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REVIEW

The role of serotonin in depression—A historical roundup and future directions

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Abstract

Depression is one of the most common psychiatric disorders worldwide, affecting approximately 280 million people, with probably much higher unrecorded cases. Depression is associated with symptoms such as anhedonia, feelings of hopelessness, sleep disturbances, and even suicidal thoughts. Tragically, more than 700000 people commit suicide each year. Although depression has been studied for many decades, the exact mechanisms that lead to depression are still unknown, and available treatments only help a fraction of patients. In the late 1960s, the serotonin hypothesis was published, suggesting that serotonin is the key player in depressive disorders. However, this hypothesis is being increasingly doubted as there is evidence for the influence of other neurotransmitters, such as noradrenaline, glutamate, and dopamine, as well as larger systemic causes such as altered activity in the limbic network or inflammatory processes. In this narrative review, we aim to contribute to the ongoing debate on the involvement of serotonin in depression. We will review the evolution of antidepressant treatments, systemic research on depression over the years, and future research applications that will help to bridge the gap between systemic research and neurotransmitter dynamics using biosensors. These new tools in combination with systemic applications, will in the future provide a deeper understanding of the serotonergic dynamics in depression.

KEYWORDS
depression, antidepressants, mechanisms, serotonin, systems, biosensors

Abbreviations: 5-HIAA, 5-hydroxyindoleacetic acid; 5-HT, serotonin, 5-hydroxytryptamin; 5-HTIAA, 5-hydroxyindoleacetic acid; 5-HT_R, serotonin receptor; 5-HTT, 5-hydroxytryptamin transporter; 5-HTTLPR, 44 bp repeat polymorphism in the 5-htt linked polymorphic region; AMY, amygdala; AN, affective network; BDNF, brain-derived neurotrophic factor; cAMP, cyclic adenosine monophosphate; CCN, cognitive control network; ChR2, channelrhodopsin 2; DA, dopamine; DBS, deep brain stimulation; dlPFC, dorsolateral prefrontal cortex; DMN, default mode network; DMT, 5-methoxy-n,n-dimethyltryptamine; DOPAC, 3, 4-dihydroxyphenylacetic acid; DREADDs, designer receptors exclusively activated by designer drugs; DRN, dorsal raphe nucleus; DSM, the diagnostic and statistical manual of mental disorders; FDA, food and drug administration; FLIM, fluorescence lifetime imaging microscopy; fMRI, functional magnetic resonance imaging; GFP, green fluorescent protein; $G_{i/o}$, inhibitory G-protein; GPCR, G-protein coupled receptors; G_q, stimulatory G-protein; G_s, stimulatory G-protein; GWAS, genome-wide association studies; GxE studies, gene–environment interaction studies; HIP, hippocampus; IGF-1, insulin-like growth factor-1; IL, infralimbic cortex; IPC, inferior parietal cortex; KO, knock-out; LSD, lysergic acid diethylamide; MAO, monoamine oxidase; MDD, major depressive disorder; mPFC, medial prefrontal cortex; MRN, median raphe nucleus; mTor, mammalian target of rapamycin; NA, noradrenaline; NMDA, glutamatergic n-methyl-d-aspartate; OFC, orbitofrontal cortex; Opto-MASS, optogenetic microwell array screening system; OR, odds ratio; PBP, periplasmic binding protein; PCC, posterior cingulate cortex; PET, positron-emission-tomography; PFC, prefrontal cortex; PrL, prelimbic cortex; RN, reward network; SNP, single nucleotide polymorphism; SNRI, serotonine noradrenaline reuptake inhibitor; SSRI, selective serotonin reuptake inhibitor; TCA, tricyclic antidepressant; TPH, tryptophane; TPH2, tryptophane hydroxylase 2; vACC, ventral anterior cingulate cortex; VEGF, vascular endothelial growth factor; vlPFC, ventrolateral prefrontal cortex; vmPFC, ventromedial prefrontal cortex; VNTR, variable-number-tandem-repeat region in the second intron.

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1 | INTRODUCTION

Depression is one of the most common mental disorders worldwide, affecting approximately 280 million people worldwide (WHO, 2023). Major depressive disorder (MDD) is characterized by the inability to feel pleasure (anhedonia), loss of interest in activities, sadness, depressed mood, loss of energy, impaired cognitive functions, and vegetative symptoms such as disrupted sleep and changes in appetite and weight (American Psychiatric Association, 2022). Over the past decades, there has been increasing evidence that depression is associated with neurotransmitter dysregulation, with serotonin playing a key role. Although depression has been studied for many years, its mechanisms and etiology remain poorly understood. The balancing act of mental health relies on the maintenance of brain homeostasis and the finely-tuned interplay of neurotransmitters, neuromodulators, hormones, and other signaling molecules that regulate complex processes such as cognition, behavior, emotion, and mood. However, disruptions to this dynamic system can lead to neurochemical imbalances, resulting in a cascade of neurobiological changes with far-reaching consequences. Mental disorders such as depression can be triggered by influences such as genetic, epigenetic, environmental, and stress-related vulnerabilities. Understanding the etiology and pathophysiology of mental disorders, such as MDD, requires a comprehensive understanding of basic signaling pathways and neurotransmitter dynamics in health and disease.

This review focuses on the role of serotonin in depression and gives an overview of the history of depression research, the development of the serotonin hypothesis, the systemic research over the years, and the technical implementation of neurotransmitter imaging with optogenetic methods and genetically encoded biosensors. It is important to note that the following manuscript is not a systematic review or meta-analysis of serotonergic evidence in depression based on a pre-defined theory. Instead, the aim is to narrate the story of how serotonin was initially linked to depression and how a whole research branch evolved around this neurotransmitter. Although systemic research provides compelling evidence, it points towards a disturbed serotonergic system in depression, highlighting the complexity of this mental disorder. This complexity is further illustrated by the growing body of evidence that the brain-gut-microbiome axis also has a role in the development of mental disorders such as depression. However, these findings will not be discussed here (for further reading see: (Foster & McVey Neufeld, 2013; Simpson et al., 2021)). Although the focus here is on serotonin, depression should not be considered exclusively as a serotonin-based disease, but rather a heterogeneous and highly complex disorder involving various biochemical systems. In this review, we further want to highlight the future of systemic research with newly advancing tools to visualize neurotransmitter and neuromodulator systems, making it possible to draw more precise conclusions about the biological underpinnings of MDD.

2 | HISTORY OF CLINICAL AND PHARMACOLOGICAL RESEARCH

This section will provide a historical overview of serotonin as a modulator of depression and the serotonin hypotheses of depression. However, serotonin as a neuromodulator is not only associated with depression but also affects aggression, anxiety, sexual behavior, gastrointestinal functions, and many other physiological functions. For more information, see the review by Olivier (Olivier, 2014).

2.1 | The early history of depression

Depression is a mental disease that was already described during the ancient era under the name Melancholia by Hippocrates (Lewis, 1934). Since melancholia was not only depression but rather a combination of several mental problems, hundreds of years later melancholia was still being discussed by various psychiatrists, historians, physicians, and more. For an overview of the milestones in the history of depression, see Figure 1. It was not before 1899 when Emil Kraepelin classified mental disorders, which were still included under the term melancholia, into dementia praecox, and manic-depressive insanity. It was Adolf Meyer, a Swiss psychiatrist, who coined the term depression six years later (Jansson, 2021; Kraepelin, 1899). When the 3rd edition of "The Diagnostic and Statistical Manual of Mental Disorders" (DSM)

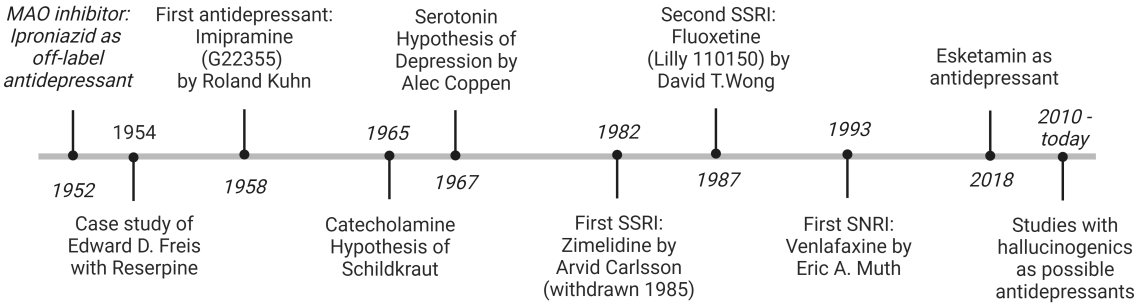

FIGURE 1 Overview of the milestones in the history of depression starting from the first evidence suggesting a serotonergic influence in depression in the 1950s up to the most recent pharmacological findings. Created with biorender.com.

was published by the American Psychiatric Association in 1980, depression as an affective disorder was included under the two diagnoses "Major Depressive Episode" and "Major Depression". While a Major Depressive Episode" reflects a single incidence of depressive symptoms such as anhedonia, fatigue, and feelings of worthlessness lasting at least 2 weeks, "Major Depression" reflects recurrent depressive episodes. (American Psychiatric Association, 1980).

2.2 | The first theories of depression

2.2.1 | The catecholamine hypothesis of affective disorders

The idea that depression is caused by serotonin (5-HT) imbalance first emerged in 1954, when Edward D. Freis made interesting observations in 5 patients who were treated with reserpine. Reserpine is an extract of *rauwolfia serpentina*, a plant from the family of *apocynaceae*. It was initially used in the treatment of hypertension because of its sympatholytic effects on blood pressure. Its antihypertensive action is modulated by the inhibition of catecholamine reuptake by binding to monoamine transporters (Cheung & Parmar, 2023). Freis analyzed the cases of 5 patients treated for hypertension. All of them showed depressive-like symptoms such as sleep disturbance, anhedonia, and suicidal thoughts after long-term treatment with high doses of reserpine. In all patients, the depressive symptoms disappeared after the withdrawal of reserpine. He, therefore, hypothesized an unknown mechanism of reserpine that could lead to depression (Freis, 1954). Freis' hypothesis was supported by several other subsequent case studies. Patients who were treated with drugs other than reserpine showed no mental symptoms, while patients treated with reserpine developed depressive symptoms (Kass & Brown, 1955; Lemieux et al., 1956; Muller et al., 1955; Nick, 1955; Quetsch et al., 1959).

Studies on the mechanisms of reserpine-induced effects revealed a direct influence of reserpine on monoamines such as serotonin, dopamine (DA), and noradrenalin (NA). In 1955 Shore, Silver, and Brodie postulated that the treatment of dogs with reserpine leads to a high amount of 5-hydroxyindoleacetic acid (5-HTIAA) excretion, which is a metabolite of serotonin. Furthermore, they suggested that the 5-HTIAA originated from internal stores, as they were not able to show 5-HTIAA excretion after a second dose of reserpine (Shore et al., 1955). In 1956, Paasonen and Vogt examined brain tissue from the hypothalamus and caudate nucleus of dogs after intraperitoneal (i.p.) injections of reserpine. The amount of 5-HT was significantly reduced in both brain regions (Paasonen & Vogt, 1956). Carlsson, who investigated the mechanism of Mg^{2+}-ATP-dependent storage of amines in the adrenal medulla, showed that the storage mechanism of DA and adrenaline was blocked by reserpine (Carlsson et al., 1962). In 1963, Häggendal and Lindqvist studied the long-term effects of reserpine on the monoamines. After treating rabbits with reserpine for several weeks, levels of monoamines decreased by 20–30 percent (Häggendal & Lindqvist, 1963). The finding that reserpine acts on monoamine metabolism was confirmed by several other studies during the following years (Ahtee et al., 1970; Bertler et al., 1961; Häggendal et al., 1967; Häggendal & Lindqvist, 1963). Later it was shown that the effect of reserpine on monoamines is mediated by inhibition of the vesicular monoamine transporter-2 (VMAT-2). This leads to the depletion of serotonin, dopamine, and noradrenalin by the monoamine oxidase (MAO), which catalyzes the oxidation of 5-HT, NA, and DA (Baumeister et al., 2003; Cheung & Parmar, 2023; Strawbridge et al., 2023).

