Molecular Mechanisms of JNKs in anxiety and depression

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ABSTRACT

Depression and anxiety disorders are among the most common causes of disability and suicide. The first hypothesis for depression was created approximately 70 years ago [1], indicating that the research behind the mechanism of mood disorders is relatively new.

Depression and anxiety disorders are thought to be caused by the dysregulation of monoamines and significantly decreased levels of serotonin and norepinephrine in the brain. These monoamines have an essential role in regulating emotional and cognitive behaviour [2]. Current antidepressants have been developed based on the monoamine hypothesis and have been shown to alleviate mood and increase adult neurogenesis, i.e., the formation of new neurons in the hippocampus [3]. Neural cells formed in neurogenesis specialise, for example, to granule cells linked to memory formation and stress reactions [4]. Impaired neurogenesis is thought to be connected to depression and anxiety [5], [6].

Other mechanisms behind mood disorders include dysregulation of the brain's inhibitory and exhibitory neurotransmitters, brain plasticity, and chronic stress [7], [8], [9] [10]. Recent studies have shown that the JNK (c-Jun N-terminal kinase) pathway is associated with controlling mood disorders. JNKs are intracellular kinases that control functions such as the brain's development, the death of nerve cells, and the state of inflammation in the brain [10].

Research shows that the brain's JNK is linked to its plasticity and the emergence of new nerve cells in the hippocampus [11], [12]. Studies have investigated the effect of JNK on the emergence of depressive states and anxiety disorders. For instance, one study demonstrated that blocking JNK in the hippocampal granule cells during adulthood reduced anxiety—and depression-like symptoms in animal models [11], [12]. Furthermore, genetic irregularities within the JNK pathway have been linked to both schizophrenia and autism spectrum disorders [13], [14].

Addressing treatment-resistant depression poses a significant challenge, as one-third of current antidepressant users do not get a proper response to treatment [15]. Consequently, new therapeutic approaches are essential to tackle this issue [16]. Recent clinical trials have emerged with gamma-aminobutyric acid (GABA)- and glutaminergic neurotransmissions and psychedelic approaches [17], [18]. Furthermore, the current antidepressants do not target the activity of JNK [11]. Thus, JNK or its downstream targets are valuable in drug development, as they may enable novel responses, especially in patients who do not benefit from existing drugs. However, further research is needed to confirm this hypothesis.

Keywords: Major Depressive Disorder, Anxiety disorder, Treatment-resistance, Neurogenesis, c-Jun N-terminal kinases, Granule cells

TIIVISTELMÄ

Masennus- ja ahdistuneisuushäiriöt ovat pitkään tunnistettuja ilmiöitä sekä yleisiä syitä työkyvyttömyydelle ja itsemurhille. Tutkimus mielenterveyshäiriöiden mekanismeista on kuitenkin verrattain uusi ilmiö, sillä ensimmäinen hypoteesi masennuksen mekanismista syntyi vasta noin 70 vuotta sitten [1].

Masennus- ja ahdistuneisuushäiriöiden arvellaan johtuvan monoamiinien säätelyhäiriöstä ja merkittävästi alentuneesta serotoniinin ja noradrenaliinin pitoisuudesta aivoissa. Monoamiineilla on olennainen rooli emotionaalisen ja kognitiivisen käyttäytymisen säätelyssä [2]. Nykyiset masennuslääkkeet on kehitetty monoamiinihypoteesin pohjalta ja niiden on osoitettu lievittävän mielialaa ja lisäävän aikuisiän neurogeneesiä eli uusien hermosolujen muodostumista hippokampuksessa [3]. Neurogeneesissä syntyneet uudet hermosolut erikoistuvat esimerkiksi jyväissoluiksi, jotka toimivat muistinmuodostuksessa ja stressireaktioissa [4]. Neurogeneesin heikentymisen ajatellaan olevan yksi mekanismeista masennuksen ja ahdistuksen taustalla [5], [6].

Muita tunnettuja taustamekanismeja ovat aivojen estävien ja kiihottavien välittäjäaineiden säätelyhäiriöt, aivojen plastisuus ja krooninen stressi [7], [8], [9] [10]. Eräs mielenterveyshäiriöihin liittyvä molekyyli, jota on hiljattain tutkittu, on JNK (c-Jun N-terminaalinen kinaasi). JNK:t ovat solunsisäisiä kinaaseja, jotka muun muassa säätelevät aivojen kehitystä, hermosolujen kuolemaa ja aivojen tulehdustilaa [10].

Tutkimukset ovat osoittaneet, että aivojen JNK:t vaikuttavat aivojen plastisuuteen ja uusien hermosolujen syntymiseen hippokampuksessa, ja näissä tutkimuksissa on pääasiassa keskitytty JNK:n vaikutukseen masennustilojen ja ahdistuneisuushäiriöiden synnyssä. Esimerkiksi on osoitettu, että JNK:n estäminen aikuisiällä erikoistuneissa jyväissoluissa vähensi ahdistuksen ja masennuksen kaltaisia käyttäytymisiä eläinmalleissa. [11], [12] Lisäksi geneettiset poikkeavuudet JNK-reitillä on liitetty skitsofreniaan ja autismispektrin häiriöihin [13], [14].

Hoitoresistenttiin masennukseen puuttuminen on merkittävä lääketieteellinen haaste, sillä kolmasosa nykyisistä masennuslääkkeiden käyttäjistä ei saa asianmukaista vastetta hoitoon [15]. Siksi onkin välttämätöntä kehittää uusia terapeuttisia lähestymistapoja. Viimeisimmissä kliinisissä tutkimuksissa on tarkasteltu gamma-aminovoihapon (GABA) ja glutamiinin neurotransmissiota ja psykedeelisten yhdisteiden käyttöä [16], [17], [18]. Nykyiset masennuslääkkeet eivät myöskään suoraan kohdistu JNK:n toimintaan [11]. Näin ollen JNK:t tai niiden reitin alavirran komponentit ovat potentiaalisesti arvokkaita kohteita lääkekehityksessä, sillä ne saattavat mahdollistaa uudenlaisia vasteita etenkin niillä potilailla, jotka eivät hyödy nykyisistä lääkityksistä. Tämän hypoteesin vahvistamiseksi tarvitaan kuitenkin lisätutkimuksia.

Avainsanat: Masennus, Ahdistuneisuushäiriö, Hoitoresistenssi, Neurogeneesi, c-Jun N-terminaalikinaasi, Jyväissolut

ABBREVIATIONS

ACTH	Adrenocorticotropic Hormone
ATP	Adenosine Triphosphate
CNS	Central Nervous System
CRH	Corticotrophin-releasing Hormone
D-JNK	JNK inhibitor
GABA	Gamma-aminobutyric Acid
GAD	Generalised Anxiety Disorder
HPA	Hypothalamus-pituitary-adrenal
JNK	c-Jun N-terminal Kinases
MAPK	Mitogen-activated Protein Kinase
MAPKK	Mitogen-activated Protein Kinase Kinase
MAPKKK	Mitogen-activated Protein Kinase Kinase Kinase
MAO	Monoamine Oxidase
MDD	Major Depressive Disorder
MRI	Magnetic Resonance Imaging
NMDA	N-methyl-D -aspartate
NRI	Noradrenaline Reuptake Inhibitor
PD	Panic Disorder
PFC	Prefrontal Cortex
SAD	Social Anxiety Disorder
SNRI	Serotonin-noradrenaline Reuptake Inhibitor
SSRI	Selective Serotonin Reuptake Inhibitor
TCAs	Tricyclic Antidepressants
TRD	Treatment-resistant Depression
VTA	Ventral Tegmental Area
5-HT	5-Hydroxytryptophan; Serotonin
LC	Locus Coeruleus

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1. INTRODUCTION

Major depressive disorder (MDD) and anxiety disorders are mood disorders that affect an individual's ability to perform daily activities. In 2019, 3.76 % of the world's population and 5 % of Finland's population suffered from MDD in all ages. In the same year, 4.05 % of all ages suffered from anxiety disorders globally; in Finland, the amount was 4.38%. [19] The significant problems that MDD and anxiety are causing are incapacity for work and suicide [20]. MDD is clinically diagnosed when a patient suffers at least two weeks of depressed mood, loss of interest or pleasure, reduced self-esteem, and changes in physical characteristics such as sleep and appetite [21]. Anxiety disorders are characterised by excessive fear and anxiety, which can lead to avoidance behaviour and somatic symptoms such as increased heart rate and shortness of breath [22].

The pathogenesis of MDD and anxiety involves biological, psychological, and social factors. The neurobiological mechanisms are not fully understood, but several hypotheses exist for the pathophysiology of MDD and anxiety disorders [23]. The first and central hypothesis is the dysregulation of the monoamine system, and most antidepressants increase the amount of monoaminergic neurotransmitters in the synaptic cleft [24]. Other hypotheses include the dysregulation of gamma-aminobutyric acid (GABA) and glutamate and changes in the brain's neuroplasticity [6], [7], [25], [26] [8], [9], [11], [27], [28]. Furthermore, the research aims to identify new pathways and molecules associated with the disorders, namely the c-Jun N-terminal Kinases (JNKs) [11], [12].

The monoamine neurotransmitters have an essential role in mood and cognition. Furthermore, as part of the limbic system, the hippocampus regulates autonomic functions, motivation, and emotions. Along with monoamine neurotransmitters, GABAergic and glutamatergic neurons form pathways in the limbic system, and maintaining a balance between the neurotransmitters, GABA and glutamate, is an integral part of the state of alertness.[29]

Additionally, neurogenesis, the process of forming new granule cells, is fundamental in the brain. Studies indicate that decreased neurogenesis can lead to anxiety- and depressive-like behaviour. These studies suggest inhibiting JNK in adult-born granule cells can potentially increase mood and cognition. [11], [12] This highlights the interplay between neurotransmitters, neurogenesis, and pathways liable for mood regulation.

Mood disorders reviewed in this thesis are major depressive disorder and anxiety disorders. MDD is a heterogeneous disease that affects the difficulty of treatments; therefore, treatment should be tailored for each individual [21]. Studies show that about 50 % of patients treated with antidepressants do not get complete remission [30], [31]. Hence, it is crucial to study the pathophysiology of MDD so that new

treatments can be provided. This thesis aims to review the possibility of JNKs as drug targets for mood disorders.

