

Serotonin and the Brain: Exploring the 5-HT system's role in Depression

By Liam McLaughlin

Department of Biological Sciences, College of Arts & Sciences

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 priming 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 supplementing psychotherapy with potentiating neuroplasticity, helping individuals relearn negative emotional associations and restoring dysfunctional neurocircuitry. 5-HT 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 Selective Serotonin Reuptake Inhibitors (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.

Introduction

Major depressive disorder (MDD) is an impairing and chronic illness. With an estimated lifetime occurrence of 16.2% in the USA while affecting more than 300 million people worldwide, MDD is the second biggest cause of disability today (Albert, 2012; Yohn, 2017). 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 (Jacobsen, 2012).

The monoamine hypothesis has had an influential role in the history of psychology (Liu, 2017). Much of the evidence supporting the depletion hypothesis comes from the efficacy of serotonin enhancing drugs, as the majority of clinically 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.

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 (Nautiyal, 2017). This, along with issues surrounding the delayed onset of typical monoamine affecting antidepressants presenting danger in cases of suicidal ideation and a meta-



Table 1: Currently Approved Antidepressant Drugs (Sheffler, 2022)

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.	<ul style="list-style-type: none"> • 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.	<ul style="list-style-type: none"> • Venlafaxine • Desvenlafaxine • Duloxetine • Milnacipran • Levomilnacipran
Atypical Antidepressants	Various effects on the 5-HT, NE, and/or dopamine (DA) systems.	<ul style="list-style-type: none"> • Bupropion • Mirtazapine • Agomelatine
Serotonin Modulators	Inhibit presynaptic 5-HT reuptake to varying degrees while also acting as 5-HT receptor agonists or antagonists.	<ul style="list-style-type: none"> • Nefazodone • 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.	<ul style="list-style-type: none"> • 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.	<ul style="list-style-type: none"> • Selegiline • Moclobemide • Tranylcypromine • Isocarboxazid • Phenelzine
NMDA Antagonists	Blockades NMDA receptors, which ultimately increases glutamatergic signaling.	<ul style="list-style-type: none"> • Esketamine • Dextromethorphan/ Bupropion

analysis that demonstrated SSRIs struggle to outperform placebo (Kirsch, 2008), has led to the development of alternate hypotheses hoping to develop more effective antidepressants (Liu, 2017). While there is evidence that 5-HT may play a role in the pathophysiology of depression (Blier, 2013), modern findings suggest the monoamine hypothesis is overly simplistic, and that serotonin should not be viewed as the

primary pathogenetic factor behind MDD (Liu, 2017).

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. First, I will explain the role 5-HT plays

in the brain and along with the history of the 5-HT deficiency hypothesis. After providing background, I will elaborate on the role 5-HT may play in stress and MDD, based on modern evidence. Next, I will describe several issues with the 5-HT hypothesis before presenting a description of the neuroplasticity hypothesis, which has been favored in current literature. Finally, I will discuss my findings holistically, presenting directions for future research into antidepressants.

Based on these findings, 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. The literature search was conducted primarily using PubMed. Papers were found in Pubmed using the website's advanced search function with the keywords, "Serotonin, 5-HT, Depression, Norepinephrine, Dopamine, Neuroplasticity, Stress." 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. This paper is an abridged version of another paper that was submitted as a Cornell Honors Thesis. The original paper can be found at <https://ecommons.cornell.edu/handle/1813/111440>. Overall, findings of 41 papers were included to conduct the abridged 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 (Berger, 2009). 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 (Jans, 2007). 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 (Jans, 2007). 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 (Berger, 2009). The primary raphe nuclei are the dorsal raphe (DR) and median raphe, located in the caudal midbrain and rostral pons (Meyer & Quenzer, 2019). Axons from these regions are not uniformly distributed, innervating areas of high dendritic and synaptic density more than white matter tracts (Meyer & Quenzer, 2019). Figure 1 contains a diagram showing serotonergic fiber distributions in the human brain.

While awake, the dorsal raphe fires tonically at a constant, slow rate. It also can fire in phasic bursts, facilitating motor output while suppressing sensory processing. Phasic firing must be triggered by excitatory inputs to the