Taken together, the research on reserpine led to the conclusion that depression is caused by a deficiency in monoamine transmission. This hypothesis has persisted to the present day, and reserpine is still used as a model for depression in mice (Greenwood et al., 2018; Kim et al., 2021; Park et al., 2018; Qian et al., 2023). Nevertheless, the assumption that reserpine induces depression is in question. In 2018, Zhu et al. failed to find a correlation between using reserpine and depressive symptoms when they conducted a cross-sectional study (Zhu et al., 2019). When Baumeister, Hawkins, and Uzelac analyzed case reports and group studies on reserpine-induced depression they concluded that there is no valid evidence for a reserpine-induced depression. They found an overall prevalence of depression of 10% in patients treated with reserpine (Baumeister et al., 2003). A recent systemic review by Strawbridge et al. also concluded that there is no direct evidence of reserpine-induced depression (Strawbridge et al., 2023).

While research on reserpine was taking place, two other agents came into focus: These agents were iproniazid and isoniazid, which were originally utilized for the treatment of tuberculosis (Bloch et al., 1954; Collins & Bowen, 1953; Selikoff & Robizek, 1952). When Zeller and Barsky studied the mechanism of both agents, they showed an inhibitory effect on MAO both in vitro and in vivo (Zeller et al., 1952; Zeller & Barsky, 1952). The same year the physicians Selikoff and Robizek studied the properties of isoniazid and iproniazid to test the medical benefits of tuberculosis and noticed a change in the mood of these patients. They evaluated not only somatic symptoms but also "the sense of strength and well-being" of the patients. The patients, especially those treated with iproniazid, showed a gain in "well-being" (Selikoff & Robizek, 1952). The antidepressant effect was further confirmed by studies done in 1957 and in 1959. Depressive patients were treated with iproniazid for several weeks. In both studies, patients showed an improvement in symptoms after treatment (Loomer et al., 1957; Pare & Sandler, 1959). Later, the inhibitory effect on MAO was identified as the antidepressant effect (Ganrot et al., 1962; Randall & Bagdon, 1959). Iproniazid was used off-label as an antidepressant until 1961 when it was withdrawn from the market due to cases of hepatitis as a side effect.

Upon the research on reserpine and its action on monoamines and the findings that the MAO inhibitor iproniazid acts as an antidepressant Schildkraut introduced the "Catecholamine Hypothesis of affective disorders [...]" in which he stated the importance of

catecholamines in psychiatric disorders. The catecholamine hypothesis suggests a deficiency of monoamines, especially noradrenaline, as the cause of affective disorders (Schildkraut, 1965).

2.3 | The serotonin hypothesis

The first commercially available antidepressant was introduced by Roland Kuhn in 1958, initially called G22355 and later named imipramine. Until that time, electroshock therapy was the only official treatment for depression other than psychotherapy.

Imipramine was synthesized as an improvement of chlorpromazine, the first antipsychotic drug. Kuhn couldn't find any improved antipsychotic symptoms of schizophrenic patients when he did clinical studies but rather observed antidepressant effects. During a three-year lasting study "over 500" patients with psychiatric disorders were treated with imipramine. The best response was observed in patients with "endogenous depression," a term used to classify depression caused by internal factors rather than external factors, as in what was called "exogenous depression" during this time (American Psychiatric Association, 1995). Several symptoms were improved after treatment like suicidal thoughts, fatigue, and hopelessness. Kuhn recommended a treatment that should last at least as long as the depression lasts (Kuhn, 1958). The efficacy of imipramine was validated by Lehmann et al. later that year. Like Kuhn, he observed the best improvement in patients with "endogenous depression". After 8 weeks, 60 percent of the patients recovered from depression or showed an improvement. Lehmann as well as Kuhn, reported only a low-side effect rate (Lehmann et al., 1958). Imipramine didn't show inhibition of MAO but inhibits the reuptake of serotonin and noradrenalin (Carlsson et al., 1968; Glowinski & Axelrod, 1964; Lehmann et al., 1958; Meek et al., 1970). As the chemical structure of imipramine consists of 3 atomic rings attached to a tertiary amine, it was named a tricyclic antidepressant (TCA).

It was Alec Coppen who published the serotonin hypothesis of depression in his review "The Biochemistry of affective disorders" (Coppen, 1967). In this paper, he analyzed the studies that were published in the last decades, including studies on reserpine, iproniazid, and other MAO inhibitors, as well as imipramine. The importance of monoamines, especially 5-HT, was finally communicated. In his summary, he mentioned the lack of antidepressant effects of the catecholamine precursor DOPAC, but that in fact tryptophan, the precursor of 5-HT, was able to increase the antidepressant efficacy of MAO inhibitors. He also noted that tryptamine, a precursor of serotonin, is decreased in depressive patients. He not only pointed to the importance of 5-HT but also discussed a possible role of electrolytes that could further influence 5-HT metabolism.

2.4 | Antidepressants

This paragraph provides a summary of the most commonly used antidepressants and their effects on depression. For more detailed information, see the review by Hillhouse and Porter (Hillhouse & Porter, 2015).

2.4.1 | Tricyclic antidepressants (TCAs)

The antidepressant effect of TCAs is modulated by the inhibition of the reuptake of serotonin and noradrenalin as mentioned above. After the Food and Drug Administration (FDA) approved imipramine (Tofranil®) in 1959, several other TCAs were developed by modifying the chemical structure of imipramine. In total, 7 other TCAs were approved by the FDA during the following years, namely trimipramine (1961), amitriptyline (1961), nortriptyline (1964), desipramine (1964), protriptyline (1967), doxepin (1969), and amoxapine (1979) (Fangmann et al., 2008). In 1961, Garattini et al. (1962) investigated the effect of imipramine and amitriptyline on the pharmacological action of reserpine. They observed not only the prevention of reserpine-induced physical symptoms such as hypothermia and gastric ulcer but also that imipramine increased brain 5-HT, while its derivative desipramine had no effect on 5-HT levels. The action of serotonin was confirmed in 1970 by Meek et al. They studied the effects of imipramine and "other drugs of the imipramine type" in rats. After injection of imipramine and clomipramine 5-HT induced effects were potentiated, whereas there was a lack of effect after injection of desipramine and protriptyline. Moreover, the effect of imipramine and clomipramine was correlated with a decreased amine level in 5-HT neurons and an increase in extracellular 5-HT (Meek et al., 1970).

Several other studies also resulted in the assumption, that imipramine as well as clomipramine are effecting 5-HT transmission (Carlsson, 1966; Gyermek & Possemato, 1960; Kivalo et al., 1961). But not only the effect of imipramine and related drugs on 5-HT was investigated. The influence on noradrenaline transmission was also of interest, since desipramine did not affect 5-HT transmission (Meek et al., 1970).

For instance, Glowinski and Axelrod investigated the influence of desipramine and amitriptyline on the uptake of NA in the brains of rats. Desipramine as well as amitriptyline treatment lead to reduced uptake of tritiated NA (Glowinski & Axelrod, 1964).

A few years later, Häggendal and Hamberger performed an in vitro study, in which they incubated slices of rat brains with reserpine (to deplete amines) and nialamide (to block MAO) and subsequently with desipramine. The desipramine incubation resulted in inhibition of NA uptake (Häggendal & Hamberger, 1967).

Later, the difference in the tendency to inhibit the uptake of NA or 5-HT was explained by the difference in the chemical structure of TCAs. The TCAs that have a higher tendency to inhibit 5-HT reuptake are those that contain a tertiary amine, such as amitriptyline, doxepin, imipramine, and trimipramine. TCAs containing a secondary amine, such as desipramine, nortriptyline, and protriptyline, have a higher affinity to inhibit NA reuptake. The affinity to inhibit the reuptake of NA or 5-HT varies depending on the metabolization of the TCAs to their active metabolite by cytochrome P450 (CYP) isoforms,

while the chemical structure of them affects this metabolization (Gillman, 2007; Rudorfer & Potter, 1989, 1999).

Tricyclic antidepressants (TCAs) not only affect the reuptake of NA or 5-HT but also impact various transmitter receptors including histamine, muscarinic, and adrenergic receptors. This broad spectrum of interactions also results in a wide range of side effects. Several studies have shown the tendency of TCAs to induce seizures in both animal models and humans (Koella et al., 1979; Peterson et al., 1985; van Merter et al., 1959; Wroblewski et al., 1990). Not only seizures are a problematic side-effect but also atropine-like effects due to the inhibitory effect on muscarinic receptors. This condition causes side effects like constipation, dry mouth, blurry vision, and even sinus tachycardia and cognitive dysfunction. There have been some reports of serious side effects and sudden death caused by an overdose of TCAs as well as by therapeutic doses of TCAs (Marshall & Forker, 1982; Moir et al., 1972; Sacks et al., 1968).

Today, TCA's are used as a second-line treatment, as they show a higher risk of side effects compared to other antidepressants that are available.

2.4.2 | Selective serotonin reuptake inhibitors (SSRIs)

The first selective serotonin reuptake inhibitor (SSRI) zimelidine (Zelmid®) was approved in Europe in 1982. It was synthesized by Arvid Carlsson in cooperation with the Swedish firm Astra in 1971.

Based on the findings that TCAs have an impact on the reuptake of serotonin, Carlsson and his colleague Hans Corrodi developed zimelidine, which was derived from pheniramine, a Histamin-H1-Receptor inhibitor. In clinical trials, zimelidine showed to be an efficient antidepressant (ÅBerg-Wistedt, 1982; Benkert et al., 1977; Carlsson, 1982).

However, zimelidine was withdrawn from market in 1983, as there were cases of Guillain–Barre syndrome, a form of polyneuropathy. Fagius et al. (1985) reviewed cases of Guillain–Barre syndrome and found a 25-fold increased risk of developing this syndrome when patients were treated with zimelidine.

While Astra was introducing zimelidine, another SSRI was developed and published in 1974 by Wong et al. which they called Lilly 110140 and was later introduced as fluoxetine. Wong et al synthesized Lilly 110140 on the basis of diphenhydramine, an antihistamine that showed antidepressant properties. In measurements using synaptosomes of rat brains Lilly 110140 showed to be a highly selective 5-HT reuptake inhibitor. Furthermore, in vivo experiments confirmed the findings of the in vitro study (Wong et al., 1974). The efficiency of fluoxetine was confirmed by several clinical studies (Emslie, 1997; Hillhouse & Porter, 2015; Wong et al., 1995, 2005). When the efficacy of fluoxetine was compared to that of imipramine it was found to have greater antidepressant effects as well as less side-effects than imipramine (Bremner, 1984). In 1985, the efficacy of fluoxetine was compared with that of amitriptyline. Although both drugs were shown to have antidepressant effects, amitriptyline was less efficient, because patients treated with amitriptyline had a wider range of side effects, including side effects that led to discontinuation of the drug (Chouinard, 1985; Feighner, 1985).

Fluoxetine was approved in 1987 and reached the market in 1988 under the name Prozac®. Following fluoxetine, the FDA approved several other SSRIs that were developed in the following years. In 1991, sertraline (Zoloft®) was introduced followed by paroxetine (Paxil®) in 1992 and citalopram (Celexa®) in 1998 (Huskamp et al., 2008). The FDA later approved 2 further SSRIs. In 2002, Escitalopram (Lexapro®) the active S-Enantiomer of citalopram was introduced. Most recently the SSRI vilazodone (Viibryd®) was approved in 2011.

A common mechanism of SSRIs is to block the human 5-HT-transporter (5-HTT), which increases 5-HT at the synaptic cleft, thereby prolonging the time that 5-HT activates postsynaptic 5-HT receptors (Hillhouse & Porter, 2015; Preskorn, 1997; Rudorfer & Potter, 1989; Xue et al., 2016). While the effect on the reuptake of 5-HT is an acute effect, the onset of antidepressants action is delayed 2–4 weeks (Hervás & Artigas, 1998; Tollefson & Holman, 1994). This discrepancy between the immediate pharmacological effects and the delayed antidepressant effect is still being discussed and not fully understood. In 2017, Fritze, Spanagel, and Noori conducted a meta-analysis of in vivo microdialysis studies that measured extracellular 5-HT levels after SSRI administration in rats. Depending on the brain area, 5-HT levels increased (e.g. prefrontal cortex, hippocampus) or decreased (frontal cortex) within 3 days (Fritze et al., 2017). To date, the delayed antidepressant effect has been attributed to modulatory effects at the synapses leading to desensitization of serotonergic 5-HT_{1A} receptors, a receptor type strongly implicated in the development and maintenance of depression (Commons & Linnros, 2019; Fritze et al., 2017; Hervás & Artigas, 1998). Recently, downstream effects are also considered. The change in 5-HT transmission may result in adaptational changes in gene expression and further in neuropsychological changes including an adaptation of an emotional bias (Harmer et al., 2009; Zhang et al., 2020).