2. MAJOR DEPRESSIVE DISORDER AND ANXIETY

2.1. SYMPTOMS

MDD and anxiety disorders are often comorbid and can have overlapping symptoms. Although anxiety and MDD share symptoms, MDD is distinguished by constant feelings of sadness, hopelessness, and loss of interest in once enjoyable activities. It can influence a person's thoughts, feelings, and behaviour and lead to various emotional and physical problems. MDD can range from mild to severe and can last for weeks, months, or even years. [21], [22]

To diagnose MDD, an individual must experience a minimum of five depressive symptoms daily for two weeks. These symptoms must be new or have worsened since the onset of the depressive episode. Two of the following symptoms must be present: persistent depressed mood, loss of interest or pleasure in activities, and significant fatigue or reduced energy levels. Additionally, at least four of the following symptoms should be identified: decreased self-confidence, unfounded self-blame, recurring thoughts of death or suicide, challenges with concentration, alterations in psychomotor activity, changes in appetite or weight, and disruptions in sleep patterns. [21]

Anxiety disorders are characterised by excessive and persistent worry or fear about everyday situations. Common symptoms of anxiety disorders include feelings of nervousness, restlessness, or tension, along with a sense of impending danger or panic. Physical symptoms may occur, such as elevated heart rate, rapid breathing, sweating, and trembling. Additional symptoms may include weakness or fatigue, trouble concentrating or sleeping, and avoiding certain situations that may trigger anxiety. It is important to note that everyone experiences anxiety on occasion, but if these symptoms persist and interfere with daily life, it may be indicative of an anxiety disorder. [22]

2.2. THE MONOAMINE HYPOTHESIS FOR MDD AND ANXIETY DISORDERS

Schildkraut first proposed the monoamine theory in 1965. The theory was based on the ability of monoamine oxidase inhibitors or tricyclic antidepressants to facilitate the monoamine system [1]. The monoamine hypothesis proposes that mood disorders are caused by the dysregulation of the brain's neurotransmission. This hypothesis has been the most influential and widely accepted theory to explain the pathophysiology of

MDD and anxiety disorders. Furthermore, it has been the basis for the development of most antidepressant medications currently available [2].

The monoaminergic neurons form the human brain's main pathways, responsible for creating feelings of reward and pleasure (**Figure 1B**). The monoamine neurotransmitters include serotonin (5-Hydroxytryptophan; 5-HT), noradrenaline, and dopamine. The brain's reward system consists of the prefrontal cortex (PFC), nucleus accumbens, ventral tegmental area (VTA), hippocampus, amygdala, hypothalamus, and thalamus. These regions are essential in managing emotional and cognitive behaviour (**Figure 1A**). [32]

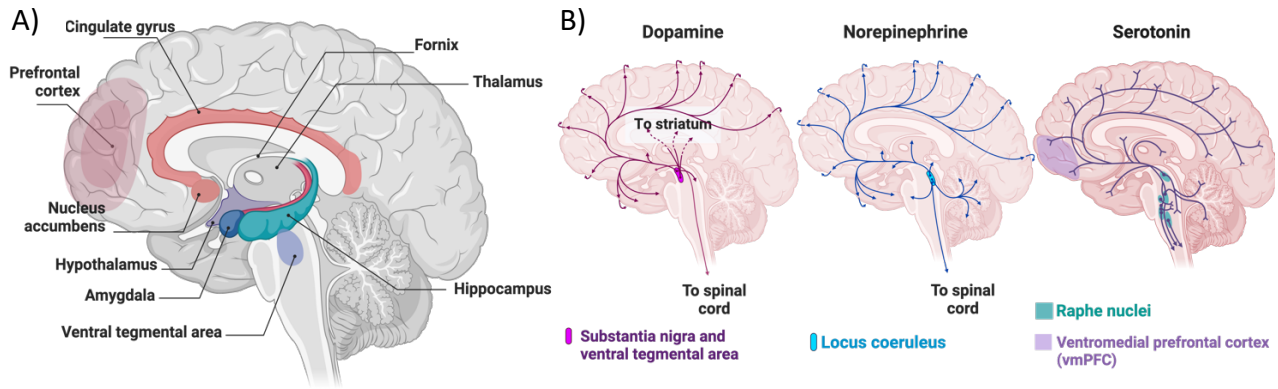

Figure 1. The limbic system and the distribution of monoamine neurotransmitters*. Brain areas that form the limbic system are shown in left (A). Dopaminergic (pink), norepinephrinergic (noradrenaline, blue), and serotoninergic (purple) pathways are shown in picture B. Created with Biorender.com*

Dopaminergic neurons in the midbrain affect behaviour, cognition, and feelings. Dopamine is associated with the reward system, pleasure, reward, motivation, and drive. Dopaminergic neurons create three pathways in the brain. From the substantia nigra to the dorsal striatum, forming the Nigrostriatal system (**figure 1B**). The nigrostriatal pathway plays an essential role in the motor movement. The mesocorticolimbic pathway begins from the VTA and projects to the limbic structures. The mesocorticolimbic pathway has a role in emotion-based behaviour, motivation, and reward systems. The tuberoinfundibular pathway controls hypophyseal activities, and it starts from the hypothalamus. [32][33]

5-HT has an essential role in anxiety-like behaviour and alleviating depressed mood. The human brain consists of 300,000 Serotoninergic neurons in the raphe nucleus (**Figure 1B**). 5-HT is an essential neurotransmitter in the central nervous system (CNS) and affects motor control, cerebellar regulation, sleep, and circadian rhythms. 5-HT regulates behavioural effects such as mood, perception, memory, anger, aggression, fear, stress response, appetite, addiction, and sexuality. [34]

There are 15 serotoninergic receptors, with 5-HT_{1A} and 5-HT_{1B} being the most studied in MDD [35]. Activation of 5-HT_{1A} receptors suppresses cyclic adenosine monophosphate levels and inhibits neuronal activity [36]. Mouse model studies have shown that 5-HT_{1A} autoreceptors have a relation with anxiety-like behaviour [37], [38], [39]. 5-HT_{1B} is primarily associated with regulating aggressive and impulsive behaviour. However, it also has a significant impact on MDD. This receptor reduces serotonin levels in the brain through its release, synthesis, and reuptake. [35] 5-HT_{1B} receptor agonists have been found to produce antidepressant effects in humans and mice [40], [41], [42], [43].

Noradrenaline is linked with stress reactions, attention, and arousal. Noradrenergic pathways partake in the state of alertness, modulation of stress responses, and central cardiovascular modulation. Locus coeruleus (LC) is an integral part of the central nervous system associated with attention and arousal. It is active during wakefulness. Noradrenergic neurons from LC project to the forebrain, thalamus, hypothalamus, cerebellum, basal forebrain, hippocampus, and also through the neocortex (**Figure 1B**). In addition, noradrenaline activates the amygdala and the hypothalamic-pituitary-adrenal (HPA) axis and, together with 5-HT, has a role in impulsive, anxiety- and irritability-like behaviour. [32] [44]

2.3. ROLE OF GABA AND GLUTAMATE

The balance between the brain's inhibitory and excitatory transmission determines the brain's state of alertness. GABA is an inhibitory neurotransmitter that reduces neurons' activity and decreases the nerve cells' responsiveness. Meanwhile, glutamate is an excitatory neurotransmitter that plays a role in synaptic plasticity, learning, and memory. The balance between GABAergic inhibition and glutamatergic excitation is crucial for maintaining mental health. Imbalances, whether due to genetic factors, environmental stressors, or other causes, can contribute to the development of anxiety and MDD.[45]

Mental disorder animal studies show some evidence of an imbalance in the excitatory and inhibitory neurotransmission associated with MDD. [46], [47] This imbalance occurs in the brain's limbic region, hippocampus, and PFC. Together with monoaminergic projections, GABAergic and glutamatergic projections form the reward circuit and regulate mood (**Figure 2**) [45].

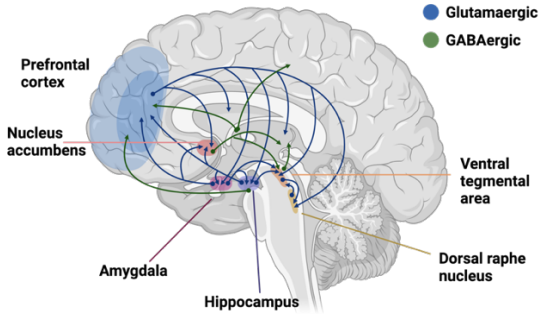

Figure 2. GABAergic and Glutamatergic pathways in the brain. *Glutamatergic pathways are shown with blue arrows. They project from the prefrontal cortex to the nucleus accumbens, amygdala, hippocampus, dorsal raphe nucleus, and ventral tegmental area. GABAergic pathways are shown with green arrows. Created with BioRender.com*

GABA is the brain's inhibitory neurotransmitter, and its dysfunction is associated with mood disorders, mainly anxiety disorders. These inhibitory neurons are pivotal in various physiological processes frequently affected by psychiatric disorders, including neural plasticity, sensory processing, memory consolidation, attention, and stress response [45]. GABAergic neurons form 20 % of total synapses in the CNS.[45] GABA binds to two receptors, ionotropic A or metabotropic B type, which have a role in sleep, memory, epilepsy, and emotion regulation; due to this, it is a target for many therapeutic profiles [48] [16]. GABAergic activity increases sedation, amnesia, and ataxia [45].

In contrast, glutamate functions as the major excitatory neurotransmitter in the brain, forming most of the synapses in the neocortex, approximately 80 %. When glutamate is released, it activates diverse downstream pathways. Glutamate activity increases alertness, sleep-wake cycle regulation, and pain management. It is also essential in memory and learning. In response to action potentials, the presynaptic neurons release glutamate, which binds to various pre- and postsynaptic receptors, including receptors on the surrounding astrocytes (**Figure 2**). [45][49]

Glutamate receptors include α-Amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid (AMPA), N-methyl-D-aspartate (NMDA), and kainate-receptors. Additionally, glutamate binds to metabotropic glutamate receptors, which are G-protein-coupled receptors. Astrocytes primarily perform synaptic glutamate reuptake. Within the astrocyte, glutamate is converted to glutamine-by-glutamine synthetase and then resupplied to the presynaptic neuron, which synthesises glutamate. NMDA receptor signalling facilitates various responses, including excitation and neurotrophic function, and can also trigger pathways leading to cell death. [45]

Magnetic resonance imaging (MRI) studies have revealed insights into glutamate and GABA levels in patients with MDD. Specifically, MRI studies have demonstrated changes in glutamate and GABA levels in MDD patients, with reduced GABA and increased glutamate compared to controls [28], [50], [51], [52].

