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Treatment-induced plasticity in the "depressed" hippocampus mediates the mood-improving actions of antidepressants

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Abstract

Major depressive disorder (MDD) is a mood disorder characterized by persistent low mood and reduced motivation. Despite decades of research, the underlying pathophysiology of MDD remains poorly understood; likewise, the mechanisms of action of antidepressants (AD). The most influential hypothesis of MDD suggests that MDD is rooted in a monoamine deficiency, and that ADs work by reversing this deficiency. However, the observed acute increase in monoamines after AD administration and the delayed clinical onset of ADs in improving mood suggest that merely increasing monoamine levels is not sufficient to improve symptoms of mood. Instead, repeated stimulation of monoamine receptors and downstream monoamine-induced gene expression may be necessary to induce changes in behaviors. A more recently proposed hypothesis of MDD states that reduced neuroplasticity/neurogenesis in the hippocampus (HC) in the presence of stress is responsible for maintaining the depressive-like phenotype. This is also supported by evidence that ADs have pro-neurogenic and neuroplastic effects in the HC, and that chronic AD treatment leads to morphological adaptations in the HC which may underlie the mood-improving actions of ADs. While mechanistically plausible, the story is more complicated. It appears that mechanisms involved in neurotransmission, stress neurobiology, and neuroplasticity, interact in complex ways to support neuronal remodeling in the HC and ultimately restore functionality in local circuits involved in mood and stress regulation.

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INTRODUCTION

Major depressive disorder (MDD; interchangeably used as "depression" and "depressive disorder" in the present essay) is a common mood disorder characterized mainly by persistent low mood and reduced motivation (also called *anhedonia*). Despite decades of research, the underlying pathophysiology of MDD remains poorly understood, although explanations for a neurobiological basis of depression have been proposed. The most influential hypothesis of depression states that reduced brain levels of monoamines (serotonin, norepinephrine, and/or dopamine) is the underlying factor for MDD, and that treatment with antidepressants (ADs) can restore this deficit and facilitate recovery. While the *monoamine hypothesis* greatly advanced our understanding of depressive disorders and yielded treatment options, it fails to address the inconsistent efficacy of ADs among sufferers and the delayed onset of therapeutic effects. This renders the monoamine paradigm as rather simplistic when faced with evidence about more intricate processes underlying AD efficacy and remission from depression.

One such process is neuroplasticity, particularly adult hippocampal neurogenesis. Adult neurogenesis (AN) is a sophisticated form of neuroplasticity that involves the generation of new neurons from adult stem cells in the mature hippocampus (HC) (Cameron & Gould, 1994). Additional processes crucial for the structural and functional integration of these newly formed cells include gliogenesis, dendritic arborization, and synapse formation. With regard to MDD, a wealth of studies shows that (1) the HC of patients with MDD is smaller relative to healthy controls (Sheline et al. 1996, 1999; Bremner, et al., 2000), and (2) ADs have neuroplastic effects, which may underlie their therapeutic effect.

While a causal relationship is difficult to establish between HC atrophy and depression, animal and human studies have shown that such atrophy can be reversed with AD treatment, at a time course that parallels the onset of clinically relevant changes in behavior, i.e., improved mood. This shifts – or rather expands – the monoamine paradigm to a *neurogenic* base for MDD (Jacobs, van Praag, & Gage, 2000) that acknowledges a more sophisticated role of monoamines in relation to stress hormones, neuroplasticity, and depressed mood (Magarinos & McEwen, 1995; Cameron, Tanapat, & Gould, 1998; Duman, Aghajanian, Sanacora, & Krystal, 2016; Karayol, et al., 2021). For instance, (based on the monoamine hypothesis) depletion of serotonin levels has been causally linked to MDD for decades; until evidence from rodent studies showed that systemic treatment with agents that target serotonin/norepinephrine promoted cell proliferation and expression of plasticity-related proteins in the HC (Duman, Nakagawa, & Malberg, 2001). This stimulated interest in the study of monoamines in relation to neural plasticity and integrity, beyond neurotransmission.

Most of AD agents used in MDD initiate biochemical changes that facilitate plasticity, neurogenesis, learning, adaptation, and more (Thome, et al., 2000), and their AD-like effects indicate that (1) MDD may arise from disrupted neural circuitry rather than solely from neurochemical imbalances (at least in certain types of depression), and (2) ADs support recovery by promoting neuronal "rewiring" through their neuroplastic effects.

The etiology of MDD makes a complex discussion that extends beyond the scope of this essay. It is, however, essential to discuss different hypotheses of depression and the premises on which they rest, particularly their neurobiological foundations. These theories will be discussed in Chapter 1 (Section 1.1), along with pharmacological therapies for depression and their mechanisms of action (Section 1.2). The second chapter will shift the focus to hippocampal involvement in mood, stress, and depression-related neurobiology. The aim of this essay is to discuss the mood-improving actions of ADs as a function of HC plasticity.

CONCEPTUAL FRAMEWORK

1. Depression

Major depressive disorder is a multifaceted psychiatric disorder characterized by a wide range of symptoms, including affective and cognitive disturbances, changes in appetite, sleep disturbances, altered sexual desire, loss of pleasure and motivation, suicidal thoughts, and psychomotor retardation. A diagnosis of MDD is established only if symptoms of low mood and/or low motivation/pleasure persist for at least two weeks and interfere significantly with one's functioning and relations (according to the DSM-5 classification of mental disorders; American Psychiatric Association, 2013).

A prominent feature of MDD is the chronic and incapacitating nature of its symptoms, coupled with sensitization to stress (Hammen, Henry, & Daley, 2000). Even when receiving medication, individuals with MDD exhibit heightened sensitivity to stress (Technow, Hazel, Abela, & Hankin, 2015), and higher rates of relapse increasing with every episode (Hardeveld, Spijker, De Graaf, Nolen, & Beekman, 2010). The onset of MDD varies among individuals, though precipitating life events and prolonged exposure to stress are common triggers or exacerbating factors for a first episode, with childhood adversity being among the strongest predictors for MDD at all ages (Green, et al., 2010).

