differing roles than presynaptic autoreceptors, whose role in antidepressant efficacy will be elaborated later in this section.

Due to the differing roles of serotonergic receptors, Carhart-Harris et al. proposed a "bipartite model of depression", where postsynaptic 5-HT_{1A}Rs are hypothesized to be involved in resistance to depression through its signaling promoting stress-coping, while 5-HT_{2A}Rs are hypothesized to be involved in antidepressant efficacy, shown by their downstream activation of neuroplastic genes in response to psychedelics.[47] This idea is summarized in Figure 2 below. Their formulation acknowledged that ignoring the roles of the other serotonin receptors represented an oversimplification, but emphasized the general idea of serotonin mediating both a coping and neuroplastic pathway through separate mechanisms.[47] With results from a 2021 study by Hesselgrave et al. demonstrating psilocybin could mediate an antidepressant and neuroplastic effect in mice despite blockade of 5-$HT_{2A/2C}$Rs with ketanserin[48], more extensive studies into the roles of other 5-HTRs are warranted to find additional pharmacological targets. For example, blockade of 5-HT_7 potentiates antidepressant effects in rats.[2] A summary of data detailing current findings about the roles of varying serotonin receptors in modulating neuroplasticity is shown in Table 3 below, adapted from Kraus et al.[49]

Table 3. The roles of various serotonin targets in neuroplasticity. Data adapted from Kraus et al.[49]

Serotonin Target	**Downstream Mechanism of Neuroplastic Activation**	**Modulates**
5-HT_{1A}	MAPK, AKT, LTD + LTP via NMDA, s100, BDNF, NF-κB, CREB	Adult neurogenesis, dendritic maturation, neuroprotection, astroglial interaction
5-HT_{1B}	AKT, ERK, LTD	Unknown
5-HT_{2A}	ERK, NMDA, kalirin−7, BDNF	Synaptic plasticity, spine morphology, dendritic morphology
5-HT_{2C}	NMDA, LTP	Synaptic plasticity.
5-HT_{3A}	PSA-NCAM, NMDA, LTD	Neuronal migration, synaptic plasticity
5-HT_{4}	ERK, LTP/LTD, BDNF, CREB, AKT	Spine morphology, synaptic plasticity, neurogenesis
5-HT_{6}	ARK, ERK, BDNF	Unknown
5-HT_{7}	MAPK, LTD, TrKB	Neurite length

SERT	BDNF	Spine density
MAO	NMDA, LTP	Neurogenesis

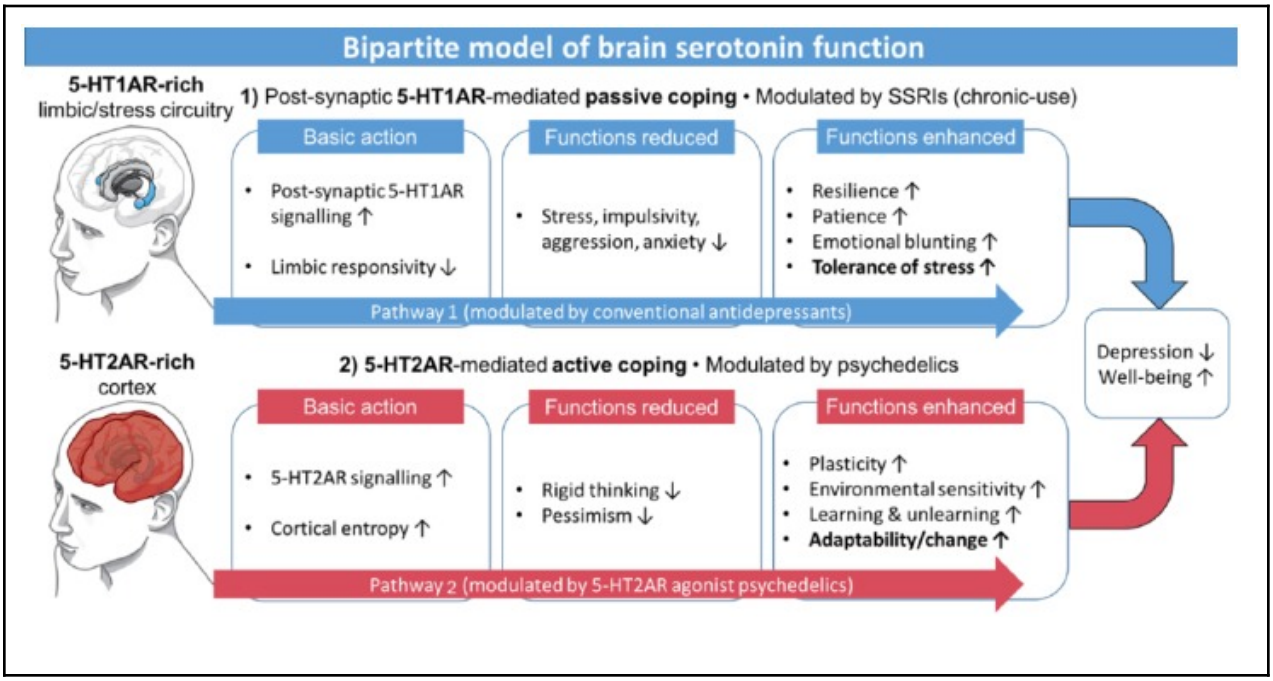

Figure 2. The proposed bipartite model of serotonin's role in depression. 5-HT_{1A} signaling corresponds with resistance to stress. 5-HT_{2A} signaling corresponds to neuroplastic changes that may help alleviate depression. Carhart-Harris et al. predicts conventional antidepressants such as SSRIs therefore act by primarily enhancing the 5-HT_{1A} pathway, while serotonergic psychedelics primarily act on pathway 2.[47] Note the findings that serotonergic neuroplasticity could occur independent of 5-HT_{2A}[48] evidence that this model is an oversimplificaton. Adapted from Carhart-Harris et al.[47]

In opposition to the 5-HT insufficiency hypothesis, a genetic study of the serotonin transporter (SERT or 5-HTT) showed increased presence of serotonin in the synapse could be tied to a depressive phenotype.[12] SERT, involved in the reuptake of serotonin at brain synapses,[12] is the main point of action of SSRIs.[4] A 2003 study found that a functional polymorphism in the promoter of the SERT gene moderated the influence of stress on depression, stating "Individuals with one or two copies of the short allele (*s*) of the SERT promoter polymorphism exhibited

more depressive symptoms, diagnosable depression, and suicidality than individuals homozygous for the long allele (*l*)".[12] While this evidence reinforces a connection between 5-HT and depression, it also implicates 5-HT's role in depression is not so simple as a deficiency leads to MDD, as the *s* allele of SERT decreases transporter function and therefore leads to higher concentrations of postsynaptic 5-HT. One explanation consistent with the 5-HT theory is that neurotransmitters have divergent roles in modulating depression during postnatal development than in adulthood, shown in one experiment where a pharmacological blockade of SERT in mice exclusively during early postnatal development led to increased adult depressive behavior.[5]

Along with SERT, most serotonin receptors have been connected to the modulation of depression. For example, rodent models have shown that 5-HT_{1A} receptor agonists can have acute antidepressant effects; effects that are blocked by 5-HT_{1A} antagonists, suggesting that the antidepressant response is specific to the 5-HT_{1A} receptor signaling. Conversely, 5-HT_{1A} autoreceptors produce a pro-depressive response, as opposed to the antidepressant response of the 5-HT_{1A} heteroreceptor. Activation of these receptors following an increase in extracellular 5-HT desensitizes the 5-HT_{1A} autoreceptor after chronic treatment, potentially explaining the delayed onset of SSRI treatment.[5] Studies have also suggested a connection between the 5-HT_{1B} receptor and the reward system, with reward dysfunction being a major symptom of MDD.[5]

While the examples above serve to support the connection between 5-HT modulation and depression, the evidence that the cause of MDD is a particular deficiency of 5-HT is inconclusive at best.[3] Nevertheless, the 5-HT system appears to be an important factor in the pathophysiology (as a potential risk factor) and treatment of MDD. For clarity, Figure 3 below depicts a serotonergic synapse, including autoreceptors and the serotonin transporter.

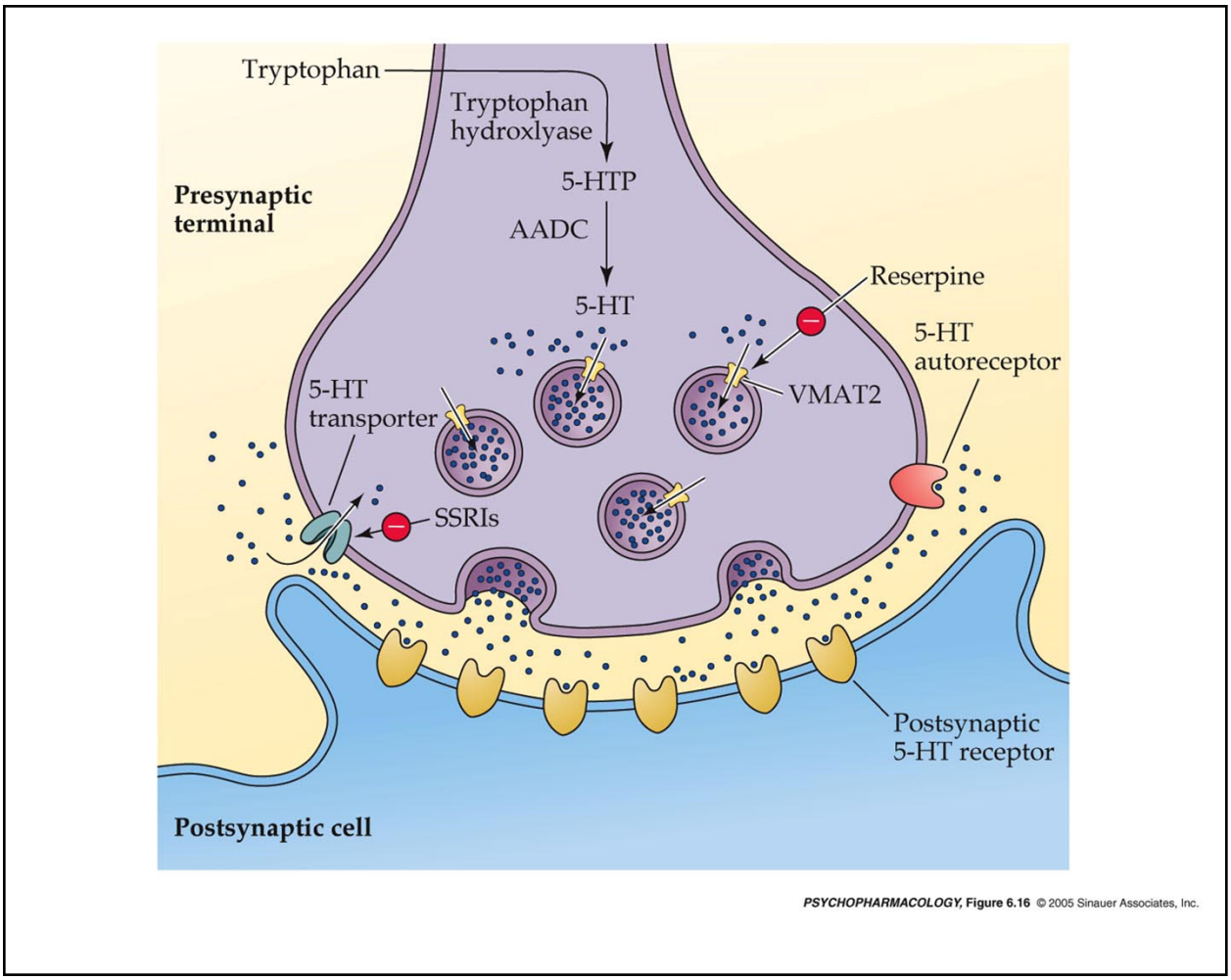

Figure 3. A serotonergic synapse. 5-HT is synthesized from tryptophan by tryptophan hydroxylase and AADC. It is packaged into vesicles by VMAT2, to be released into the synapse. The inhibition of this process by reserpine leading to depressive symptoms in a subset of patients served as important evidence for Alec Coppen's 5-HT deficiency theory.[11] The 5-HT transporter (SERT) mediates reuptake from the synapse and is the primary target for SSRIs. Presynaptic 5-HT autoreceptors maintain the extracellular tone of 5-HT. Postsynaptic 5-HT receptors receive serotonergic signals. Adapted from *Psychopharmacology.* Sunderland, MA, U.S.A. Sinauer Associates.[25]