Furthermore, exposure to chronic stress may exacerbate these neurotransmitter imbalances. It can cause neuronal atrophy in cortical and limbic regions, potentially due to stress-induced excitotoxicity, elevated glucocorticoids, and inflammatory cytokines affecting excitatory and inhibitory neurotransmission [46], [53][54]. Chronic stress can elevate glutamate levels in the synapses, causing overexcitation of NMDA receptors [55].

2.4. ROLE OF THE HPA AXIS AND STRESS

HPA axis is critical in the body's stress response. It is a complex communication system between the hypothalamus, pituitary gland, and adrenal glands that produces and regulates hormones such as corticotrophin-releasing hormone (CRH), adrenocorticotropic hormone (ACTH), and cortisol. The HPA axis is crucial for maintaining homeostasis and adapting to stress. However, prolonged stress can lead to dysregulation of the axis and contribute to the development of mental health disorders.[56]

In response to stress, the paraventricular nucleus neurons in the hypothalamus secrete CRH, which causes stimulation in ACTH synthesis in the pituitary gland. ACTH activates glucocorticoid synthesis, and cortisol is released from the adrenal cortex. Cortisol is a hormone that regulates blood pressure, blood sugar, inflammation, neuronal survival, and neurogenesis. Additionally, cortisol terminates the stress response by negative feedback on the HPA axis, inhibiting further CRH release. However, chronic stress can disrupt feedback regulation, leading to prolonged HPA axis activation. [57]

Persistent activation of the HPA axis can lead to hypersecretion of ACTH and cortisol, potentially resulting in hippocampal atrophy. While glucocorticoids typically enhance hippocampal activity during acute stress, chronic stress may damage hippocampal neurons. [57] Research on hippocampal atrophy in rodent models indicates that elevated cortisol levels resulting from stress can negatively affect the hippocampus [58]. Furthermore, MRI studies have revealed that individuals with MDD have smaller hippocampal volumes, suggesting a potential link between HPA axis dysregulation and the pathophysiology of mood disorders. [59][60].

2.5. HIPPOCAMPAL ADULT NEUROGENESIS

Nervous system plasticity refers to the brain's response and adaptation to stimuli such as stress. The hippocampus and the subventricular zone are the only places where new cell formation occurs in adults. This formation is called Hippocampal adult neurogenesis and is an essential part of an adaptive response that mediates the HPA axis. Reduced neurogenesis in the hippocampus has become one of the hallmarks of MDD. [8]

The hippocampus consists of two distinct domains: the ventral and the dorsal. The ventral hippocampus is responsible for emotional processing and regulation, while the dorsal hippocampus plays a crucial role in spatial navigation and memory consolidation. The dorsal hippocampus corresponds to cognitive functions, whereas the ventral part corresponds to stress, affection, and emotions. [61] Therefore, neurogenesis has different responses in the ventral and the dorsal regions of the hippocampus. In the dorsal region, neurogenesis has an impact on spatial memory. For instance, an increase in neurogenesis results in enhanced spatial memory. Whilst in the ventral region, increased neurogenesis can alleviate anxiety-like behaviour. [62].

Adult hippocampal neurogenesis occurs in the dentate gyrus of all mammalian species, with a daily formation of 0.004% dentate gyrus neurons in humans [62]. The immature granule cells in the hippocampus are highly responsive to input from the perforant path, a neural pathway that connects the entorhinal cortex to the hippocampus in the brain. This neural pathway is essential for transferring information between the neocortex and the hippocampus, which is critical for learning and memory. Unlike resident granule cells, immature cells have a lower activation threshold due to a particular configuration. These immature granule cells play a crucial role in memory formation and consolidation by negatively regulating the overall activity of resident dentate granule cells through the recruitment of local GABAergic inhibitory neurons. Increasing the number of adult-born granule cells or their activity can decrease the glutamatergic projections activity from the ventral hippocampus. The excitatory output from the ventral hippocampus to the medial prefrontal cortex is necessary for anxious behaviour [63], [64], [65]. However, a decrease in activity within this area is linked with stress resilience in the chronic social defeat model of MDD [66] [67].

Studies have shown that adult hippocampal neurogenesis plays a critical role in enhancing the effectiveness of antidepressant drugs [3], [68], [69]. This discovery resulted in more investigations about adult hippocampal neurogenesis effects on mood regulations, leading to the hypothesis that increasing neurogenesis alleviates anxiety and depressive-like symptoms [70]. The hypothesis remains controversial due to some studies indicating that neurogenesis is not the primary function of depression, and therefore, it is not necessary for antidepressive drugs to alter neurogenesis [71], [72], [73]. However, newer studies conducted on mice suggest that chronic antidepressant treatment can enhance neurogenesis levels in the

dentate gyrus subregion [71], [74], indicating that neurogenesis is a crucial factor in the effectiveness of antidepressants, raising the possibility that stimulating adult hippocampal neurogenesis could potentially alleviate symptoms of anxiety and MDD.

3. TREATMENTS

3.1. TREATMENT PLAN

MDD is categorised by its severity into four types: mild, moderate, severe, and psychotic depression [21]. Based on the Current Care Guidelines, Anxiety Disorders are classified into generalised anxiety disorder (GAD), social anxiety disorder (SAD), and panic disorder (PD), with or without agoraphobia[22].

The most used treatment methods are medical and psychotherapy (**Table 1**). The best response is often obtained when the methods are used simultaneously. In addition, online therapy can be a beneficial option for people who are experiencing mild to moderate MDD and anxiety disorders [21], [22]. Online therapy is a form of therapy done individually online with specific themes, and the therapist comments on the progress [75]. In contrast, psychotherapy requires close interaction with the patient and psychotherapist [76]. Medication is not always necessary for mild MDD, although it can be beneficial. For patients with psychotic conditions, antipsychotics may be added to the treatment plan. Psychotic MDD also requires electrotherapy or other neuromodulation therapy. [21], [22]

Table 1. *Treatment indications for different severity of MDD and anxiety disorders* [21], [22]

Treatment format	Mild MDD	Moderate MDD	Severe MDD	Psychotic MDD	Anxiety Disorders
Online therapy	x	x			x
Psychotherapy	x	x	(x)		x
Antidepressants	x	x	x	(x)	x
Antidepressant + antipsychotics				x	
Electrotherapy (ECT)			x	x	

x determines which treatment format is used for anxiety or MDD type. It can be used as a separate treatment or together.
(x) determines that treatment can be used, but not it is not effective on its own.

The majority of antidepressants are targeting serotonergic and noradrenergic functions [77]. However, it remains unclear whether they are functional enough to treat MDD and anxiety. Antidepressant drugs fall into the following pharmacological categories: Inhibitors of monoamine reuptake, receptor-blocking antidepressants, monoamine oxidase inhibitors, melatonin receptor agonists, and rapid-acting

antidepressants [78]. Current medications used for MDD and anxiety are shown in **Table 2**. Each x shows the suitability of the treatment for various diagnoses. Antidepressants are also used in anxiety disorders. For example, GAD is usually treated with non-sedating anxiolytics or with antidepressants. [21], [22]

***Table 2**. Overview of the drug categories in the treatment of MDD and anxiety disorders.* [21], [22]

Antidepressant/Anxiolytic	Indicated for:
SSRIs	MDD, GAD, SAD, PD
SNRIs	MDD, GAD
TCAs	MDD, PD
NRIs	MDD
Receptor blocking antidepressants	MDD, SAD
MAO-inhibitors	MDD, SAD
Melatonin Receptor agonist	MDD, SAD
Rapid acting antidepressants	MDD
Benzodiazepines	GAD, SAD, PD
Gabapentinoids	SAD
Antipsychotic agents	MDD, GAD, SAD, PD
Azapirones	GAD
β-Adrenoceptor Antagonists	GAD, SAD, PD
MDD: Major depressive disorder GAD: Generalized anxiety disorder SAD: social anxiety disorder PD: panic disorder	

3.2. ANTIDEPRESSANTS

3.2.1. Inhibitors of monoamine reuptake

Inhibitors of monoamine reuptake include selective 5-HT reuptake inhibitors (SSRIs), 5-HT and noradrenaline reuptake inhibitors (SNRIs), tricyclic antidepressants (TCAs), and noradrenaline reuptake inhibitors (NRIs) [78].

SSRIs (e.g., citalopram, escitalopram, sertraline, etc.) bind to the serotonin transporter, inhibiting serotonin uptake back to the neurons. SSRIs are widely used in MDD and anxiety disorders, as seen in **Table 2**. Although they are generally well-tolerated, the most common side effects of SSRIs include nausea, agitation, and insomnia. It is important to note that it may take a few weeks to improve mood due to the desensitisation of the raphe 5-HT_{1A} receptors. SNRIs (e.g., duloxetine, venlafaxine), unlike SSRIs, affect not only serotonin but also the reuptake of noradrenaline. Venlafaxine has similar side effects to SSRIs, while duloxetine has fewer side effects, including sedation and dizziness.[78]

Classic TCAs (e.g., clomipramine, amitriptyline) have varying activity and selectivity concerning the 5-HT and noradrenaline reuptake inhibition. Additionally, TCAs affect dopamine, acetylcholine, and histamine levels by modulating the reuptake of norepinephrine and serotonin. However, TCAs are notorious for causing many side effects, some of which are severe, such as seizures and a risk of overdose. Conversely, NRIs (e.g., bupropion, atomoxetine, reboxetine) inhibit the presynaptic uptake of noradrenaline, increasing the amount of noradrenaline in the synaptic cleft. Reboxetine is less effective than TCAs, and it can cause, for instance, anticholinergic effects. Bupropion inhibits both norepinephrine and dopamine. It is mainly used for MDD with anxiety disorder. Common side effects include headache, dry mouth, agitation, and insomnia.[78]

3.2.2. Receptor-blocking antidepressants

Regarding receptor-blocking antidepressants, mirtazapine and mianserin inhibit a range of amine receptors, including α2 adrenoceptors and 5-HT_2 receptors. Mirtazapine has a faster onset of action than other antidepressants, and the common side effects are dry mouth, sedation, and weight gain. Trazodone has mixed agonist and antagonist effects on monoamine receptors and weakly affects 5-HT uptake inhibitors. Side effects include sedation, hypotension, and cardiac dysrhythmias.[78]

