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REVIEW

Genetically encoded sensors for in vivo detection of neurochemicals relevant to depression

Yulin Zhao[1,2] | Jinxia Wan[1,2] | Yulong Li[1,2,3,4,5]

[1]State Key Laboratory of Membrane Biology, School of Life Sciences, Peking University, Beijing, China

[2]PKU-IDG/McGovern Institute for Brain Research, Beijing, China

[3]National Biomedical Imaging Center, Peking University, Beijing, China

[4]Peking-Tsinghua Center for Life Sciences, Academy for Advanced Interdisciplinary Studies, Peking University, Beijing, China

[5]Chinese Institute for Brain Research, Beijing, China

Correspondence
Yulong Li, State Key Laboratory of Membrane Biology, Peking University School of Life Sciences, 100871 Beijing, China.
Email: yulongli@pku.edu.cn

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Abstract

Depressive disorders are a common and debilitating form of mental illness with significant impacts on individuals and society. Despite the high prevalence, the underlying causes and mechanisms of depressive disorders are still poorly understood. Neurochemical systems, including serotonin, norepinephrine, and dopamine, have been implicated in the development and perpetuation of depressive symptoms. Current treatments for depression target these neuromodulator systems, but there is a need for a better understanding of their role in order to develop more effective treatments. Monitoring neurochemical dynamics during depressive symptoms is crucial for gaining a better a understanding of their involvement in depressive disorders. Genetically encoded sensors have emerged recently that offer high spatial–temporal resolution and the ability to monitor neurochemical dynamics in real time. This review explores the neurochemical systems involved in depression and discusses the applications and limitations of current monitoring tools for neurochemical dynamics. It also highlights the potential of genetically encoded sensors for better characterizing neurochemical dynamics in depression-related behaviors. Furthermore, potential improvements to current sensors are discussed in order to meet the requirements of depression research.

KEYWORDS
depression, neurochemical, genetically-encoded sensor

Abbreviations: 5-HT, serotonin, 5-hydroxytryptamin; ACh, acetylcholine; ACTH, adrenocorticotrophic hormone; BA, basal amygdala; BDNF, brain-derived neurotrophic factor; BF, basal forebrain; cAMP, cyclic adenosine monophosphate; CMS, chronic mild stress; CNiFERs, cell-based neurotransmitter fluorescent engineered reporters; cpGFP, circularly permuted green fluorescent protein; CRF/CRH, corticotropin-releasing hormone; CSI, chronic social isolation; DA, dopamine; DAT, DA reupdate transporter; DRN, dorsal raphe nucleus; FPs, fluorescent proteins; FRET, fluorescence resonance energy transfer; FSCV, fast-scan cyclic voltammetry; GABA, gamma-aminobutyric acid; GECIs, genetically encoded calcium indicators; Glu, glutamate; GPCRs, G-protein-coupled receptors; HPA, hypothalamic–pituitary–adrenal; HPLC, high-performance liquid chromatography; ICL3, third intracellular loop; IPN, interpeduncular nucleus; LDCVs, large dense core vesicles; mPFC, medial prefrontal cortex; MS, mass spectrometry; NAc, nucleus accumbens; NE, norepinephrine; NET, norepinephrine transporter; NIR, near-infrared; NMDA, N-methyl-D-aspartate; PBP, periplasmic binding protein; PFC, prefrontal cortex; RFP, red fluorescent protein; SERT, serotonin transporter; SNR, signal-to-noise ratio; SNRIs, serotonin-norepinephrine reuptake inhibitors; ssDNAs, single-stranded DNAs; SSRIs, selective serotonin reuptake inhibitors; SWCNTs, single-walled carbon nanotubes; TF, transcription factor; VTA, ventral tegmental area.

Yulin Zhao and Jinxia Wan contributed equally to this work.

This article is part of the special issue "Depressive Disorders".

1 | INTRODUCTION

Depressive disorders are among the most prevalent types of mental illnesses that affect millions of people worldwide (WHO, 2023). An estimated 4.4% of the global population experience depression, with more than 700000 people dying because of suicide every year (American Psychiatric Association, 2013). The economic costs associated with major depression are approximately US$2.5 trillion and are expected to be over US$6 trillion by 2023 (Bloom et al., 2011). However, because of the complexity of depressive disorders and the fact that they are caused by a diverse range of factors, including genetic, environmental, and neurochemical influences, the etiology and pathophysiology of depressive disorders remain largely unknown. As a consequence, despite the widespread prevalence of depressive disorders, there remains a lack of efficient treatments that can effectively alleviate symptoms (Krishnan & Nestler, 2008; Nestler et al., 2002).