The 5-HT_{1A} Receptor and SSRI Efficacy

Attempts to explain the several weeks before SSRI efficacy begins have identified the serotonin autoreceptors (such as 5-HT_{1A}) as possible culprits mediating the delayed therapeutic onset.[4] This hypothesis attempts to explain the delayed onset of SSRIs by identifying the key

mechanism behind antidepressant efficacy as the downregulation or desensitization of somatodendritic monoamine autoreceptors, leading to a eventual increase in 5-HT concentration after less autoreceptors are present to downregulate serotonin release.[4] The 5-HT_{1A} receptor is present both pre- and post-synaptically, coupled to Gi/o proteins that cause hyperpolarization when activated.[1] Central to this idea is the fact that presynaptic 5-HT_{1A} activation attenuates 5-HT release through negative feedback inhibition, regulating serotonin's extracellular tone.[1] Pharmacological evidence has shown pre-synaptic 5-HT_{1A} receptors to be pro-depressive when activated, while postsynaptic 5-HT_{1A}Rs are anti-depressive when activated.[17] For example, pindolol, a 5-HT_{1A}R partial agonist, was initially shown to accelerate the effects of SSRIs when co-adminsitered,[17] although this theory has not since demonstrated clinical efficacy.[19]

Upon SSRI administration, this theory proposes 5-HT reuptake inhibition initially suppresses 5-HT release by indirect activation of its autoreceptor.[18] Evidence from electrophysiological studies demonstrated that prolonged administration of an SSRI would reduce the sensitivity of 5-HT_{1A}Rs[18], allowing for an eventual elevation of serotonergic transmission. Thus, the several days to two weeks these autoreceptors take to desensitize would explain the delayed onset of SSRIs.[4] A summary of these ideas is shown in Figure 4 below.

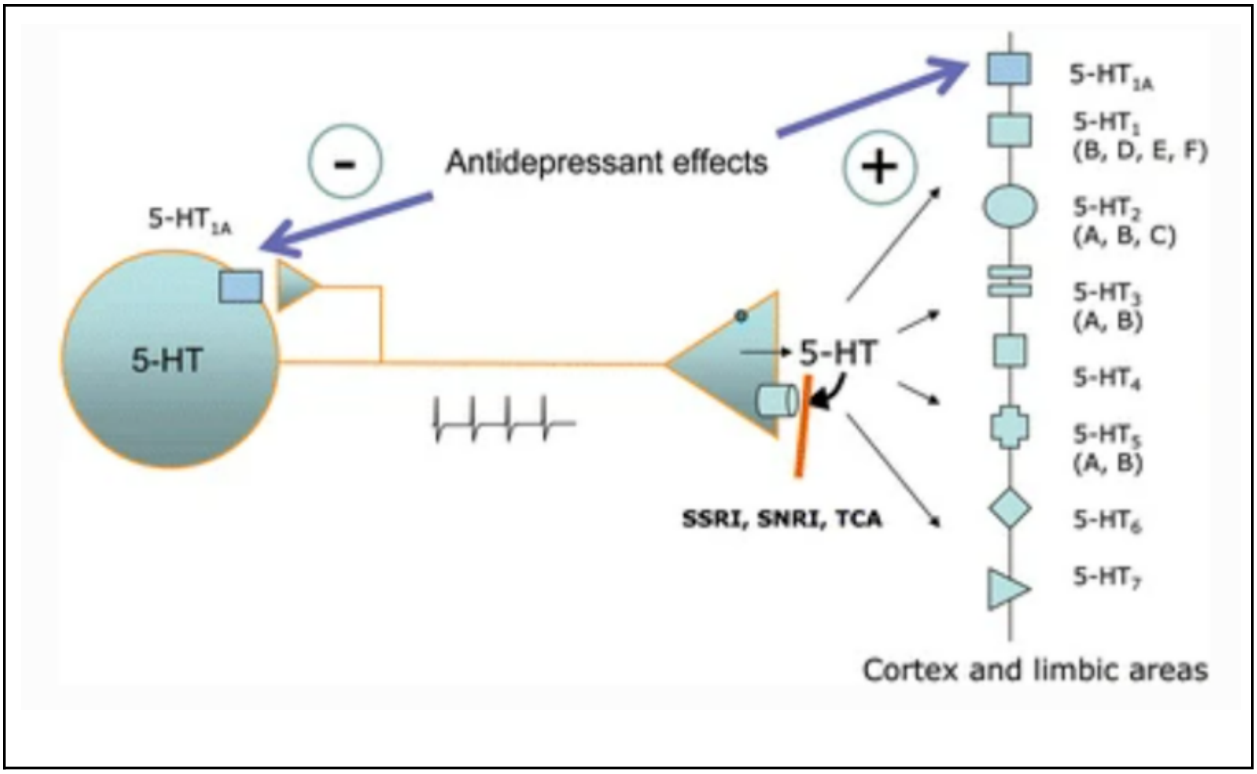

Figure 4. The differing roles of presynaptic 5-HT_{1A} autoreceptors and postsynaptic 5-HT_{1A} receptors in antidepressant response. Serotonin enhancing antidepressants (SSRI, SNRI, TCA) initially lead to increased autoreceptor activation which maintains serotonin's extracellular tone. Only after these receptors become desensitized may serotonin release into the synaptic cleft increase above baseline, explaining the delayed efficacy of SSRIs. The corresponding increase in postsynaptic serotonin receptor signaling mediates the antidepressant response. Adapted from Celada et al.[17]

The role of 5-HT_{1A}Rs in depression is evidenced by the fact that reducing presynaptic but not postsynaptic 5-HT_{1A}Rs is sufficient for an antidepressant effect in mice. Correspondingly, activation of postsynaptic 5-HT_{1A}Rs in the hippocampus is an important target in many antidepressant therapies, and may be related to hippocampal neurogenesis[17], as 5-HT signaling in the hippocampus appears to be necessary for exercise-induced neurogenesis there.[49] However, 5-HT_{1A}R KO mice show baseline antidepressant responses, and since hippocampal neurogenesis is modulated by other 5-HT receptors, it appears postsynaptic 5-HT_{1A}R activation is not entirely necessary for antidepressant action.[17] The role of hippocampal neurogenesis is further explained below in the section "The contribution of Neuroplastic and Neurogenic Dysfunctions". Finally,

postmortem studies in MDD patients have failed to find evidence supporting alterations of 5-HT_1A, suggesting a better theory may be needed.[4]

Hjorth et. al (2000) describes how preclinical evidence that autoreceptor blockade could potentiate SSRI effects raised hopes that an adjunctive therapy would help alleviate many of the problems associated with SSRI treatment alone, such as its delayed effectiveness and non-ideal response rate.[18] Sixteen years later, however, and adjunctive therapies with 5-HT_{1A}R antagonists failed to demonstrate clinical effectiveness.[19] 5-HT_{1A} agonists, aiming to take advantage of the observed antidepressant effect of postsynaptic 5-HT_{1A}Rs also failed, due to agonism towards presynaptic 5-HT_{1A}Rs and gastrointestinal side effects.[17] The observed SSRI potentiation of pindolol may be a result of its partial agonist properties that allow it to both maintain postsynaptic 5-HT_{1A}R signaling, while at least partially inhibiting presynaptic 5-HT_{1A} autoreceptors, rather than full inhibition of an antagonist.[19] The development of drugs with varying selectivity towards various 5-HT receptors is one avenue of future research. For example, Vortioxetine is a newer antidepressant agent that combines SERT inhibition with a number of 5-HTR agonist, antagonist, or partial agonist properties.[19]

The Role of Other Monoamines: Norepinephrine and Dopamine in Depression

In addition to a dysfunction of the 5-HT system, there is evidence of disturbances in the neurotransmission of the monoamines NE and DA.[32] Drugs targeting the NE and DA systems have been shown to have antidepressant potential. For example, NE specific tricyclics and SNRIs both demonstrate antidepressant efficacy[32], while anti-dopaminergic agents have shown efficacy as adjuncts in antidepressant therapy.[31] The roles both the NE and DA systems play in depression are may be tied to their roles in stress and reward, respectively.

Noradrenergic pathways originate from the locus coeruleus (LC) in the pons and project diffusely throughout the brain, including to limbic regions like the hippocampus, AMG, and hypothalamus, to cortical regions, and down the spinal cord.[32] Along with 5-HT, the widespread innervation of NE allows it to coordinate responses across multiple brain regions, such as fight-or-flight or approach-avoidance behaviors.[33] Also modulated by CRH[34], the NE system is important in coordinating the stress response, and its consequent innervation of limbic regions known to be disturbed in depression, such as the amygdala and hippocampus,[32] implicates it could play a mediating role in MDD.

There have been several findings in support of NE disturbances in depression. Alterations in signaling of the β-adrenergic receptor and the α2-autoreceptors were observed in the frontal cortices of suicide victims.[32] These findings are coupled with the observation that chronic antidepressant treatment in animals leads to the downregulation of both α2- and β-receptors at adrenergic synapses, although the fact these two receptors have opposite effects on NE release has made the outcome of these changes unclear.[25] Notably, β-receptor downregulation occurs after a delay of 7-21 days, mirroring the lag in antidepressant response in patients taking SSRIs.[25] However, other studies have found not all antidepressants downregulate these receptors, implicating that these changes are not always necessary for the antidepressant response.[25] Changes in NE metabolite concentrations in depression have been observed but are inconsistent[35], however the principle metabolite of NE, MPGH, is often elevated in patients undergoing antidepressant treatment, suggesting a higher rate of NE turnover.[25] Finally, patients treated with adrenergic antidepressants display a relapse in depressive symptoms if depleted of the NE precursor tyrosine.[25] As tryptophan depletion causes a depressive relapse in patients

treated with SSRIs, it appears the therapeutic effects of monoamine antidepressants may be reversed by depleting the monoamine affected by that antidepressant.[35]

The role of NE in depression may be tied to its control over behavioral stress responses. Both acute stressors such as foot shock and direct CRH infusion into rats stimulates tyrosine hydroxylase (TH), the enzyme that synthesizes NE, increasing NE turnover.[34] In addition to rapid upregulation of NE signaling following acute stressors, chronic stress leads long lasting disturbances of the NE system[34], as described in the above paragraph. For example, a study observed patients with melancholic MDD had significantly higher plasma levels of NE and cortisol, which were positively correlated.[35] Additionally, TH in the locus coeruleus was found to be 108-172% higher in untreated suicide victims releative to controls, linking NE to both depression and stress.[34] Leonard (2001) describes the idea that a "biochemical lesion" in the NE system is an important factor in depression.[34] Besides its role in stress, NE also peripherlaly affects the immune and endocrine systems, stimulating cytokine and glucocorticoid overproduction in depression. Leonard notes the convergence of disruptions in the sympathetic, immune, and endocrine systems underscore how NE dysfunction contributes to the association of physical ill-health and the depressed state.[34] An overview of this concept is shown in Figure 5 below.