2.4.3 | Serotonin noradrenalin reuptake inhibitors (SNRIs)

As discussed above, the antidepressant effect of some agents is not only mediated by inhibition of 5-HT reuptake but may also be mediated by inhibition of NA reuptake, as in the case of desipramine and nortriptyline. The assumption that 5-HT reuptake inhibition together with NA reuptake inhibition may produce more effective antidepressant effects led to the development of agents that inhibit both 5-HT reuptake and NA reuptake, the serotonin-noradrenaline reuptake inhibitors (SNRIs).

In 1993, the FDA approved the first developed SNRI, venlafaxine (Effexor®). When Muth et al. screened for agents capable of inhibiting "rat brain imipramine receptors", which is the later named 5-HT-transporter 5-HTT, they found the ethylcyclohexanol

derivative Wy-45 030. Examination of the binding profile of Wy-45 030 using rat brain homogenates revealed a higher affinity to bind the "imipramine receptors" compared to desipramine and an equal affinity compared to imipramine itself. Wy-45 030 also showed high selectivity to reuptake 5-HT, NA, and to a small extent dopamine, without any affinity for other receptors.

Based on these properties, the author suggested a possible antidepressant effect of Wy-45 030 (Muth et al., 1986). Wy-45 030 is the agent that was later approved under the name venlafaxine. A double-blind study in 1998 demonstrated not only the antidepressant effect of venlafaxine but also an early onset of the antidepressant effect compared to SSRIs. In a study in which patients with MDD were treated with venlafaxine for 6 weeks, a significant number of patients showed an onset of action within the first 2 weeks, which was considered early onset, as other antidepressants have an onset of action of 2–4 weeks (Entsuah et al., 1998). The effect of venlafaxine treatment was compared with the effect of fluoxetine treatment over several weeks in clinical trials. Depending on the dose administered, venlafaxine showed comparable antidepressant effects (75 mg) and increased antidepressant effects (150 mg) compared to fluoxetine, while the incidence of side effects was similar regardless of dose. For both treatments, venlafaxine and fluoxetine, the most common side effects were nausea, headache, and dry mouth (Diaz-Martinez et al., 1998; Dierick et al., 1996). Several other studies confirmed the dose-dependent superiority of Wy-45 030 over fluoxetine and other SSRIs (Bauer et al., 2009; de Nayer et al., 2002; Smith et al., 2002; Stahl et al., 2002).

Up to date, there are five SNRIs available. Duloxetine (Cymbalta®) was the second SNRI that was approved in 2004, 4 years later the single active metabolite of venlafaxine, desvenlafaxine (Pristiq®) was approved, milnacipran (Savella®) was approved in 2009 and the active l-enantiomer of milnacipran, levomilnacipran (Fetzima®) was the last SNRI approved in 2013. It should be noted, that milnacipran is not approved for the treatment of depression but for treatment of fibromyalgia, while all other named SNRIs have an approval for the treatment of MDD (Sansone & Sansone, 2014).

2.4.4 | Other antidepressants

The most recent available antidepressant is ketamine. Initially, ketamine was introduced as an anesthetic drug. Compared to other available antidepressant agents, ketamine has a rapid onset of action, only one dose is necessary for an antidepressant effect in less than 24 h. In clinical trials treatment with low doses of intravenous ketamine resulted in a significant reduction in symptoms within hours (Berman et al., 2000; DiazGranados et al., 2010; Zarate et al., 2006).

Ketamine antagonizes the glutamatergic N-methyl-D-aspartate receptor (NMDA) and has no direct influence on 5-HT or NA transmission, like other approved antidepressants. However, it was discovered that ketamine increases 5-HT levels as well as NA levels inside the medial prefrontal cortex (mPFC) of mice. Furthermore, ketamine increased glutamate efflux within the dorsal raphe nucleus (DRN) and the mPFC (López-Gil et al., 2019; Pham et al., 2017). Ketamine also affects several other signaling molecules inside the brain. Growth factors such as the vascular endothelial growth factor (VEGF), the insulin-like growth factor-1 (IGF-1), the brain-derived neurotrophic factor (BDNF), and the mammalian target of rapamycin (mTOR) are increased by ketamine. These factors have been suggested to be decreased in patients with MDD (Deyama & Kaneda, 2023; Iadarola et al., 2015; Pham et al., 2020). In 2018, esketamine, the S (+) enantiomer of ketamine was approved by the FDA as a nasal spray only for the treatment of treatment resistant MDD. Esketamine should be used in combination with an oral antidepressant (FDA, 2019).

Not only ketamine as an antidepressant has come into the focus of interest, but also hallucinogens such as psilocybin, mescaline, lysergic acid diethylamide (LSD) and 5-methoxy-N,N-dimethyltrypta mine (DMT) have recently been explored in micro doses as antidepressant agents. Most of these agents act on different neurotransmitter systems not only glutamate dopamine but also serotonin (De Gregorio et al., 2018). LSD for instance, seems to act mainly by binding to serotonin receptors with a high affinity for the 5-HT_{2A} receptor (Baumeister et al., 2014). DMT is known to act through the 5-HT_{2A}, 5-HT_{2C}, and 5-HT_{1A} receptors (Riga et al., 2016).

Currently, there are not many completed clinical studies on microdosing. The few clinical studies with some hallucinogens are inconsistently. In 2021, Davis et al. published a study in which they investigated the effect of psilocybin. They found a significant decrease in depression after 1 week of treatment for patients diagnosed with MDD (Davis et al., 2021). When Kuypers reviewed 14 clinical studies in which low doses of LDS or psilocybin were administered, it was concluded that both agents showed "no, to very subtle" effects on mood state and cog-*99 + nitive functions. Furthermore, LSD may increase anxiety and "cycling pattern of depression and euphoric mood state" (Kuypers, 2020). Recently, the FDA published its first guidance on clinical research with hallucinogens. They point out the importance of further investigations on the promising psychedelic drugs (FDA, 2023).

3 | SYSTEMIC RESEARCH ON THE RELATIONSHIP BETWEEN THE SEROTONERGIC SYSTEM AND DEPRESSION OVER THE COURSE OF THE YEARS

The findings that antidepressant medications influence serotonergic neurotransmission motivated systemic research about the role of serotonin in the etiology of depression. Different branches of research can be assigned to this objective, with the following three being the core areas outlined in this subchapter. First, genetic studies will be sketched. Starting immediately after the findings on antidepressant mechanisms, genetic studies focus on serotonin-related genetic predispositions for depression. Secondly, molecular studies will be described which took off almost simultaneously to genetic

research. The focus here lies in investigating the implications of the serotonergic transporter and the serotonergic receptors in depression. While one of the main focuses of these two branches is to identify "spots of interest,", revealing the most promising components of the serotonergic system, the last area comprising connectivity studies set out to better understand the global role of serotonin and connect its influence to aberrant brain circuits within the depressed brain. The most important findings of each research area are summarized in Table S1. It is important to clarify that the following section should not be considered a meta-analysis of systemic research studies. Other systemic reviews and meta-analyses have evaluated each aspect of systemic research individually, and these will be provided in the following chapter in the appropriate sections. This chapter serves as an overview of the evidence regarding serotonin and depression, as indicated by systemic research over the years. It aims to demonstrate the evolution of the serotonin theory of depression since its first description in the 1960s to its evolvement through advancements in basic research and to numerous sub-hypotheses.

At this point, let it be shortly described how such a complex disorder as depression can be modeled in animals, more specifically, in rodents. First of all, it must be clear that "major depressive disorder" as a diagnostic term cannot be fully modeled in animals as such due to its differential psychological and physiological variations and implications in human patients. Instead, researchers aim to elicit "depressive-like states" in animals through different methodological approaches. One approach is to generate genetic depression models via the genetic knock-out (KO) of a risk allele. Since chronic stress is considered a key factor for causing depression, the second approach for modeling is through inducing chronic stress in rodents. Various paradigms exist for this purpose, which make use of either environmental stress (through a paradigm called the chronic mild stress test) (Willner, 2017) or social stress. Different approaches can be used to trigger social stress both in early-life, as well as in adulthood. Examples of the most often used ones are maternal separation (Vetulani, 2013) and chronic social defeat stress (Golden et al., 2011). The choice of which paradigm to use depends on the strengths and limitations of each test, as reviewed by Becker et al. (Becker et al., 2021).

How to assess the actual success to elicit a depressive-like state, the so-called validity of animal models, was first reviewed by McKinney and Bunney in 1969 (McKinney, 1969) and later postulated in the form of three assessment categories by Willner (Willner, 1984). The three categories are summarized in Figure 2 and comprise (1) construct validity, assessing whether pathophysiological processes, such as genetic and molecular ones, in a model resemble those in humans; (2) face validity, assessing whether a model recapitulates depression-related phenotypic characteristics like anhedonia; and (3) predictive validity, assessing whether a model responds to different types of antidepressant treatment (Willner, 1984). Even though these values got even more refined throughout the years (Belzung & Lemoine, 2011; Gururajan et al., 2019), the three basic assessment criteria still need to be met whenever using animal models of depression.

3.1 | Getting to know the serotonergic system

As a neurotransmitter, serotonin (5-HT) is involved in various processes, like mood, sleep, and arousal, as well as learning and memory (Berger et al., 2009). The main root of the serotonergic system projecting to the forebrain can be found in the raphe nuclei, more precisely, in the median and dorsal raphe nuclei (MRN and DRN, resp.) which are located in the midbrain. There, serotonin gets synthesized from its precursor tryptophan (Trp) whose rate-limiting enzyme is the brain-specific isoform of the tryptophane hydroxylase 2 (TPH2; Walther et al., 2003). Once synthesized, serotonin is released from serotonergic neurons in the MRN and DRN to target other neurons all over the forebrain. Most of the collaterals go to the prefrontal cortex (PFC) and limbic regions, such as the amygdala (AMY) and the hippocampus (HIP), where serotonin exhibits a mostly inhibitory effect on neuronal activity (Courtney & Ford, 2016; Saulin et al., 2012; Smith et al., 2021). Next to collaterals that are sent out from the raphe nuclei, there are also feedback collaterals to the raphe nuclei whose activity is regulated by target regions such as the PFC (Aghajanian & Wang, 1977; Hajós et al., 1998; Lingawi et al., 2019; López-Terrones et al., 2022).

Unsurprisingly, the PFC and limbic regions have the highest abundance of serotonergic receptors which make signaling possible in the first place (Albert et al., 1990; Barnes & Sharp, 1999). The serotonergic receptors (5-HTR) comprise one of the largest neurotransmitter receptor families categorized in seven main receptor types and 14 subtypes (Nichols & Nichols, 2008). With the exception of 5-HT_3 receptors which are ligand-gated ion channels, all 5-HTR are G-protein coupled. $5\text{-HT}_{1/5}$ receptors are coupled to the $G_{i/o}$ pathway which inhibits adenylyl cyclases, leading to a decreased production of the intracellular messenger cyclic adenosine monophosphate (cAMP). With this, $5\text{-HT}_{1/5}$ receptors act inhibitory on their target neurons (Nichols & Nichols, 2008). On the contrary, $5\text{-HT}_{4/6/7}$ receptors bind to a G_s protein exerting a stimulatory effect on their target neurons by activating adenylyl cyclases, thereby increasing cAMP levels (Nichols & Nichols, 2008). The 5-HT_2 receptors are the only ones coupled to the G_q pathway which, via elevating the intracellular calcium level, also acts stimulatory (Nichols & Nichols, 2008). Interestingly, the $5\text{-HT}_{1A/B}$ receptors exist both as heteroreceptors and as autoreceptors. While $5\text{-HT}_{1A/B}$ heteroreceptors can be found all over the brain, 5-HT_{1A} autoreceptors are located on the soma of serotonergic neurons; 5-HT_{1B} autoreceptors on the contrary are located on nerve terminals (Barnes & Sharp, 1999). Both autoreceptors aid in negatively self-regulating neurons.