The imbalances in neurochemical systems, specifically serotonin (5-HT), norepinephrine (NE), and dopamine (DA), have been associated with the development and perpetuation of depressive symptoms. These neuromodulators play crucial roles in regulating mood, emotion, and behavior, all of which are believed to be disrupted in patients with depressive disorders (Krishnan & Nestler, 2008; Perez-Caballero et al., 2019; Russo & Nestler, 2013). Current treatments for depressive disorders often involve medications that target these neuromodulator systems, such as selective serotonin reuptake inhibitors (SSRIs) or serotonin-norepinephrine reuptake inhibitors (SNRIs) (Berton & Nestler, 2006; Trivedi et al., 2006). Therefore, delving deeper into the role of these neuromodulator systems in depression could lead to the development of novel treatments. To gain a better understanding of the involvement of neurochemicals in depressive disorders, it is essential to be able to monitor the neurochemical dynamics during various depressive symptoms. Yet, current monitoring tools for neurochemicals in animal models of major depression have limitations and do not allow for real-time spatially-defined monitoring in freely moving animals. As a result, new technologies, including genetically encoded sensors, have emerged. These sensors offer high spatial–temporal resolution, allowing for the monitoring of rapid fluctuations in neurochemical levels, and providing insights into the dynamics of these neurochemicals associated with certain depressive states.

This review aims to explore the detection methods for neurochemicals involved in depression, highlight the limitations of previously developed monitoring tools, and discuss how recently developed genetically encoded sensors can contribute to a better characterization of the neurochemical dynamics in depression-related behaviors. Additionally, potential improvements to current sensors will be explored to meet the requirements of depression research.

1.1 | Monoamine systems are involved in depressive disorders

The revolutionized medications for depression, tricyclic antidepressants, and monoamine oxidase inhibitors were discovered more than half a century ago (Nestler et al., 2002; Schuckit et al., 1971). Shortly after, it was identified that these agents primarily function through the monoamine systems, specifically the 5-HT and NE systems. By either inhibiting the reuptake transporters of monoamines or monoamine oxidase, they are able to increase the synaptic levels of these neuromodulators (Coppen, 1967; Frazer, 1997; Schildkraut, 1965). This led to the proposal of the monoamine hypothesis of depression, which suggests that depression is caused by a deficiency in these monoamine neuromodulators (Figure 1). In response to this hypothesis, second-generation antidepressants, such as SSRIs, were developed. SSRIs specifically increase 5-HT levels in the brain and are still widely used in the treatment of depression today (Hillhouse & Porter, 2015; Morilak & Frazer, 2004).

5-HT, which is mainly produced by serotonergic neurons in the raphe nuclei, has been traditionally linked to depressive disorders based on the pharmacological effects of antidepressant drugs. 5-HT has various roles in the mammalian brain, including