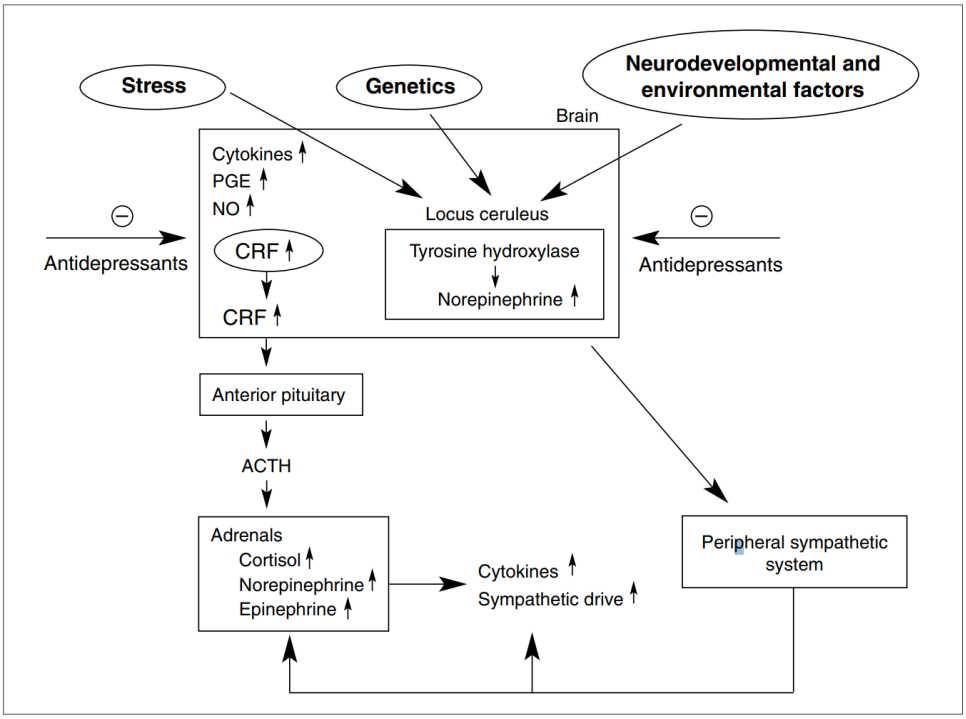

Figure 5. How NE may modulate depression. The large ovals represent factors that could cause a "biochemical lesion", raising the risk of developing depression. Depression is associated with chronic dysregulation of the stress axis, mediated by CRH in the brain, which stimulates TH in the LC and disrupts normal NE function. This feeds into a vicious cycle of stress activity in the periphery that contributes to atrophy in brain regions consistent with depression, reversible by antidepressant activity. Adapted from Leonard (2001).[34]

In contrast to NE, DA neurons project to specific rather than diffuse brain regions, allowing information flow about discrete physiological states and behaviors.[33] In rats, reward pathways arise from the VTA and innervate the ventral striatum and the nucleus accumbens (NAc).[33] DA neurons on the border of the lateral VTA and substantia nigra project to the associative striatum.[33] Lastly, DA neurons front the lateral substantia nigra project to motor regions in the dorsolateral striatum and habit-forming regions in the dorsomedial striatum.[33] Primates by contrast have a small VTA and therefore DA neurons projecting to limbic, cortical, and associative striatum are located in the substantia nigra instead.[33] Since anhedonia and

amotivation are common symptoms of depression, the influence DA circuits exert over motivational states may play an important role in MDD.[33]

Molecular and electrophysiological studies evidence changes in DA signaling after stress. VTA DA neurons typically fire at a slow, phasic pace, but may also fire rapid tonic discharges in response to environmental stimuli.[33] In rats, prolonged stressors increase VTA firing and elevate DA levels in the nucleus accumbens, which could be to enhance motivation to overcome stressful situations, and may be reversed by long term antidepressant administration.[31] This is at first transiently driven by the hippocampus, which distinguishes context, followed by a long-term downregulation in the responsiveness of the DA system driven by the basolateral amygdala (BLA).[33] The infralimbicPFC (ilPFC) exerts control over this network, regulating the opposing modulatory actions of the hippocampus and the BLA in the DA system.[33] Under prolonged stress, hyperactivity in the ilPFC drives the BLA, which attenuates reward activity in the VTA, diminishing the ability to connect reward to its stimulus.[33] Similarly, in human depression there is observed hyperactivity of the subgenual cingulate area 25, the human analog of the ilPFC, leading to a failure to activate the pedunculopontine tegmentum, which is involved in reward associations.[33] Grace (2016) proposed that after stressor withdrawal, the maintenance of VTA down regulation may be maintained, leading to depression and anhedonia. The antidepressant ketamine meanwhile was shown to restore DA neuron activity in helpless rats.[33] This concept is depicted below in Figure 6.

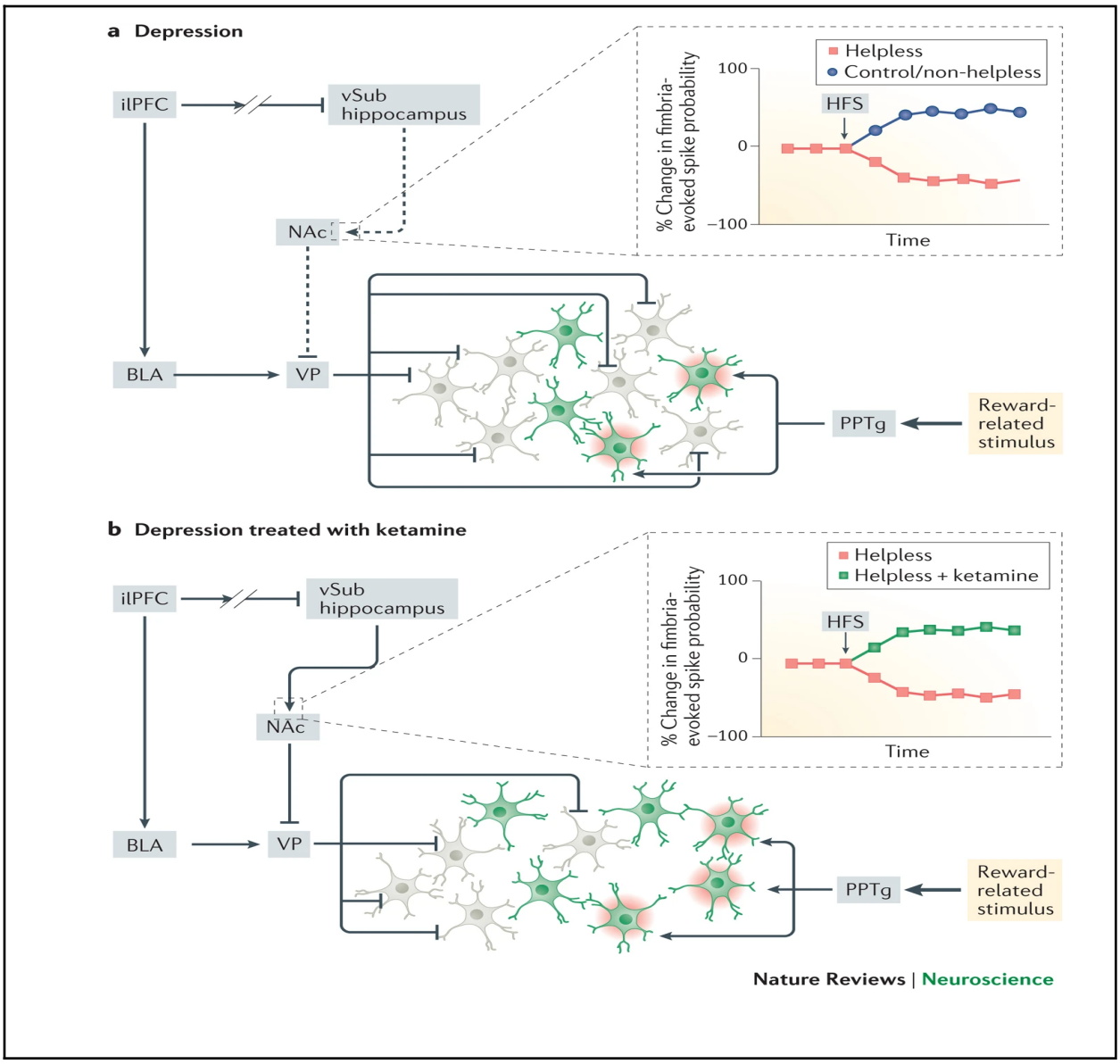

Figure 6. a. In depressed rodent-models, hyperactivity in the ilPFC stimulates the BLA. Depressed humans likewise show hyperactivity in the subgenual cingulate area 25, the functional analog of the rodent ilPFC. Through the ventral pallidum, the BLA attenuates reward-related DA activity in the VTA, reducing phasic stimulation of the pedunculopontine tegmentum, disrupting the formation of reward associations. Control rats display high-frequency stimulation LTP of the vSub Hippocampus -> NAc pathway, which can be prevented by BLA -> VP mediated inhibition of the VTA. However, in rats undergoing the learned helplessness paradigm, high-frequency stimulation produces LTD instead, representing a reward pathway dysfunction. b. The fast acting antidepressant effects of ketamine normalize DA action and re-establish stimulus-induced LTP of

the vSub hippocampus -> NAc pathway, demonstrating how antidepressant efficacy can resolve dopaminergic circuit dysfunctions. Adapted from Grace (2016).[33]

In the context of neuroplasticity, variations in the plasticity of VTA DA neurons may contribute to individual differences in responsiveness to stress.[31] Stress susceptible mice are seen to have enhanced VTA activity and subsequent BDNF release following social defeat, while stress-resilient mice resist this activity change by upregulating potassium channel subunits in the VTA to maintain normal tonic firing.[31] Correspondingly, stress induced increases of BDNF in the nucleus accumbens may contribute to a remodification of in the reward circuit to associate a negative-valence with normally positive social interactions following aversive social encounters.[31] As the development of dysfunctional reward pathways following stress corresponds with an increase in VTA to nucleus accumbens activity, this may both explain why anti-dopaminergic agents have shown efficacy as antidepressant adjuncts and the significance comorbidity of substance abuse in depressive disorders.[31] Depressed humans displaying anhedonia are associated with nucleus accumbens hypoactivation and reduced volume, and consequently deep brain stimulation in this and nearby regions have shown success in treatment resistant-depression,[31] likely by altering the dysfunctional circuit through coordinated firing and inhibition.

As they frequently coregulate each other, the activities of the NE, DA, and 5-HT system are hard to separate. Anatomical and functional interactions exist between noradrenergic pathways from the LC and 5-HT pathways of the raphe nuclei, with both modulating eacother.[25] Dopaminergic input tends to upregulate seroternegic and downregulate noradrenergic activity, serotonergic activity tend to mostly inhibit both NE and DA, and lastly NE increases tend to suppress DA and modulate 5-HT in either direction.[35] Since chronic antidepressant treatment

consistently downregulates both 5-HT_2 receptors and β-receptors, a serotonin-norepinephrine theory of depression was proposed by Sulser in 1989.[25] Consequently, drugs targeting any of these three monoamine systems have antidepressant potential.