The clearance of serotonin from the synaptic cleft after transmission is managed by the serotonin transporter (5-HTT), which is located on the soma of serotonergic neurons and re-uptakes it so it can be reused for later releases (Nichols & Nichols, 2008). It is important to note at this point that, despite the main focus here will be on neuronal cells, there is ever-growing evidence that suggests also involvement of glial cells in the (aberrant) homeostasis of the serotonergic system. Microglia and astrocytes have been put into perspective during the last years, pointing to a mutual influence of

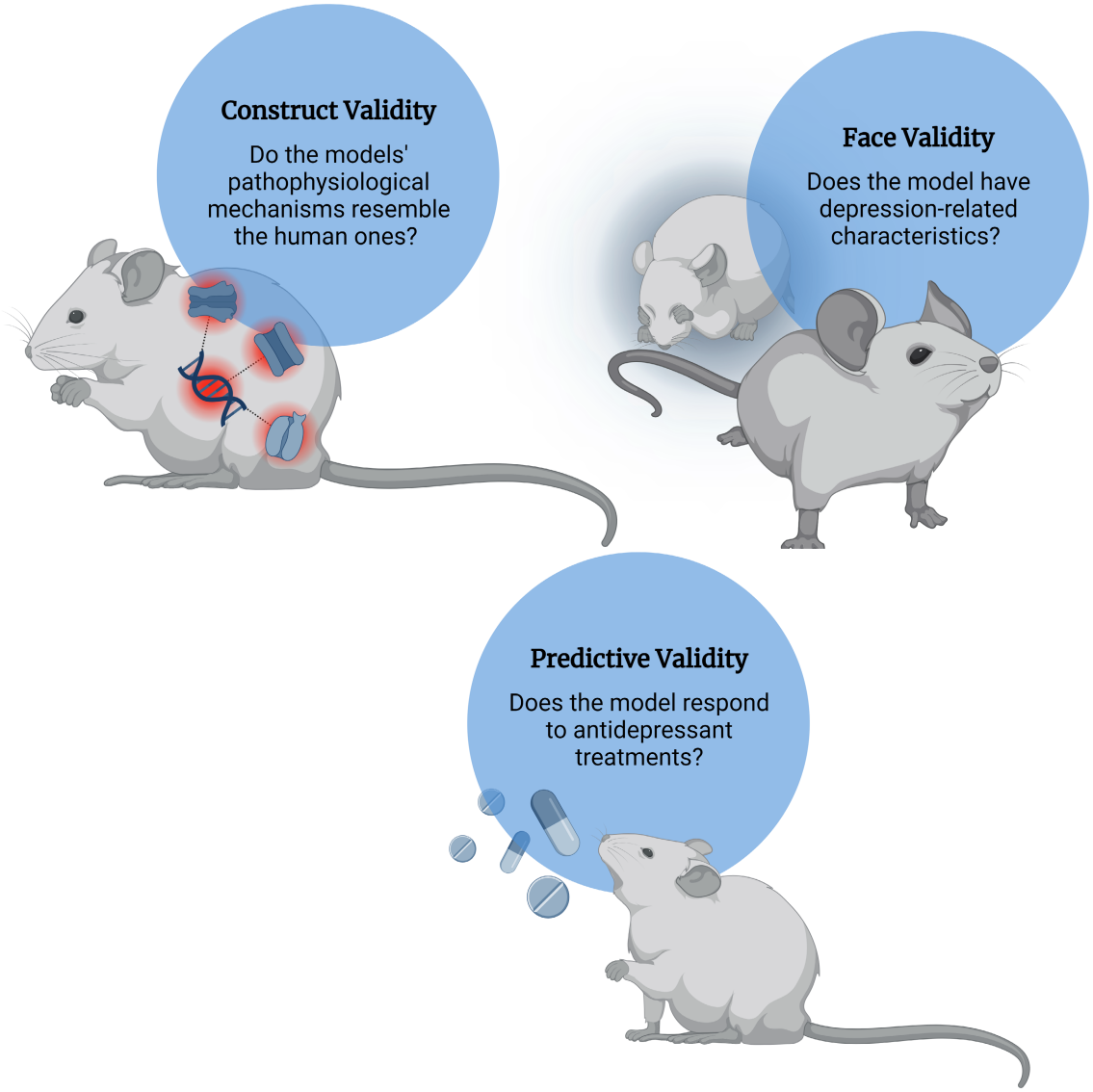

FIGURE 2 Validity criteria for animal models of depression. Construct-, Face-, and Predictive validity must be met for modeling depression in animals. Created with biorender.com.

serotonergic neurotransmission and astrocytic and microglial activity (González-Arias et al., 2023; Wang et al., 2022).

3.2 | Genetic findings

Genetic factors have long been implicated in the pathophysiology of depression and started with twin and family studies 70 years ago, which investigated which shared familial factors contribute to the etiology of depression (Bellivier et al., 1998; Berrettini, 2004). These yielding rather inconsistent results about possible candidate genes, the advancement of genome-wide association studies (GWASs) and gene–environment interaction studies (G×E studies) made it possible to narrow down candidate genes more precisely. Moreover, these studies helped elucidating which variants constitute a high risk due to environmental factors such as chronic stress. The most closely involved candidates are genetic loci associated with the 5-HTT, the 5-$HT_{1A/2A}$ receptors, and TPH2.

3.2.1 | Human studies

The first and possibly most described genetic variant in depression was linked to the 5-HTT gene and constitutes a 44 bp repeat polymorphism in the 5-HTT linked polymorphic region (5-HTTLPR) and the variable-number-tandem-repeat (VNTR) region in the second intron (from here on referred to as: 5-HTTLPR-VNTR) (Bellivier et al., 1998). 5-HTTLPR-VNTR was later on often confirmed to be associated with depressive disorders (Bellivier et al., 1998; Goldman et al., 2010; Heils et al., 1996; Kunugi et al., 1997; Lesch et al., 1996; López-León et al., 2008; Uher & McGuffin, 2010). Another variant often associated with MDD is the single nucleotide polymorphism

(SNP) rs25531, also in the 5-HTTLP region (Fratelli et al., 2020). Until today, genetic variants of the 5-HTTLPR get linked to depression, new discoveries revealing variations in the allelic frequency which "tune" the extent of susceptibility to developing depression (Fratelli et al., 2020). The notion of an involvement of the 5-HTTLPR-VNTR variant in depression is further substantiated by GxE studies which found individuals with this variant at increased risk of depression developed through stressful life events, such as childhood trauma (Caspi et al., 2003; Li et al., 2019; Ressler et al., 2010; Simonyte et al., 2023; Talati et al., 2017). There are meta-analyses that confirm this notion (Bleys et al., 2018; Fratelli et al., 2020; Karg et al., 2011; Kiyohara & Yoshimasu, 2010; Newman-Tancredi & Albert, 2011; Oo et al., 2016), which demonstrate an association between 5-HTTLPR and depression particularly through gene-by-environment interactions rather than a direct genetic association. However, it should be noted that other meta-analyses report no such association (Border et al., 2019; Culverhouse et al., 2018; Howard et al., 2019).

In conclusion, the association between 5-HTTLPR and depression remains contentious, with evidence both supporting and omitting a clear link. The contradictory findings suggest a nuanced role of 5-HTTLPR in depression, emphasizing the complexity of MDD. We will not delve into a detailed discussion of this evidence, as it has already been covered in previous reviews (Caspi et al., 2010; Gatt et al., 2015; Kenna et al., 2012; McIntosh et al., 2019; Norkeviciene et al., 2022; Sharpley et al., 2014). However, we still believe that 5-HTTLPR is important in depression and will explain why the focus should not solely be on meta-analyses. Large sample sizes in meta-analyses, while advantageous, may oversimplify results and overlook important study differences. The potential for significant differences in small effects underscores the need for caution in interpreting meta-analyses, be it analyses reporting or omitting evidence of the 5-HTTLPR variant in depression. Additional methodological considerations, such as the measure of depression and the ethnicity of the assessed individuals, further complicate the interpretation. Ethnicity, particularly in Caucasian populations, has been linked to differences in stress susceptibility among carriers of the 5-HTTLPR variant, revealing a positive correlation with depression development (Kiyohara & Yoshimasu, 2010; Murphy et al., 2013; Simonyte et al., 2023). Similarly, studies focusing on specific stressors rather than general stressors consistently yield positive findings (reviewed by (Caspi et al., 2010)), highlighting the influence of included factors on statistical power. Recognizing the limitations of meta-analyses and systematic reviews, it is thus crucial to value individual studies which provide evidence for the association of 5-HTTLPR and depression. Future investigations should address these methodological concerns, employing standardized assessments to facilitate meaningful comparisons across diverse studies, as already noted by previous reviews (Fratelli et al., 2020; Sharpley et al., 2014). While acknowledging compelling evidence, it is necessary to conduct further investigations to fully understand the complex interaction involving 5-HTTLPR in depression. Until then, it is important to highlight the involvement of 5-HTTLPR in depression. This complexity aligns with the broader understanding of genetic factors in MDD (Shadrina et al., 2018).

Other promising targets can be found in genes coding for serotonergic receptors. Polymorphisms in the 5-HT_{1A} and 5-HT_{2A} receptor genes have most often been described. Especially the 5-HT_{1A} rs6295 C(-1019)G single nucleotide polymorphism (SNP), which was first described in 1999 (Wu & Comings, 1999), was found to be associated with depression and suicide (Lemonde et al., 2003; Obermanns et al., 2023; Ying et al., 2008). Meta-analyses and reviews could confirm a risk association between 5-HT_{1A} polymorphisms and depression (Kishi et al., 2013; Le François et al., 2008; Newman-Tancredi & Albert, 2011). It has further been hypothesized that patients with both 5-HTTLPR and 5-HT_{1A} risk alleles may be more vulnerable to MDD in a synergistic manner (Arias et al., 2005; Zhang et al., 2009).

Genetic variations in the 5-HT2A receptor have also been found to be associated with depression and suicide mostly through gene × environment interactions, with the most commonly described SNPs being rs7997012, rs6311, and rs6313 and 102 T/C (Brezo et al., 2010; Choi et al., 2004; Du et al., 2000; Jokela, Lehtimäki, & Keltikangas-Järvinen, 2007; Kamata et al., 2011; Obermanns et al., 2023). Moreover, also gene–gene interactions between the 5-HT_{1A} and 5-HT_{2A} genes have been described and associated to the development of depression (Jokela, Keltikangas-Järvinen, et al., 2007).

Yet another polymorphism, in the gene coding for TPH2, was found to be a potential risk factor for depression (Van Den et al., 2006; Zhang et al., 2005; Zill et al., 2004). More specifically, the SNPs rs120074175 on the A allele and rs4290270 on the T allele of the TPH2 gene were associated with the etiology of depression (Liu et al., 2022). Yang et al. even described co-occurring polymorphisms in TPH2 and 5-HT_{2A} which were correlated with the development of depression (Yang et al., 2019).

Similar to the genetic evidence for 5-HTTLPR in depression, there is also literature reporting different conclusions about the association between serotonergic receptor polymorphisms and the risk of developing depression (Höfer et al., 2016; Kishi et al., 2009). We maintain the opinion that such an association exists. Methodological considerations may obscure the inherent genetic predisposition, as reviewed by Newman-Tancredi and Albert (Newman-Tancredi & Albert, 2011). The authors noted that studies failing to find an association between 5-HT_{1A} polymorphisms and depression were mainly conducted in the Caucasian populations and that there may be a gender bias towards female susceptibility (Newman-Tancredi & Albert, 2011). Moreover, the pooling of patients with different genotypes may cause divergent results in meta-analyses, as individual genetic profiles are under-represented (Newman-Tancredi & Albert, 2011). Wasserman et al. also discovered that 5-HT1A variation only contributes to suicidal behavior when individuals have a history of traumatic events (Wasserman et al., 2006), emphasizing the significant impact that the selection of factors can have.