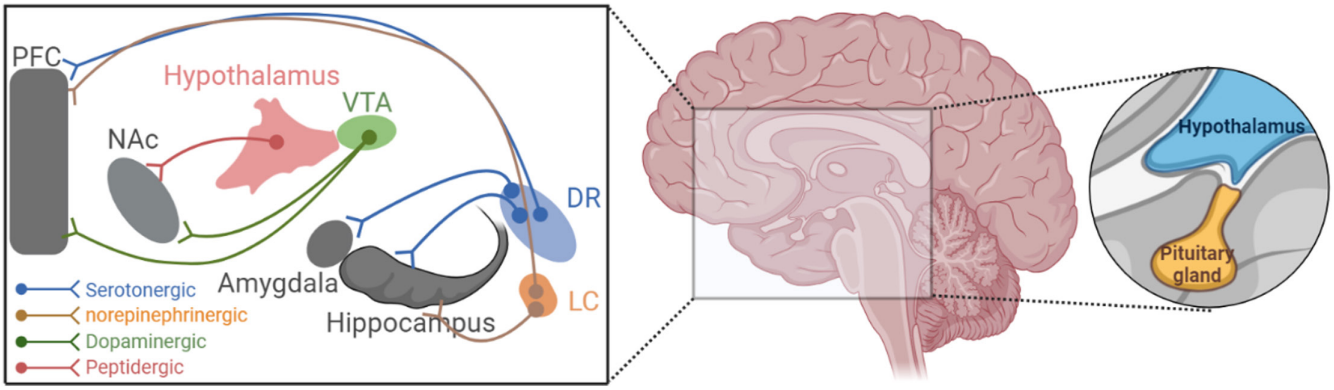

FIGURE 1 Neurochemical systems involved in depression. The figure provided a summary of specific neurochemical systems that have been previously shown to contribute to depression, including monoamine systems (left), neuropeptide systems (left), and the hypothalamic–pituitary–adrenal axis (right). Figure prepared in Biorender.com. PFC, prefrontal cortex; NAc, nucleus accumbens; VTA, ventral tegmental area; DR, dorsal raphe nucleus; LC, locus coeruleus.

the regulation of emotion and mood (Dahlstroem & Fuxe, 1964; Okaty et al., 2019; Soubrié, 1986). It has been shown that 5-HT has a mood-stabilizing effect by promoting feelings of contentment, happiness, and relaxation (Cools et al., 2008; Dayan & Huys, 2009), and the involvement of 5-HT in the pathophysiology of depression has been extensively studied. One of the main theories of depression suggests that a deficiency of 5-HT in the synaptic cleft is responsible for the development of depressive symptoms (Asberg et al., 1976; Leake et al., 1991). As a result, the antidepressant effect of SSRIs has been attributed to their ability to inhibit the serotonin transporter (SERT), which leads to an increase in the synaptic 5-HT level (Frazer, 1997). Additionally, it has been speculated that the delayed onset of antidepressant action of SSRIs may be because of the inhibition of serotonergic neurons induced by the 5-HT1A receptor (Artigas et al., 1996; Sun et al., 2022). Some studies have also suggested that 5-HT dysfunction may be a predisposing factor for depressive disorders, as certain SERT gene variants have been associated with major depression (Belmaker & Agam, 2008; Craddock & Forty, 2006). Furthermore, the SERT promoter polymorphism has been linked to the effectiveness of SSRI treatment in patients with depressive disorders (Serretti et al., 2007). However, the relationship between 5-HT and depressive disorders is complex and still not fully understood. Further research is needed to elucidate the exact mechanisms underlying this association.

Similarly, NE has also been implicated in the pathogenesis of depression. As one of the major neuromodulators, NE is involved in the regulation of arousal, motivation, and mood (Aston-Jones & Cohen, 2005; Moore & Bloom, 1979). Studies have shown that individuals with depression often have lower levels of NE activity in certain regions of the brain, which may contribute to symptoms such as lethargy, low motivation, and loss of pleasure (Anand & Charney, 2000; Bunney & Davis, 1965; Delgado & Moreno, 2000; Goddard et al., 2010). Additionally, stress can lead to increased production of cortisol, a hormone that can decrease NE levels in the brain. This may explain why individuals experiencing chronic stress or trauma are at a higher risk of developing depression (Roy et al., 1988). Antidepressants that target NE, such as SNRIs, have proven to be effective in treating depression. By inhibiting the reuptake of NE, these medications increase its availability in the synapse, thereby improving mood and reducing depressive symptoms. SNRIs vary in their relative potency to the norepinephrine transporter (NET) and/or SERT, with Levomilnacipran (brand name Fetzima) being an example that preferentially inhibits NET (Auclair et al., 2013). It has been demonstrated that SNRIs exhibit clinical efficacy than standard doses of SSRIs. However, currently available SNRI antidepressants are known to show some adverse effects, such as hypertension and weight gain (Morilak & Frazer, 2004; Nemeroff et al., 2002).