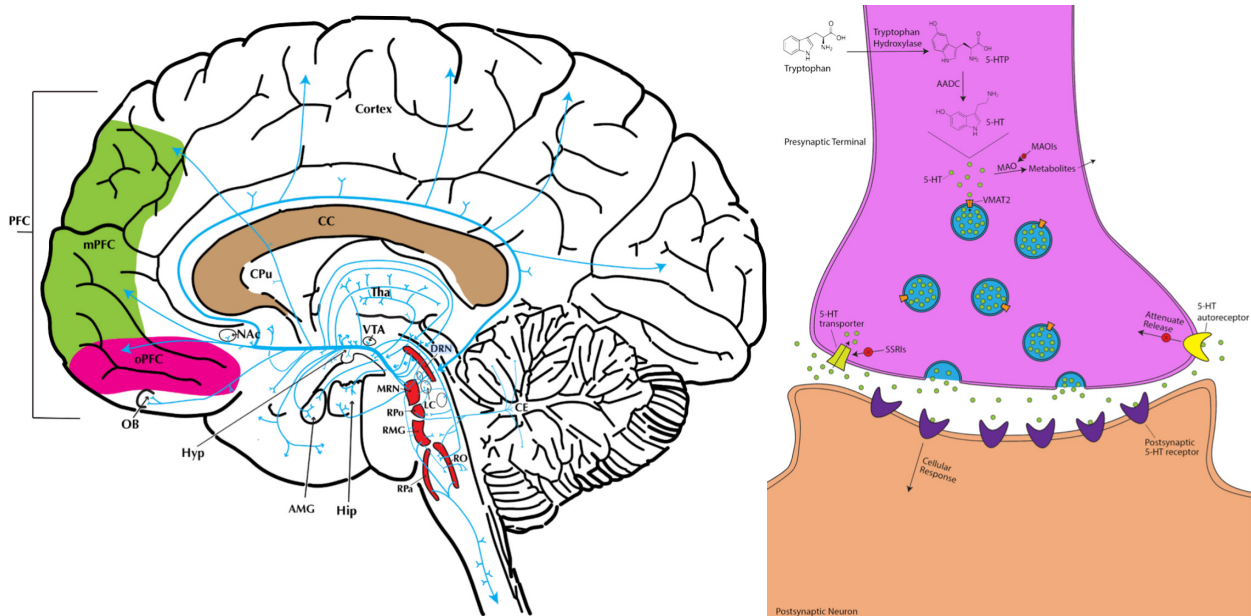


Figure 1 (left): A sagittal view of human serotonergic neurocircuitry. The raphe nuclei are shown in red. Blue tracts represent serotonergic projections from the raphe nuclei, with extensive limbic and cortical innervation. Raphe Nuclei: DRN, dorsal raphe nuclei, MRN, median raphe n, RPo, raphe pontis n, RMG, raphe magnus n, RPa, raphe pallidus n, RO, raphe obscurus n; LC, locus coeruleus, Tha, thalamus, Hip, hippocampus, AMG, amygdala, Hyp, hypothalamus, CPu, caudate putamen, VTA, ventral tegmental area, NAc, nucleus accumbens, OB, olfactory bulb, CC, corpus callosum, CE, cerebellum, PFC, prefrontal cortex: mPFC, medial prefrontal c, oPFC, orbitofrontal prefrontal c. Adapted from Charnay, 2010.

Figure 2 (right): A serotonergic synapse. 5-HT is synthesized from tryptophan by tryptophan hydroxylase and AADC (Aromatic L-Amino Acid Decarboxylase). It is packaged into vesicles by VMAT2 (Vesicular Monoamine Transporter 2), to be released into the synapse. MAO (Monoamine Oxidase) breaks down 5-HT into metabolites. MAOI antidepressants inhibit this process. The 5-HT transporter (SERT or 5-HTT) 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 Meyer & Quenzer, 2019.

DR, such as through glutamatergic pathways from the PFC, lateral habenula, hypothalamus, and various brainstem areas. The DR also receives cholinergic input from the pons, and inhibitory GABA inputs from different areas including the DR itself. 5-HT is also regulated by the monoamine neurotransmitters DA and NE. During slow wave sleep, DR firing becomes slower and irregular, and effectively ceases firing during REM sleep (Meyer & Quenzer, 2019).

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. In addition, an alteration of 5-HT function has been observed in a plethora of clinical conditions, including

anxiety and suicide (Jans, 2007). Serotonergic tracts have been robustly connected to aggression and impulse control. For example, mice prevented from synthesizing 5-HT in the brain demonstrate a large increase in aggression and impulsivity, but decreased anxiety, social communication, and maternal care (Meyer & Quenzer, 2019). For clarity, Figure 2 depicts a serotonergic synapse, including autoreceptors and the serotonin transporter.

Table 2 shows the 14 serotonin receptors and their studied functions. 5-HT_{1A} and 5-HT_{2A} have been widely studied in depression, due to their high expression in limbic and cortical regions respectively (Nichols, 2008). The majority of serotonin receptors have been connected to the modulation of depression (Nautiyal, 2017).

Table 2: The Functions of the 5-HT Receptors (Meyer and Quenzer, 2019; Nichols, 2008)

5-HT Receptor	Type	Mechanism	Effect	Notes
5-HT _{1A}	G _{i/o} coupled	Decreases cellular cAMP	Inhibitory	Presynaptically expressed on raphe cells as an autoreceptor, but highly postsynaptically expressed in limbic regions.
5-HT _{1B}	G _{i/o} coupled	Decreases cellular cAMP	Inhibitory	Terminal raphe cell 5-HT autoreceptor.
5-HT _{1D}	G _{i/o} coupled	Decreases cellular cAMP	Inhibitory	Terminal raphe cell 5-HT autoreceptor.
5-HT _{1E}	G _{i/o} coupled	Decreases cellular cAMP	Inhibitory	Expressed cortically, not expressed in mice.
5-HT _{1F}	G _{i/o} coupled	Decreases 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 IP3 and DAG	Excitatory	Important for heart and brain development, knockout is lethal, involvement in certain cardiac pathologies.
5-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-HT ₃	Cation channel	Depolarize cell	Excitatory	The only ionotropic 5-HT receptor, located on peripheral terminals of vagus nerve, antagonists reduce nausea and are 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 cAMP	Excitatory	Highly 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 attributed to its ability to inhibit monoamine oxidase (MAO) A and B, the enzyme which metabolizes 5-HT and NE (Jacobsen, 2012). 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. His formulation heavily relied on drug-based evidence, recognizing the theory was likely an oversimplification of a complex biological state (Schildkraut, 1965). 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 of 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. 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 (Coppen, 1967). Today, the theory remains influential in the pharmaceutical industry, and SSRI antidepressants are now among the best-selling drugs in medical practice (Lacasse, 2005).

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. Both MAOIs and tricyclics increase synaptic monoamine concentrations and demonstrate antidepressant efficacy. On the other hand, 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 (Yohn, 2017), and serving as a first line treatment for depression (Saavedra, 2021).

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. Additionally, low 5-HT was found to have a robust correlation with suicide patients, although its correlation to MDD has been inconsistent (Jacobsen, 2012).