The Role of the Stress Axis: Onset and Maintenance of MDD

A widely accepted model for studying depression in animals is the chronic unpredictable stress (CUS) paradigm. Under CUS, "multiple varied, non-debilitating, inescapable, and uncontrollable physical, psychological, and circadian stressors are applied in an unpredictable and randomized fashion for several week, whereas control animals are not exposed to any of the stressors and may be housed in pairs throughout the course of the experiment."[24] While it is currently impossible to say simply introducing CUS in animals is an equivalent to human depression, CUS is valued for its "quite remarkable predictive validities in screening for antidepressants"[24], and inducing depressive-like behaviors such as anhedonia.[24] Correspondingly, stress often precedes depressive episodes in humans.[25] This is not always the case for recurrent depression, however, and the implications of this are elaborated in the discussion section. Chronic stress induces alterations in dendritic spine densities of various regions, shrinkage of the PFC and hippocampus, and a decrease of hippocampal neurogenesis[24], all of which is seen to reverse with antidepressant treatment. Interest about the role of stress in depression has spurred research into the dysregulation of the stress activated hypothalamic-pituitary-adrenal (HPA) axis in depressed patients.[24]

Several important observations provide evidence that depression is frequently, although not always[26], associated with HPA dysregulation. Depressed patients often show elevated levels of the stress hormone cortisol. This is a potential result of abnormalities in neuroregulation due to oversecretion of the stress-regulating peptide CRH in the hypothalamus.[25] The hypersecretion

of CRH is then seen to decrease with antidepressant treatment and electroconvulsive therapy.[25] CRH acts both in the brain and on the receptors CRH_1 and CRH_2 in the anterior pituitary, stimulating the release of ACTH into circulation.[26] ACTH stimulates the release of glucocorticoids (GC) like cortisol from the adrenal glands. Maintenance of homeostasis is controlled by glucocorticoid receptors (GR) in the hippocampus, which bind GCs in a negative feedback mechanism. However in MDD, the sensitivity of GRs are impaired, leading to increased CRH and GC production.[26] This has been demonstrated in some depressed patients failing to respond to dexamethasone challenges, which is a synthetic glucocorticoid that should normally suppress CRH release through negative feedback.[25] This vicious cycle of increased cortisol levels may exacerbate hippocampal atrophy and decrease neurogenesis.[31]

As shown in Figure 7, disruptions of circadian control over cortisol are also present in depression, with a general flattening of cortisol levels throughout the day. Whereas cortisol levels normally decline in the morning and evening in healthy individuals, depressed patients show less overall fluctuation.[25] Altered sleep rhythms can also be observed in depression, with patients experiencing more frequent awakenings, less deep rhythm sleep, and early onset REM sleep. Overall, it may be said that depression contributes to a “phase-shifting” of biological rhythms.[25] Since 5-HT and NE also fluctuate with circadian rhythms, these dysfunctions evidence disruptions of these systems in depression as well.[25]

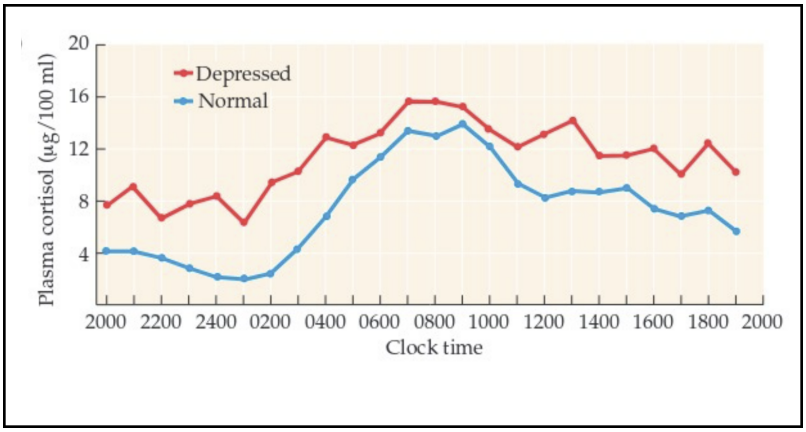

Figure 7. Humans displayed altered circadian fluctuations in plasma cortisol levels throughout the day. Healthy individuals show a large decrease in cortisol level corresponding with sleeping hours followed by a large increase in waking hours. Depressed individuals by contrast show a general flattening and overall of cortisol levels throughout the day. Adapted from *Psychopharmacology.* Sunderland, MA, U.S.A. Sinauer Associates.[25]

The abnormalities in stress regulation have led to a "glucocorticoid hypothesis" of depression, focusing on the role of CRH and HPA dysregulation in initiating and maintaining depression, as well as possible antidepressant treatments targeting the stress axis.[25] Notably, administration of CRH in preclinical models produces behavioral effects similar to depression in humans, which are attenuated by CRH receptor antagonists.[26]

Despite the substantial evidence of HPA dysregulation in depression, however, clinical trials of drugs that target it have been largely mixed at best[26] In his review, Andreas Menke describes the current state of many of these potential drugs. GR antagonists have had inconsistent success treating depression, but have demonstrated antipsychotic properties in treating psychotic depression. A promising CRH1 antagonist R121919 significantly reduced depressive symptoms, but was withdrawn due to inducing liver enzyme elevations.[26] Further CRH1 antagonists have failed to demonstrate significant effects at relieving symptoms, but may be useful in patients who demonstrate significant CRH dysfunction. Other HPA-affecting drugs

such as TDO inhibitors and FKBP5 antagonists show promise but are largely preclinical.[26] Overall, evidence heavily indicates the HPA axis dysfunction is involved in depression, but lack of clinical efficacy may implicate long-term HPA dysfunctions are a downstream consequence of depression, and drugs targeting it may not be treating the underlying pathology. Despite the current lack of clinical effectiveness of HPA-targeting drugs, they may hold promise as an adjunctive therapy, or a case-specific treatment in patients with demonstrable HPA abnormalities, and therefore warrant further research.

In a review by Mahar et. al, the role of stress induced serotonergic dysfunction in causing depressive symptoms is discussed at length. 5-HT is observed to modulate the stress response. Under acute stress, extracellular levels of 5-HT in the mPFC are seen to increase with in-vivo microdialysis. This may be in part a result of increased glutamatergic drive from the mPFC onto the dorsal raphe, evidencing the role of the mPFC in interpreting and responding to acute stressors. After CUS, studies have found decreases in global 5-HT in the brain, a reduction in spontaneous firing of the DR, and a downregulation 5-HT_{1A} autoreceptor receptor function.[24] As it has been hypothesized that 5-HT_{1A} autoreceptor desensitization is necessary for the therapeutic action of SSRIs, it has been proposed that stress induced 5-HT_{1A} downregulation is associated with an opposing behavior profile as downregulation due to SSRI treatment. A mouse study demonstrated individuals with high 5-HT_{1A} autoreceptor expression were non-responsive to fluoxetine despite 5-HT_{1A} autoreceptor downregulation, but that individuals with low 5-HT_{1A} expression were more responsive.[24] Therefore, one explanation is that low 5-HT_{1A} expression is associated with more severe depression and increased responsiveness to SSRIs, but that the presence and downregulation of this receptor is still required to some degree for SSRI efficacy.[24] Finally, since 5-HT_{1A} downregulation is observed in the mPFC, Mahar et al. hypothesized that

disturbances of the mPFC-DR circuit would lead to impaired cognitive appraisal of stressful situations, and an increase in the negative cognitive distortions seen in depression.[24]

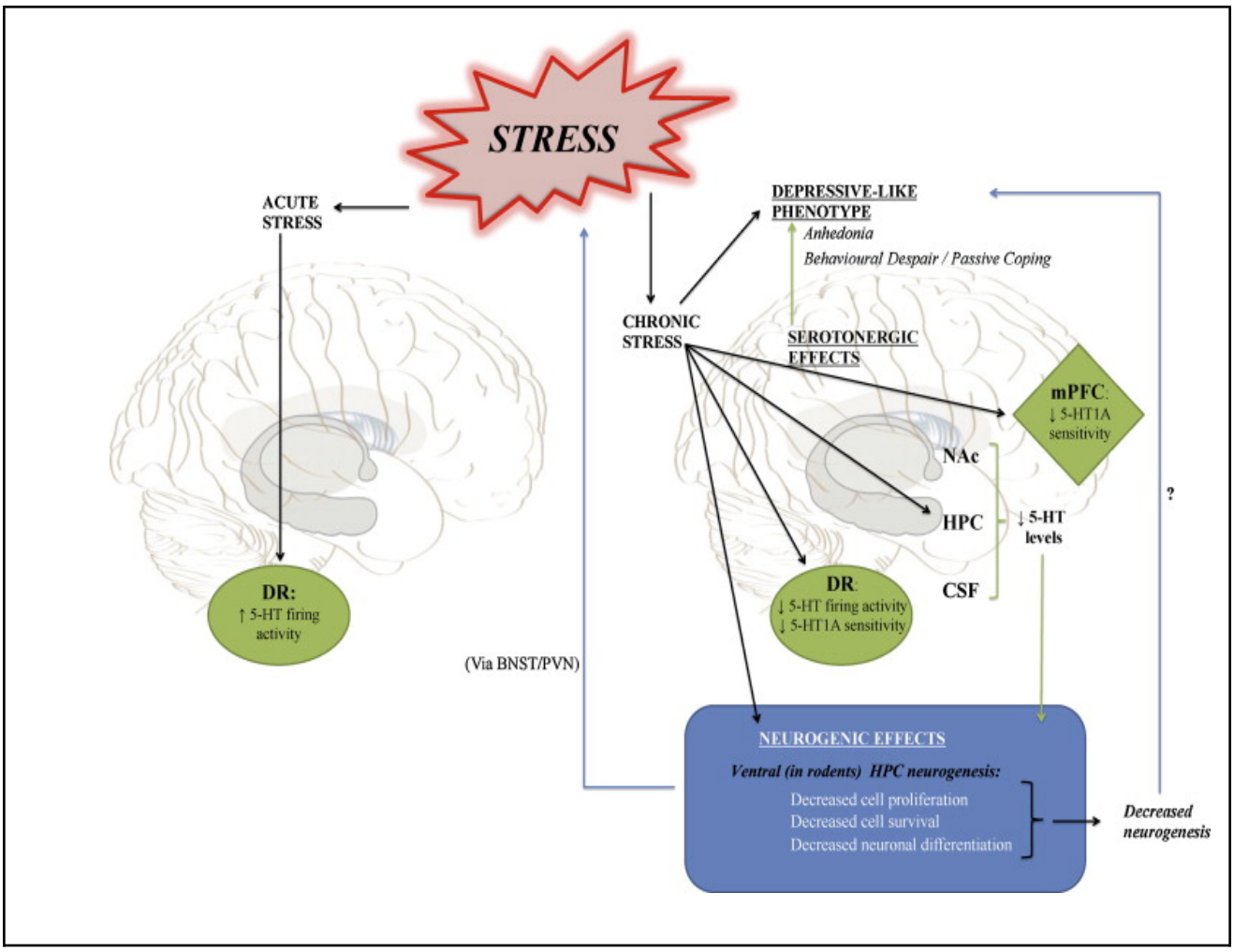

Figure 8. A model of how chronic stress contributes to serotonergic and neurogenic dysfunction in the brain. Acute stress increases DR firing onto the mPFC as a way to interpret and respond to stressors. Chronic stress causes changes in the serotonergic circuit, decreasing DR activity, while down regulating pre- and post- synaptic $5\text{-}HT_{1A}R$ sensitivity. It also decreases hippocampal neurogenesis, which may further impair regulation of the HPA axis, as the glucocorticoid receptors regulating negative feedback inhibition of the HPA axis are located in the

hippocampus. An upregulation of HPA further increases stress, maintaining dysfunctions in serotonin. Serotonergic antidepressant treatment modulates hippocampal neurogenesis, restoring HPA regulation there and alleviating depression. "BNST, bed nucleus of the stria terminalis; CSF, cerebrospinal fluid; HPC, hippocampus; mPFC, medial prefrontal cortex; NAc, nucleus accumbens; PVN, paraventricular nucleus of the hypothalamus". Adapted from Mahar et al.[24]