3.2.3. Monoamine oxidase inhibitors

Selective MAO inhibitors increase monoamine (serotonin, noradrenaline, and dopamine) levels in synapses and are often used when regular antidepressants are ineffective. MAO inhibitors Inhibit MAO-A and/or MAO-B.[78] Irreversible and non-competitive inhibitors (e.g., phenelzine, tranylcypromine) have a prolonged duration of action as they bind irreversibly. However, they have a severe side effect known as a cheese reaction. It is acute hypertension due to the interaction of the MAO inhibitors with tyramine formed in cheese. Fortunately, there are safer alternatives to earlier MAO inhibitors, such as reversible, MAO-A selective inhibitors (e.g., moclobemide). While these alternatives may still have side effects like nausea, insomnia, and agitation, there are no reported incidents of cheese reactions. [78]

3.2.4. Melatonin receptor agonist

Agomelatine is a melatonin receptor MT1 and MT2 agonist and a weak 5-HT_{2C} antagonist. In addition to raising a depressed mood, it is suitable for promoting sleep and balancing circadian rhythms. The side effects include headache, dizziness, and fatigue. [78]

3.2.5. Rapid-acting antidepressant

Ketamine is a rapid-acting antidepressant. It is a non-competitive NMDA receptor channel blocker and effective for patients who are resistant to other antidepressants. Its metabolites may cause the antidepressant effects of ketamine. However, it can have side effects, such as the psychotomimetic effect, which mimics the symptoms of psychosis, including delusions. [78]

3.2.6. Anxiolytic drugs

Anxiolytic drugs are used to treat anxiety disorders. Among these medications are benzodiazepines, which are GABA-α -agonists and are helpful for short-term or acute anxiety due to their characteristics of tolerance and dependence. The main effects of benzodiazepines include induction of sleep, reduction of muscle tone, anticonvulsant effect, and reduction of anxiety and aggression. Additionally, gabapentinoids (e.g., gabapentin, pregabalin) can be used to treat anxiety disorders. They work by binding to the alpha-2-delta subunit of voltage-gated calcium channels. This reduces calcium influx into neurons, decreasing excitatory glutamate release. This mechanism of action is thought to underlie the drugs' therapeutic effects in managing anxiety disorders. In forms of anxiety that appear as physical symptoms such as sweating, tremors, and tachycardia, β-adrenoceptor antagonists (e.g., propranolol) can be added. [79]

Antipsychotic agents (quetiapine) are used in severe or psychotic MDD. Quetiapine is an atypical antipsychotic medication that works by blocking dopamine and serotonin receptors in the brain. By doing so, it helps to regulate the levels of these neurotransmitters in the brain, which can relieve delirium and other psychotic symptoms, as well as equalise mood. Additionally, quetiapine has been shown to have sedative effects, which can be helpful for individuals who have difficulty sleeping due to their condition.[79]

Antidepressants are not always beneficial as they sometimes have unwanted side effects, even severe ones. In addition, they do not work for everyone; about a third of patients who use antidepressants do not get a proper response. [21], [80]

3.3. CLINICAL TRIALS

It is vital to investigate more drugs to provide more proficient treatment for patients without uncomfortable side effects. Even though there are several different drugs available, treatment-resistant depression (TRD) remains a massive problem among MDD patients [16]. Furthermore, for current antidepressant SSRIs, the onset of action with these medicines is approximately four weeks, and therefore, the non-monoaminergic approach would be essential [2].

Advantageous strategies for patients suffering from TRD are glutaminergic and GABAergic neurotransmissions. Another promising approach is hallucinogenic drugs for medical use. [2] Some potential medicines for MDD and anxiety include SAGE-217 and psilocybin [81], [82].

3.3.1. SAGE-217

Zuranolone (Sage-217) is a positive allosteric modulator of $GABA_A$ receptors and neuroactive steroids. These neuroactive steroids enhance GABAergic neurotransmission. By increasing GABA levels, SAGE-217 may help to reduce the activity of excitatory neurotransmitters, such as glutamate, which are associated with MDD and anxiety.[83], [84] A Phase 3, multicenter, double-blind, randomised, placebo-controlled study aimed at evaluating the efficacy of SAGE-217 in treating major depressive disorder (MDD) in adult subjects. The study was completed in 2020 and aimed to confirm and extend the positive findings of a previous study in a larger population. The results of this study show a promising potential to be a treatment option for individuals with MDD. [18], [82]

3.3.2. Psilocybin

In 2023, a Phase III multicenter, randomised, double-blind, controlled study aimed to evaluate the effectiveness of psilocybin (COMP360) in improving depressive symptoms in adult participants with TRD when combined with psychological support. [81]

Psilocybin is a compound that is found in certain fungi and can cause psychedelic effects. Psilocybin (3-[2-(Dimethylamino)ethyl]-1H-indol-4-yl dihydrogen phosphate) resembles serotonin, an essential factor in mood regulation. Psychedelics are drugs that can alter the mind and emotions, often by producing hallucinations. There are two main types of hallucinogens: dissociative drugs and classic serotonergic and dopaminergic hallucinogens. Psilocybin belongs to the latter group, affecting $5\text{-}HT_{2A}$ receptors. According to researchers, psilocybin is the least dangerous of psychedelics and has the least potential for drug abuse compared to other psychedelics. However, it should be noted that the patient should have the correct dose and the right environment. [17], [85], [86], [87]

4. C-JUN N-TERMINAL KINASES

4.1. PATHWAY

Different stress responses mainly activate the c-Jun N-terminal kinase (JNK) pathway. JNKs are a subfamily of mitogen-activated protein kinases (MAPK) consisting of three JNK isoforms: JNK1, JNK2 and JNK3. These

MAPKs interact with the final effectors responsible, such as inflammation responses and apoptosis. The pathway is activated by apoptotic stimuli that transmit signals through G-protein-coupled receptors. MAP kinase pathway includes MAPK kinase kinases (MAPKKK), MAPK kinases (MAPKK), and MAPKs. MAPKKKs are liable for activating and phosphorylating MAPKK, which activates and phosphorylates MAPKs.[10], [88]

Stress-induced changes in the membrane transmit signals to adaptor proteins Rac1/Cdc42. These stress-induced mechanisms can be receptor-dependent or receptor-independent, for example, oxidative stress, DNA damage, inflammatory cytokines, and growth factors. G-proteins are vital in activating MAPKKKs, a group of 13 proteins responsible for feeding information to the JNK pathway. For instance, MEKK1 phosphorylates and activates the downstream of MKK4 and MKK7 at the MAPKK level. Once MKK4 and MKK7 are activated and phosphorylated, the signal is transmitted further in the pathway upon activation by phosphorylation of the typical Ser-Xaa-Ala-Xaa-Ser/Thr motif. After the activation, JNK in the cytosol translocate into the nucleus or the mitochondria.[88]

The JNK pathway promotes two different death signalling pathways. Another is the activation of death signals such as c-Jun or apoptosis signals such as BIM, BAD, BAX protein or active p53 transcription. Another route is the inhibition of the cell survival signalling, such as STATs and CREB (**Figure 3**) [88]. In the first mechanism, activated JNK translocate to the nucleus and transactivates transcription factors. This leads to an increase in the expression of pro-apoptotic genes and ultimately results in apoptosis. JNK can also translocate in the mitochondria where mitochondrial apoptotic proteins, Bim, Bax, Bcl-2 and Bad, are phosphorylated by active JNK.[11], [88]

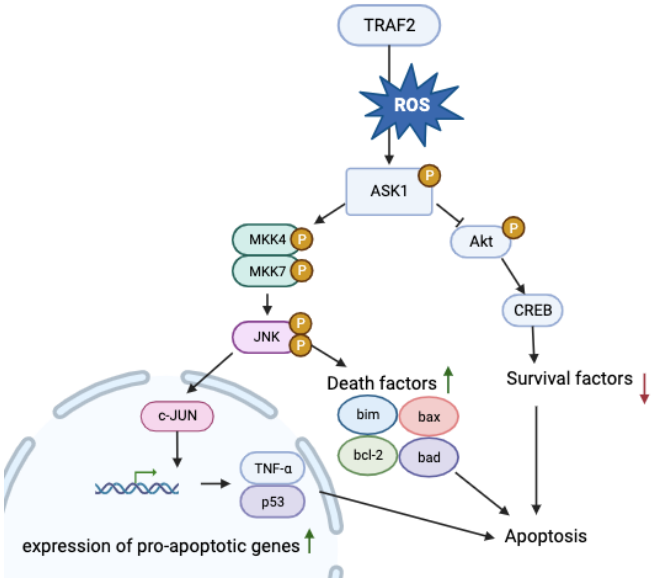

Figure 3. JNK signalling pathway to promote apoptosis*. Two main pathways are highlighted: the death factor and c-JUN transcription pathways on the left, and on the right, the survival factors pathway* [88]*. Created in BioRender.com.*

4.2. JNK FUNCTION IN THE BRAIN

JNK is one of the signalling pathways that has a role in the brain's development. It regulates several cellular processes, such as apoptosis, inflammation, and stress response. Although JNK can be found in both the brain and peripheral tissues, the brain's JNK activity differs from that found in the heart, spleen, lungs, and liver. While JNK activity is relatively low during stress in these tissues, it increases significantly in the brain. [11]

The protein kinase JNK plays a crucial role in activating the c-Jun gene through phosphorylation. JNK1 is a significant component of physiologically active JNK in the brain, while JNK2 and JNK3 isoforms show lower basal activity and increased stress activity. JNK1 and JNK2 are more associated with the brain's plasticity, memory formation, excitotoxicity and axonogenesis. JNK3 is a pro-apoptotic pathway in the hippocampal neurons. [10], [11]

JNK's roles suggested that the JNK pathway could be involved with neurodegenerative diseases. JNK plays a role in brain development [89] but has also been studied concerning Parkinson's and Alzheimer's diseases [90].