While the above findings support 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 rather than a simple reduction in 5-HT. Said mood disorders could result from either hyper- or hypo- function of serotonin pathways, depending on the brain region, stage of neurodevelopment, and 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 to suicidality (Jacobsen, 2012). This receptor is correspondingly seen to be reduced after successful antidepressant treatment, coinciding with the onset of clinical efficacy (Vollenweider, 2010).

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. 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. Indeed,

potentiation of this receptor with the hormone CRH, which regulates the stress response, led to increased anxiety-like behavior in mice in response to the 5-HT_{2A} agonist DOI. 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. 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 MDD (Vollenweider, 2010).

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 (Jacobsen, 2012). This corresponds with

an observation of postsynaptic 5-HT_{1A}Rs mediating anxiolytic effects. It has been theorized that the postsynaptic 5-HT_{1A} receptor is also involved in impulse control, such as by increasing patience and anti-aggression (Carhart-Harris, 2017). These postsynaptic 5-HT_{1A}Rs have differing roles than the presynaptic autoreceptors.

Due to the differing roles of serotonergic receptors, Carhart-Harris et al. (2017) 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. This idea is summarized in Figure 3 below.

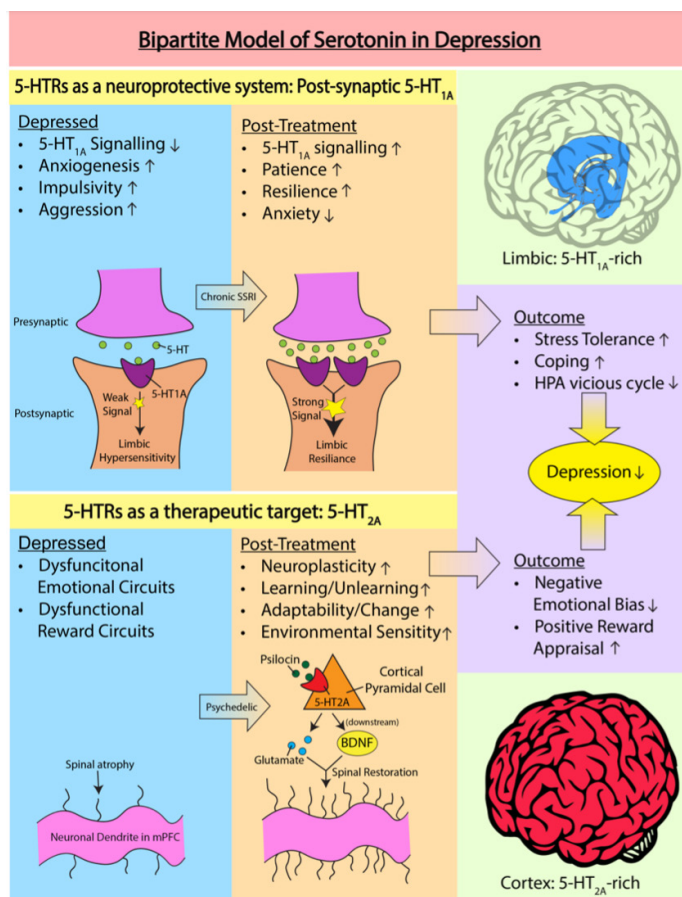


Figure 3: The proposed bipartite model of serotonin’s role in depression. 5-HT_{1A} signaling corresponds with resistance to stress. 5-HT_{2A} signaling corresponds to neuroplastic changes that may help alleviate depression. Carhart-Harris et al. predicts conventional antidepressants such as SSRIs therefore act by primarily enhancing the 5-HT_{1A} pathway, while serotonergic psychedelics primarily act on pathway 2. Note the findings that serotonergic neuroplasticity could occur independent of 5-HT_{2A} (Hesselgrave, 2021) evidence that this model is an oversimplification. Adapted from Carhart-Harris et al., 2017.

This formulation acknowledges 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. With results from a study by Hesselgrave (2021) demonstrating psilocybin could mediate an antidepressant and neuroplastic effect in mice despite blockade of

5-HT_{2A/2CRs} with ketanserin, more extensive studies into the roles of other 5-HTRs are warranted to find additional pharmacological targets. For example, blockade of 5-HT₇ potentiates antidepressant effects in rats (Yohn, 2017). A summary of data detailing current findings about the roles of varying serotonin receptors in modulating neuroplasticity is shown in Table 3 below (Kraus, 2017).

Table 3: *The roles of various serotonin targets in neuroplasticity (Kraus, 2017).*

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

While the examples above serve to support the connection between a general dysfunction in 5-HT modulation and depression, the evidence that the cause of MDD is a particular deficiency of 5-HT is inconclusive at best (Jacobsen, 2012). Nevertheless, the 5-HT system appears to be an important factor in both the pathophysiology (as a risk factor) and treatment of MDD.

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. This hypothesis identifies the downregulation of 5-HT autoreceptors, which eventually increases synaptic 5-HT, as the key mechanism of SSRI action. As shown in Figure 4, the several days to two weeks these

autoreceptors take to desensitize would explain the delayed onset of SSRIs (Liu, 2017).

5-HT May Contribute to Dysregulation of the Stress Axis in Depression

Stress often precedes depressive episodes in humans (Meyer & Quenzer, 2019). Chronic stress induces alterations in dendritic spine densities of various regions, shrinkage of the PFC and hippocampus, and a decrease of hippocampal neurogenesis, 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 (Mahar, 2013).