Due to its high heterogeneity and complex underlying mechanisms, the identification of reliable biomarkers for MDD has remained elusive. Nevertheless, several theories proposing a neurobiological basis for depression have been put forward, with varying levels of scientific support.

1.1 Neurobiology of depression: theory and evidence

1.1.1 Monoamine-Serotonin hypothesis

The most influential theory of depression emerged over 50 years ago from the discovery that certain anti-tuberculosis medications, namely iproniazid and isoniazid (a type of monoamine oxidase inhibitors; MAOIs), had psychostimulant effects. Patients with tuberculosis and depressive-like behaviors experienced enhanced mood, improved sleep, increased appetite and sociability, and an overall boost in vitality after weeks of iproniazid treatment. Around the same time, research on

chlorpromazine, an antihistaminic substance, revealed unexpected psychiatric effects, and by the end of the 1950s, similar compounds (today known as tricyclic antidepressants or TCAs) were introduced for the treatment of depression (Hillhouse & Porter, 2015).

The remarkable mood-enhancing effects observed with MAOIs and TCAs gave rise to the monoamine hypothesis of depression (Hirschfeld, 2000). According to this, depression is caused by a deficiency of monoamine neurotransmitters (such as serotonin, dopamine, and/or norepinephrine) in the brain, and using agents that elevate monoamine levels, like MAOIs and TCAs, would alleviate the core symptoms of MDD. Over time, new medications have been developed to target monoamine neurotransmitters preferentially, such as selective serotonin reuptake inhibitors (SSRIs) or serotonin/norepinephrine reuptake inhibitors (SNRIs), and these two slowly replaced MAOIs and TCAs as first-line treatments. As a result, the monoamine hypothesis evolved into a serotonin-focused perspective, based on which serotonin (5-HT) is the main player in the monoamine deficit associated with depression (Coppen, 1967).

The monoamine-serotonin paradigm enjoyed substantial support due to its significant impact on the field of psychiatry at that time. However, reducing depression to a mere neurochemical imbalance is overly simplistic, and to this day, the hypothesis lacks robust scientific support. Despite some evidence that depleting serotonin, norepinephrine (NE), or dopamine levels can lead to decreased mood in patients following AD treatment, or unmedicated individuals with a family history of MDD, no direct correlation has been found between monoamine levels and depressed mood. Besides, the hypothesis does not address the delayed efficacy of ADs.

These observations suggest that stimulating monoaminergic transmission with AD agents has at best mediating – rather than direct – therapeutic effects, and that other downstream neurobiochemical effects related to the regulation of monoamines, such as gene transcription and protein synthesis, may be ultimately responsible for AD efficacy. This aligns with alternative theories of depression, namely the *stress hypothesis* of depression, and the *neurogenic/neuroplastic hypothesis,* which is discussed below.

1.1.2 Stress hypothesis

Stress refers to the physiological and behavioral reactions triggered by a stressor to maintain body homeostasis and facilitate adaptation (referred to as “allostasis”; McEwen, 2003). These responses begin with the activation of the hypothalamus-pituitary-adrenal (HPA) axis (a neuroendocrine system crucial for stress and mood regulation) and autonomic nervous system, leading to hormone release (such as adrenaline and glucocorticoids) and other cellular responses necessary for survival. While stress responses primarily serve primitive functions such as ensuring survival, in humans stress often takes on a psychological nature. Nonetheless, acute stress responses to life threats or psychological challenges are essential for overcoming obstacles and are generally beneficial. However, prolonged exposure to stress is harmful, particularly for the brain. This is

because increased levels of glucocorticoids (e.g., cortisol, the stress-associated steroid hormone in humans) have neurotoxic effects and can even lead to atrophy in brain regions crucial for stress and mood regulation, such as the hippocampus (Magarinos & McEwen, 1995; Bremner, et al., 2000; Duman R. S., 2006; Kim, Pellman, & Kim, 2015)

The stress hypothesis of depression, thus, asserts that dysregulated function of the HPA axis leads to elevated levels of glucocorticoids, which ultimately impact mood regulation and other processes essential for well-being (e.g., digestion, sleep, and stress response), as well as brain structures involved in mood regulation (Brown, Rush, & McEwen, 1999; McEwen B.S., 2001-2015). Indeed, depression has been consistently linked to psychosocial stress (Hammen, 2005; Gilman, et al., 2013; Tafet & Nemeroff, 2016), childhood trauma, and/or prolonged exposure to adversity (Buckman, et al., 2022). Furthermore, individuals with MDD often exhibit rumination (i.e., excessive focus on one's negative feelings and worries), and negative biases in perceiving others' emotions (Bourke, Douglas, & Porter, 2010; Dai & Feng, 2012), which intensify stress perception and sustain stress-induced physiological responses even in the absence of actual threats.

Consistent with the stress hypothesis, studies on patients with MDD and in animal models of depression show hyperactivity of HPA axis (Mikulska, Juszczyk, Gawronska-Grywacz, & Herbet, 2021), including elevated cortisol levels beyond normal, disrupted regulation of cortisol secretion, resistance of the HPA axis to suppression, and increased secretion of proinflammatory cytokines (Young, et al., 1994; Deuschle, et al., 1997, 1998; Holsboer, 2000; Dowlati, et al., 2010; Stetler & Miller, 2011; Iob, Kirschbaum, & Steptoe, 2020) (Proinflammatory cytokines are initially upregulated by stress for their neuroprotective roles, yet in conditions of chronic activation can disrupt neurotransmitter function and lead to dysregulation in neural circuits and behavior, as discussed by Miller, Haroon, Raison, & Felger, 2013).

Additionally, stress-induced hypercortisolemia and inflammation lead to diminished neurotrophic support through downregulation of brain derived neurotrophic factor (BDNF) – a crucial protein for neural growth and integrity (Schaaf, De Kloet, & Vreugdenhil, 2000; Murakami, Imbe, Morikawa, Kubo, & Senba, 2005; Duman & Monteggia, 2006). Altogether, these have been associated with dendrite atrophy and reduced neurogenesis in the HC (Sousa, Madeira, & Paula-Barbosa, 1998).