4.3. JNK IN MDD AND ANXIETY DISORDERS

Recent studies have revealed that JNKs are implicated in the pathogenesis of mood disorders [11]. JNK hyperactivity results in increased inflammation and apoptosis in the brain, which can lead to neuronal loss and contribute to MDD and anxiety disorders [91]. Additionally, JNKs are found to be activated by glutamate through NMDA receptors [92]. According to the previous hypothesis, stress and the overactivated HPA axis are crucial factors in the development of MDD and anxiety, and the excessive activation of NMDA receptors can lead to excitotoxicity, as well as JNK hyperactivity [92].

Studies conducted on animals indicate that JNK is hyperactivated in the hippocampus and prefrontal cortex in chronic variable stress models of depression and acute stress models [12][93]. Additionally, in animals susceptible to stress, JNK activity is increased, whereas in those that are resilient in the social defeat stress model of depression, JNK activity decreases [93]. These findings indicate that JNK activity may play a role in the development of MDD. Furthermore, social isolation in a model for depression appears to decrease JNK activity in the hippocampus and PFC slightly. Taken together, the evidence strongly suggests that JNK activation is a common feature in animal models of depression. The function of JNK1 in the adult brain has been studied extensively using animal models. [12]

According to a study by H. Mohammad et al. published in 2018, inhibiting JNK in the hippocampal neurogenic niche can help reduce anxiety-like behaviour and increase the number of adult-born granule cells. H. Mohammad et al. subjected mice to various behavioural tests. Inhibition of JNK was achieved through different methods, including the genetic removal of *Jnk1*, infusion of DJNKI-1 into the brain ventricles, and delivery of JNK inhibitor to granule cells of the dentate gyrus using retrovirus. Results show that *Jnk1*-/- mice exhibited less anxiety-like behaviours in tests such as the open field, elevated plus maze, light-dark tests, and increased neurogenesis. When JNK1 is blocked globally, it boosts the creation of new neurons in the hippocampus. Interestingly, blocking JNK, specifically in immature granule cells, decreased anxiety-like behaviour without affecting neurogenesis. This suggests that JNK inhibition has distinct effects in the hippocampal neurogenic area in anxiety-like and depressive-like behaviour. [12] A theory that needs testing is whether JNK controls immature granule cells' properties, resulting in increased ventral hippocampal output and anxiogenic behaviour. [12]

The association between the JNK pathway, the HPA axis, stress, and mood disorders is becoming increasingly evident. Corticosteroids have been found to promote JNK activation, while glutamate receptor-mediated responses can also activate JNK pathways, thereby contributing to stress-mediated responses [94], [95], [96]. Therefore, in addition to its involvement in granule cells [12], JNK is associated with depression due to its connection with glucocorticoids, prolonged stress, and excessive glutamate activity, all of which play roles in the development of mood disorders.

Researchers are now investigating using JNK inhibitors as a potential treatment for mood disorders. Targeting JNKs may be viable in reducing inflammation and apoptosis in the brain and essentially alleviating symptoms of MDD [12]. Additionally, studies have shown that ketamine may modulate the JNK signalling pathway, which helps protect nerve cells from excitotoxicity and apoptosis [92].

4.4. JNK AS POSSIBLE THERAPEUTIC TARGETS

There are several possible molecular mechanisms for JNK to affect anxiety, including influencing the behaviour of newborn granule cells and altering the activity of circuits that control mood.

JNK inhibitors can be designed to be either adenosine triphosphate (ATP) competitive, covalent, allosteric, or peptide inhibitors. ATP competitive inhibitors bind to ATP-binding sites in kinases, resulting in poor selectivity of these inhibitors, which can lead to toxicity and other side effects. However, developing a potential selective ATP competitive inhibitor may be possible. Covalent inhibitors bind irreversibly against Cys154 of JNK3, allowing the inhibitor to provide longer potency and selectivity. Allosteric inhibitors induce

conformational changes in the binding pocket of ATP, thereby changing the activity of JNKs. Peptide inhibitors can specifically bind to the peptide sequence of the JNK binding domain and exert an inhibitory effect. D-JNKI-1 is an example of a small peptide inhibitor that competes for substrate binding by binding to the common docking domain of JNK. It's a specific JNK-1 inhibitor that does not inhibit ERK or p38 kinases. [97] Studies have shown its ability to penetrate the blood-brain barrier and persist in the brain for up to one week [98]. Depending on the therapy window, this could provide medicine taken only once a week. In addition, the inhibition of JNK is expected to benefit several diseases—for instance, cancer and diabetes. [99]

There are several issues regarding JNK as a therapeutic target. Due to their massive role in brain development, it is not profitable to inhibit JNK non-specifically. JNKs are activated by stress in the brain and act as essential kinases in immune response; consequently, silencing the pathway is not beneficial. The problem with these inhibitors is substrate specificity and potential side effects [100]. Therefore, JNK isoform-specific inhibitors could be potential therapeutics.

Currently, there are no available JNK-targeting drugs for mood disorders. Two clinical trials with small-molecule ATP-competitive JNK inhibitors were carried out. However, it is worth noting that these clinical trials were not for mood disorders. Both trials aimed to test the efficacy but were terminated due to a poor risk/benefit ratio [101], [102], [103], [104].

As the current antidepressants have the same mechanisms that target the monoaminergic pathways, an exploration of a new pathway would be a new milestone for the research field regarding mood disorders. This novel pathway would provide an avenue for targeted interventions. Moreover, the potential therapeutic focus doesn't necessarily have to be directly on JNK itself; instead, targeting downstream components of the JNK pathway could be equally effective. For instance, Ketamine, which is an effective treatment for TRD, is linked to JNKs. Consequently, another approach for possible targeting is NMDA-inhibiting drugs that affect the activation of JNKs. [92]

5. SUMMARY AND CONCLUSIONS

Neurotransmitter interactions in mental health are complex. Various factors contribute to anxiety disorders and MDD, including genetic predisposition, environmental influences, and individual differences in brain function. Many hypotheses for the mechanism behind these disorders are being increasingly studied. The first hypothesis discovered, the dysregulation of monoamines, has been driving drug development. However,

some patients' limited response to treatments for anxiety and MDD, as well as TRD, underscore the need for novel therapeutic approaches.

In response to these challenges, researchers have turned their attention to mechanisms such as hippocampal neurogenesis and brain plasticity, which may offer promising avenues for more effective treatments. Among these, the role of JNK in mood regulation and ongoing studies on its therapeutic implications have garnered significant interest. Recent research has highlighted the precise localisation of JNK anxiogenic action to immature granule cells in the hippocampus. [12] This may present a targeted approach with the potential to alleviate mood without the side effects of current drugs.

Notably, the JNK pathway intertwines with the existing hypothesis. Evidence suggests a correlation between JNK activity and neurogenesis, indicating that patterns of neuronal activity can intricately modulate intracellular signalling cascades implicated in cell survival and stress response mechanisms [12]. Moreover, pivotal in mediating calcium influx, NMDA receptors play an essential role in various signalling pathways involved in learning, memory, and synaptic remodelling [105]. NMDA can, in turn, activate the JNK pathway. Additionally, ketamine and esketamine, being NMDA receptor antagonists, have shown promise in rapidly alleviating depressive symptoms, particularly in individuals who have not responded to other treatments. However, their potential side effects and abuse potential must be considered. Importantly, their mechanism of action involves a link to JNK via the NMDA pathway [92], [106].

By integrating these novel findings with existing knowledge, ongoing endeavours aim to refine our understanding of mental health disorders' complex mechanisms and pave the way for more effective and personalised treatment approaches. JNK kinases could be valuable targets for future aspects of mood disorders and drug development. They would provide a novel response, especially for patients who do not benefit from current therapies. Furthermore, it is not necessary for the drug to specifically target JNK, as the downstream components of the JNK pathway can also be targeted for the treatment of mood disorders. However, more research is required to unveil the potential therapeutic target of JNK.

References

[1] J. J. Schildkraut, “THE CATECHOLAMINE HYPOTHESIS OF AFFECTIVE DISORDERS: A REVIEW OF SUPPORTING EVIDENCE,” *https://doi.org/10.1176/ajp.122.5.509*, vol. 122, no. 5, pp. 509–522, Apr. 2006, doi: 10.1176/AJP.122.5.509.

[2] J. M. Ritter *et al.*, “Antidepressant drugs - Rang & Dale’s Pharmacology - ClinicalKey Student,” in *Rang & Dale’s Pharmacology*, vol. 10th edition, pp. 640–662. Accessed: Feb. 21, 2024. [Online]. Available: https://www.clinicalkey.com/student/content/book/3-s2.0-B9780323873956000482#hl0000669

[3] C. Anacker *et al.*, “Antidepressants increase human hippocampal neurogenesis by activating the glucocorticoid receptor,” *Mol Psychiatry*, vol. 16, no. 7, p. 738, Jul. 2011, doi: 10.1038/MP.2011.26.

[4] K. D. Carlson, F. Rothganger, and J. B. Aimone, “Computational Perspectives on Adult Neurogenesis,” *The Rewiring Brain: A Computational Approach to Structural Plasticity in the Adult Brain*, pp. 425–441, Jan. 2017, doi: 10.1016/B978-0-12-803784-3.00020-2.

[5] J. L. Warner-Schmidt and R. S. Duman, “Hippocampal neurogenesis: Opposing effects of stress and antidepressant treatment,” *Hippocampus*, vol. 16, no. 3, pp. 239–249, Jan. 2006, doi: 10.1002/HIPO.20156.

[6] S. Becker, G. MacQueen, and J. M. Wojtowicz, “Computational modeling and empirical studies of hippocampal neurogenesis-dependent memory: Effects of interference, stress and depression,” *Brain Res*, vol. 1299, pp. 45–54, Nov. 2009, doi: 10.1016/J.BRAINRES.2009.07.095.

[7] C. Nissen *et al.*, “Learning as a Model for Neural Plasticity in Major Depression,” *Biol Psychiatry*, vol. 68, no. 6, pp. 544–552, Sep. 2010, doi: 10.1016/J.BIOPSYCH.2010.05.026.

[8] W. Liu *et al.*, “The Role of Neural Plasticity in Depression: From Hippocampus to Prefrontal Cortex,” *Neural Plasticity*, vol. 2017. Hindawi Limited, 2017. doi: 10.1155/2017/6871089.

[9] S. R. Wainwright and L. A. M. Galea, “The neural plasticity theory of depression: Assessing the roles of adult neurogenesis and psa-ncam within the hippocampus,” *Neural Plast*, vol. 2013, 2013, doi: 10.1155/2013/805497.