Several important observations provide evidence that depression is frequently, although not always (Menke, 2019), associated with HPA dysregulation. Depressed patients often show elevated levels of the stress hormone cortisol, resulting from oversecretion of the stress hormone CRH (Meyer & Quenzer, 2019) along

with disrupted negative-feedback mechanisms (Menke, 2019). A vicious cycle of dysregulated cortisol levels may exacerbate hippocampal atrophy, decrease neurogenesis (Krishnan, 2010), and disrupt circadian rhythms (Fig. 5). However clinical trials targeting HPA targets have been largely mixed at best (Menke, 2019).

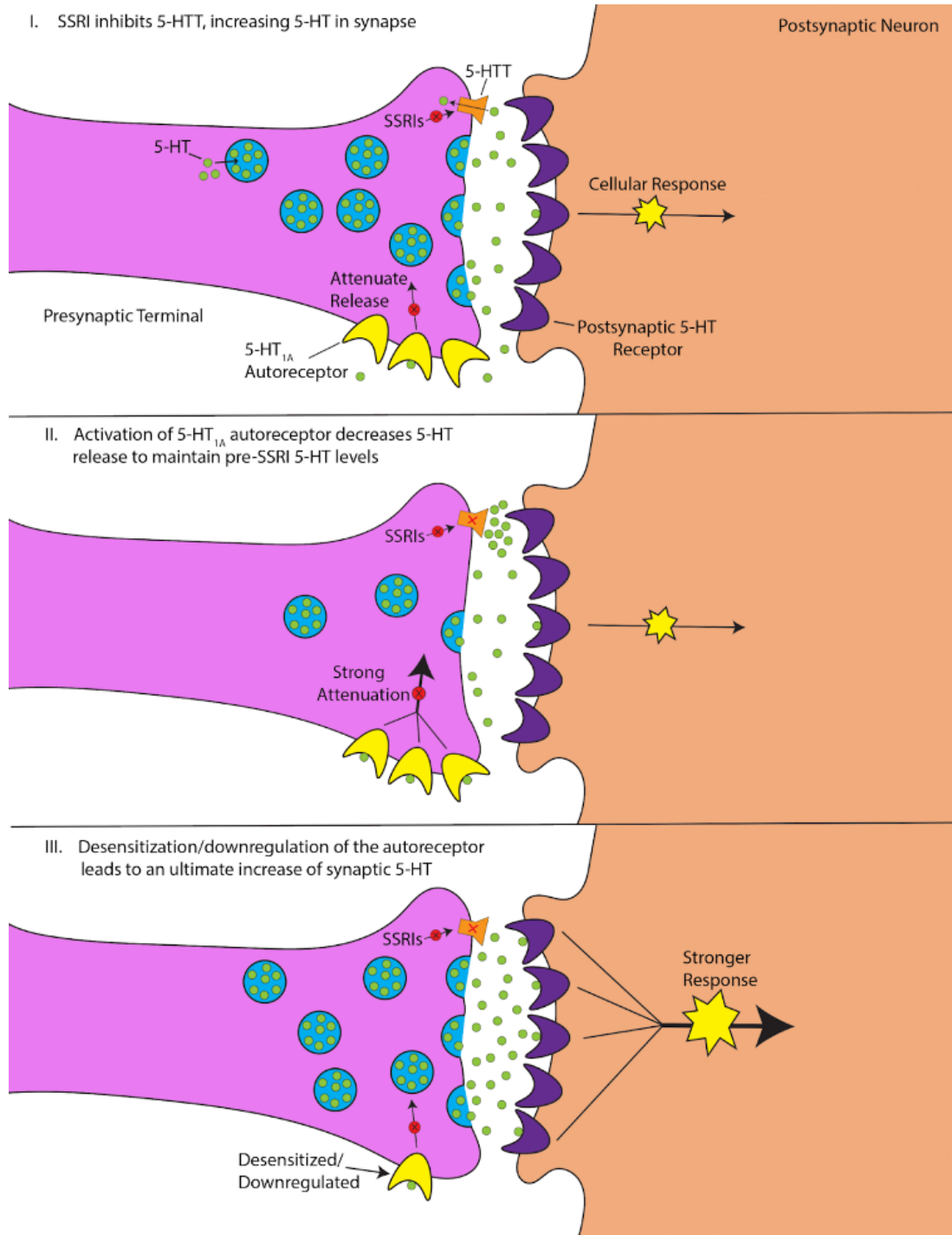
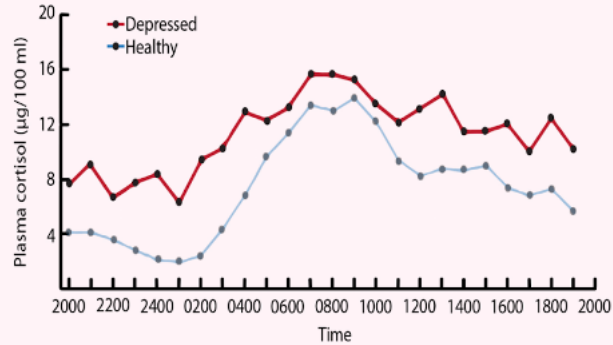


Figure 4: How 5-HT_{1A} autoreceptor downregulation is necessary for SSRI efficacy. Serotonin enhancing antidepressants (SSRI, SNRI, TCA) block 5-HTT and initially lead to increased autoreceptor activation which maintains serotonin’s extracellular tone. Only after these receptors become desensitized may serotonin release into the synaptic cleft increase above baseline, explaining the ~2 week delayed efficacy of SSRIs. The corresponding increase in postsynaptic serotonin receptor signaling mediates the antidepressant response. Adapted from Celada, 2013.