Importantly, stress triggers the release of glutamate, the primary excitatory neurotransmitter involved in neuroplasticity and adaptation. However, high levels of glutamate activity can have the opposite effect, causing overexcitation and eventual neuronal atrophy (Popoli, Yan, McEwen, & Sanacora, 2011). In people with MDD, glutamate levels are significantly higher than in healthy controls and are positively related to the severity of depression (Mitani, et al., 2006).

The impact of stress on the brain essentially comes down to stimulating the growth and function of neurons through stress-induced biochemical processes (Aberg, et al. 2000), which results in neuronal and behavioral adaptations. However, excessive activation of these processes can lead to abnormal adaptations and subsequent structural and functional alterations. While such alterations can occur anywhere in the brain, they are especially pronounced in the HC (see **Fig 1**). This has been consistently shown in brain scans of people with MDD exhibiting smaller HC volume compared to healthy controls, shifting attention to a role of HC plasticity in the development and treatment of depression (Duman, 2004).

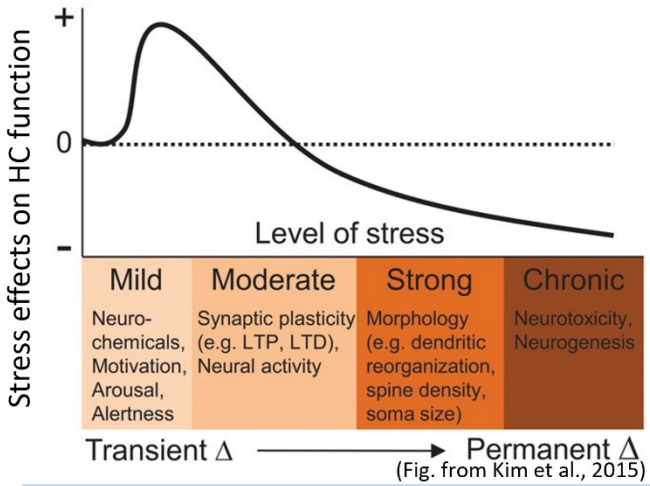

Fig.1 Stress effects in the hippocampus. From mild levels of stress to chronic exposure to stress. As the severity/duration of stress increases, severity and chronicity of neuronal damage increases.

1.1.3 Neurogenic-Neuroplastic hypothesis

The neurogenic and neuroplastic hypotheses, although distinct, share significant similarities in the aspects they address, and will therefore be discussed together. The two theories emerged from the consistently replicated finding that individuals with MDD have smaller hippocampi on brain scans compared to healthy controls (Nolan, Roman, & Roddy, 2020), which has been attributed to reduced generation of new neurons in the HC (Opel, et al., 2014). Supporting evidence comes from studies on animal models of MDD showing that ADs increase neurogenesis in the HC (Malberg, Eisch, Nestler, & Duman, 2000), whereas inhibiting neurogenesis through irradiation prevents the behavioral effects of ADs. These findings gave rise to the neurogenic hypothesis of depression, which proposes that decreased neurogenesis leads to morpho-functional atrophy in the HC, subsequently causing depressive symptoms. Accordingly, AD treatment can reverse such atrophy and facilitate recovery (Czeh, et al., 2001).

The neurogenic hypothesis is mechanistically plausible as the hippocampal dentate gyrus (DG), the site of neurogenesis, plays a vital role in mood and anxiety regulation; and impaired neurogenesis would result in altered structure and function within this region (the involvement of the HC in mood and depression is discussed in Section 2.2).

However, other studies have shown that blocking neurogenesis does not induce depressive symptoms, as assumed by the hypothesis, nor does it hinder the therapeutic effectiveness of ADs in rats with a depressive-like phenotype (Bessa, et al., 2009). Additionally, it is estimated that only around 20-30% of new cells ultimately survive, representing only a fraction (0.03%) of the entire

granule cell population in the dentate gyrus and even less (0.017%) in relation to the overall neuron population in the HC. Considering that neurogenesis exclusively occurs in the DG, which constitutes only 6% of the volume of the human HC, it is unlikely that reductions in neuronal renewal significantly contribute to the observed 10-15% reduction in HC volume among patients with MDD.

These observations suggest that reduced neurogenesis may be one of several contributing factors for MDD rather than a primary cause, and its role in AD efficacy is important but not indispensable – as dendritic remodeling and synaptic connectivity are also observed following AD treatment. Hippocampal atrophy in individuals with MDD may therefore result from neuroplastic alterations other than neurogenesis *per se,* such as dendrite retraction, synaptic loss, inadequate neurotrophic support, and more (McEwen, Nasca, & Gray, 2016). Interestingly, glia cells seem to be involved as well in these dysfunctions and may relate to the HC atrophy, as explained further.

Glia cells slightly outnumber neurons in the human HC, with astroglia (also called *astrocytes*) accounting for approximately one-third of the brain's mass. They play central roles in the structural and functional organization of neurons, as well as in modulating inflammatory processes and stress-induced neurotransmission.

Astroglia provide energy and nutrients to neurons, clear neuronal waste, and regulate synaptic strength, synaptogenesis, and neurogenesis in the adult DG. Moreover, astroglia are responsible for glutamate clearance in the brain, and dysfunction therein can lead to abnormally high levels of glutamate, causing neuronal overexcitation (Pittenger, Sanacora, & Krystal, 2007). Dysfunction in astroglia not only impacts the structure and function of neurons. Because these cells express receptors for neurotransmitters and steroid hormones, they can directly contribute to the pathophysiology of MDD by affecting the monoaminergic system and disrupting the balance between excitation-inhibition, and between neurotrophic-neurotoxic states in brain areas crucial for mood and stress regulation (Martin, Bajo-Graneras, Moratalla, Perea, & Araque, 2015; Ma, Stork, Bergles, & Freeman, 2016; Wang, Jie, Yang, & Gao, 2017). Microglia, on the other hand, are primarily involved in immune responses and neuronal homeostasis, yet in pathological conditions can adopt a neurotoxic phenotype via excessive release of glutamate (Barger & Basile, 2001).