[10] X. Antoniou and T. Borsello, “The JNK signalling transduction pathway in the brain,” 2012.

[11] P. Hollos, F. Marchisella, and E. T. Coffey, “JNK Regulation of Depression and Anxiety,” *Brain Plasticity*, vol. 3, no. 2, pp. 145–155, Apr. 2018, doi: 10.3233/bpl-170062.

[12] H. Mohammad *et al.*, “JNK1 controls adult hippocampal neurogenesis and imposes cell-autonomous control of anxiety behaviour from the neurogenic niche,” *Mol Psychiatry*, vol. 23, no. 2, pp. 362–374, Feb. 2018, doi: 10.1038/mp.2016.203.

[13] A. J. Funk, R. E. McCullumsmith, V. Haroutunian, and J. H. Meador-Woodruff, “Abnormal Activity of the MAPK- and cAMP-Associated Signaling Pathways in Frontal Cortical Areas in Postmortem Brain in Schizophrenia,” *Neuropsychopharmacology 2012 37:4*, vol. 37, no. 4, pp. 896–905, Nov. 2011, doi: 10.1038/npp.2011.267.

[14] F. Marchisella, E. T. Coffey, and P. Hollos, “Microtubule and microtubule associated protein anomalies in psychiatric disease,” *Cytoskeleton*, vol. 73, no. 10, pp. 596–611, Oct. 2016, doi: 10.1002/CM.21300.

[15] G. I. Papakostas, M. Fava, and M. E. Thase, “Treatment of SSRI-Resistant Depression: A Meta-Analysis Comparing Within- Versus Across-Class Switches,” *Biol Psychiatry*, vol. 63, no. 7, pp. 699–704, Apr. 2008, doi: 10.1016/J.BIOPSYCH.2007.08.010.

[16] S. J. Rizvi *et al.*, “Treatment-Resistant Depression in Primary Care across Canada,” *http://dx.doi.org/10.1177/070674371405900702*, vol. 59, no. 7, pp. 349–357, Jul. 2014, doi: 10.1177/070674371405900702.
[17] R. L. Carhart-Harris *et al.*, “Psilocybin with psychological support for treatment-resistant depression: six-month follow-up,” *Psychopharmacology (Berl)*, vol. 235, no. 2, p. 399, Feb. 2018, doi: 10.1007/S00213-017-4771-X.
[18] A. Clayton *et al.*, “A Phase 3, Multicenter, Double-Blind, Randomized, Placebo-Controlled Study Evaluating the Efficacy of SAGE-217 in the Treatment of Adult Patients With Major Depressive Disorder,” *Biol Psychiatry*, vol. 87, no. 9, p. S86, May 2020, doi: 10.1016/j.biopsych.2020.02.242.
[19] “VizHub - GBD Results.” Accessed: Feb. 21, 2023. [Online]. Available: https://vizhub.healthdata.org/gbd-results/?params=gbd-api-2019-permalink/d780dffbe8a381b25e1416884959e88b
[20] T. Vos *et al.*, “Years lived with disability (YLDs) for 1160 sequelae of 289 diseases and injuries 1990–2010: a systematic analysis for the Global Burden of Disease Study 2010,” *The Lancet*, vol. 380, no. 9859, pp. 2163–2196, Dec. 2012, doi: 10.1016/S0140-6736(12)61729-2.
[21] Working group set up by the Finnish Medical Society Duodecim and the Finnish Psychiatric Association, “Depression,” *Current Care Guidelines*, 2023, Accessed: Nov. 06, 2023. [Online]. Available: www.käypähoito.fi
[22] the F. P. A. and the F. Y. P. A. Working group set up by the Finnish Medical Society Duodecim, “Anxiety disorders,” *Current Care Guidelines*, 2019, Accessed: Nov. 06, 2023. [Online]. Available: www.käypähoito.fi
[23] G. S. Malhi and J. J. Mann, “Depression,” *The Lancet*, vol. 392, no. 10161, pp. 2299–2312, Nov. 2018, doi: 10.1016/S0140-6736(18)31948-2/ATTACHMENT/E53E28B2-D634-41C0-A987-C1495A02F4CB/MMC1.PDF.
[24] J. J. Schildkraut and S. S. Kety, “Biogenic amines and emotion,” *Science (1979)*, vol. 156, no. 3771, pp. 21–30, 1967, doi: 10.1126/SCIENCE.156.3771.21.
[25] N. L. Lopez-Duran, M. Kovacs, and C. J. George, “Hypothalamic–pituitary–adrenal axis dysregulation in depressed children and adolescents: A meta-analysis,” *Psychoneuroendocrinology*, vol. 34, no. 9, pp. 1272–1283, Oct. 2009, doi: 10.1016/J.PSYNEUEN.2009.03.016.
[26] K. E. M. Godfrey, A. C. Gardner, S. Kwon, W. Chea, and S. D. Muthukumaraswamy, “Differences in excitatory and inhibitory neurotransmitter levels between depressed patients and healthy controls: A systematic review and meta-analysis,” *J Psychiatr Res*, vol. 105, pp. 33–44, Oct. 2018, doi: 10.1016/J.JPSYCHIRES.2018.08.015.
[27] A. J. Levinson, P. B. Fitzgerald, G. Favalli, D. M. Blumberger, M. Daigle, and Z. J. Daskalakis, “Evidence of Cortical Inhibitory Deficits in Major Depressive Disorder,” *Biol Psychiatry*, vol. 67, no. 5, pp. 458–464, Mar. 2010, doi: 10.1016/J.BIOPSYCH.2009.09.025.
[28] G. Sanacora *et al.*, “Reduced Cortical γ-Aminobutyric Acid Levels in Depressed Patients Determined by Proton Magnetic Resonance Spectroscopy,” *Arch Gen Psychiatry*, vol. 56, no. 11, pp. 1043–1047, Nov. 1999, doi: 10.1001/ARCHPSYC.56.11.1043.
[29] E. Pralong, P. Magistretti, and R. Stoop, “Cellular perspectives on the glutamate–monoamine interactions in limbic lobe structures and their relevance for some psychiatric disorders,” *Prog Neurobiol*, vol. 67, no. 3, pp. 173–202, Jun. 2002, doi: 10.1016/S0301-0082(02)00017-5.
[30] J. Undurraga and R. J. Baldessarini, “Randomized, Placebo-Controlled Trials of Antidepressants for Acute Major Depression: Thirty-Year Meta-Analytic Review,”

Neuropsychopharmacology 2012 37:4, vol. 37, no. 4, pp. 851–864, Dec. 2011, doi: 10.1038/npp.2011.306.
[31] H. Melander, T. Salmonson, E. Abadie, and B. van Zwieten-Boot, "A regulatory Apologia — A review of placebo-controlled studies in regulatory submissions of new-generation antidepressants," *European Neuropsychopharmacology*, vol. 18, no. 9, pp. 623–627, Sep. 2008, doi: 10.1016/J.EURONEURO.2008.06.003.
[32] "Other transmitters and modulators - Rang & Dale's Pharmacology - ClinicalKey Student." Accessed: Jan. 22, 2024. [Online]. Available: https://www.clinicalkey.com/student/content/book/3-s2.0-B9780323873956000391
[33] D. Braverman, "Dopamine agonists and antagonists," *Reference Module in Biomedical Sciences*, pp. 923–928, Jan. 2024, doi: 10.1016/B978-0-12-824315-2.00614-X.
[34] P. Wright and M. F. O'Neill, "Psychopharmacology," *Core Psychiatry: Third Edition*, pp. 585–615, Jan. 2012, doi: 10.1016/B978-0-7020-3397-1.00039-2.
[35] R. Hen and K. M. Nautiyal, "Serotonin receptors in depression: from A to B," *F1000Res*, vol. 6, 2017, doi: 10.12688/F1000RESEARCH.9736.1.
[36] R. Xiong *et al.*, "Pharmacological characterization of the 5-HT1A receptor of Bombyx mori and its role in locomotion," *Comp Biochem Physiol A Mol Integr Physiol*, vol. 231, pp. 56–65, May 2019, doi: 10.1016/J.CBPA.2019.01.020.
[37] B. L. Oliver *et al.*, "Acute serotonin 1B/1A receptor activation impairs behavioral flexibility in C57BL/6J mice," *Behavioural Brain Research*, vol. 427, p. 113865, Jun. 2022, doi: 10.1016/J.BBR.2022.113865.
[38] V. Martin *et al.*, "Key role of the 5-HT1A receptor addressing protein Yif1B in serotonin neurotransmission and SSRI treatment," *J Psychiatry Neurosci*, vol. 45, no. 5, p. 344, Sep. 2020, doi: 10.1503/JPN.190134.
[39] M. Toth, "5-HT1A receptor knockout mouse as a genetic model of anxiety," *Eur J Pharmacol*, vol. 463, no. 1–3, pp. 177–184, Feb. 2003, doi: 10.1016/S0014-2999(03)01280-9.
[40] J. W. Murrough *et al.*, "Reduced ventral striatal/ventral pallidal serotonin1B receptor binding potential in major depressive disorder," *Psychopharmacology (Berl)*, vol. 213, no. 2–3, pp. 547–553, Feb. 2011, doi: 10.1007/S00213-010-1881-0/FIGURES/1.
[41] M. F. O'Neill and M. W. Conway, "Role of 5-HT1A and 5-HT1B Receptors in the Mediation of Behavior in the Forced Swim Test in Mice," *Neuropsychopharmacology 2000 24:4*, vol. 24, no. 4, pp. 391–398, 2001, doi: 10.1016/s0893-133x(00)00196-2.
[42] J. P. Redrobe and M. Bourin, "Evidence of the activity of lithium on 5-HT(1B) receptors in the mouse forced swimming test: Comparison with carbamazepine and sodium valproate," *Psychopharmacology (Berl)*, vol. 141, no. 4, pp. 370–377, 1999, doi: 10.1007/S002130050846/METRICS.
[43] E. Tatarczyńska, L. Antkiewicz-Michaluk, A. Kłodzińska, K. Stachowicz, and E. Chojnacka-Wójcik, "Antidepressant-like effect of the selective 5-HT1B receptor agonist CP 94253: A possible mechanism of action," *Eur J Pharmacol*, vol. 516, no. 1, pp. 46–50, May 2005, doi: 10.1016/J.EJPHAR.2005.04.025.
[44] Y. Jiang *et al.*, "Monoamine Neurotransmitters Control Basic Emotions and Affect Major Depressive Disorders," *Pharmaceuticals*, vol. 15, no. 10, Oct. 2022, doi: 10.3390/PH15101203.
[45] J. M. Ritter *et al.*, "Amino acid transmitters - Rang & Dale's Pharmacology - ClinicalKey Student," in *Rang & Dale's Pharmacology*, vol. 10th edition, pp. 509–523. Accessed: Feb. 26, 2024. [Online]. Available: https://www.clinicalkey.com/student/content/book/3-s2.0-B978032387395600038X#hl0000426

[46] M. Banasr *et al.*, “Characterization of GABAergic Marker Expression in the Chronic Unpredictable Stress Model of Depression,” *Chronic Stress*, vol. 1, Aug. 2017, doi: 10.1177/2470547017720459/ASSET/IMAGES/LARGE/10.1177_2470547017720459-FIG4.JPEG.