Depressed:

- Disrupted circadian control of cortisol
- Average cortisol levels \uparrow
- Flattening of cortisol fluctuations
- Early onset REM
- Frequent awakenings
- Less deep sleep rhythms
- Hippocampal atrophy \uparrow
- Neurogenesis \downarrow



Healthy:

- Lower overall cortisol
- Cortisol spike in the morning
- Cortisol drop in the evening.
- Cortisol stays low throughout night.

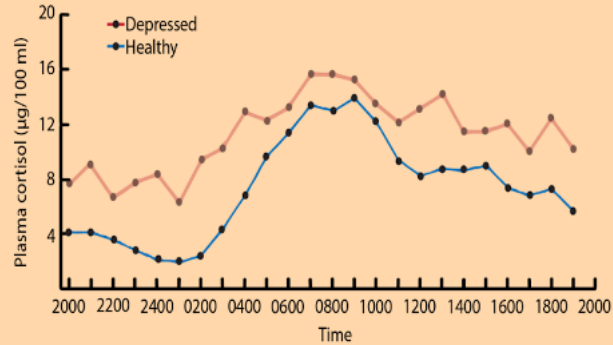


Figure 5: How depression affects daily cortisol fluctuations. Healthy individuals show a large decrease in cortisol level corresponding with sleeping hours followed by a large increase in waking hours. Depressed individuals by contrast show a general flattening and overall increase of cortisol levels throughout the day. Adapted from Meyer & Quenzer, 2019.

In a review by Mahar et al. (2013), 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 chronic unpredictable stress, 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. 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, with some amount of downregulation of this receptor still being necessary for antidepressant efficacy.

Finally, since 5-HT1A downregulation is observed in the mPFC, Mahar et al. (2013) 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. A summary of this is shown in Figure 6 below.

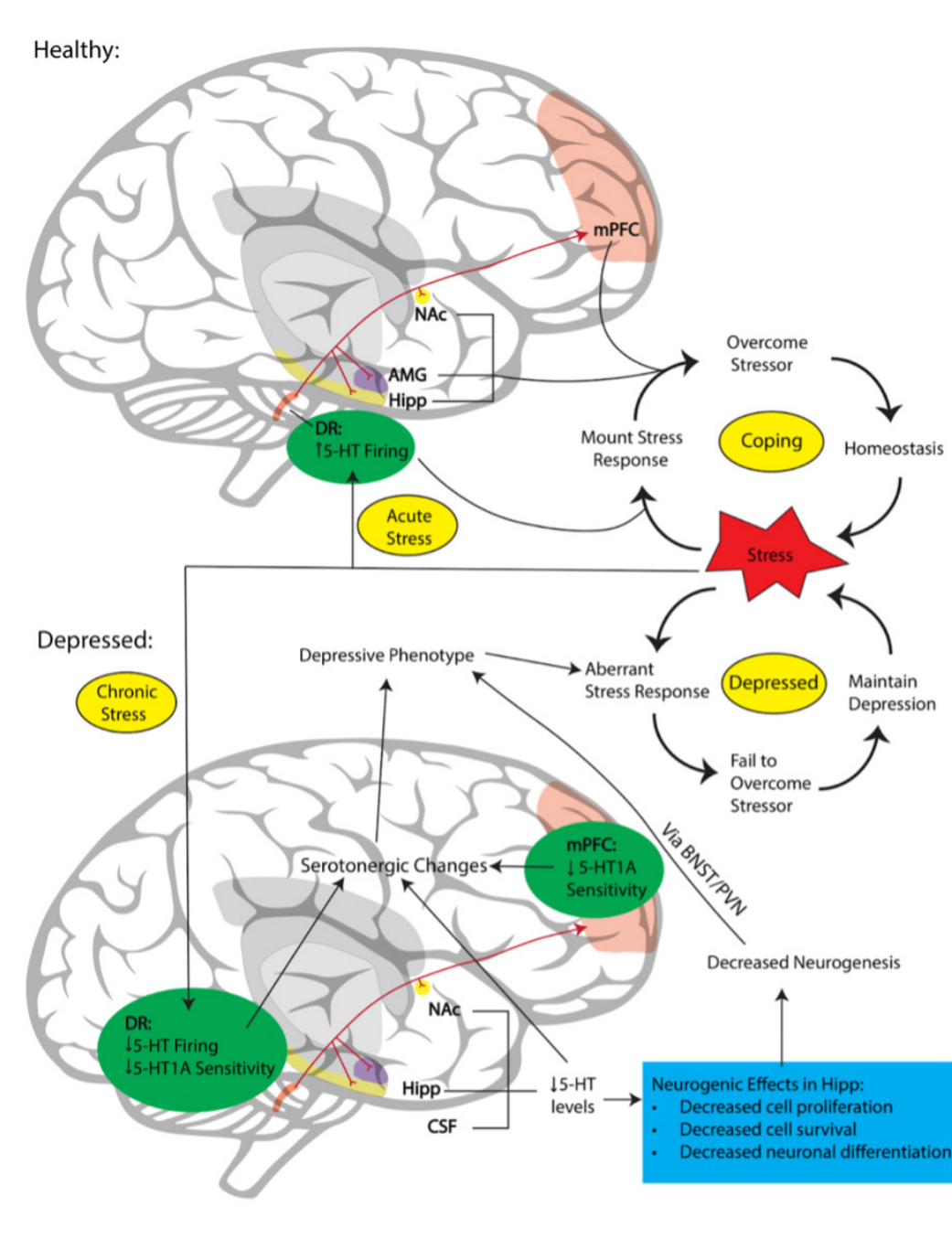


Figure 6: A model of how chronic stress contributes to serotonergic and neurogenic dysfunction in the brain. Acute stress increases DR firing onto the mPFC as a way to interpret and respond to stressors. Chronic stress causes changes in the serotonergic circuit, decreasing DR activity, while down regulating pre- and post- synaptic 5-HT1AR 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. The resulting dysfunction of the HPA axis contributes to a vicious cycle, where aberrant stress responses maintain serotonergic dysfunctions in the depressed brain. Serotonergic antidepressant treatment modulates hippocampal neurogenesis, restoring HPA regulation there and alleviating depression. DR, Dorsal Raphe; BNST, bed nucleus of the stria terminalis; CSF, cerebrospinal fluid; Hipp, hippocampus; AMG, amygdala; mPFC, medial prefrontal cortex; NAc, nucleus accumbens; PVN, paraventricular nucleus of the hypothalamus. Adapted from Mahar, 2013.