The Contribution of Neuroplastic and Neurogenic Dysfunctions

A promising way to describe the pathophysiology of MDD is through neuroplasticity. Under this model, the pathology of depression is due to a disruption of the brain's neurocircuitry, rather than a neurotransmitter imbalance. Relying on evidence connecting the changes in neuroplasticity underlying the connection between stress and depression, it states that an improvement of neuroplasticity in brain regions altered by MDD serves as the "final common pathway" of antidepressant efficacy. Antidepressants would therefore act through regulating release of postsynaptic glutamate, enhancing NMDA to AMPA receptor output, improving neuroplasticity through an LTP-like process, and improving hippocampal neurogenesis[4], although possibly through separate mechanisms. Central to this hypothesis are alterations in neuronal spines seen in MDD.[20] Spines, which are small protrusions on a dendrite's surface, greatly increase the surface area for synaptic transmission, and therefore enhance functional connectivity. They are highly plastic structures that are enlarged and stabilized when used, but eliminated when inactive.[20] Chronic stress models used to study depression in animals have been shown to decrease spine densities, along with cellular and dendritic atrophy, in hippocampal CA1 and CA3 cells. The mPFC also experiences a loss of spines and dendritic atrophy due to stress, which was partially reversible by a 21 day stress-free period.[20] Correspondingly, the overall volumes of the PFC and hippocampus are observed to decrease in depression.[20] Conversely, the amygdala reliably increases its spine density due to stress, contributing to dendritic hypertrophy there, and potentially an increased sensitivity to anxiety and fear.[20] Spine

densities have also been shown to increase in the orbitofrontal cortex (a subregion of the PFC), as well as the nucleus accumbens (NAc), the latter being associated with increased social avoidance behavior.[20]

Chronic, but not acute, administration of classical antidepressants that target monoamine systems has been shown to reverse these synaptic deficiencies. The novel antidepressants ketamine, scopolamine, and psilocybin demonstrated a rapid and robust restoration of AMPA mediated neuroplasticity in depressed patients.[20] The discovery of the rapid antidepressant effects of ketamine has been crucial to the formulation of the neuroplasticity theory, and can be considered "the biggest breakthrough for the treatment of depression in over 60 years".[21]

Although the mechanism is being debated[56], ketamine is observed to increase glutamate release and increase AMPA signalling, thus potentiationg LTP.[22] One explanation is that inhibiting NMDA receptors on GABAergic interneurons leads to disinhibition of excitatory glutamatergic neurons.[22] A meta-analysis of ketamine as an antidepressant showed a single dose after 24 hours produced a response rate of 52.6%, with repeated ketamine infusions associated with an even higher response rate (70.8%) that lasted about 18 days[4], demonstrating drugs acting on the glutamate system exhibit far faster and somewhat stronger antidepressant effects than those acting on 5-HT, whose first line antidepressants likewise produce a remission rate of 60-70% when combined with cognitive beahvioral therapy, with an average 2 week delay before drug efficacy represnting a danger in cases of suicidal ideation.[4] A similar glutamate burst may also underlie the antidepressant effects of 5-HT_{2A} stimulating hallucinogens such as psilocin or LSD, whose downstream signaling causes a robust increase in glutamatergic synaptic activity in the PFC.[22]

The neuroplasticity theory explains the efficacy of 5-HT enhancing drugs both through their indirect regulation of glutamate receptors and the slow, weaker role in neuroplasticity played by monoamines.[4] Evidence has shown several serotonin receptors to be regulatory of LTP, hippocampal neurogenesis, and cytoskeletal rearrangement.[49] Additionally, 5-HT has demonstrated a link to levels of Brain Derived Neurotrophic Factor (BDNF), a member of a group of proteins called neurotrophins that signal for increased neurogenesis and plasticity. When coupled with the findings that chronic SSRI treatment restores plasticity in depressed patients and elevates BDNF levels[49], it is plausible the efficacy of monoaminergic agents for MDD are reliant on these processes. These ideas are displayed in Figure 9 below.

Separate from spine density changes, hippocampal neurogenesis appears important in antidepressant functioning. It must be noted that the exact role of hippocampal neurogenesis in depression is not entirely clear.[49] While evidence of impaired neurogenesis has been found in depression, inhibiting neurogenesis does not affect depressive or anxiety-like behavior in rodents, although it may underlie the cognitive deficits seen in depression.[49] As the PFC and AMG are also key regions involved in depression, it has been proposed decreased hippocampal neurogenesis is not necessary to trigger depressive behaviors.[49] On the other hand, evidence has shown that restoration of neurogenesis is necessary for antidepressant efficacy[25], with chronic but not acute SSRI treatment coinciding with an upregulation of hippocampal neurogenesis.[49]

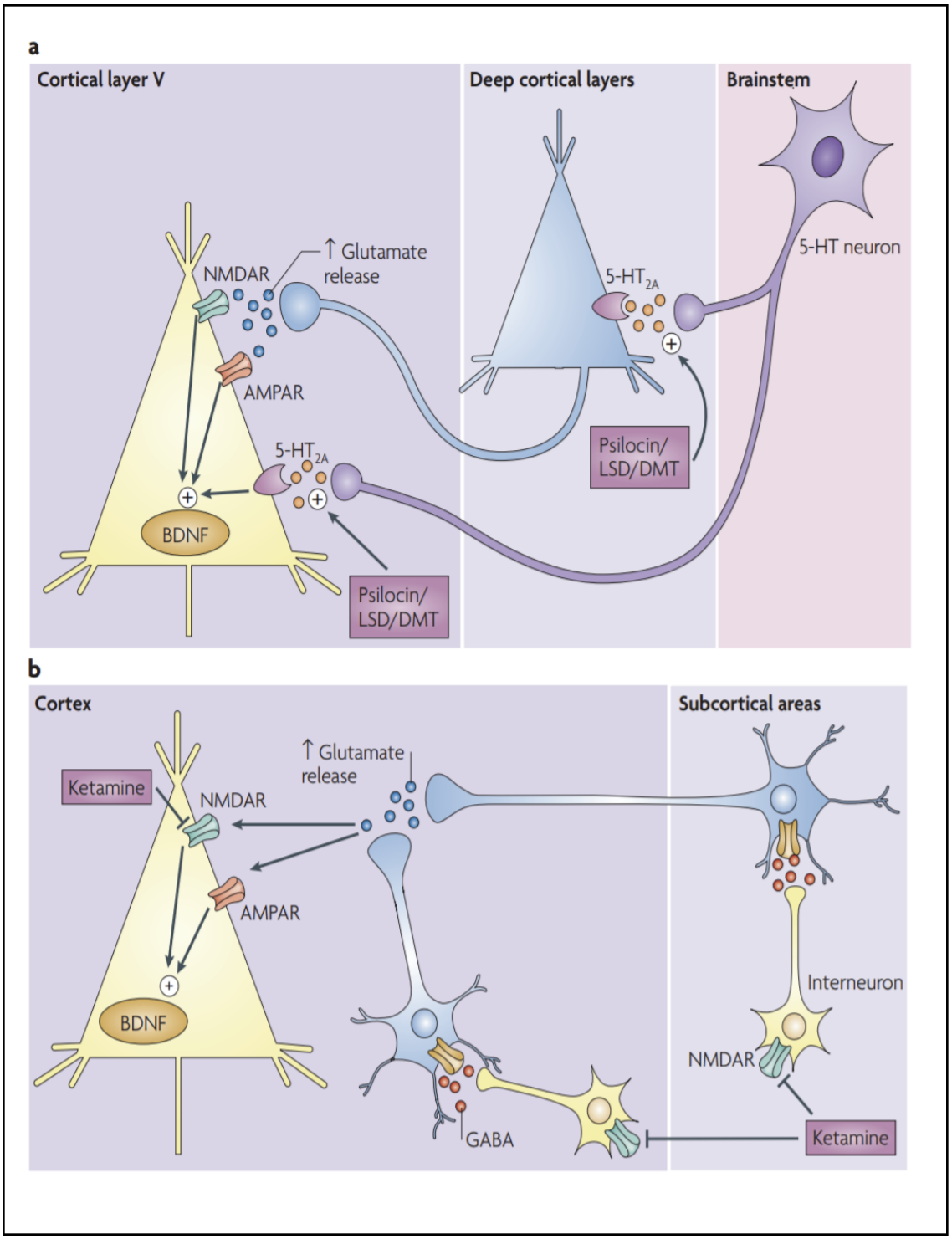

Figure 9. a. Hallucinogens such as LSD, psilocin, or DMT, indirectly upregulate glutamate signaling in the PFC by stimulating postsynaptic 5-HT_{2A}Rs. The resulting activation of AMPA and NMDA receptors on cortical pyramidal neurons, along with direct 5-HT_{2A}R stimulation, may lead to increased expression of BDNF, mediating neuroplasticity necessary to alleviate depression. b. Ketamine blockades NMDA receptors on GABAergic interneurons in cortical and subcortical regions, upregulating glutamatergic firing and increasing extracellular glutamate in

the PFC. This activity increases AMPA signaling, enhancing NMDA throughput through LTP, and activating BDNF to mediate neuroplasticity. Adapted from Vollenweider et al.[22]

Under this model, all antidepressants function by upregulating glutamatergic signaling in affected brain regions, leading to an increase in neurotrophins, and ultimately restoring the altered neurocircuitry of the depressed brain. The action of BDNF is necessary, as deletion of the BDNF receptor TrkB in progenitor cells blocks both the neurogenic and antidepressant actions of exercise, fluoxetine, and the TCA imipramine.[21] Also important is the neurotrophin VEGF, whose deletion in the forebrain blocks the behavioral antidepressant effects of ketamine. VEGF release is stimulated by BDNF, so it may play an important mediating role.[21]

Efforts to find a common chemical pathway underlying neuroplastic antidepressant function have discovered the crucial importance of the second messenger mammalian target of rapamycin (mTOR). Its downstream targets S6K, 4E-BP, and eEF2K regulate transcription and translation of synaptogenic proteins and BDNF.[23] Directly responsive to AMPA and TrkB, mTOR serves as an important regulatory center of plastic and neurogenic responses. Notably, mTOR appears both upstream of BDNF translation, and downstream BDNF signalling[23], suggesting it may contribute to a positive feedback mechanism important for plastic responses. A summary of the mTOR pathway is shown in Figure 10.

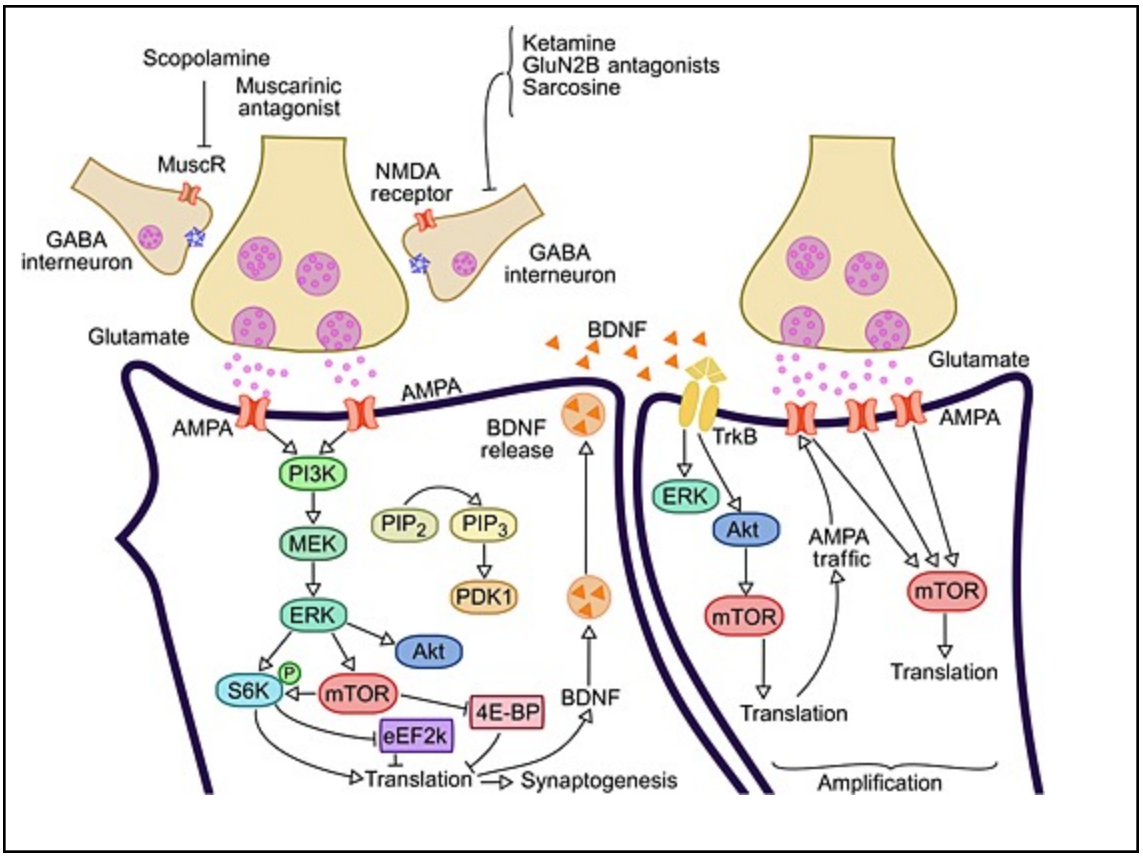

Figure 10. A mechanism of how the mTOR pathway responds to fast acting antidepressants, such as ketamine. Inhibition of NMDAR GABAergic interneurons disinhibits glutamate neurons. The subsequent increase in AMPAR stimulation activates mTOR through ERK. mTOR stimulates S6K and inhibits 4EBP, promoting translation. S6K activates eEF2k, promoting translation. BDNF is released in vesicles and further stimulates the mTOR pathway through TrKB Receptors. Adapted from Ignácio et al.[23]