[47] P. K. Mishra, M. Adusumilli, P. Deolal, G. F. Mason, A. Kumar, and A. B. Patel, “Impaired neuronal and astroglial metabolic activity in chronic unpredictable mild stress model of depression: Reversal of behavioral and metabolic deficit with lanicemine,” *Neurochem Int*, vol. 137, Jul. 2020, doi: 10.1016/j.neuint.2020.104750.

[48] O. F. O’Leary and J. F. Cryan, “GABAB receptors, depression, and stress resilience: a tale of two isoforms,” *Stress Resilience: Molecular and Behavioral Aspects*, pp. 63–79, Jan. 2020, doi: 10.1016/B978-0-12-813983-7.00005-7.

[49] G. Sanacora, G. Treccani, and M. Popoli, “Towards a glutamate hypothesis of depression: An emerging frontier of neuropsychopharmacology for mood disorders,” *Neuropharmacology*, vol. 62, no. 1, pp. 63–77, Jan. 2012, doi: 10.1016/J.NEUROPHARM.2011.07.036.

[50] G. Hasler, J. W. Van Der Veen, T. Tumonis, N. Meyers, J. Shen, and W. C. Drevets, “Reduced Prefrontal Glutamate/Glutamine and γ-Aminobutyric Acid Levels in Major Depression Determined Using Proton Magnetic Resonance Spectroscopy,” *Arch Gen Psychiatry*, vol. 64, no. 2, pp. 193–200, Feb. 2007, doi: 10.1001/ARCHPSYC.64.2.193.

[51] G. Sanacora *et al.*, “Reduced Cortical γ-Aminobutyric Acid Levels in Depressed Patients Determined by Proton Magnetic Resonance Spectroscopy,” *Arch Gen Psychiatry*, vol. 56, no. 11, pp. 1043–1047, Nov. 1999, doi: 10.1001/ARCHPSYC.56.11.1043.

[52] G. Sanacora *et al.*, “Subtype-Specific Alterations of γ-Aminobutyric Acid and Glutamatein Patients With Major Depression,” *Arch Gen Psychiatry*, vol. 61, no. 7, pp. 705–713, Jul. 2004, doi: 10.1001/ARCHPSYC.61.7.705.

[53] Y. I. Sheline, P. W. Wang, M. H. Gado, J. G. Csernansky, and M. W. Vannier, “Hippocampal atrophy in recurrent major depression.,” *Proceedings of the National Academy of Sciences*, vol. 93, no. 9, pp. 3908–3913, Apr. 1996, doi: 10.1073/PNAS.93.9.3908.

[54] T. C. Ho *et al.*, “Higher Levels of Pro-inflammatory Cytokines Are Associated With Higher Levels of Glutamate in the Anterior Cingulate Cortex in Depressed Adolescents,” *Front Psychiatry*, vol. 12, p. 642976, Apr. 2021, doi: 10.3389/FPSYT.2021.642976/BIBTEX.

[55] C. G. Abdallah, G. Sanacora, R. S. Duman, and J. H. Krystal, “The Neurobiology of Depression, Ketamine and Rapid-Acting Antidepressants: Is it Glutamate Inhibition or Activation?,” *Pharmacol Ther*, vol. 190, no. 5, p. 148, Oct. 2018, doi: 10.1016/J.PHARMTHERA.2018.05.010.

[56] J. A. Sheng *et al.*, “The Hypothalamic-Pituitary-Adrenal Axis: Development, Programming Actions of Hormones, and Maternal-Fetal Interactions,” *Front Behav Neurosci*, vol. 14, p. 601939, Jan. 2021, doi: 10.3389/FNBEH.2020.601939/BIBTEX.

[57] F. P. Varghese and E. S. Brown, “The Hypothalamic-Pituitary-Adrenal Axis in Major Depressive Disorder: A Brief Primer for Primary Care Physicians,” *Prim Care Companion J Clin Psychiatry*, vol. 3, no. 4, p. 151, 2001, doi: 10.4088/PCC.V03N0401.

[58] Y. Luo *et al.*, “Dynamic study of the hippocampal volume by structural MRI in a rat model of depression,” *Neurological Sciences*, vol. 35, no. 11, pp. 1777–1783, Nov. 2014, doi: 10.1007/S10072-014-1837-Y/FIGURES/3.

[59] S. MacMillan *et al.*, “Increased Amygdala: Hippocampal Volume Ratios Associated with Severity of Anxiety in Pediatric Major Depression,” *https://home.liebertpub.com/cap*, vol. 13, no. 1, pp. 65–73, Jul. 2004, doi: 10.1089/104454603321666207.

[60] S. W. Y. Chan, C. J. Harmer, R. Norbury, U. O'Sullivan, G. M. Goodwin, and M. J. Portella, "Hippocampal volume in vulnerability and resilience to depression," *J Affect Disord*, vol. 189, pp. 199–202, Jan. 2016, doi: 10.1016/J.JAD.2015.09.021.

[61] D. M. Bannerman, M. A. Good, B. K. Yee, M. J. Heupel, S. D. Iversen, and J. N. P. Rawlins, "Double dissociation of function within the hippocampus: A comparison of dorsal, ventral, and complete hippocampal cytotoxic lesions," *Behavioral Neuroscience*, vol. 113, no. 6, pp. 1170–1188, 1999, doi: 10.1037/0735-7044.113.6.1170.

[62] K. L. Spalding *et al.*, "Dynamics of hippocampal neurogenesis in adult humans," *Cell*, vol. 153, no. 6, p. 1219, Jun. 2013, doi: 10.1016/J.CELL.2013.05.002.

[63] K. M. Christian, H. Song, and G. L. Ming, "Functions and Dysfunctions of Adult Hippocampal Neurogenesis," *Annu Rev Neurosci*, vol. 37, p. 243, 2014, doi: 10.1146/ANNUREV-NEURO-071013-014134.

[64] M. S. Fanselow and H. W. Dong, "Are the Dorsal and Ventral Hippocampus Functionally Distinct Structures?," *Neuron*, vol. 65, no. 1, pp. 7–19, Jan. 2010, doi: 10.1016/J.NEURON.2009.11.031.

[65] C. Anacker and R. Hen, "Adult hippocampal neurogenesis and cognitive flexibility — linking memory and mood," *Nat Rev Neurosci*, vol. 18, no. 6, p. 335, Jun. 2017, doi: 10.1038/NRN.2017.45.

[66] C. C. Chen, C. C. Huang, and K. Sen Hsu, "Chronic Social Stress Affects Synaptic Maturation of Newly Generated Neurons in the Adult Mouse Dentate Gyrus," *International Journal of Neuropsychopharmacology*, vol. 19, no. 3, pp. 1–10, Apr. 2016, doi: 10.1093/IJNP/PYV097.

[67] B. Bassett *et al.*, "Minocycline alleviates depression-like symptoms by rescuing decrease in neurogenesis in dorsal hippocampus via blocking microglia activation/phagocytosis," *Brain Behav Immun*, vol. 91, pp. 519–530, Jan. 2021, doi: 10.1016/J.BBI.2020.11.009.

[68] J. E. Malberg and R. S. Duman, "Cell Proliferation in Adult Hippocampus is Decreased by Inescapable Stress: Reversal by Fluoxetine Treatment," *Neuropsychopharmacology 2003 28:9*, vol. 28, no. 9, pp. 1562–1571, May 2003, doi: 10.1038/sj.npp.1300234.

[69] J. M. Encinas, A. Vaahtokari, and G. Enikolopov, "Fluoxetine targets early progenitor cells in the adult brain," *Proc Natl Acad Sci U S A*, vol. 103, no. 21, pp. 8233–8238, May 2006, doi: 10.1073/PNAS.0601992103/SUPPL_FILE/01992FIG7.PDF.

[70] A. S. Hill, A. Sahay, and R. Hen, "Increasing Adult Hippocampal Neurogenesis is Sufficient to Reduce Anxiety and Depression-Like Behaviors," *Neuropsychopharmacology 2015 40:10*, vol. 40, no. 10, pp. 2368–2378, Apr. 2015, doi: 10.1038/npp.2015.85.

[71] J. E. Malberg, A. J. Eisch, E. J. Nestler, and R. S. Duman, "Chronic Antidepressant Treatment Increases Neurogenesis in Adult Rat Hippocampus," *Journal of Neuroscience*, vol. 20, no. 24, pp. 9104–9110, Dec. 2000, doi: 10.1523/JNEUROSCI.20-24-09104.2000.

[72] D. J. David *et al.*, "Article Neurogenesis-Dependent and-Independent Effects of Fluoxetine in an Animal Model of Anxiety/Depression," *Neuron*, vol. 62, pp. 479–493, doi: 10.1016/j.neuron.2009.04.017.

[73] F. A. Henn and B. Vollmayr, "Neurogenesis and depression: etiology or epiphenomenon?," *Biol Psychiatry*, vol. 56, no. 3, pp. 146–150, Aug. 2004, doi: 10.1016/J.BIOPSYCH.2004.04.011.

[74] A. Surget *et al.*, "Antidepressants recruit new neurons to improve stress response regulation," *Molecular Psychiatry 2011 16:12*, vol. 16, no. 12, pp. 1177–1188, May 2011, doi: 10.1038/mp.2011.48.