Glial activity and its impact on synaptic dysfunctions and neurotoxicity have gained currency in the study of MDD from several lines of evidence (Yirmiya, Rimmerman, & Reshef, 2015). First, postmortem studies have shown changes in glial cell morphology, density, and astrocyte loss in individuals with MDD (Peng, Verkhratsky, Gu, & Li, 2015). Additionally, glial apoptosis and overactivation of microglia have been observed in conditions of prolonged stress and have been associated with anxiety and depression (Stein, Vasconcelos, Albrechet-Souza, Cereser, & de Almeida, 2017). Conversely, ADs seem to inhibit the neurotoxic activity of glia, potentially through the upregulation of BDNF and its receptor (Björkholm & Monteggia, 2017).

To summarize, these findings highlight a complex interplay between neurotransmitters, neurogenesis, neuroplasticity, and glial dysfunction in conditions of stress and depression, and each

contributes to the structural and functional impairments observed in brain regions responsible for mood regulation.

- How do the theories compare?

The theories of depression have evolved over time without being mutually exclusive. Instead, each theory represents one step closer in our understanding of MDD. The early hypotheses centered on monoamine deficiency were criticized for their simplicity yet laid the foundation for further exploration of the roles of monoamines beyond neurotransmission. Likewise, the stress hypothesis fails to account for all cases of MDD yet provided unprecedented insight into the neuroendocrine aspects of mood disorders and the significance of stress. Finally, the neurogenic hypothesis may overstate the role of neurogenesis in causing atrophy yet sparked interest in the role of neuroplasticity – especially hippocampal plasticity – in the pathogenesis of MDD.

Although still a subject of debate, it appears that at the fundamental level MDD is associated with impairments in structural plasticity and cellular resilience to stress (Fuchs, Czeh, Kole, Michaelis, & Lucassen, 2004), maintained by interactions between different factors of vulnerability (Tafet & Nemeroff, 2015), such as: genetic and epigenetic mechanisms (Alshaya, 2022), stress-induced neurotoxicity, inadequate neurotrophic support, altered monoamine neurotransmission, heightened glutamate activity, and inflammation, to name a few. Interestingly, ADs seem to restore normal functioning in these areas through various mechanisms that converge into promoting neuroplasticity and providing neuroprotection against stressors (Czeh, et al., 2001).

1.2 Antidepressants: clinical, biochemical, neuroplastic effects

Typical antidepressant medications work by increasing the levels of monoamine neurotransmitters like serotonin, dopamine, and/or norepinephrine, through mechanisms that involve either inhibiting their breakdown, or blocking their reuptake into the presynaptic neuron. Commonly prescribed ADs for mood disorders are the selective serotonin reuptake inhibitors (SSRIs) and the serotonin norepinephrine (NE) reuptake inhibitors (SNRIs). Despite facing criticism for their inconsistent efficacy and delayed therapeutic effect, they remain the primary treatment option for MDD and generally produce successful outcomes.

The therapeutic effects of ADs are diverse and include improving mood, reducing anxiety and obsessive thoughts (e.g., rumination), increasing motivation, enhancing cognitive function, and regulating sleep and appetite. While some individuals may experience improvements in all aspects, others may only experience mild or no therapeutic effect with AD treatment. However, the improvement in mood is central to AD efficacy, and the use of SSRIs/SNRIs as first-line treatment suggests a role for modulating serotonergic neurotransmission for achieving clinical effectiveness.

The precise mechanisms by which enhancing serotonergic transmission leads to improved mood are not fully understood, apart from increasing the availability of monoamines and promoting neurotransmission. Accumulating evidence shows that upon stimulating monoamine neurotransmission, ADs promote neuroplasticity in brain regions crucial for mood regulation (prefrontal cortex and the hippocampus; (Castren & Hen, 2013), as follows.

Upon ligand binding, ADs trigger a series of biochemical reactions involved in signal transduction and ending in gene expression. One of the pathways involved in this regulation starts with the activation of adenyl cyclase (AC) and further production of the second messenger cyclic AMP (cAMP); which in turn activates protein kinase A (PKA). Downstream of PKA, activation of transcription factor CREB enables gene expression of many proteins involved in neuroplasticity, such as BDNF.

Brain-derived neurotrophic factor promotes neuroplasticity in cortical and limbic structures and stimulates adult neurogenesis in the HC (Numakawa, Odaka, & Adachi, 2018). Moreover, it regulates serotonin transmission by supporting the growth, maturation, and differentiation of serotonergic neurons (Rumajogee, et al., 2004) and dysfunction of BDNF is strongly associated with psychiatric disorders (Numakawa, Odaka, & Adachi, 2018). Upregulation of BDNF by AD treatment not only promotes neuroplasticity and serotonergic transmission but also protects against incoming stress, eventually restoring normal functionality in local circuits (Duman & Monteggia, 2006).

Besides increasing neurotrophic support, ADs promote plasticity via pro-neuroplastic functions of serotonin receptors as well. For example, SSRI stimulation of 5-HT2B receptor results in increased cell proliferation and AD-like effects, whereas ablation of 5-HT2B blocks the neurogenic and therapeutic effects of SSRIs. Notably, not all 5-HT receptors are involved in neurogenesis, showing that 5-HT mediated neurogenesis is receptor subtype-specific (Banasr, Hery, Printemps, & Daszuta, 2004). Nevertheless, plenty of evidence coming from rodent, human, and non-human primate studies shows that chronic AD treatment promotes cell proliferation in the HC (Malberg, Eisch, Nestler, & Duman, 2000; Duman R. S., 2006; Anacker, et al., 2011; Perera, et al., 2011; de Oliveira, Bolzan, Surget, & Belzung, 2020; Leschik, et al., 2022).

Another point of evidence for a neuroplastic mechanism underlying AD efficacy relates to their delayed clinical onset. While these drugs increase serotonin or norepinephrine levels within hours (Hervas & Artigas, 1998), behavioral changes occur weeks later. Initially, this delay has been attributed to properties of 5-HT receptors (Frey, Rosa-Neto, Lubarsky, & Diksic, 2008): Initial stimulation of serotonin by ADs would increase feedback inhibition from the 5-HT1A receptor, and chronic administration may be necessary for the desensitization of 5-HT1A and overall increased serotonergic transmission (Hensler, 2002).