Indeed, patients with MDD show impaired mTOR signaling in the PFC[23], associated with decreased synaptic proteins and spines.[21] Studies have shown mTOR to regulate the antidepressant effects of classical antidepressants[23], and inhibition of this pathway with rapamycin blocks the increase in spine synapses and antidepressant behavioral effects of ketamine in rodents.[21] Drugs affecting various targets in the mTOR pathway may therefore be an important subject of future antidepressant research. These ideas are depicted in Figure 11 below.

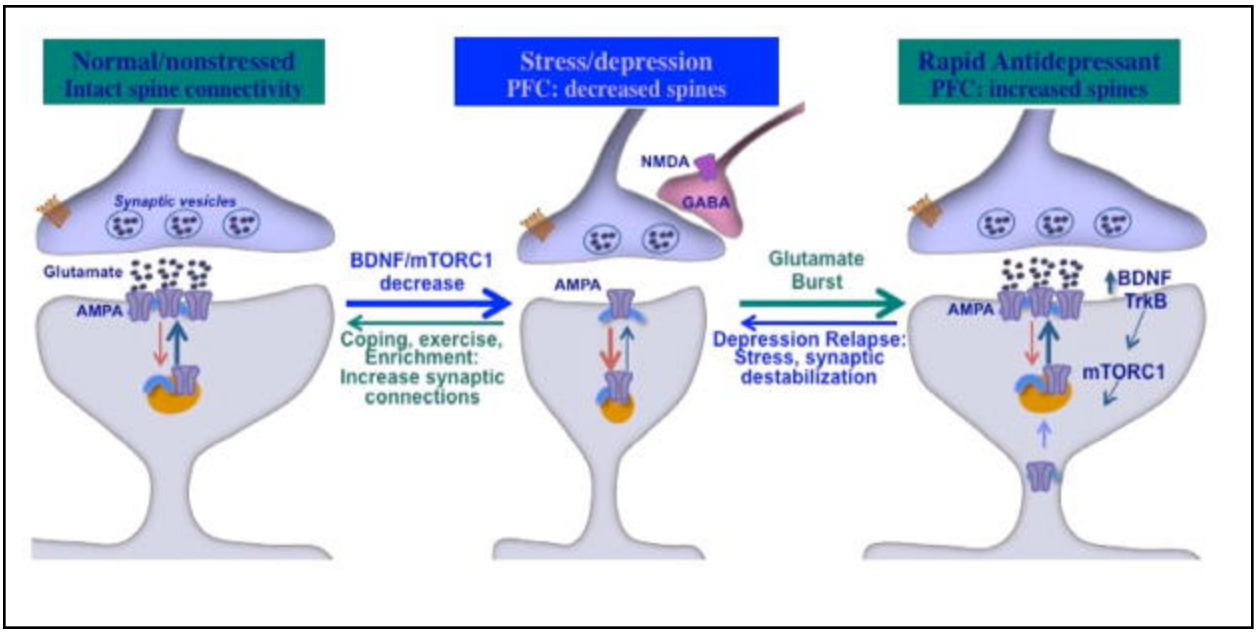

Figure 11. How mTOR signaling underlies the effects of fast-acting antidepressants. Under nonstressed conditions, spine synapse connections are normal and contribute to control over mood, emotion, and cognition. Chronic stress and depression decrease BDNF and downstream mTOR signaling, ultimately decreasing spine density in the mPFC. Ketamine reverses spine deficits via a glutamate burst. An increase in AMPA activity leads to release of BDNF and stimulation of mTOR, resulting in a restoration of spine levels. Adapted from Duman et al.[20]

While the antidepressant effects of ketamine and the associated role of the glutamatergic system have provided the greatest change in the way the pathology of depression is viewed, drugs targeting this system are not yet ideal. The S-enantiomer of ketamine, esketamine, has been approved as a nasal spray for treatment resistant depression in the United States, however it demonstrates undesirable side effects such as an abuse potential[21] and dissociative effects.[22] While the robust and fast acting antidepressant action of glutamatergic antidepressants should not be ignored, more research must be done to find better alternatives than ketamine. For example, rodent studies have already shown that (R)-ketamine and its metabolite (2R, 6R)-HNK produce rapid antidepressant effects with fewer side effects,[21] theoretically not requiring NMDAR blockade.[14]

The Contribution of Genetics

Differences in individual responses to daily trauma and stress are influenced by genetic factors.[25] A metaanalysis found 40% heritability in depression[26], and twin study estimates have averaged a heritability of 35%[37], although environmental factors appear to be the primary factor driving depressive onset.[26] Nonetheless, research has been done attempting to find polymorphisms that confer a risk for depression. Several polymorphisms in serotonergic and glucocorticoid systems were identified to confer greater tendency to develop depression after childhood trauma.[24] This included the 5-HT transporter-linked promoter region, the 5-HT transporter-encoding SLC6A4 gene, and Htr1A promoter region on the 5-HT1A-encoding gene, and the HPA regulating genes CRF-R1 and NR3C1.[24] Other single nucleotide polymorphisms associated with MDD have been found in systems not as heavily studied, such as GNB3 (guanine nucleotide-binding protein-3) or MTHFR (methylene tetrahydrofolate reductase), possibly providing new insights into the disease.[31]

Until recently, candidate gene studies had struggled to find replicable variants for general MDD onset.[37] This can be attributed both to the heterogeneity of MDD and the fact culprit genes often have widespread downstream effects, making their exact role in MDD hard to narrow down.[37] However, a genome-wide association study (GWAS) by CONVERGE found two robust loci on chromosome 10 in a large sample of han Chinese women with recurrent MDD.[38] The first was near *SIRT1*[38], a gene involved in mitochondrial biogenesis and cellular metabolism.[38] The second was in an intron of *LHPP*[38], whose polymorphisms a recent study showed may contribute to the gray matter disruptions seen in MDD.[39]

An extensive GWAS in European patients conducted by Wray et al. in 2018 identified 44 “independent and significant loci” associated with clinical features of major depression.[40] Many

of these genes were in extended major histocompatibility complex regions, involved with immune function, while others were found near "druggable" targets, such as genes involved in calcium signaling, dopaminergic neurotransmission (DRD2, a primary antipsychotic target), glutamate neurotransmission, and presynaptic vesicle trafficking.[40] Four more key genes (*OLFM4*, *NEGR1*, *RBFOX1*, *LRFN5*) were identified, with the first two involved in associations with obesity, *RBFOX1* possibly with HPA hyperactivation, and *LRFN5* with presynaptic differentiation and neuroinflammation.[40] It must be noted that none of these polymorphisms included coding regions, suggesting a dysfunction of regulatory processes.[40] These results led Wray et al. to conclude MDD was a disorder of the brain rather the periphery, that its genetic associations were conserved across placental mammals, and that MDD had significant genetic overlap with many other psychiatric disorders, such as schizophrenia.[40] Finally, it appears these variants each only slightly increase the risk for depression, making it tricky to characterize MDD with a genetic model.

Overall, genetic analysis has identified polymorphisms in systems known to be involved in MDD, such as 5-HT, as well as in others not as widely studied, warranting future research into other systems. Despite this, MDD is a heterogeneous disorder that is not caused by any specific polymorphism. A more accurate description is that all individuals carry some degree of genetic risk for MDD[40], with individuals carrying a higher degree of associated polymorphisms or rare genetic variants being more susceptible to stress induced depressive episodes.

Epigenetics: Connecting Genes and the Environment

There is evidence that epigenetic modifications in response to stress mediate the relationship between genes and the environment in depression.[36] This is especially relevant in periods of neural development, where the epigenome is more responsive to both hormonal and

environmental stimuli.[41] Consequently, prenatal stress and early adverse experiences can lead to long-lasting epigenetic changes that can negatively impact future resistance to stress, and thus represent a vulnerability factor to MDD, as shown in Figure 12. As not all depression is a factor of childhood trauma and several neuroendocrine features of depression differ as a function of early adverse experiences, Heim et al. proposed separating childhood trauma associated depression as its own distinct subtype.[28] Considering epidemiological studies have established a strong connection between childhood trauma and future risk of depression[28], research into the epigenome may establish an important underlying link between early stress and depression.

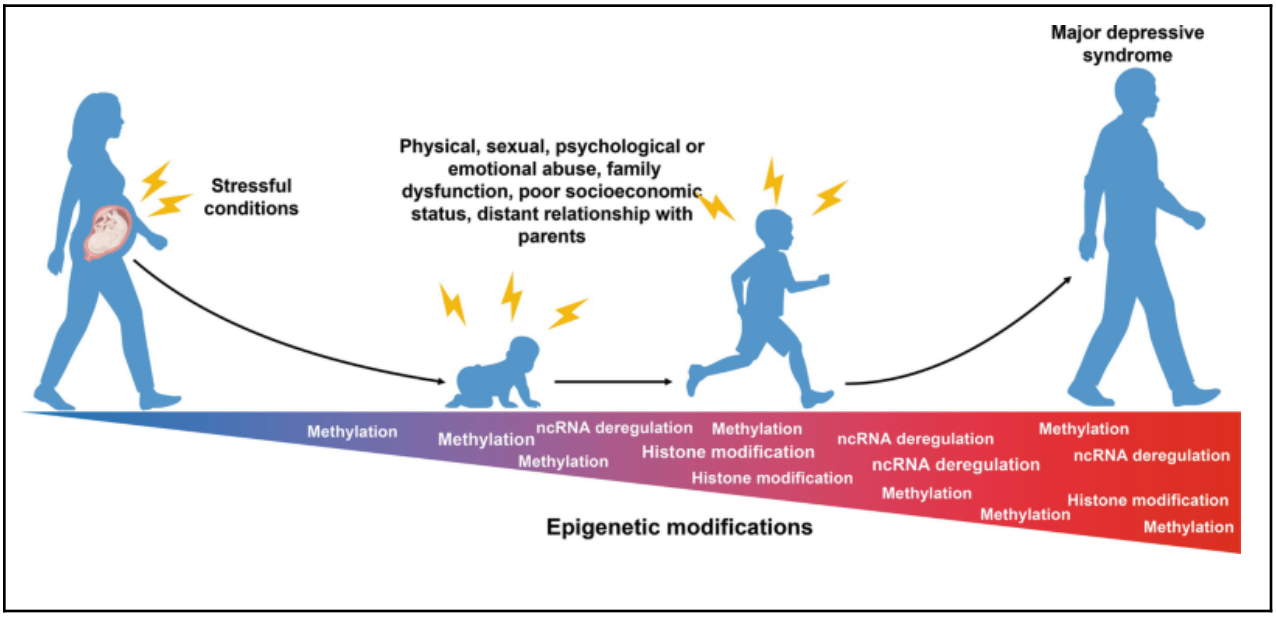

Figure 12: Early life trauma increases the risk of mood disorders in adult life by dysregulation of epigenetic factors. Adapted from Saavedra et al.[41]