[75] J.-H. Stenberg, K. Joutsenniemi, and M. Holi, “Nettiterapiat - mitä tiedetään toimivuudesta,” Lääketieteellinen Aikakausikirja Duodecim. Accessed: Feb. 21, 2024. [Online]. Available: https://www.duodecimlehti.fi/duo12324
[76] H. Eerola, “Psykoterapian aloittaminen ja psykoterapian muodot - Terveyskirjasto,” Lääkärikirja Duodecim. Accessed: Feb. 21, 2024. [Online]. Available: https://www.terveyskirjasto.fi/dlk01311
[77] M. J. Owens, “Selectivity of Antidepressants: From the Monoamine Hypothesis of Depression to the SSRI Revolution and Beyond,” 2004.
[78] “Antidepressant drugs - Rang & Dale’s Pharmacology - ClinicalKey Student.” Accessed: Jan. 17, 2024. [Online]. Available: https://www-clinicalkey-com.ezproxy.utu.fi/student/content/book/3-s2.0-B9780323873956000482#hl0000769
[79] J. M. Ritter *et al.*, “Anxiolytic and hypnotic drugs,” in *Rang & Dale’s Pharmacology*, vol. 10th Edition, 2024, pp. 602–612. Accessed: Jan. 17, 2024. [Online]. Available: https://www-clinicalkey-com.ezproxy.utu.fi/student/content/book/3-s2.0-B9780323873956000457#hl0000288
[80] E. Isometsä and E. Syvälahti, “Lääkeresistentin depression lääkehoidon suuntaviivoja,” Lääketieteellinen Aikakausikirja Duodecim. Accessed: Feb. 21, 2024. [Online]. Available: https://www.duodecimlehti.fi/duo94192
[81] “Efficacy, Safety, and Tolerability of COMP360 in Participants With TRD - Full Text View - ClinicalTrials.gov.” Accessed: Feb. 21, 2024. [Online]. Available: https://classic.clinicaltrials.gov/ct2/show/NCT05624268?term=psilocybin&cond=Depression&phase=2&draw=2&rank=3
[82] “Study Details | A Study to Evaluate the Efficacy of SAGE-217 in the Treatment of Adult Participants With Major Depressive Disorder | ClinicalTrials.gov.” Accessed: Nov. 01, 2023. [Online]. Available: https://clinicaltrials.gov/study/NCT03672175?intr=SAGE-217&cond=depression&aggFilters=results:with&rank=2
[83] A. L. Althaus *et al.*, “Preclinical characterization of zuranolone (SAGE-217), a selective neuroactive steroid GABAA receptor positive allosteric modulator,” *Neuropharmacology*, vol. 181, p. 108333, Dec. 2020, doi: 10.1016/J.NEUROPHARM.2020.108333.
[84] Y. W. Lin *et al.*, “Efficacy and safety of zuranolone in major depressive disorder: a meta-analysis of factor effect and dose-response analyses,” *EClinicalMedicine*, vol. 66, Dec. 2023, doi: 10.1016/j.eclinm.2023.102308.
[85] L. X. Shao *et al.*, “Psilocybin induces rapid and persistent growth of dendritic spines in frontal cortex in vivo,” *Neuron*, vol. 109, no. 16, p. 2535, Aug. 2021, doi: 10.1016/J.NEURON.2021.06.008.
[86] A. E. Calder and G. Hasler, “Towards an understanding of psychedelic-induced neuroplasticity,” *Neuropsychopharmacology*, vol. 48, no. 1, p. 104, Jan. 2023, doi: 10.1038/S41386-022-01389-Z.
[87] H. Lowe *et al.*, “The Therapeutic Potential of Psilocybin,” *Molecules*, vol. 26, no. 10, May 2021, doi: 10.3390/MOLECULES26102948.
[88] “JNK Signaling Pathway - Creative Diagnostics.” Accessed: Oct. 11, 2023. [Online]. Available: https://www.creative-diagnostics.com/JNK-Signaling-Pathway.htm
[89] C. Y. Kuan, D. D. Yang, D. R. Samanta Roy, R. J. Davis, P. Rakic, and R. A. Flavell, “The Jnk1 and Jnk2 Protein Kinases Are Required for Regional Specific Apoptosis during Early Brain Development,” *Neuron*, vol. 22, no. 4, pp. 667–676, Apr. 1999, doi: 10.1016/S0896-6273(00)80727-8.

[90] Y. Zhao *et al.*, “Hypothesis: JNK signaling is a therapeutic target of neurodegenerative diseases,” *Alzheimer’s & Dementia*, vol. 18, no. 1, pp. 152–158, Jan. 2022, doi: 10.1002/ALZ.12370.

[91] J. Zhang *et al.*, “Inhibition of JNK ameliorates depressive-like behaviors and reduces the activation of pro-inflammatory cytokines and the phosphorylation of glucocorticoid receptors at serine 246 induced by neuroinflammation,” *Psychoneuroendocrinology*, vol. 113, p. 104580, Mar. 2020, doi: 10.1016/J.PSYNEUEN.2019.104580.

[92] P. Hollos, J. M. John, J. V. Lehtonen, and E. T. Coffey, “Optogenetic Control of Spine-Head JNK Reveals a Role in Dendritic Spine Regression,” *eNeuro*, vol. 7, no. 1, 2020, doi: 10.1523/ENEURO.0303-19.2019.

[93] S. G. Rosa, A. P. Pesarico, and C. W. Nogueira, “m-Trifluoromethyl-diphenyl diselenide promotes resilience to social avoidance induced by social defeat stress in mice: Contribution of opioid receptors and MAPKs,” *Prog Neuropsychopharmacol Biol Psychiatry*, vol. 82, pp. 123–135, Mar. 2018, doi: 10.1016/J.PNPBP.2017.11.021.

[94] A. Q. Qi, J. Qiu, L. Xiao, and Y. Z. Chen, “Rapid activation of JNK and p38 by glucocorticoids in primary cultured hippocampal cells,” *J Neurosci Res*, vol. 80, no. 4, pp. 510–517, May 2005, doi: 10.1002/JNR.20491.

[95] G. M. Thomas, D. T. Lin, M. Nuriya, and R. L. Huganir, “Rapid and bi-directional regulation of AMPA receptor phosphorylation and trafficking by JNK,” *EMBO Journal*, vol. 27, no. 2, pp. 361–372, Jan. 2008, doi: 10.1038/SJ.EMBOJ.7601969/SUPPL_FILE/EMBJ7601969-SUP-0014.DOC.

[96] P. K. Mukherjee, M. A. DeCoster, F. Z. Campbell, R. J. Davis, and N. G. Bazan, “Glutamate receptor signaling interplay modulates stress-sensitive mitogen-activated protein kinases and neuronal cell death,” *Journal of Biological Chemistry*, vol. 274, no. 10, pp. 6493–6498, Mar. 1999, doi: 10.1074/jbc.274.10.6493.

[97] R. K. Barr, T. S. Kendrick, and M. A. Bogoyevitch, “Identification of the Critical Features of a Small Peptide Inhibitor of JNK Activity,” *Journal of Biological Chemistry*, vol. 277, no. 13, pp. 10987–10997, Mar. 2002, doi: 10.1074/JBC.M107565200.

[98] Y. Zhu *et al.*, “Unraveling the Design and Discovery of c-Jun N-Terminal Kinase Inhibitors and Their Therapeutic Potential in Human Diseases,” *J Med Chem*, vol. 65, no. 5, pp. 3758–3775, Mar. 2022, doi: 10.1021/ACS.JMEDCHEM.1C01947/ASSET/IMAGES/MEDIUM/JM1C01947_0014.GIF.

[99] Q. Wu, W. Wu, V. Jacevic, T. C. C. Franca, X. Wang, and K. Kuca, “Selective inhibitors for JNK signalling: a potential targeted therapy in cancer,” *J Enzyme Inhib Med Chem*, vol. 35, no. 1, pp. 574–583, Jan. 2020, doi: 10.1080/14756366.2020.1720013.

[100] D. Zhang, J. Li, L. Song, W. Ouyang, J. Gao, and C. Huang, “A JNK1/AP-1-dependent, COX-2 induction is implicated in 12-O-tetradecanoylphorbol-13-acetate-induced cell transformation through regulating cell cycle progression,” *Molecular Cancer Research*, vol. 6, no. 1, pp. 165–174, Jan. 2008, doi: 10.1158/1541-7786.MCR-07-0181.

[101] “Study Results | A Study to Evaluate the Efficacy and Safety of CC-90001 in Subjects With Idiopathic Pulmonary Fibrosis | ClinicalTrials.gov.” Accessed: Feb. 23, 2024. [Online]. Available: https://clinicaltrials.gov/study/NCT03142191?intr=jnk&aggFilters=status:ter&rank=2&tab=results#publications

[102] Z. Popmihajlov *et al.*, “CC-90001, a c-Jun N-terminal kinase (JNK) inhibitor, in patients with pulmonary fibrosis: design of a phase 2, randomised, placebo-controlled trial,” *BMJ Open Respir Res*, vol. 9, no. 1, p. e001060, Jan. 2022, doi: 10.1136/BMJRESP-2021-001060.

[103] A. Messoussi *et al.*, “Recent Progress in the Design, Study, and Development of c-Jun N-Terminal Kinase Inhibitors as Anticancer Agents,” *Chem Biol*, vol. 21, no. 11, pp. 1433–1443, Nov. 2014, doi: 10.1016/J.CHEMBIOL.2014.09.007.
[104] “Study Details | PGL5001 Proof of Concept Study in Inflammatory Endometriosis | ClinicalTrials.gov.” Accessed: Feb. 23, 2024. [Online]. Available: https://clinicaltrials.gov/study/NCT01630252?intr=PGL5001&rank=1
[105] O. Dick and H. Bading, “Synaptic activity and nuclear calcium signaling protect hippocampal neurons from death signal-associated nuclear translocation of FoxO3a induced by extrasynaptic N-methyl-D-aspartate receptors,” *Journal of Biological Chemistry*, vol. 285, no. 25, pp. 19354–19361, Jun. 2010, doi: 10.1074/jbc.M110.127654.
[106] R. S. McIntyre *et al.*, “Synthesizing the Evidence for Ketamine and Esketamine in Treatment-Resistant Depression: An International Expert Opinion on the Available Evidence and Implementation,” *Am J Psychiatry*, vol. 178, no. 5, p. 383, May 2021, doi: 10.1176/APPI.AJP.2020.20081251.