However, explanations with more scientific support suggest that adaptations in post-receptor signaling and gene expression induced by repeated stimulation of serotonergic transmission may be in fact necessary to initiate the desired changes in mood and behavior (Duman, Aghajanian, Sanacora,

& Krystal, 2016). These adaptations involve neurogenesis and remodeling of neuronal connectivity in cortico-limbic structures, especially in the hippocampus.

2. Why the hippocampus and depression?

The HC communicates with various brain regions involved in depression, such as the prefrontal and cingulated cortices, as well as the amygdala, playing central roles in mood regulation and stress-mediated adaptive behaviors, both affected in depression. Additionally, the HC is directly influenced by stress hormones, making it susceptible to stress-induced atrophy. On the other hand, ADs have pro-neurogenic and neuroprotective roles in the HC by increasing neurotrophic support, decreasing glutamate toxicity, and overall normalizing the balance between inhibitory-excitatory states in HC regions.

2.1Anatomical and functional organization in the hippocampus

The HC is segregated along the longitudinal axis into posterior and anterior regions in primates and humans, and analogous dorsal and ventral regions in rodents, each with distinct functional connectivity patterns. The dorsal HC (dHC) is primarily involved in cognitive and spatial processing and connects with the retrosplenial and posterior parietal cortices. In contrast the ventral HC (vHC) connects with the amygdala and orbitofrontal cortex, and is primarily associated with stress and mood regulation, particularly anxiety-related behaviors (Canteras & Swanson, 1992). Further subdivision within the HC includes the dentate gyrus (DG), the cornu Ammonis subfields (CA1, CA2, CA3) and the subiculum regions.

Although the functional division of the HC has been debated (Risold & Swanson, 1996; Strange, Witter, Lein, & Moser, 2014), there is increasing evidence for the involvement of the vHC in processing affective information. In anxiety paradigms for rodents, this distinction is observed by the recruitment of the vHC in modulating anxiety-related behaviors, but not (by the recruitment) of the dHC. Interestingly, gene expression profiles also seem to differ between dorsal and ventral HC: while dHC gene expression is associated with information processing in cortical areas, vHC gene expression correlates with emotion processing in the amygdala and hypothalamus (Bertagna, et al., 2021).

Furthermore, the ventral HC is densely innervated by serotonergic receptors. At least 14 5-HT subtype receptors have been identified in the HC, exhibiting region-dependent activity profiles, and having complementary or opposing functions within circuits and even on the same neuron (Hoyer, et al., 1994; Dale, et al., 2016). While 5-HT is known to regulate stress and mood (Törk , 1990), it also plays important roles in HC function. In particular, the 5-HT1A and 5-HT4 receptors regulate serotonin signaling in the HC in opposite ways, and coordinated activity between the two is necessary for mood and stress regulation, as well as for neurogenesis.

The 5-HT1A receptor subtype has the highest affinity for 5-HT and modulates the entire 5-HT system through feedback inhibition (Valdizan, Castro, & Pazos, 2010). Knock-out of 5-HT1A

receptors in the mouse HC significantly reduces the AD-like effects of cytisine (Mineur, et al., 2015), a substance used for smoking cessation that exhibits AD-like properties (Gotti & Clementi, 2021). Besides modulating AD effects, 5-HT1A is also involved in neurogenesis, as seen in increased cell proliferation and birth of new neurons after administration of 5-HT1A agonists (Huang & Herbert, 2005). Additionally, 5-HT1A receptors also regulate corticosterone activity and implicitly HPA axis activity (Fuller, 1990).

On the other hand, 5-HT4 receptors increase neuronal excitability and facilitate neurotransmission, and stress-induced overexpression may have opposing effects. In animals with a depressive-like phenotype, ablation of 5-HT4R in the HC or chronic AD treatment show similar AD effects as seen in better stress resilience, perhaps by normalizing excitatory signaling (Karayol, et al., 2021).

To conclude, the HC displays dense serotonergic (but also norepinephrinergic and mesolimbic dopaminergic) innervation, as well as abundant expression of glucocorticoid receptors, especially in the vHC. Moreover, the placement of the vHC in the temporal lobe makes this brain region an important player in motivational and emotional behavior (Fanselow & Dong, 2010).

2.2 Hippocampus in stress and mood: implications for depression

Traditionally known as the center of learning and memory, the HC is a key modulator of stress and emotions due to its placement in the central nervous system. It is involved in the formation of emotional and autobiographical memory (Audrain, Gilmore, Wilson, Schacter, & Martin , 2022), in the contextual allocation of emotional memories, as well as in the processing of social emotions and facial expressions (Immordino-Yang & Singh, 2011). The importance of the HC in emotional processing and stress regulation is exerted via several, interconnected ways.

First, via its connections with cortico-limbic structures. As mentioned earlier, the HC connects with the amygdala and the prefrontal cortex. Contrary to previous knowledge that emotional memories rely solely on the amygdala, turns out that reciprocal interactions between the HC and amygdala are necessary (Richardson, Strange, & Dolan, 2004). Modulation of HC activity by the amygdala facilitates the encoding of aversive memories (Costa, et al., 2022), which are a crucial component of MDD associated with psychosocial stress. Similarly, modulation of amygdala activity by HC is necessary for coping. Lesions in the vHC alter stress responses and emotional behavior in rats, whereas strengthening of synaptic connectivity in the HC-amygdala pathway promotes stress coping (Henke, 1990). Additionally, the HC is bidirectionally connected with the prefrontal cortex to receive top-down regulation on emotions (e.g., through cognitive reappraisal), but also to send bottom-up information about emotional memories and cues that inform the PFC about the relevance and context of these emotions for further regulation.

Another way in which the HC is involved in mood is through the neurotransmitter systems. As discussed earlier, the HC is densely innervated by serotonergic, noradrenergic, and dopaminergic neurons. The three monoamines are linked to the two core symptoms of depression, namely depressed

mood (associated with dysruptions in serotonin/norepinephrine neurotransmission) and anhedonia/loss of pleasure (related to dysfunctions in the dopamine system).