Expanding Beyond 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. 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 (Blier, 2013), as a lack of dopaminergic signaling is believed to contribute to anhedonia (Grace, 2016). 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 (Blier, 2013). 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 (Albert, 2013). Although controversial, the pooled results of FDA clinical trials of SSRIs showed placebo was able to duplicate the antidepressant response of SSRIs by 80% and demonstrated that SSRIs exactly demonstrate superiority to placebo in severe depression only (Kirsch, 2008). Another review found long-term antidepressant therapy with drugs such as SSRIs to be generally ineffective (Burcusa, 2007). 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 (Liu, 2017). 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 (Blier, 2009). As a result of these contradictory findings, modern research efforts have sought to expand models of depression beyond 5-HT to better understand the disorder and improve treatment options (Lacasse, 2005).

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 and 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 (Liu, 2017). Central to this hypothesis are alterations in neuronal spines seen in MDD. 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 (Duman, 2015).

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 (Duman, 2015). The discovery of the rapid antidepressant effects of ketamine has been crucial to the formulation of the neuroplasticity theory, which Deyama (2020) called "the biggest breakthrough for the treatment of depression in over 60 years."

Although the mechanism is being debated (Kohtala, 2021), ketamine is observed to increase glutamate release and increase AMPA signaling, thus potentiating LTP. One explanation is that inhibiting NMDA receptors on GABAergic interneurons leads to disinhibition of excitatory glutamatergic neurons (Vollenweider, 2010). 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 (Liu, 2017), 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 behavioral therapy, with an average 2 week delay (Liu, 2017) before drug efficacy representing a danger in cases of suicidal ideation. 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 (Vollenweider, 2010).

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 (Liu, 2017). Evidence has shown several serotonin receptors to be regulatory of LTP, hippocampal neurogenesis, and cytoskeletal rearrangement (Kraus, 2017). 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 (Kraus, 2017), it is plausible the efficacy of monoaminergic agents for MDD are reliant on these processes. These ideas are displayed in Figure 7 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. 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. As the PFC and AMG are also key regions involved in depression, it has been proposed that decreased hippocampal neurogenesis is not necessary to trigger depressive behaviors (Kraus, 2017). On the other hand, evidence has shown that restoration of neurogenesis is necessary for antidepressant efficacy (Meyer & Quenzer, 2019), with chronic but not acute SSRI treatment coinciding with an upregulation of hippocampal neurogenesis (Kraus, 2017).

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 (Deyama, 2020). 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), which regulates synaptogenesis and BDNF (Ignácio, 2016). An example of this pathway enabling antidepressant therapy is shown below in Figure 8.