3.2.2 | Rodent studies

Rodent studies in genetic research about depression are surprisingly sparse. Most genetic animal models comprise the complete

or partial knock-out (KO) of one of the candidate genes and their resulting altered abundancy in the brain. These molecular changes will be described in a later part. Studies on KO animals do not specifically link genetic alterations such as polymorphisms to behavioral traits indicating depressive states and hence could not give definitive conclusions about their role in depression vulnerability. The only study that aimed in doing so was Piszczek et al. who modeled the 5-HTTLPR-VNTR variant in mice but could not provide any behavioral outcomes (Piszczek et al., 2019). As they stated, it is technically challenging to create such an animal model, which is probably why it is done to such a small extent, and most evidence is still brought about by investigations on the human genome.

Nevertheless, genetic studies identified genes of interest by assessing the brain of MDD patients. Furthermore, they linked genetic alterations in the form of polymorphisms in the 5-HTT, 5-$HT_{1A/2A}$, and the TPH2 gene to the susceptibility to develop depression.

3.3 | Molecular findings

Almost simultaneously with genetic studies, also molecular studies emerged. These concentrate on differences in the availability and distribution of the serotonergic transporter and serotonergic receptors in the depressed brain. Similar to genetic findings, the 5-HTT and the serotonergic receptors 5-HT_{1A} and 5-HT_{2A} were found to be most involved.

3.3.1 | Human studies

Both, imaging studies on depression patients (such as positron-emission-tomography, PET and functional magnetic resonance imaging, fMRI) and post-mortem studies on patients with MDD have provided early evidence of abnormal levels of 5-HTT (Kambeitz & Howes, 2015; Malison et al., 1998; Mann et al., 2000; Reimold et al., 2008) and serotonergic receptors, mainly the types 5-$HT_{1A/B}$ and 5-$HT_{2A/C}$, but also 5-$HT_{3/4/6/7}$ (assessed by (Amidfar et al., 2018)).

These abnormalities could be found in the brain regions heavily connected to the serotonergic system. As such, post-mortem studies found increased levels of 5-HT_{1A} in the PFC, HIP, and AMY of patients with MDD (Arango et al., 1995; Matsubara et al., 1991; Underwood et al., 2012). Imaging studies on the contrary yielded mixed results reporting increased levels of 5-HT_{1A} mainly in the ventrolateral PFC (vlPFC) and the raphe (Arango et al., 2001; Parsey et al., 2010; Stockmeier et al., 1998), which is substantiated by meta-analyses reporting increased levels of 5-HT_{1A} in the globus pallidus (Nikolaus et al., 2016). In contrast, decreased levels of 5-HT_{1A} were found in the medial temporal cortex, ventral anterior cingulate cortex (vACC) and dorsolateral prefrontal cortex (dlPFC) (Sargent et al., 2000), as well as in the raphe, HIP, and AMY (Arango et al., 2001; Drevets et al., 1999) and also other brain regions (Hirvonen et al., 2008). Meta-analyses confirmed decreased levels of 5-HT_{1A} in the midbrain, as well as the mesiotemporal cortex, HIP, raphe, and insular cortex (Nikolaus et al., 2016; Wang et al., 2016).

Similar to 5-HT_{1A}, also 5-HT_{2A} levels were found to be increased in the PFC, AMY, HIP in post-mortem brains (PFC: (Arango et al., 1990; Arango et al., 1995; Arora & Meltzen, 1989; Mann et al., 1986; Pandey et al., 2002; Stanley & Mann, 1983; Turecki et al., 1999); AMY (Hrdina et al., 1993; Laruelle, 1993); HIP (Cheetham et al., 1988; Rosel et al., 2000; Underwood et al., 2018)). Imaging studies reported mixed results about the abundance of 5-HT_{2A} in those brain regions pointing to either increased, decreased or unchanged levels in patients with MDD (increase in PFC (D'haenen et al., 1992; Massou et al., 1997); decrease in PFC (Attar-le et al., 1999; Sargent et al., 2000); no change in AMY and HIP: (Meltzer et al., 1999; Meyer et al., 2001)).

Regarding the serotonin transporter, both, post-mortem and imaging studies uniformly confirmed decreased levels in the PFC and ACC, as well as in the thalamus, DRN and brainstem (Arango et al., 1995, 2001; Austin et al., 2002; Leake et al., 1991; Malison et al., 1998; Mann et al., 2000; Reimold et al., 2008; Underwood et al., 2012, 2018; Yeh et al., 2015), also reviewed in (Gryglewski et al., 2014; Kambeitz & Howes, 2015; Nikolaus et al., 2016; Rajkowska, 2000).

It appears that post-mortem studies and imaging studies of depressed patients reveal some discrepancies in their analysis, especially imaging studies vary in their results regarding the differences in serotonergic component levels in depression. This is probably due to the heterogeneity of depression in humans (different diagnostics, different underlying causes, comorbid diseases, individual variation), which makes it difficult to state definitive conclusions about possible implications, let alone correlate behavioral traits to the findings on serotonergic components. However, molecular imaging studies clearly indicate that the serotonergic system in depression is perturbed yet dynamic and have identified regional hotspots in the brains of depressed patients. Studies using genetic animal models specified to one component provide a more consistent view in that regard, showing the implication of serotonergic receptor and transporter levels in different aspects that come with depression.

3.3.2 | Rodent studies

Żmudzka et al. nicely documented the behavioral outcomes elicited by the KO, blockage or stimulation of serotonergic receptors in different rodent lines (C57BL/6J and 129/Sv mice and Swiss-Webster rats; Żmudzka et al., 2018). The most explicit focus was on the 5-HT_{1A} receptor, which revealed that the KO of the 5-HT_{1A} heteroreceptor elicits depressive-like behavior, while the blockage or KO of 5-HT_{1A} autoreceptors show to have antidepressant-like effects (Żmudzka et al., 2018). As for other receptors, Żmudzka et al. assessed almost all serotonergic receptors and concluded that blockage of postsynaptic 5-HT_{1A}, 5-HT_{1B}, 5-HT_{2B}, 5-HT_4, or stimulation of presynaptic 5-HT_{1A}, 5-HT_{1B}, 5-HT_{2A}, 5-HT_3, 5-HT_{5A}, and 5-HT_7 result in depressive-like behavior (Żmudzka et al., 2018).

Also 5-HTT KO rats were found to have an increased stress vulnerability which leads to depressive- and anxiety-like behavior (Olivier et al., 2008; Schipper et al., 2011). Interestingly, it was recently shown that 5-HTT KO mice with a homozygous genotype show increased levels of anxiety while their heterozygous counterparts showed to be less anxious (Krakenberg et al., 2019). This contradiction suggests a genetically variable role of 5-HTT in anxiety and depression. The interested reader is referred to the so-called "differential susceptibility hypothesis," which attempts to explain the occurrence of such a differential phenotype by the susceptibility of heterozygous 5-HTTLPR rodents to both positive and negative environmental factors while their homozygous littermates remain susceptible to negative events (Belsky et al., 2009).

In conclusion, molecular studies from human and rodent studies could attest to the same components of the serotonergic system to be involved in depression as the genetic studies. The most implicated factors being the 5-HTT, as well as the serotonergic receptors, all of which seem to be involved in depressive- and anxiety-like behavior, with the most extensive studies on the 5-HT_{1A} and 5-HT_{2A}. However, conclusive interpretations on which factors are decisive for the development of depression cannot be made due to diverging evidence. It is clear from both human and animal studies that the serotonergic system is perturbed in depression. Our view of the importance of 5-HT receptors in depression is also supported by recent research on serotonergic psychedelics. Compounds such as psilocybin and LSD have been found to interact with 5-HT1A, 5-HT2A, and 5-HT2C receptors and are increasingly being investigated as potential therapeutics (nicely reviewed by (Cameron et al., 2023)). As there is literature suggesting no disruption of serotonergic molecular components (such as (Moncrieff et al., 2022)), it is important to acknowledge the limitations of large meta-analyses and systematic reviews again, which were discussed previously. Specifically, the choice of which studies to include often excludes certain studies at the expense of others, resulting in a loss of sensitivity to the dynamic nature of serotonergic aberration in depression which was shown to be the case here. Next to conclusions about the prominent involvement of 5-HTT, 5-HT_{1A}, and 5-HT_{2A}, molecular findings in humans also underlined the involved brain regions linked to aberrant serotonergic signaling in depressive states. The most prominent ones being the PFC, AMY, and HIP, whose connectivity with the serotonergic system is discussed in the following.

3.4 | Connectivity findings

During the last years it is becoming more and more clear that the leading cause of depression cannot be found solely in the dysregulation of single neurotransmitter and neuromodulator systems. It is rather on the level of brain circuits which are in an altered balance where neurotransmitter and neuromodulator systems influence and are influenced to create pathological states. The following part thus constitutes the most cutting-edge research area on serotonergic influence in the etiology of depression. It aims to connect the molecular incidents about serotonin to brain activity and pathological brain circuits.

3.4.1 | Human studies

Connectivity studies in humans can be divided into three subareas: (1) structural connectivity, which describes the volume of white matter; (2) functional connectivity, which focuses on undirected correlations between the activity of two brain regions; and (3) effective connectivity, which investigates the directed influences among brain regions within a network (Li et al., 201w8). Since the scope of this review is about serotonergic modulation in depression, functional, and especially effective studies will be more in focus on the following.

The consistent findings of altered structural connectivity found in post-mortem brains of patients with MDD (i.e. reduced volume of the PFC, HIP, and AMY (Cao et al., 2012; Helm et al., 2018; Koolschijn et al., 2009; Liu et al., 2017; MacQueen & Frodl, 2011; Price & Drevets, 2010; Savitz & Drevets, 2009; Schmaal et al., 2017; Shajahan et al., 2002; Sheline et al., 1996; Tahmasian et al., 2013)) confirms the molecular implications regarding the involvement of the PFC, AMY, and HIP in depression. Next to these structural findings though, numerous lines of evidence point to an aberrant functional and effective connectivity of the PFC to limbic regions and the DRN, pointing to a connection to the serotonergic system. Evidence starts with functional imaging studies in the 1990s which report an aberrant PFC-limbic circuitry in depressed patients (Mayberg, 1997). Likewise, it is known for over a decade now that serotonergic abnormalities within this circuit are apparent (Franklin et al., 2012; Ramirez-Mahaluf et al., 2017). Hence, it comes as no surprise that PFC-limbic networks are in the spotlight of connectivity research on depression.

Starting with functional studies on the PFC, there is literature about different subpopulations of PFC neurons that mediate anxiety and depression (Krishnan & Nestler, 2008; Ressler et al., 2008; Savitz et al., 2009). Further, a disturbed activation of the medial PFC (mPFC) in patients was described (Sheline et al., 2010), which proves to be especially true for the ventromedial PFC (vmPFC) (de Kwaasteniet et al., 2013; Drevets et al., 2008; Hamilton et al., 2012; Johnstone et al., 2007; Liao et al., 2012; Mayberg, 1997; Mayberg, 2003; Murray et al., 2011). Early tracing studies with antero−/retrograde tracers further revealed direct afferents from the vmPFC to the DRN, underlining the functional connectivity of frontal areas to this serotonergic hotspot (Chiba et al., 2001; Freedman et al., 2000; Gabbott et al., 2005; Gonçalves et al., 2009; Hajós et al., 1998; Jankowski & Sesack, 2004; Vertes, 2004).

As for the limbic regions, especially AMY- and HIP-, but also the vACC activity have been shown to be altered in the depressed brain. As such, increased activity was reported for the vACC and the AMY (Cao et al., 2012; Mayberg, 2009; Savitz & Drevets, 2009; Shajahan et al., 2002). In contrast, a decreased functional connectivity was reported between HIP and PFC (Drevets et al., 1992; Genzel et al., 2015).

Coming to effective connectivity, there are mainly four core networks that can nowadays be assorted to be involved in depression (Li et al., 2018). These networks are: the affective network AN (orbitofrontal cortex OFC, ACC, AMY, HIP), the reward network RN (frontal cortex, striatal regions), the default mode network DMN (precuneus, posterior cingulate cortex PCC, mPFC, inferior parietal cortex IPC) and the cognitive control network CCN (dlPFC, ACC, parietal cortex; Li et al., 2018). Unsurprisingly, the most promising candidates described before (the PFC, HIP and AMY) are part of at least one of these networks (for an overview, see Figure 3).