Third, the HC is directly involved in stress regulation by receiving input from the HPA axis. In response to stress, the HPA axis stimulates glucocorticoid production, which in normal conditions peaks within 30 minutes of stress onset and returns to baseline within 120 min (Spencer & Deak, 2016); the HC is responsible for sending inhibitory feedback on the production of glucocorticoids and help the system return to homeostasis. Hyperactivation of the HPA axis, and/or hypoactivity of the HC, can dysregulate this process and maintain heightened stress neurochemicals and psychological stress. Moreover, the HC responds to gonadal, thyroid, and adrenal hormones, which control mood but also DG volume during development and in adult life.

Lastly, all the above are maintained with a plastic, structurally functional HC. The roles of hippocampal plasticity in stress adaptation and stress vulnerability are discussed further in relation to MDD.

2.3Hippocampal plasticity: implications for depression

Information processing in the brain is not merely the exchange of chemicals between neurons. Instead, it is the result of repeated stimulation of neurons, resulting in neuroplastic adaptations. The process of neuroplasticity begins with the release of the excitatory neurotransmitter glutamate, ultimately leading to long-term remodeling of brain circuits (long-term potentiation; LTP). Glutamate binds to the postsynaptic NMDA receptor, which gates the calcium ion channel. The entry of calcium ions into the cell initiates a cascade of changes that impinge on the transcription factor CREB, and further expression of proteins involved in plasticity, such as BDNF. In short, glutamate receptors together with neurotrophic factor BDNF and transcription factor CREB are important players in neuroplasticity, and upon repeated stimulation promote neurogenesis, increase in glial cells, increase in spine density and complexity, and increase in synapse formation (Blendy, 2006; Yang, et al., 2020).

While the entire nervous system participates in these neuroplastic changes, the hippocampus is particularly specialized in neuroplasticity, since it is the main site of neurogenesis, and is directly targeted by stress hormones. This malleability of the HC makes it both resilient, and highly susceptible to the effects of stress. During acute stress, glucocorticoids along with excitatory amino acids increase neuronal excitability and facilitate neuroplastic adaptations. However, in conditions of chronic, or inescapable stress, glutamate activity levels become excessively high and cause opposite effects. In animal models, chronic stress or administration of glucocorticoids can cause histological alterations in the HC, including retraction or loss of dendritic spines in neurons of the CA1, CA3, and DG regions, synaptic loss, reduction in glial cells, suppression of neurogenesis, and in extreme cases, apoptosis (McEwen B. S., 1999; Czeh, et al., 2001; McEwen, Nasca, & Gray, 2016).

In addition, repetitive stress-induced reduction of BDNF levels and resulting poor neurotrophic support contributes to neuronal atrophy/death, and to the HC reductions observed in both human and

animals experiencing chronic stress and/or depression. Conversely, overexpression of BDNF in adult 5-HT neurons provides protection and mitigates the behavioral responses induced by the chronic social defeat stress in animal models. This protective effect is accompanied by increased sprouting of serotonergic axons and enhanced adult neurogenesis in the DG (Leschik, et al., 2022).

Interestingly, some human studies revealed a decrease in the number of granule cells and volume in the anterior and mid-dentate gyrus (Boldrini, et al., 2009, 2013), but not in the posterior DG, among unmedicated MDDs compared to healthy controls. Moreover, SSRI treatment showed an increase in neural progenitor cells in the anterior DG of medicated versus unmedicated subjects with MDD. This relates to the functional division within the HC discussed in Section 2.1. These findings are also supported by animal studies, which show that chronic or inescapable stress selectively reduces neurogenesis in the vDG, while ADs increase neurogenesis in this area (Elizalde, et al., 2010; Tanti, et al., 2013). Additionally, there are studies showing that enhancing neurogenesis specifically in the vHC produces antidepressant-like effects (Mahar, et al., 2011). These findings may be related to the fact that the vHC receives more serotonergic, norepinephrinergic, and mesolimbic dopaminergic input compared to the dHC (Bannerman, et al., 2003, 2004), which would make this area of the HC more responsive to AD medications that target the monoamines, such as SSRIs and SNRIs.

DISCUSSION & CONCLUDING REMARKS

What is the neurobiology of depression? No reliable neural biomarker has been found to date. However, some findings are more consistent than others. Among the most replicated are changes in *hippocampal plasticity*. Such changes are seen in brain scans revealing reduced HC volume, reduction that correlates with the progression of the illness (Cao, et al., 2017). Other studies also reveal changes in synaptic plasticity, number of synapses, glial dysfunction, reduced neurogenesis, and changes in glutamate receptors (Sheline, Liston, & McEwen, 2019). Notably, among the most consistently found markers of impaired plasticity is reduced expression of BDNF – the main neurotrophic factor involved in neuronal growth and survival. Conversely, chronic AD use has shown increases in HC volume in proportion to symptom relief (Maller, et al., 2017). Another well-replicated finding is *dysregulation of HPA axis* (Pariante & Lightman, 2008; Pariante, 2017). The main biological markers found are hypercortisolemia, increased secretion of proinflammatory cytokines, reduced neurotrophic support by downregulation of BDNF, and overall dysregulation of stress systems, all correlating with chronic and/or early life stress in MDD (Buckman, et al., 2022). Moreover, *disrupted serotonin signaling* seems to be at play, though in more intricate ways than initially thought (Banasr, Hery, Printemps, & Daszuta, 2004; Dale, et al., 2016). It appears that merely increasing 5-HT with SSRIs/SNRIs is not sufficient to achieve clinical efficacy. Instead, repeated stimulation of 5-HT receptors (with chronic AD treatment) and activation of downstream transcriptional events may be required to induce neuroplastic adaptations and ‘rewiring’ of circuits that support mood regulation, in order to finally induce behavioral changes (Blendy, 2006; Vahid-Ansari & Albert, 2021).

It seems that, at least in *this* type of depression, excessive stress, disrupted 5-HT signaling (by heightened glutamate activity, degeneration of 5-HT neurons, and dysfunctions in 5-HT receptors), inadequate neurotrophic support (downregulated by stress) and HC atrophy (induced or sustained by stress toxicity) maintain a depressive-like phenotype, which can be reversed with chronic AD treatment (Malberg, Eisch, Nestler, & Duman, 2000; Maller, et al., 2017).