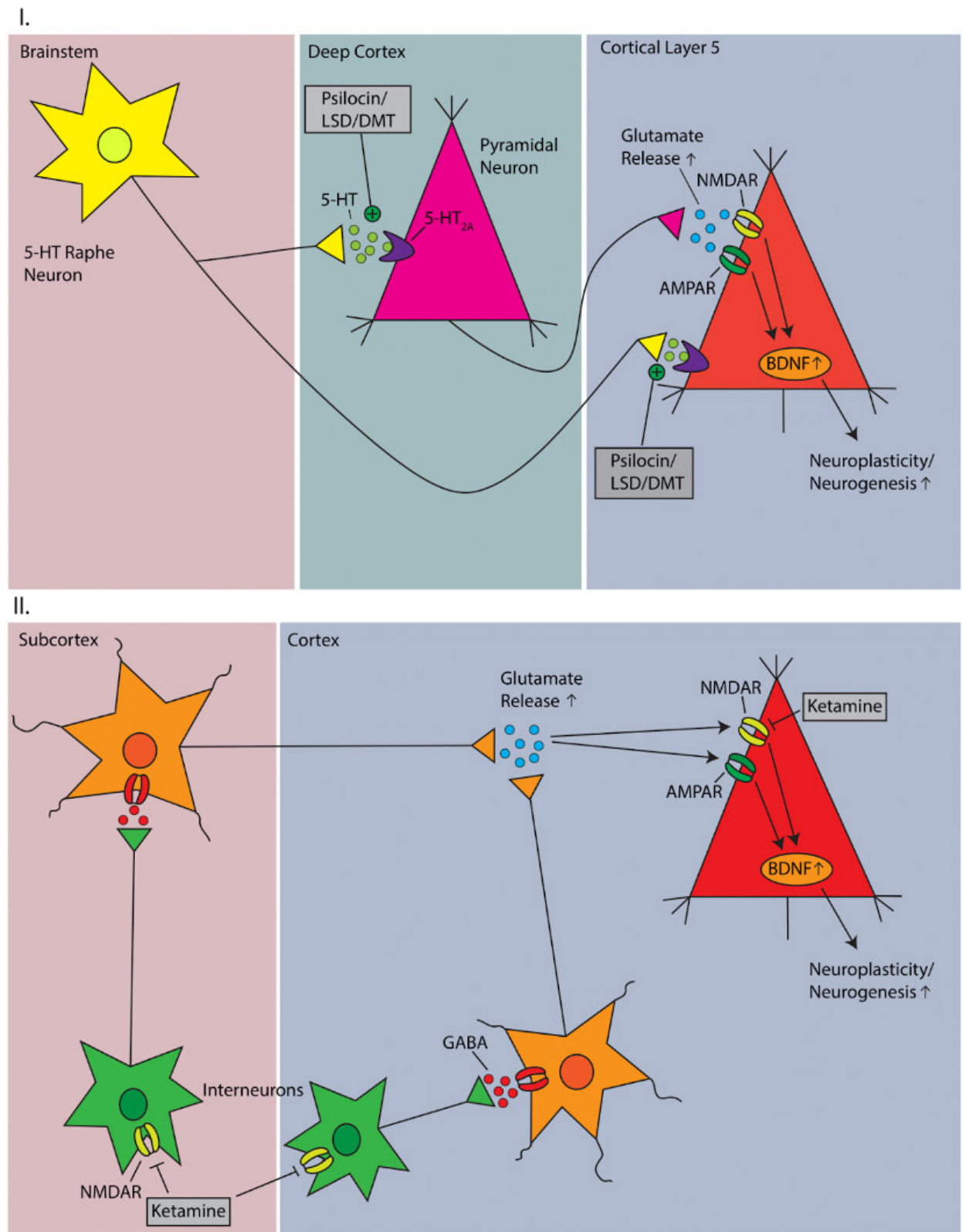


Figure 7: How hallucinogens may cause a glutamate burst through serotonergic signaling.

I. 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} stimulation, may lead to increased expression of BDNF, mediating neuroplasticity necessary to alleviate depression. II. 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, 2010.

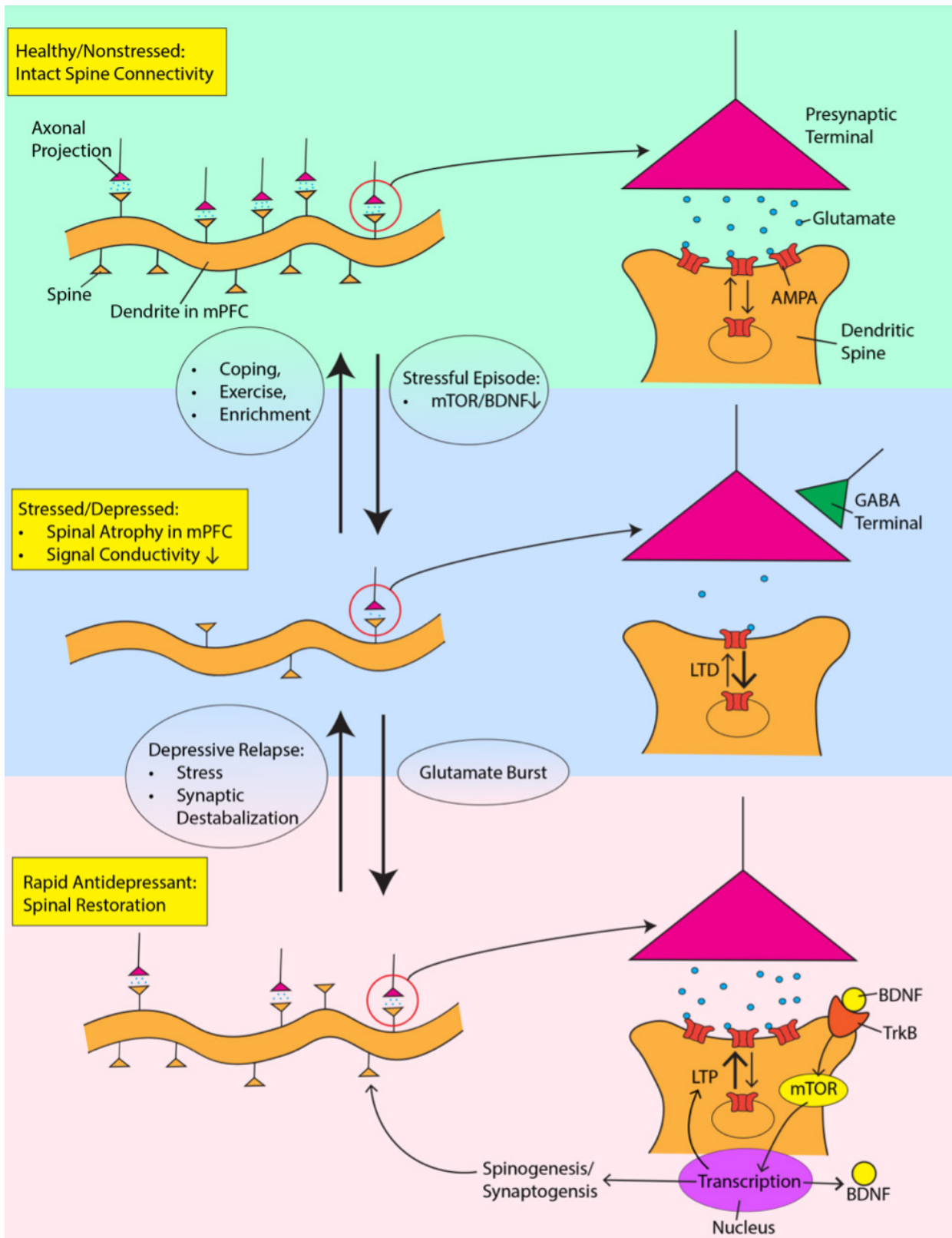


Figure 8: How *mTOR* signaling mediates the effects of fast-acting antidepressants. Under nonstressed conditions, spine synapse connections are normal and contribute to control over mood, emotion, and cognition. Chronic stress and depression decrease BDNF and downstream *mTOR* signaling, ultimately decreasing 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. (Duman, 2015).