Already, recent studies have revealed epigenetic changes associated with DNA methylation, histone methylation and acetylation, and miRNA levels that differ between depressed individuals and controls.[36] Recent candidate gene studies, for example, have shown patients with MDD have hypermethylation in the BDNF encoding loci, and SLC6A4, the

serotonin transporter gene, displaying early evidence of altered DNA methylase function in depression.[36] Epigenetic alterations in HPA elements such as *NCR31* and *CRF* genes have also been observed[42], potentially explaining how early trauma translates to future stress vulnerability. Additionally, chronic social defeat stress has been shown to cause long lasting decreases in BDNF in certain brain regions by inducing a fourfold increase in histone methylation, which reduces gene expression.[25] The antidepressant imipramine was shown to restore BDNF levels by increasing histone acetylation and downregulating histone deacetyltransferase, opening the chromatin to increase gene expression.[25] Investigation of miRNA level alterations in MDD have yielded inconsistent results, however a downregulation of miR-1202, which regulates a glutamate receptor (*GRM4)* was found in the PFC of suicide victims with MDD. This finding was replicated in two more independent cohorts, and miR-1202 levels were shown to be restored with antidepressant treatment, indicating miRNA imbalances hold potential as a biomarker for treatment.[41] The role of chromatin remodeling in BDNF expression in stress is shown in Figure 13 below.

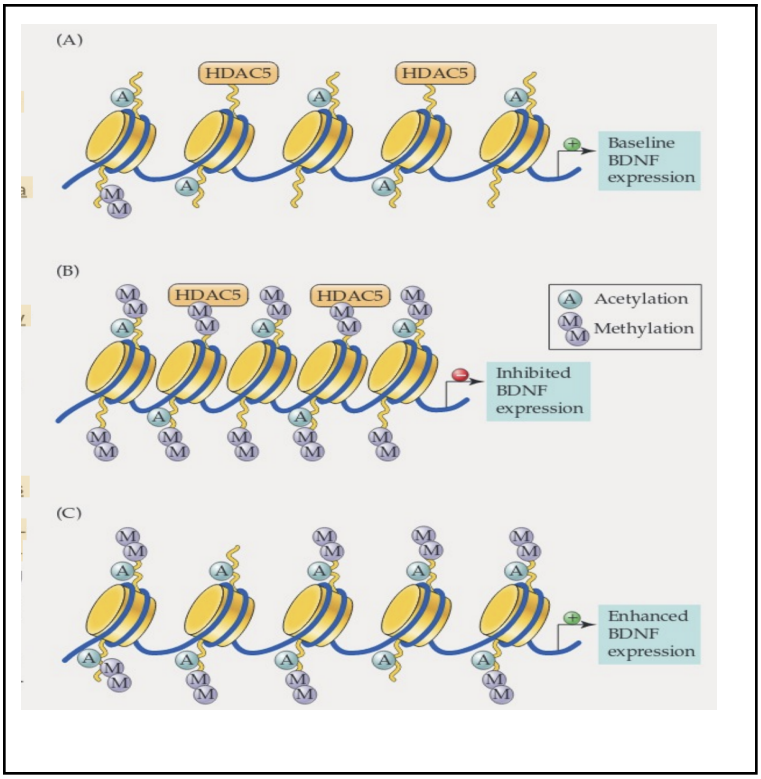

Figure 13. a. Under nonstress, BDNF chromatin has low levels of acetylation and virtually no methylation, representing basal BDNF expression. b. Histone methylation following prolonged defeat stress restricts chromatin and blocks BDNF expression. c. Chronic antidepressant treatment increases acetylation without alleviating stress-induced methylation, with a net effect of opening repressed chromatin and transcribing the BDNF gene, which may be necessary for antidepressant efficacy. HDA5C, histone deacetylase 5. Adapted from *Psychopharmacology.* Sunderland, MA, U.S.A. Sinauer Associates.[25]

Since endocrine results indicate evidence of increases in HPA hyperactivity after childhood abuse[28], these studies indicate adverse early life experiences cause liability for future mood disorders by inducing epigenetic changes which upregulate the stress response, and alter plasticity and serotonergic signaling, ultimately leading to neural network changes which confer depressive risk.[28] They also highlight the role epigenetic machinery such as DNA methylase, histone acetyltransferases and deacetyltransferases, and miRNAs play in depression. Presently, research on histone and miRNA changes in MDD is comparatively lacking, and therefore deserves further investigation.[41] Additionally, the underlying epigenetic pathways may hold promise for finding future therapeutic targets, such as in the glucocorticoid regulating genes

NR3C1 and *FKBP5*, or the serotonergic signaling regulator *SLC6A4*,[42] although finding drugs specific to these targets may be a challenge.

Modern Understanding

The multitudinous studies that take issue with the 5-HT deficiency hypothesis of depression combined with its lack of solid evidence highlight the need for medical understanding to distance itself from the simple theory that low 5-HT is the primary cause for depression. Modern research concludes 5-HT still likely plays some kind of role in the pathophysiology of depression but looks for alternate explanations of what that role exactly is.[6] It is important to consider the role other catecholamine systems, such as NE and DA, may play in depression as well, with drugs targeting these systems demonstrating efficacy.[31,32]

As for the importance of 5-HT itself, there exist studies that suggest 5-HT dysfunction remains relevant as a risk factor of MDD[1], even if not the direct cause. A more dimensional approach is that 5-HT explains, in part, the vulnerability to mood liability across diagnoses has come to replace the view that low 5-HT is specific for depression. Under this lens, 5-HT may have an important role in the triggering and maintenance of a mood disorder, but is not sufficient nor necessary for depression.[8] A study by Jans et al. defined the idea of serotonergic vulnerability: that the 5-HT system may be disrupted by a variety of factors, and pathology occurs once a threshold is reached whereby the 5-HT system may no longer compensate.[8] Under this lens, the modulation of the stress response by serotonin systems represents a neuroprotective effect from depression during adversity in healthy patients[24], while genetic and epigenetic risk factors involving the serotonin system and other relevant genes reduce an individual's ability to cope with stress[40]. Depression is consequently the result of a failure to properly overcome stress, whereby the HPA axis becomes unresponsive to negative feedback[25], contributing to hypotrophy

of dendritic spines in certain regions associated with coping such as the PFC and hippocampus, while causing hypertrophy in other areas, such as the AMG, NAc, and orbitofrontal cortex.[20]

Under the lens of the neuroplasticity hypothesis, depression is better described as a dysfunction of the neurocircuitry of the brain, especially in areas and tracts associated with emotional regulation. Through the serotonergic innervation of limbic circuitry, especially the amygdala, hippocampus, and mPFC, 5-HT dysfunction may change how the brain appraises emotionally laden information.[15] This viewpoint connects 5-HT to the negatively biased emotional responses seen in depressed patients and sees 5-HT not as directly improving mood. Instead, the antidepressant role of 5-HT is viewed as a secondary effect of positive shifts in emotional responses. Coinciding with the neuroplasticity hypothesis, the use of SSRIs indirectly potentiates synaptic plasticity and helps the brain relearn emotional associations. Overtime, this can lead to a positive biasing of emotional experience.[15] A 2013 study by Branchi et al. substantiates this hypothesis with evidence that SSRI effectiveness is largely dependent on the environment during ongoing antidepressant administration.[27] In their experiment, adult male mice exposed to chronic stress were administered fluoxetine in either an enriching environment, or a stressful environment. At the end of treatment, the mice in the enriching environment displayed an improvement in their depression-phenotype, associated with enhanced BDNF levels and reduced corticosterone levels. Interestingly, mice in the stressful environment displayed worsening depressive symptoms, including reduced BDNF and enhanced corticosteroids, despite the fluoxetine treatment.[27] Studies on the role of the environment in antidepressant efficacy in humans are few, but they have shown that living conditions modulate patient response to antidepressants. This may explain why low-income groups are less responsive than higher income groups.[27] It therefore appears SSRIs prime the brain for increased plasticity to be shaped

by environmental factors, whether positive or negative, and therefore have the potential to both relieve or exacerbate depressive symptoms. Although the possibility of antidepressant-induced exacerbation of depression has not been directly tested in humans for ethical reasons, it would explain some findings demonstrating paradoxical worsening of mood disorders after antidepressant treatment.[30]

The above findings emphasize the crucial role of the environment during antidepressive treatment, and underscore why combination treatment with psychotherapy and antidepressants are shown to be significantly more effective than either antidepressant or psychotherapy alone.[28] A failure to properly control for environmental factors calls into question the meta-analysis that demonstrated antidepressants such as SSRIs struggle to outperform placebo,[29] as one might expect depressed patients to be dealing with a higher degree of stress compared to healthy individuals. In the future, further studies investigating the connection between the environment and antidepressant efficacy in humans are warranted.

Along with its potential to alter emotional appraisal, low 5-HT has a robust connection to suicide.[3] This factor may have to do with impulse control, especially due to 5-HT's association with the reward system. 5-HT_{1B} receptor KO mice display aggression and increased impulsivity, while 5-HT_{1B} receptor agonists decrease aggression. 5-HT_{2C} receptor agonists decrease impulsivity and motivation for food and drug consumption[5], and some suicide victims were observed to have an abnormally high expression of 5-HT_{2C} in the prefrontal cortex.[2] A study by Underwood et al. compared 83 suicide and 149 nonsuicide brains post-mortem, observing lower SERT binding in suicides across all ages and sexes, as well as increased 5-HT_{1A} binding in suicides, independent of MDD. Although lower SERT binding was found to be more related to MDD than suicide in the PFC, it was suggested that suicide effects are tied to a pronounced

difference in the ventral PFC, an area of the brain important in restraint. An increase of 5-HT_{1A} receptors in the PFC may indicate an inhibition of the excitatory cortical outputs that mediate executive function and behavioral restraint. This top-down reduction of restraint may increase risk of suicidal behavior.[16]

Another important role of 5-HT in MDD may lie in its ability to regulate neurotrophic factors and adult hippocampal neurogenesis. Coinciding with this is more recent data from studies that hypothesize neurotrophic factors such as brain derived neurotrophic factor (BDNF) and decreases in adult hippocampal neurogenesis are involved with the pathophysiology of depression.[2] The restoration of these mechanisms is therefore critical for the therapeutic effects of antidepressants.[2] This is supported by studies showing the effects SSRIs have on 5-HT_{1A}Rs in the mature granule cells of the dentate gyrus of the hippocampus are critical mediators of the effects of SSRIs on behavior, neurotrophic factors, and neurogenesis.[2]

Discussion

Major Depressive Disorder is often characterized by its relationship to stress. In general, stressful episodes are frequent in the initial onset of depression.[25] The development of MDD depends on an individual's resistance to stress and adversity. As shown by social defeat studies of mice, depression can be considered an aberrant form of an adaptive mechanism to avoid future stress and defeat, where influence of the stress axis realigns neurocircuitry to avoid pursuing reward after an association has been established with punishment. Healthy individuals have neuroprotective mechanisms in place to resist the onset of this pathology, but depressed individuals may become prone to a vicious cycle of stress dysregulation, combined with resulting dysfunctional neurocircuitry, that makes it difficult to unlearn negative emotional associations,

maintaining the depressive state. Stress is not always required for depressive episodes, in particular in cyclical recurrent depression.[55] One proposed explanation is that stressful episodes remain important for initial depressive onset and early recurrent episodes, but that resultant biological changes in the brain cause stressful life events to matter less as a trigger, which could be due to an increased mood liability to once negligible stressors.[55]

Vulnerability to stress induced depression is an outcome of both genetic and environmental factors. In the case of genes, there are several common polymorphisms that may confer some depressive risk, such as the short allele of the SERT promoter.[12] However, depression is a heterogeneous disorder[37], with such polymorphisms only becoming a significant risk when present in a sufficient load to disrupt the neuroprotective mechanisms against stress. Rare genetic variants may pose significant risk by themselves, but are not frequent enough in the overall population to properly characterize a common genetic model of depression, although they may help elucidate the overall pathophysiology of the disorder[52]. Environmental factors are responsible for establishing the epigenome during prenatal and early childhood development[41], explaining the significant association of childhood trauma and adult depression. Besides contributing to depressive risk, epigenetic mechanisms appear to be involved in the physiological onset of depression, as shown by histone methylation of the BDNF gene restricting its transcription after chronic social defeat stress[25].