Mainly functional imaging studies in patients with MDD revealed changes in these core networks, starting with an increased connectivity in the AN (Sheline et al., 2010), while the RN showed to have a decreased network connectivity (Cheng et al., 2016). Studies on the default-mode network and the cognitive control network outweigh the previous two: Several incidences point towards an increased activity in the DMN (Berman et al., 2011; Greicius et al., 2007; Ho et al., 2015; Li et al., 2013), while the CCN exposes a decreased connectivity in patients with MDD (Kaiser et al., 2015; Kerestes et al., 2015; Vasic et al., 2009; Wang et al., 2014).

Knowing of the reciprocal connection between the PFC-limbic regions and the DRN, it is further not surprising that also there, huge evidence points to an aberrant connectivity. Early evidence already pointed to the involvement of the PFC-limbic connectivity to the DRN in stress-related behavior and anxiety (Barnes & Sharp, 1999; Donaldson et al., 2013; Garcia-Garcia et al., 2014; Gross et al., 2002; Warden et al., 2012). There is further evidence that serotonergic signaling modulates emotional behavior through effects on PFC-limbic connectivity (LeDoux, 2003; Savli et al., 2012). A more recent study found definitive relations between the PFC-limbic circuit and serotonin, reporting an increased connectivity strength between PFC-limbic- and the DRN-regions in depressed patients which was decreased when administering SSRIs to the test persons (Arnone et al., 2018). Kitamura et al. confirmed the significance of a serotonergic dysfunction in the activity of limbic regions in the pathophysiology of depression and antidepressant treatment (Kitamura et al., 2023).

To strengthen this notion, let it be allowed at this point to shortly bridge back to the genetic and molecular findings about serotonin to review studies that linked these to aberrant connectivity. As such, differential corticolimbic responses in MDD patients were often reported to be related to 5-HTT and TPH2 polymorphisms (Brown et al., 2005; Haarir et al., 2002; Volman et al., 2013). Moreover, Fisher et al. (2006) reported a negative correlation between 5-HT_1 abundance in the DRN and the reactivity of the AMY. Other PET studies found disturbed 5-HT neurotransmission to be linked to abnormal 5-HTT levels and 5-HT_{1A} availability (Kaufman et al., 2015; Parsey et al., 2010). More specifically, 5-HTT levels were also linked to the activity of the AMY (Kobiella et al., 2011; Schneck et al., 2016) and most recently even to the dynamics between AMY and the dlPFC and ACC (Janet et al., 2023).

In summary, functional and effective connectivity studies on humans (mainly using fMRI and PET techniques) could show the link between serotonergic abnormalities and altered activity in the PFC-limbic circuit. Even though only human studies can conclusively give

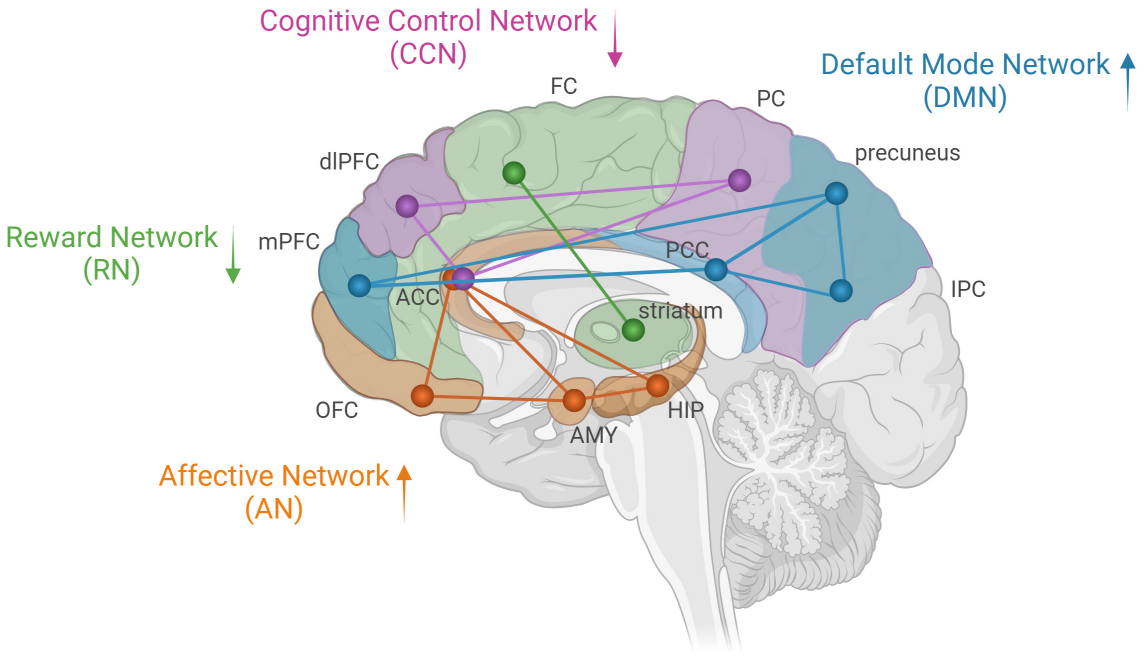

FIGURE 3 The four core networks involved in depression. Connectivity studies in MDD patients found increased connectivity in the AN; decreased connectivity in both, the RN and CCN circuits; and increased connectivity in the DMN. The regions considered "hotspot areas" in depression are the PFC and limbic areas which show a huge overlap with the core networks. ACC, anterior cingulate cortex; AMY, amygdala; dlPFC, dorsolateral prefrontal cortex; FC, frontal cortex; HIP, hippocampus; IPC, inferior parietal cortex; mPFC, medial prefrontal cortex; OFC, orbitofrontal cortex; PCC, posterior cingulate cortex; PC, parietal cortex. Created with biorender.com.

evidence about the "true" situation in the depressed brain, they are limited in their circuit modulatory approaches. That is, a modulation of brain networks is only possible with antidepressant medication or deep brain stimulation (DBS), the first one having a huge time-constraint while most DBS is very invasive and requires an elaborate surgery on voluntary test persons. Furthermore, the star of the show, serotonin, cannot be visualized directly but only through tracers.

3.4.2 | Rodent studies

To really investigate the extent of aberrant connectivity within depressed states and especially, how serotonergic modulation plays into this, rodent experiments are needed. With the advent of chemo- and optogenetics (i.e., introducing chemically or light-inducible receptor proteins making them modulable by the experimenter either by chemicals or light), areas of interest can be controlled in a high-spatiotemporal manner. Especially optogenetics allows for high-temporal fidelity. Combining optogenetics with the simultaneous recording of neuronal activity (i.e., in vivo electrophysiology), it is possible to elucidate the contribution of brain circuits and serotonin to depressive states in vivo in real-time. This can be done to the extent to create whole connectomes specific for certain physiological or pathophysiological states, displaying potential patient screening and treatment approaches. Thus, rodent studies combining behavioral analyses with the on-site situation in the brain using in-vivo recording approaches may display the most important form of basic research in the field of depression.

As an initial remark, there is no common notion as to which extent the human and rodent PFC are similar. In this review, the following homologs are considered: the rodent mPFC comprising the infralimbic and prelimbic cortices (IL and PrL, respectively) are the homologs for the human vACC and dorsolateral PFC, respectively. Furthermore, since the network activities studied in rodents are not of an undirected nature, the term "connectivity" in the following can be seen as the equivalent of "effective connectivity" studies in humans.

The role of the rodent mPFC, especially the IL, in mood disorders and antidepressant treatment was often described in the literature, just alike the influence of 5-HT in these pathological states (nicely analyzed by (López-Terrones et al., 2022)). For better overview, the findings on connectivity are categorized in (1) Electrical (2) Molecular, and (3) Optogenetic approaches in the following.

(1) *Electrical approaches*: Before the advent of chemo- and optogenetics, many studies used electrical stimulation of certain brain areas to modulate brain activity patterns and to study behavioral outcomes.

Very early already, Celada et al. elucidated that the mPFC controls the DRN and showed that electrical stimulation of the mPFC exerts an antidepressant effect which depends on an intact 5-HT system through the involvement of 5-HT_{1A} (Celada et al., 2001). Other studies could confirm the antidepressant effect of electrical mPFC stimulation, most often studied in animal models of social defeat stress (Challis et al., 2013; Hamani et al., 2010).

(2) *Molecular approaches*: Molecular approaches comprise modulation of brain activity via chemogenetics or the targeted blocking of certain proteins via molecular agents. Chemogenetic approaches use so-called Designer Receptors Exclusively Activated by Designer Drugs (DREADDs) to activate genetically engineered receptors by application of their specific ligands (Masseck et al., 2011; Smith et al., 2016). Also in these studies, dysregulations between PFC-limbic areas and the DRN were reported to be linked to depressive states. As such, stimulating the mPFC to AMY connectivity was found to exert an antidepressant effect (Hultman et al., 2016), and activation of 5-HT neurons in the DRN by the IL has a reported antidepressant-like effect in rats (Gasull-Camós et al., 2018). A study on ketamine reported a PrL-DRN connection influenced by ketamine which had a stress-buffering effect in female rats (Dolzani et al., 2018). As stress is one of the most potent factors in the development of MDD, this study further highlights the importance of PFC–DRN connections in depression. It is also noteworthy, that next to these afferent pathways from the forebrain towards the DRN, also efferent pathways from the DRN were reported to be involved in depression. As such, a pharmacogenetic study concluded a causal relationship between DRN and MRN activity with depressive-like behavior in a mouse model of altered emotional behavior (Teissier et al., 2015). The study found that decreasing the DRN and MRN activity led to increased depression-like behavior, while increased MRN activity resulted in increased anxiety-like behavior, pointing to differential roles of the raphe nuclei in depression.

While the aforementioned studies concentrated on neuronal implications, two molecular studies also pointed to the role of glia cells. Glutamatergic modulation by astrocytes in the IL was found to elicit an antidepressant effect, likely by activating the DRN (Gasull-Camós, Arrés-Gatius, et al., 2017; Gasull-Camós, Soto-Montenegro, et al., 2017). This depicts how widespread the pathophysiological apparatus in depression actually is.

(3) *Optogenetic approaches*: Nowadays, optogenetic stimulation is preferred over electrical and chemogenetic stimulation due to both its high spatial and temporal resolution and its lower invasiveness. Optogenetical modulation of brain regions involves expressing light-inducible proteins, the following reviewed studies make use of the ion channel Channelrhodopsin 2 (ChR2), in the brain region of interest which can be activated by light via an implanted fiber (Boyden et al., 2005; Deisseroth, 2015; Li et al., 2005). This renders the activity of the cells expressing the optogenetic tool.

By genetically engineering optogenetic tools to be expressed under a specific promoter, even cell-specific modulation is possible. Hence, this technique enables the modulation of the serotonergic system by light in brain areas of interest and to study the effect on behavior and neuronal activity. Several studies have reported that stimulating the mPFC projections to the DRN leads to antidepressant effects in animal models of depression (Challis et al., 2014; Covington et al., 2010; Fuchikami et al., 2015; Warden et al., 2012). The Dzirasa group could even show that a decreased 5-HT signaling leads to

hypersensitivity of the PFC–AMY connection (Dzirasa et al., 2013). In a later study, the same group could correlate different synchrony states between PFC and limbic areas to depression vulnerability, enabling them to predict the susceptibility outcome in a social defeat mouse model (Kumar et al., 2014), which they did unfortunately not link to 5-HT. Another study also stimulated the collaterals from the ventral HIP to the mPFC and reported an antidepressant effect along with an inactivation of the DRN, elucidating a functional implication of the HIP on the mPFC (Carreno et al., 2016). Lastly, a very recent study confirmed the interdependency of the mPFC and the serotonergic system. López-Terrones et al. reported that both, optogenetic and electrical stimulation in the IL and PrL enhances 5-HT release which points to the potentially important role of the mPFC in MDD (López-Terrones et al., 2023).