How is the hippocampus affected in stress and depression? The HC of individuals with MDD and/or with a history of life stress is often smaller than in healthy controls. Whether this reduction is the result of decreased neurogenesis or of other neuroplastic alterations, is still unclear. On one hand, the production rates of new neurons in the DG seems to be too small in relation to the total HC volume to account for the 15-20% hippocampal volume loss. At the same time, these estimations come mainly from rodents or non-human primates, whereas in humans it is believed that neuron turnover rates are higher (Ernst & Frisen, 2015). Moreover, heightened levels of stress hormones and glutamate activity can lead to hippocampal atrophy through inflammatory processes, downregulation of BDNF and inadequate neurotrophic support, consequent neuron endangerment or neuron degradation, reduced neurogenesis, and overall atrophy. In animal models of stress and depression, exposure to severe stress results in decreased BDNF expression in the HC and prefrontal cortex. In humans with MDD, postmortem studies show reduced levels of BDNF in these regions. Loss of structure/function in the HC would not only disrupt functioning in local circuits, but also impair functionality in downstream areas (HC projects to the dorsolateral prefrontal cortex, ventral tegmental area, hypothalamus, all central in the regulation of stress, emotions, and motivational behavior).

What are the effects of AD drugs on the hippocampus? Most antidepressants have neuroplastic and neuroprotective effects in the HC, and chronic treatment with ADs has been shown to promote neurogenesis and restore HC atrophy (Malberg, Eisch, Nestler, & Duman, 2000). While the mechanisms at play are not fully elucidated, one explanation relates to normalizing 5-HT signaling. While early research on monoaminergic activity was focused on neurotransmission, nowadays it is clear that 5-HT signaling and especially 5-HT receptors are involved in the regulation of neurotrophic factors and neurogenesis, which are crucial components of neuroplasticity. Chronic treatment with SSRIs results in increased BDNF levels (Duman & Monteggia, 2006), which is required for neurogenesis, synaptic plasticity, and neuronal remodeling. Although not discussed here, novel AD agents developed for treatment-resistant depression seem to also exert their AD effects through increasing BDNF, and knockout of BDNF and its receptors blocks the AD-like effects of these drugs (Björkholm & Monteggia, 2017). Furthermore, chronic AD treatment increases cell proliferation and differentiation in the DG and supports the maturation and functional integration of new cells into the DG circuitry (Wang, David, Monckton, Battaglia, & Hen, 2008). Nevertheless, although a causal link between neurogenesis and remission from depression has not been established, a recent meta-analysis finds that independent of the compound, ADs significantly increase HC neurogenesis in rodents, and these effects may be described as “more-dependent” or “less-dependent” on neurogenesis (de Oliveira, Bolzan, Surget, & Belzung, 2020).

Is hippocampal plasticity the road to "feeling better"? The short answer is *yes.* The longer answer is *it depends.* The HC is the most plastic brain area, and it is particularly susceptible to stress and depression. Whether one causes the other is unknown, yet consistent evidence shows that ADs have pro-neurogenic, neuroplastic, and neuroprotective effects, and that these effects mirror the time necessary for improvements in mood. Crucially, the vHC seems to be especially affected by stress, whereas AD-induced neuroplastic adaptations occur particularly (but not only) in this area. This indicates that, at least in areas involved in circuits for emotion regulation, reduced neuroplasticity and alterations may significantly contribute to the depressed mood; and that promoting plasticity with ADs may be necessary to rescue normal functioning.

Other types of therapies, such as physical exercise have also been shown to promote plasticity by increasing neurogenesis and neurotrophic factors, and reduce depressive and anxiety behaviors (Olson, Eadie, Ernst, & Christie, 2006; Nokia, et al., 2016; Singh, et al., 2023). Moreover, cognitive behavioral therapy (CBT) is one of the most effective psychotherapies for mood disorders, and the combination of AD treatment and CBT seems to be more effective than drug treatment alone (Cuijpers, et al., 2014; Li, Wang, Wang, & Yang, 2021). This suggests that CBT may help learn and imprint new and more beneficial behaviors on the neuroplastic changes initiated by ADs, boosting effectiveness in a bottom-up manner – from neuronal remodeling to changes in behavior.