Discussion

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 (Blier, 2013).

MDD is often characterized by its relationship to stress. In general, stressful episodes are frequent in the initial onset of depression (Meyer & Quenzer, 2019). The development of MDD after these episodes 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, realigning neurocircuitry to favor negative emotional associations. Stress is not always required for depressive episodes, in particular in cyclical recurrent depression. 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 (Burcusa, 2007).

Vulnerability to stress induced depression is an outcome of both genetic and environmental factors. Environmental factors are responsible for establishing the epigenome during prenatal and early childhood development (Saavedra, 2021), 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 (Meyer & Quenzer, 2019).

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 (Mahar, 2013), likely involved in evaluating stressors and planning the stress response. Serotonergic activation normally promotes patience for reward and inhibits impulsivity (Carhart-Harris, 2017), 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 (Leonard, 2001), helping the brain coordinate a widespread stress response. Finally, dopaminergic circuits projecting from the VTA in rats upregulate dopamine signaling onto the nucleus accumbens under acute stress (Grace, 2016), 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 (Carhart-Harris, 2017), have been seen in studies to be downregulated as a result of chronic stress (Mahar, 2013). The 5-HT_{2A} receptor, which has been shown to be anxiogenic (Vollenweider, 2010), is seen to be upregulated on the other hand (Jacobsen, 2012). Although an oversimplification, these changes may serve to promote increased anxiety in the response to stressors, translating into an inability to overcome stressful obstacles. LC pathways that innervate the entire brain, including relevant limbic and cortical regions, are disrupted in their noradrenergic signaling after chronic stress (Moret, 2011). Finally, chronic stress downregulates dopaminergic signaling, which

disrupts the ability to form reward associations and may be largely responsible for symptoms of amotivation and anhedonia (Grace, 2016).

Carhart-Harris's (2017) bipartite theory is incomplete, but may aptly characterize 5-HT's specific role in depression as both a risk factor and therapeutic target through separate mechanisms. Hesselgrave's (2021) study 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.

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, a likely contributor of depressive pathophysiology (Grace, 2016). 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 reduce this capacity by increasing anxious and impulsive behaviors, leading to a disinclination or even inability to face future stressors and contributing to feelings of low self-worth, amotivation, and reduced concentration consistent with depressive pathology.

Depression is presently best explained by changes in the functional connectivity of different brain regions. Dendritic spine hypotrophy and volume loss in the mPFC (Duman, 2015) 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 (Kraus, 2017) and a bias favoring negative labeling of external stimuli. Spine hypertrophy in the amygdala and nucleus accumbens may be responsible for negative reward associations (Grace, 2016) and fear (Duman, 2015) of normally rewarding stimuli. Finally, hypertrophy of spines in the orbitofrontal cortex may also contribute to reward-association disruption (Edmund, 2020).

The actions of neurotrophins such as BDNF appear necessary to mediate the gene transcription of neuroplastic factors in neurons (Deyama, 2020). In the case of ketamine, BDNF transcription has been connected to the actions of the mTOR pathway after a glutamate burst (Ignácio, 2016), raising the question of whether mTOR may be a common factor in all antidepressant efficacy, for example mediating similar glutamate bursts downstream of serotonin signaling (Vollenweider, 2010).

Under the lens of the neuroplasticity hypothesis, depression is better described as a dysfunction of the neurocircuitry of the brain, especially in areas 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. 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. The use of SSRIs may indirectly potentiate synaptic plasticity and help the brain relearn emotional associations. Over time, this would lead to a positive biasing of emotional experience (Cowen, 2015).

Branchi et al. (2013) substantiates this hypothesis with evidence that SSRI effectiveness in mice is largely dependent on the environment during ongoing antidepressant administration,

with fluoxetine actually potentiating depression in negative environments. 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. It therefore appears SSRIs prime the brain for increased plasticity to be shaped by environmental factors, whether positive or negative. 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 (Fava, 2003).

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 (Heim, 2008). A failure to properly control for environmental factors calls into question the meta-analysis that demonstrated antidepressants such as SSRIs struggle to outperform placebo (Kirsch, 2008), as one might expect depressed patients to be dealing with a higher degree of stress compared to healthy individuals.

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 (Heim, 2008). Similarly, thyroid disorders may lead to HPA hyperactivation, and have been associated with a higher risk of depression (Hage, 2012). Resultantly, whether the mechanism of depressive onset changes which treatment options are most effective is a question worth considering.

A recent study published in *Nature* (Taliaz, 2021) substantiated this hypothesis, demonstrating that antidepressant prescription done by an algorithm fed an assortment of patient demographic, clinical, and genetic data was able to predict a patient's response between different antidepressants with an accuracy of 70.1% compared to the 46.8% initial antidepressant response rate of the participants. This holds clinical relevance, as providing initial test screenings for genetic, demographic, and symptomatic markers of patients could lead to more effective initial response rates to antidepressants. This is especially important in patients suffering suicidal ideation. Moving away from always initially prescribing SSRIs, when superior treatments may exist, may help decrease suicide rates.

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. This can be seen as a side effect of increased neuroplasticity, 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 (Lacasse, 2005). This is especially important in instances where an alternative treatment may be superior. While SSRIs are among the bestselling drugs, expanding beyond serotonin regulating treatments may help discover more successful treatments against MDD.

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