While these studies mainly focus on the input connections to the DRN, there are also studies that directly examine the connection from the DRN to regions of the forebrain, highlighting the position of an entire connectivity network mediated by serotonin in depressive states, rather than just bi-current interactions between specific brain areas. As an example, a study by Liu et al. found that optogenetical activation of DRN Pet-1 neurons reinforces behavior and learning in mice, among others reducing anhedonic behavior (Liu et al., 2014). Two other optogenetic studies reported that serotonergic activation in the DRN had antidepressant effects in both mice (Nishitani et al., 2019; Ohmura et al., 2020). Ohmura et al. also found that stimulation of the MRN induced anxiety-like behavior (Ohmura et al., 2020), which is consistent with the aforementioned pharmacogenetic study by Teissier et al. that DRN and MRN exert opposing effects on depression and anxiety behavior. A fiber-optic study by Ren et al. supports the notion of complex connectivity between the raphe nuclei and the forebrain in anxiety and depression, finding two parallel serotonergic pathways from the DRN to the AMY that promote anxiety-like behavior, while the other pathway to the frontal cortex has antidepressant effects (Ren et al., 2018).

In summary, connectivity studies in rodents have found evidence for antidepressant effects involving afferent connections to serotonergic neurons, such as increased activity of the PFC toward the DRN; a 5-HT-dependent hyperconnectivity between the mPFC and AMY in depression, and an excitatory modulation of the HIP toward the PFC, which exerts an antidepressant effect. Evidence for efferent mechanisms reveals different pathways from the DRN and MRN to the forebrain, which appear to play opposing roles in depression and anxiety behavior. Even though explicit correlations between PFC-limbic circuitries and the serotonergic system could be shown, the exact role of 5-HT in the generation and maintenance of these networks remains unknown. That is, the dynamics of the serotonergic system during pathological states still need to be elucidated.

A big relief in that regard is the advancement of in vivo imaging approaches, such as Miniscopes, two-photon in vivo imaging, and fiber photometry (Markicevic et al., 2021). All of these rely on a microscope-like optic apparatus chronically implanted in the rodent brain which makes it possible to image real-time brain dynamics in vivo. They have already been used for imaging brain dynamics, mostly on the basis of the intracellular signaling molecule calcium. However, they reach their limitations when it comes to imaging neurotransmitter and neuromodulator dynamics. Because the biology of these is so versatile and their receptors are so abundant, it is very challenging to get direct evidence of serotonergic dynamics in vivo. Due to this, the focus of this subchapter was on electrophysiology to study the connectivity of the PFC-limbic circuit. Biosensors will be described in the next subchapter in more detail, directing to the future of illuminating neurotransmitters and neuromodulators in the brain connectivity of the depressed brain. Undoubtedly, connecting the local processes of biochemical signaling to the global scale of circuit activity will lead to a broader understanding of the pathophysiology and treatment effectiveness of depression.

4 | NEW AVENUES IN DEPRESSION RESEARCH

4.1 | Measuring neurotransmitter dynamics in vivo: A question of method

In the past, several methods have been developed to study neurotransmitter and neuromodulator dynamics as well as neuroreceptor mechanisms (Kubitschke & Masseck, 2023; Zhao & Piatkevich, 2023). However, each of these methods has its own limitations. For example, fast-scan cyclic voltammetry provides high temporal resolution but poor spatial resolution (Baur et al., 1988; Millar et al., 1981, 1985; Robke et al., 2020). Microdialysis provides high molecular specificity but is limited in spatiotemporal resolution (Delgado et al., 1972; Ungerstedt & Pycock, 1974). The limitations of these conventional techniques make real-time measurements of neurotransmitters such as serotonin challenging. To gain a detailed and precise understanding of serotonergic dynamics in healthy and pathological states, it is important to measure with high spatial and temporal resolution. With the progressive improvement of fluorescence microscopy, it became possible to visualize neurotransmitter and neuromodulator using three-photon microscopy and the natural UV fluorescence of monoamines such as serotonin. Thus, the concentration and level of serotonin in rat single granule cells (Maiti et al., 1997) and the quantitative 5-HT release in serotonin neurons of acute brain slices (Kaushalya et al., 2008) could be measured. However, the suboptimal signal-to-noise ratio and temporal resolution of these label-free imaging approaches are not suitable for in vivo measurements.

The recent development of PBP- and GPCR-based genetically encoded fluorescent biosensors has combined the advantages of previous conventional techniques such as voltammetry and microdialysis to image neurotransmitter and neuromodulator in vivo with high spatiotemporal resolution, sensitivity, and specificity. Over the years, optical imaging techniques such as wide-field fluorescence imaging, two-photon imaging, miniscopes (Ghosh et al., 2011; Park et al., 2011), and fiber photometry (Adelsberger et al., 2005, 2014; Gunaydin et al., 2014) have been developed and refined to enable applications in vivo. The combination of modern optical methods

with genetically encoded fluorescence biosensors enables the systemic observation of complex biochemical processes in real-time and the precise tracking of neurotransmitter dynamics in freely moving and behaving animals.

4.2 | Leaving the dark side? Genetically encoded biosensors as a new Hope

Genetically encoded fluorescent biosensors are molecules that produce a measurable fluorescent signal through a conformational change in their sensing moiety when their respective specific ligand is bound. These sensors can be introduced into specific cell types or cell populations of transgenic animals through minimally invasive viral delivery systems. There, the sensors are expressed as transmembrane proteins in the cell membrane of the target cells and act as a measuring tool for extracellular ligands. They indicate the presence or absence of their specific ligand through fluorescence changes (see Figure 4). This approach provides real-time insight into cellular events and enables the analysis of biological processes in living cells and organisms.

The history of biosensors begins with the discovery and purification of the green fluorescent protein from the jellyfish *Aequorea victoria* (GFP) (Shimomura, 1979; Shimomura et al., 1962). After it was proven in 1994 that GFP could be used as a genetically encoded fluorescent marker (Chalfie et al., 1994), the starting signal for the further development of this protein was given. By modifying the biochemical and fluorescent properties of GFP, different variants were generated (Heim & Tsien, 1996). The discovery of circularly permuted fluorescent proteins was the basis for the development of later biosensors. In a circularly permuted fluorescent protein, the original N- and C-termini are fused through a linker. This creates new termini in close proximity to the chromophore. As a result, the chromophore is exposed and becomes accessible to protons from outside the protein. This makes the fluorescence of the protein very sensitive to even small changes in the conformation of the protein (Baird et al., 1999; Nagai et al., 2001). As the genomes of other organisms were explored, more fluorescent proteins were extracted and fine-tuned, gradually expanding the color palette of biosensors. Over the years, several approaches have been developed to construct biosensors for physiologically relevant molecules, neurotransmitter, and neuromodulator based on either bacterial periplasmic binding proteins (PBPs) (Borden et al., 2020; Keller et al., 2021; Marvin et al., 2013, 2019; Unger et al., 2020) or G-protein coupled receptors (GPCRs; Deng et al., 2023; Dong et al., 2021, 2022; Jing et al., 2020; Kagiampaki et al., 2023; Kubitschke et al., 2022; Nakamoto et al., 2021; Patriarchi et al., 2018; Sun et al., 2018). In recent years, the site-directed mutagenesis technique has been

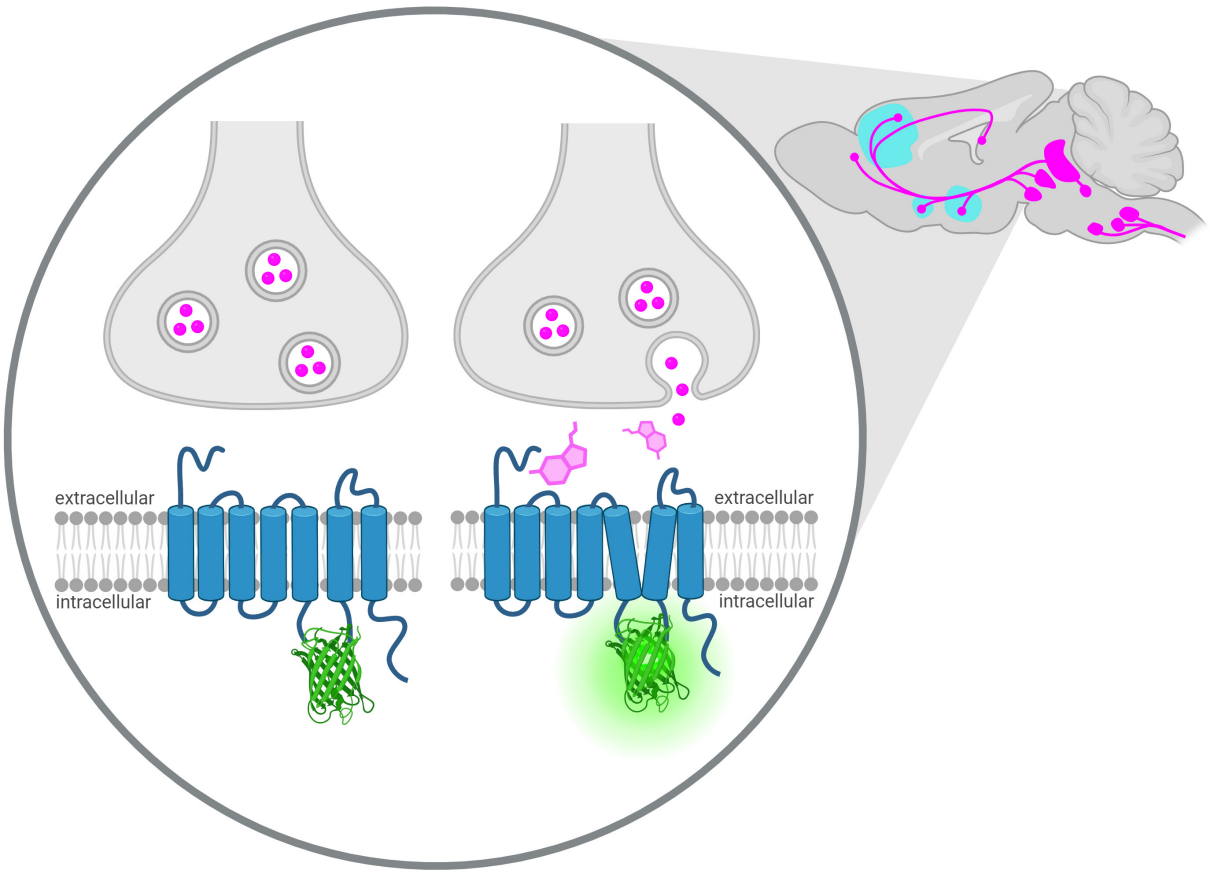

FIGURE 4 Illuminating the brain. Biosensors as new tools to image neurotransmitter and neuromodulator dynamics. Created with biorender.com.

considered to be the gold standard for the development of biosensors and the improvement of their ligand-binding properties. However, a drawback of this technique is that unanticipated allosteric interactions can occur in the proteins, making the success of the sensors a guessing game (Kubitschke & Masseck, 2024). A major turning point in biosensor development is the recent advent of machine learning and the combination with computational design strategies for predicting allosteric signals (Keri et al., 2021; Unger et al., 2020). These technologies, combined with modern screening methods such as Opto-MASS (Rappleye et al., 2022), facilitate the design of genetically encoded biosensors.

4.3 | The expanding toolbox of biosensors for neurotransmitters: The agony of choice

In recent years, significant progress has been made in the development of genetically encoded biosensors, providing a growing toolkit for a wide range of neurotransmitter, neuromodulator, and physiologically relevant molecules offering increasing application possibilities (Kubitschke & Masseck, 2024; Sabatini & Tian, 2020). The serotonergic system is often the focus of attention in the study of depression. Therefore, the various serotonin sensors available today, such as iSeroSnFR (Unger et al., 2020), psychLight (Dong et al., 2021), $GRAB_{5\text{-}HT}$ (Deng et al., 2023; Wan et al., 2021), and sDarken (Kubitschke et al., 2022) are of great benefit.