Fig. 2

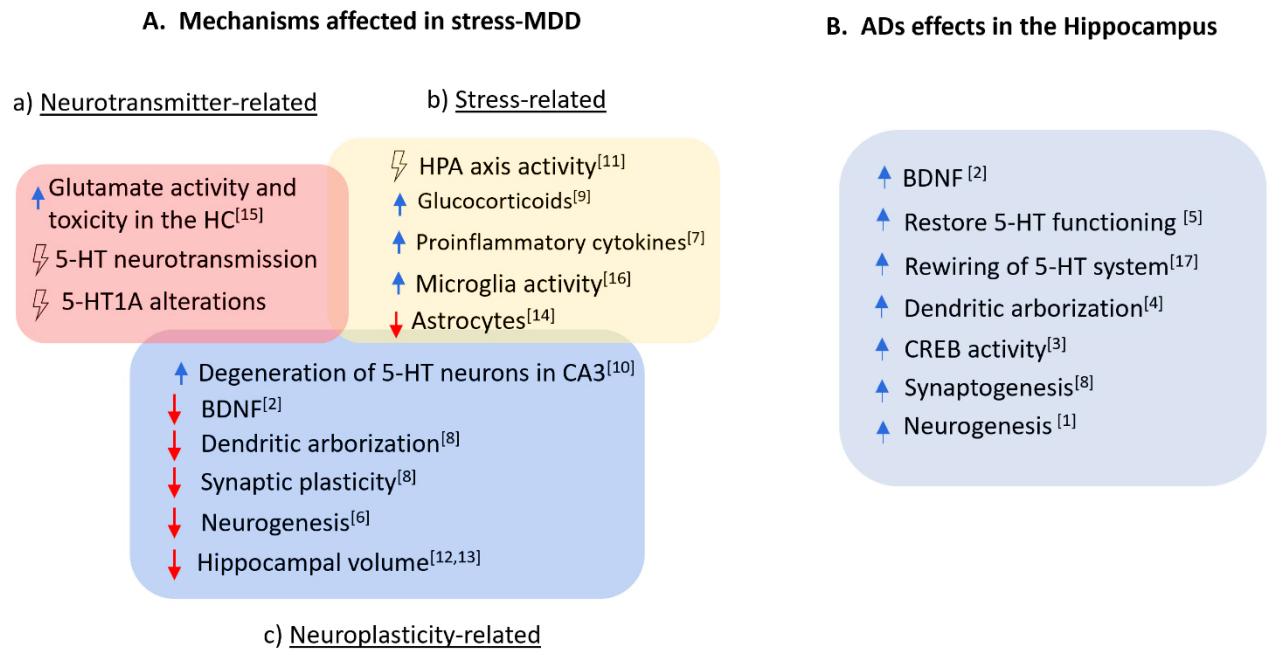

Fig.2A Main biological markers affected in MDD and/or following exposure to severe/chronic stress.
Fig.2B Main findings on the effects of ADs at cellular, molecular, and morphological level in the HC.
↯ = dysregulated. Findings show either hypo- or hyperactivity.

Limits and considerations

- *genetic and epigenetic factors.* Although not addressed in the present essay, genetic and epigenetic mechanisms ultimately predispose one to depression. While stress plays a role as a precipitating factor, its impact on the development of MDD ultimately depends on genetic factors. As such, the "stress-induced" alterations in the HC, disrupted serotonin signaling, and inadequate neurotrophic support, are likely a result of stress-induced modifications in risk genes like: polymorphisms of SERT (the serotonin transporter), GR (glucocorticoid receptor) and BDNF (neurotrophic factor) (Ding & Dai, 2019), to name a few candidates discussed throughout. Epigenetic modifications can lead to structural and functional alterations in the brain and to reduced (cellular and psychological) stress resilience, thus increasing vulnerability to MDD.

- *inconsistent AD efficacy.* Regarding the *nature vs. nurture* discussion above, "nature" may also explain why (1) ADs are not effective in everyone, (2) even in successfully medicated individuals, MDD relapse rates are high (Kishi, et al., 2023), and (3) HC volume loss is not seen in all individuals with MDD (which has been attributed to differential effects of monoamine-related gene polymorphisms in Phillips, et al., 2015).

- *hyperactive amygdala.* While ADs have been demonstrated to reverse the HC atrophy and restore neurotrophic support in some cases, they do not reverse the volume increase and overactivation of the amygdala (Saleh, et al., 2012). Consequently, an overly active amygdala could further enhance susceptibility to stress, anxiety, and overall emotion dysregulation, ultimately lowering the threshold for the onset of subsequent depressive episodes (Kim, Kim, Park, Cho, & Kim, 2012).

- *stress-related effects.* ADs appear to be particularly effective in patients with MDD and stress factors (Hrtanek, et al., 2021). Hence, their effect may lie in reversing a neuroplasticity deficit often accompanied by, or following stress. It may also be why ADs (at least SSRIs) are particularly effective in MDDs with a history of life stress, and why HC atrophy could be in fact a marker of childhood maltreatment (Opel, et al., 2014).

- *opposing effects.* The present essay is (mainly) focused on MDD associated with stress and AD effects by SSRIs and SNRIs. It is important to note that other types of depression (e.g., with somatic causes or stress-unrelated neurobiology) may not exhibit any connection to hippocampal atrophy. Similarly, ADs that have been shown to promote plasticity in the HC may have no impact on these types of depression. Furthermore, ADs other than SSRIs and SNRIs, which act through different pathways, may have different or opposite effects. A relevant consideration is for instance the differential effects of CREB activation in the brain (Carlezon, Duman, & Nestler, 2005). Many ADs act on the cAMP-PKA pathway, inducing CREB-mediated gene expression. While AD-induced CREB transactivation promotes plasticity in the HC and is associated with symptom alleviation in MDD, in other brain areas can have opposite effects. In reward circuits, e.g., in the ventral tegmental

area, drug-induced activation of CREB is associated with addiction and drug-seeking behaviors (McPherson & Lawrence, 2007). Similarly, the multitude of 5-HT receptors with diverse and even opposing activity profiles, and the limited specificity of ADs for the various 5-HT receptors pose challenges in fully understanding the precise mechanisms by which ADs work in some, but not all cases. Interestingly, although uncommon, side effects of SSRI antidepressants even include worsening depressive symptoms or inducing suicidal thoughts (Edinoff, et al., 2021). While the reason for this paradoxical effect is unknown, it is not excluded that mechanisms like the ones described above and more (e.g., opposing roles of 5-HT receptors, opposing effects of CREB activation in the brain, etc) may be at play for such side effects.

Conclusion

The neurobiology of depression is complex and so are the mechanisms of action of ADs. However, there is consistent evidence towards a combination of stress, disrupted monoamine signaling, and reduced plasticity in the HC for a neurobiological basis of MDD. Likewise, there is consistent evidence for the neuroplastic and neurogenic effects of ADs in reversing HC atrophy and restoring connectivity in the HC and facilitating communication with the amygdala and prefrontal cortex. These changes align with the timeframe required for ADs to initiate clinical improvements in mood. Given the high heterogeneity of MDD, it is truly challenging, if realistic, to pinpoint a single unified mechanism underlying the development and recovery from depression.

Nonetheless, in cases of depression associated with stress and inflammatory markers (such as glia overactivation, reduced BDNF levels, hypercortisolemia), it seems like ADs effectively support remission through opposing effects on stress. Through mechanisms like increasing neurotrophic support, restoring the structure and function of 5-HT receptors, stimulating 5-HT signaling, normalizing the secretion of stress hormones by modulation of glucocorticoid receptors and glutamate activity, and overall promoting neurogenesis and neuroplasticity in the HC, ADs seem to reverse the effects of stress and provide protection. Ultimately, this enables morphological and functional restoration of the HC, and re-establishment of its connectivity.

In conclusion, in cases of MDD characterized by stress-related “faulty wiring” and neurobiology, the mood-enhancing effects of ADs likely arise from “rewiring” within the HC. By reclaiming its structural integrity and thus reinstating its roles in stress and mood regulation, the hippocampus plays a central role in the efficacy of ADs towards *feeling better.*

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