Monoamine systems appear to be involved heavily in the stress response. For example, acute stress transiently increases serotonergic drive from the dorsal raphe to the mPFC[24], likely involved in evaluating stressors and planning the stress response. Serotonergic activation normally promotes patience for reward and inhibits impulsivity[47], allowing individuals to maintain goal-directed psychological states necessary to overcome stress and adversity.

Noradrenergic fibers from the LC upregulate NE signaling after acute stress[34], helping the brain coordinate a widespread stress response. Finally, dopaminergic circuits projecting from the VTA in rats (functional analog is the subgenual cingulate area 25 in humans) upregulate dopamine signaling onto the nucleus accumbens under acute stress[33], likely important for establishing motivation to face stress and challenge.

Effects of chronic stress on monoaminergic systems show how stress-induced disruptions of these symptoms helps maintain depressive pathophysiology. In the case of serotonin, postsynaptic 5-HT_{1A} receptors, which are observed to be anxiolytic and may serve a role in resisting stress[47], have been seen in studies to be downregulated as a result of chronic stress[24]. The 5-HT_{2A} receptor, which has been shown to be anxiogenic[22], is seen to be upregulated on the other hand[3]. These changes may serve to promote increased anxiety in the response to stressors, translating into an inability to overcome stressful obstacles. It must be noted that this is an oversimplification, and it is likely the several other serotonin receptors play similarly important roles. LC pathways that innervate the entire brain, including relevant limbic and cortical regions, are disrupted in their noradrenergic signaling after chronic stress.[32] This change may increase stress sensitivity and reduce adaptive responses to stressful stimuli, help maintain HPA dysregulation, and lead to the development of peripheral symptoms such as chronic fatigue.[34] It should be noted that the exact impact of alterations of noradrenergic receptors seen in MDD has not been clarified.[25] Finally, chronic stress downregulates dopaminergic signaling through the BLA, which disrupts the ability to form reward associations and may be largely responsible for the symptoms of amotivation and anhedonia characteristic of MDD.[33] Since there is significant crosstalk between monoaminergic pathways[25], it is plausible that a disruption of one of these systems may translate to disruptions of another. Consequently, this is a possible way for

depression to differ in its neural mechanism of onset between cases, while ultimately presenting a similar pathology. In the future, it may be worth studying how disruptions of specific monoamine systems in depression (ie. comparing tryptophan depletion to tyrosine depletion) affects which antidepressants an individual is most responsive to.

Individual variation in how monoaminergic circuitry regulates the stress response describes how these symptoms can serve as risk factors for development of depression. Furthermore, individuals more resistant to depression likely have protective pathways that prevent maladaptive changes to monoamine systems after chronic stress, as shown by stress resilient mice being able to upregulate K^+ channels in the VTA after social defeat to prevent hyperactivation of the nucleus accumbens[33] (a likely contributor of depressive pathophysiology[33]). When considering serotonin's role in patience for reward and impulsivity, I would like to propose that the maintenance of these pathways is crucial to maintain goal-directed behavior in the face of stress. The changes in serotonergic activity observed in MDD reduces this capacity by increasing anxious and impulsive behaviors. The consequence of this is a disinclination or even inability to face future stressors, contributing in humans to feelings of low self-worth, amotivation, and reduced concentration consistent with depressive pathology. I want to clarify that this is specific to serotonin-dysregulation induced depression, but that it is likely disruptions in other neural systems, such as dopamine or norepinephrine, represent alternative pathways for depressive onset. Additionally, in the future, I would be interested in investigating how serotonin's modulation of goal-directed states ties in with its facilitation of motor output[25].

Regardless of the triggering mechanism, the ultimate resulting pathophysiology in depression is presently best explained by changes in the functional connectivity of different brain regions. Dendritic spine hypotrophy and volume loss in the mPFC[20] may explain the loss of

self-control, suicidal ideation, and negative ruminations seen in depression. Spine hypotrophy and reduced neurogenesis in the hippocampus meanwhile may contribute to cognitive deficits[49] and a bias favoring negative labeling of external stimuli. Spine hypertrophy in the amygdala and nucleus accumbens may be responsible for negative reward associations[33] and fear[20] of normally rewarding stimuli. Finally, the orbitofrontal cortex is associated with assignment of reward value, implicated in action-outcome and goal-directed learning, and also innervates DA neuron bodies in the brainstem.[50] As the lateral orbitofrontal cortex has been modeled in studies to represent non-reward and punishment[50], it is possible hypertrophy of spines seen there in MDD are another basis of reward-association disruption.

As a result of the above, the best descriptor of a common pathway in antidepressant efficacy is by facilitating neuroplasticity, which allows for the realignment of dysfunctional neurocircuitry that may otherwise be caught in a vicious cycle of depression. As shown by Branchi et al. (2013)[27], there is evidence antidepressant treatment rather than simply relieving the depressed state instead makes patients particularly attuned to emotional-circuit changes as a result of the environment. This corresponds to alleviation of depression in positive environments, but a risk of failing to treat or even furthering depression in negative, stressful ones. Effective treatment plans consequently should be paired with psychotherapy and supportive care to find the greatest efficacy.[28]

As shown by numerous studies of antidepressant-induced neuroplasticity, the actions of neurotrophins such as BDNF appear necessary to mediate the gene transcription of neuroplastic factors in neurons[21]. In the case of ketamine, BDNF transcription has been connected to the actions of the mTOR pathway after a glutamate burst[23]. Under the assumption that all antidepressant-induced neuroplasticity results from increased glutamatergic signaling, the

question is raised of whether mTOR may be a common factor in all antidepressant efficacy, for example as a result of similar glutamate bursts downstream of serotonin signaling.[22]

Concerning serotonin specifically, Carhart-Harris et al.'s bipartite model[47] is incomplete but may aptly characterize the neurotransmitters' specific role in depression as being both a risk factor and a therapeutic target through separate mechanisms. Hesselgrave et al.[48] demonstrates that prior theories of how exactly serotonin modulates neuroplasticity, for example via 5-HT_{2A} signaling, do not yet fully characterize its mechanism. Further research in how other serotonin receptors combine neuroplastic action and antidepressant potential is warranted.

Finally, it appears the biological culprits responsible for the onset of MDD differs between individuals. For example, individuals with adult depression as a result of childhood adversity likely develop it as a result of epigenetic alterations laid down during critical periods of childhood neural development, that are not present in cases of adult depression without prior childhood trauma. Similarly, thyroid disorders may lead to HPA hyperactivation, and have been associated with a higher risk of depression[51]. Resultantly, whether the mechanism of depressive onset changes which treatment options are most effective is a question worth considering.

Conclusion and Future Directions

The discovery of the antidepressant efficacy of serotonin enhancing drugs was central to the development of the theory that low 5-HT was the primary factor in MDD. Over time, the theory began to receive scrutiny due to a growing body of counterevidence, coupled with a lack of solid evidence to directly tie low 5-HT to depression. Despite this, 5-HT still demonstrates a connection to depression, suggesting it may still play a role, even while not being a direct cause of MDD. In a more modern understanding, 5-HT abnormalities are considered as a potential risk factor for MDD. New theories about the pathophysiology of depression consider how 5-HT

interacts with the complex systems of the brain, such as its involvement with other monoamine neurotransmitters. The 5-HT neurotransmitter itself has become less of the central focus as evidence instead connects its numerous receptors to the alleviation of depression with SSRIs, such as through the desensitization of the 5-HT_{1A} autoreceptor allowing for increased serotonergic signaling. Abnormalities in 5-HT are a risk factor for suicidal behavior, evidenced by differences in the PFC of suicidal patients. Additionally, the alleviation of depression seen in SSRIs may be a side effect of increased neuroplasticity due to 5-HT's regulation of neurotrophic factors and hippocampal neurogenesis, rather than simply a result of a correction of 5-HT levels. In the future, studies into alternative treatments of depression are warranted, stressed by the prevalence of misleading SSRI advertisement campaigns that cloud public perception about potential antidepressants.[9] This is especially important in instances where an alternative treatment may be superior.

Future directions of antidepressant research may want to look for drugs that vary in their agonism between monoaminergic receptors. For example, efficacy has already been found with Vortioxetine, which acts as an agonist, partial agonist, or antagonist depending on the type of 5-HT receptor. Further clarifying the exact role of the differing 5-HT receptors in depressive onset and treatment will assist this process. The noradrenergic receptor changes associated with depression are also poorly characterized in their role in depressive behavior, warranting further investigation. The neuroplastic pathways resulting from all antidepressants similarly deserve clarification, which may assist in finding additional antidepressant targets, for example along the mTOR pathway. It may also be worthwhile to investigate how the environment affects antidepressant efficacy in humans, although such a study may be hard to perform ethically. Finally, research establishing a link between the biological culprit of depressive onset and what

treatments are most effective will validate the idea that plans to treat depression should begin with diagnostic screenings for specific physiological disruptions. For example, an individual with pronounced HPA hyperactivation may better benefit from adjunctive treatment inhibiting this pathway.

While 5-HT restoring treatments are among the bestselling drugs[9], I advise that both popular culture and medical literature distance themselves from the 5-HT deficiency theory of depression. By further expanding beyond serotonin regulating treatments, more successful drugs and adjunctive therapies may be found to help treat the debilitating Major Depressive Disorder.

Glossary

MDD, Major Depressive Disorder. 5-HT, 5-Hydroxytryptophan. PFC, Prefrontal Cortex. mPFC, Medial Prefrontal Cortex. SSRI, Selective Serotonin Reuptake Inhibitor. SNRI, Selective Norepinephrine Reuptake Inhibitor. DSM-V, The Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition. NE, Norepinephrine. DA, Dopamine. DR, Dorsal Raphe Nuclei. VTA, Ventral Tegmental Area. MAOI, Monoamine Oxidase Inhibitor. TCA, Tricyclic Antidepressant. AMG, Amygdala. SERT, Serotonin Transporter. LC, Locus Coeruleus. CRF, Corticotropin-releasing Factor. CRH, Corticotropin-releasing Hormone. TH, Tyrosine Hydroxylase. NAc, Nucleus Accumbens. BLA, Basolateral Amygdala. ilPFC, Infralimbic Prefrontal Cortex. BDNF, Brain Derived Neurotrophic Factor. VEGF, Vascular Endothelial Growth Factor. CUS, Chronic Unpredictable Stress. HPA, Hypothalamic-Pituitary-Adrenal. ACTH, Adrenocorticotropic Hormone. GC, Glucocorticoid. GR, Glucocorticoid Receptor. LTP, Long Term Potentiation. LTD, Long Term Depression. mTOR, Mammalian Target of Rapamycin. GWAS, Genome-Wide Association Study. miRNA, microRNA.

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