The first approach to develop a GPCR-based serotonin sensor was described by validating the design strategy of the dopamine sensor dLight for other neurotransmitter and neuromodulator such as serotonin, resulting in a serotonin sensor based on the $5\text{-}HT_{2A}$ receptor (Patriarchi et al., 2018). Slightly later, the first PBP-based serotonin biosensor, iSeroSnFR (Unger et al., 2020), was developed using a computational redesign of the acetylcholine binding pocket of iAChSnFR0.6 (Borden et al., 2020) to improve protein-ligand binding specificity and affinity for serotonin. iSeroSnFR is a fluorescent reporter for extracellular serotonin with a relatively low affinity of 390 μM and a two-component kinetics (τ_{On} = 0.5–10 ms and τ_{OFF} = 4 ms (fast); τ_{On} = 5000–18 000 ms and τ_{OFF} = 150 ms (slow)). iSeroSnFR has been confirmed for in vitro and in vivo applications in the mouse brain (Hon et al., 2022; Jang et al., 2023; Unger et al., 2020). Further fine-tuning of the design strategy for dLight and its variants (Patriarchi et al., 2018) led to the development of the serotonin biosensor psychLight1 (Dong et al., 2021), which is based on the $5\text{-}HT_{2A}$ receptor (Dong et al., 2021). Further development of psychLight1 by fusing an endoplasmic reticulum export motif to the C terminus of psychLight1 led to the psychLight2 variant with an improved membrane expression. PsychLight2 exhibits a high affinity (K_d = 26.3 nM) and relatively slow off kinetics (τ_{OFF} = 997 ± 37.6 ms (fast); τ_{OFF} = 3998 ± 310.3 ms (slow)) (Dong et al., 2021). The $5\text{-}HT_{2A}$ receptor has been shown to play an important role in the hallucinogenic effects of psychedelic drugs. In addition, ligands of the $5\text{-}HT_{2A}$ receptor represent some of the most important drugs in neuropsychology. There is growing evidence that psychedelics can be used to treat depression and post-traumatic stress disorder (Chi & Gold, 2020). Since psychLight can be used for drug screening, this biosensor has a relevant practical application (Dong et al., 2021), such as in the selection and microdosing of psychedelics as a treatment of depression (Kuypers, 2020; Polito & Liknaitzky, 2022). $GRAB_{5\text{-}HT1.0}$ is another GPCR-based serotonin sensor based on the 5-HT2C receptor with high affinity for serotonin (K_d = 22 nM) and moderate kinetics (τ_{On} = 200 ms, τ_{OFF} = 3130 ms; Wan et al., 2021). This sensor has been further developed resulting in the improved green version g5HT3.0 variant (K_d = 150 nM; τ_{On} = 290 ms, τ_{OFF} = 1660 ms) and a red version, r5-HT1.0 (K_d = 790 nM; τ_{On} = 50 ms, τ_{OFF} = 510 ms) (Deng et al., 2023). The recently developed serotonin sensor sDarken is based on the $5\text{-}HT_{1A}$ receptor and has been confirmed for in vitro and in vivo applications (Kubitschke et al., 2022). sDarken belongs to a family of turn-off sensors that exhibit a high-baseline fluorescence in the unbound state and a decrease in fluorescence as soon as 5-HT binds. sDarken shows a high affinity to serotonin (K_d = 127 nM) and fast on and off kinetics (τ_{ON} = 43.5 ± 9.7 ms, τ_{OFF} = 323 ± 61.5 ms; Kubitschke et al., 2022). To cover different in vivo applications, variants of sDarken have been developed that exhibit either high affinity (H-sDarken; K_d = 57 nM) or low affinity (L-sDarken; K_d = 45 μM) to serotonin (Kubitschke et al., 2022). The sDarken variant H-sDarken exhibit similar kinetics as the original sDarken (τ_{ON} = 57.2 ± 19.3 ms, τ_{OFF} = 324.8 ± 48.5 ms) while the L-sDarken variant showed slower on and faster off kinetics (τ_{ON} = 95.3 ± 17.8 ms, τ_{OFF} = 156.0 ± 27.0 ms; Kubitschke et al., 2022). However, there is evidence that other neurotransmitter and neuromodulator like norepinephrine, dopamine, and acetylcholine are also involved in the development of depression (Fogaça et al., 2023; Glowinski & Axelrod, 1964; Häggendal & Hamberger, 1967; Schildkraut, 1965; Willmore et al., 2022). Genetically encoded biosensors for norepinephrine such as $GRAB_{NE}$ (Feng et al., 2019, 2023) and nLight (Kagiampaki et al., 2023), for dopamine such as dLight (Patriarchi et al., 2018) and $GRAB_{DA}$ (Sun et al., 2018, 2020; Zhuo et al., 2023) or for acetylcholine such as $GRAB_{Ach}$ (Jing et al., 2020) make it possible to study the influence of these transmitters on depression with high spatiotemporal resolution. For a more detailed overview of the growing variety of genetically encoded biosensors for neurotransmitter, neuromodulator, and other neurochemicals, see Kubitschke and Masseck (2023). As the development of biosensors is still quite new, to our knowledge there are currently no systemic studies using biosensors to investigate neurotransmitter dynamics in depression.

4.4 | Limitations, challenges, and future perspectives of genetically encoded biosensors

In addition to the previously mentioned advantages that biosensors offer, they also have their limitations. A central element of the criticism of biosensors is their dependence on the expression level. The use of biosensors requires physical manipulation of brain tissue, as genetically encoded biosensors are introduced into the brain via minimally invasive viral transduction systems.

Possible consequences of this manipulation include changes and differences in expression levels, overexpression of the sensor, membrane accumulation, or cytotoxicity. By diluting the virus prior to injection, some of these risks can be limited in advance. Especially the time-dependent change of expression levels of biosensors is often a point of criticism. Chronic imaging can lead to changes in sensor expression levels or the measured intensity. However, to understand the role of tonic serotonin levels over long behaviorally relevant time periods other readouts, such as fluorescence lifetime might be advantageous. However, in general, current serotonin biosensors have lower reported fluorescence intensities and smaller response amplitudes compared to biosensors for calcium, dopamine, or glutamate, the genetically encoded biosensors (Zhao & Piatkevich, 2023).

All intensity-based sensors are limited by their dependence on expression level, excitation power, photobleaching, and sensitivity to pH changes, which affect the possible interpretations that can be derived from the intensity readout. However, these limitations could be overcome by using fluorescence lifetime imaging microscopy (FLIM) as a more robust readout. Fluorescence lifetime measures the time between the excitation and emission of a fluorophore and is independent of expression level and excitation power, photobleaching, or pH changes. Some, but not all, GPCR-based sensors for neuromodulators have been shown to exhibit changes in a lifetime upon ligand binding and can be used to robustly compare neuromodulator dynamics across brain regions, animals, disease models, and time (Kubitschke et al., 2024; Ma et al., 2023).

In addition, the invasiveness of the optical imaging techniques that are essential for the measurement of biosensors is also discussed. Imaging of biosensor responses is often achieved by implanting optical fibers or by two-photon microscopy. Placing an optical implant in the brain is an invasive procedure and the amount of physical damage to the brain depends on the experimental design and the probes used. In addition, optical probes are limited in their spatial resolution and cannot provide further details such as subcellular resolution and cell types within the brain regions imaged. The use of two-photon microscopy requires a cranial window created by craniotomy or bone thinning.

Depression is also linked to several monoamines and physiologically relevant signaling molecules besides serotonin. Thus, it is important to expand the range of sensors for all types of signal molecules. The use of modern techniques such as machine learning and computational design approaches facilitates the design of future genetically encoded biosensors. One advantage of the increasing variety of biosensors is the possibility to study the interplay and crosstalk of different monoamine and signaling molecule dynamics. However, a major challenge with this multiplexed imaging approach is that although several different biosensors have been published for a variety of signaling molecules, most are GFP-based and therefore overlap in the spectrum. To address this issue, work has already begun to extend the color range of biosensors, with red-shifted biosensors currently being developed. Red-shifted calcium indicator like R-GECO (Dana et al., 2016) and RCaMP (Akerboom et al., 2013) are currently available, but they still suffer from a rather low signal-to-noise ratio, photobleaching, and photoswitching. First red-shifted single wavelength fluorescent GPCR-based biosensors for serotonin (Deng et al., 2023), glutamate (Wu et al., 2018), dopamine (Kim et al., 2022; Nakamoto et al., 2021; Patriarchi et al., 2020; Sun et al., 2020; Zhuo et al., 2023), and norepinephrine (Kagiampaki et al., 2023) are also available.

5 | CONCLUSION

Even though the serotonin hypothesis of depression was first described in the 1960s and initiated a whole field of research that found evidence for serotonin in depression, the involvement of serotonin in depression has been the subject of debate for a number of years, with the most critical review being the umbrella review by Moncrieff (Moncrieff et al., 2022).

We would like to take this opportunity to give our opinion on this umbrella review and its relevance in the field of serotonergic research in depression. We believe that this review has certain limitations and agree with what other authors have already criticized (Bartova et al., 2023; Jacobsen, 2023; Jauhar et al., 2023; Möller & Falkai, 2023). Alongside the methodological and interpretative limitations, such as the unusual pooling of study types included and the assessment of a mixture of metrics for quality analysis, there is also the notion of overly simplistic interpretations of the available evidence by these authors. We would like to address as a limitation the actual aim of this review, which was to assess the validity of the serotonin theory of depression. We recognize that the serotonin theory of depression has long since ceased to be a grand theory to be proved or disproved. Rather, the original serotonin theory of depression, as formulated in the 1960s, initiated a whole new direction of research into the role of the serotonergic system in depression. This research has evolved into various specific hypotheses about specific parts of the serotonergic system and their association with depression. The history of clinical, pharmacological, and systemic research over the years that we have presented in this review clearly points to serotonin as one of the key factors in the pathophysiology of depression. However, this research has also demonstrated the biological complexity of this condition, as indicated by the conflicting evidence on serotonin. In our opinion, meta-analyses and systematic reviews may not be sensitive enough to capture the full dynamics of serotonin in depression. Theoretically driven approaches with large sample sizes in meta-analyses and systematic reviews are advantageous in terms of statistical power. However, they run the risk of oversimplifying results and overlooking important marginal data due to publication bias. That is, the effects reported in meta-analyses are often multivariate rather than univariate, and the data extracted from the included studies may not be homogeneous (Eysenck, 1994). We acknowledge the importance of meta-analyses and systematic reviews but it is also important to consider individual studies and narrative reviews, which have the potential to reveal significant

differences in smaller effects. It is acknowledged that narrative reviews, like the present one, may provide a subjective perspective on the field. However, this approach has the advantage of conveying an opinion that may be shared by a large proportion of people, but which may be lost through methodological generalization by systematic reviews. Therefore, we recommend that systematic reviews, such as the umbrella review by Moncrieff et al., should be assessed alongside narrative reviews, but not solely in the search for serotonergic evidence in depression. For these reasons, it is important to clarify that our review is not intended to provide empirical evidence for the serotonin theory of depression. Instead, it aims to describe the development of serotonergic research in depression, the strong correlation between depression and abnormalities in the serotonergic system that has been consistently found through systematic research over the years, and how we can benefit from the use of biosensors in the future. Drawing conclusions about the specific involvement of serotonin alone in depression is difficult due to the many intertwined transmitter systems, such as dopamine and glutamate, and other cell types, such as astrocytes and microglia, that are increasingly coming into focus. Therefore, it is important to focus on serotonin in depression research, but it should not be considered the sole contributor. The collection of genetically encoded fluorescent biosensors presented here can help to clarify the dynamics of neurotransmitters, neuromodulators, and signaling molecules involved in MDD. This can pave the way for more targeted treatment strategies for depression.

AUTHOR CONTRIBUTIONS

Svenja Bremshey: Writing – original draft; writing – review and editing; visualization. **Juliana Groß:** Writing – original draft; visualization; writing – review and editing. **Kim Renken:** Writing – original draft; visualization; writing – review and editing. **Olivia Andrea Masseck:** Conceptualization; supervision; writing – review and editing.

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DECLARATION OF GENERATIVE AI AND AI-ASSISTED TECHNOLOGIES IN THE WRITING PROCESS

During the preparation of this work, the author(s) used DeepLWrite to improve language and readability. The free browser version available at https://www.deepl.com/write was used. After using this tool/service, the author(s) reviewed and edited the content as needed and take(s) full responsibility for the content of the publication.

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SUPPORTING INFORMATION

Additional supporting information can be found online in the Supporting Information section at the end of this article.

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