As discussed above, most preclinical and clinical studies have focused on the involvement of 5-HT/NE in depression. However, while 5-HT and NE are considered as essential neurochemicals in depression, other neurochemicals also play important roles in the generation and treatment of depression. The DA system, which is critical for reward processing, has recently been linked to depression. Dysfunction in the DA system has been associated with anhedonia, a key symptom of depression characterized by a loss of interest or pleasure in normally enjoyable activities (Fouriezos & Wise, 1976; Pizzagalli, 2014; Wise, 1977). Studies in rodents have shown that chronic stressors, which are used to generate models of depression, can decrease the activity of DA neurons in the ventral tegmental area (VTA) (Chang & Grace, 2014; Grace, 2016). The optogenetic inhibition of VTA DA neurons has also been found to induce depressive-like behaviors in rodents (Tye et al., 2013). However, multiple studies have shown that animals predisposed to depression exhibit increased excitability in VTA DA neurons (Cao et al., 2010; Friedman et al., 2014). Additionally, the phasic optogenetic activation of VTA DA neurons has been linked to the development of a depression-susceptible phenotype (Chaudhury et al., 2013). These conflicting findings warrant further investigation. In humans, patients with major depressive disorder have been found to have reduced DA metabolites in the cerebrospinal fluid, suggesting dysfunction in the DA system (Dunlop & Nemeroff, 2007; Russo & Nestler, 2013). Studies have also shown that drugs that increase DA release, such as bupropion, have antidepressant effects in patients with major depressive disorder who did not respond adequately to SSRIs (Rush et al., 2006). Furthermore, altered availability of DA receptors has been observed in individuals with depression, particularly in areas of the brain involved in reward processing (D'haenen & Bossuyt, 1994; Rocca et al., 2002). However, the exact role of the DA system in depression is still not fully understood, and additional research is required to clarify its involvement in various depressive symptoms.

However, the monoamine hypothesis, particularly the 5-HT hypothesis, has been debated for several decades. Some researchers have suggested that the theory oversimplifies the complex neurochemical mechanisms involved in depression and that the role of 5-HT in depression is more intricate than the hypothesis suggests. Conversely, others maintain that the 5-HT hypothesis still holds some validity, and selective SSRIs remain an effective treatment for many individuals with depression (Berton & Nestler, 2006). Besides, almost all of the medications that target monoamine systems require several weeks of administration to achieve effective treatment (Ferguson, 2001). This delay in therapeutic response presents a limitation in effectively treating patients with suicidal ideation. Nonetheless, there remains a lack of understanding regarding the underlying mechanisms of the monoamine deficiency theory of depression, and further research is needed to elucidate the complex interactions between monoamines, other neuromodulators, and various neurobiological systems in the development and treatment of depression. To address this question, it is important to elucidate the neurochemical dynamics during specific behaviors and determine whether these events are dysregulated in the context of depression. It is especially crucial to be able to image the neurochemicals that are implicated in the pathophysiology of depressive disorders in living brain. Recent development

of calcium indicators enables in vivo measurements of calcium dynamics of neurons, such as monoaminergic neurons. While calcium recordings can provide valuable insights as a proxy for neuronal activity or neurotransmitter release, it is essential to acknowledge that they are not a direct readout of either. Furthermore, calcium dynamics can be uncoupled from action potential firing and neurotransmitter release. This highlights the importance of employing other techniques that allow for a more comprehensive understanding of neurochemical dynamics.

1.2 | Other neurochemicals that are involved in depressive disorders

Dysfunction of glutamate system has been implicated in the pathophysiology of depression (Duman et al., 2019; Murrough et al., 2017). Early studies have indicated that depressed patients show increased glutamate levels in both the serum and cerebrospinal fluid (Kim et al., 1982; Levine et al., 2000). Genetic studies have also identified a high correlation between genes involved in glutamatergic synaptic neurotransmission and the etiology of major depressive disorder (Lee et al., 2012). Following the discovery of ketamine as an important antidepressant, extensive research has focused on the role of glutamatergic system in depression and the development of related therapeutics. Over the past half-century, ketamine, a non-competitive N-methyl-D-aspartate (NMDA) receptor antagonist (Anis et al., 1983), has emerged as one of the most important advances in the depression field. In contrast to the delayed onset of action seen with first-line antidepressants such as SSRI and SNRI, ketamine exhibits a rapid antidepressant effect (Berman et al., 2000; Zarate et al., 2006). Originally developed as an anesthetic, ketamine was first reported to have profound clinical effects on depressive symptoms in 2000 (Berman et al., 2000). Subsequently, numerous studies have been dedicated to identifying the potential mechanisms underlying the antidepressant effects of ketamine (Autry et al., 2011; Li et al., 2010; Ma et al., 2023; Yang et al., 2018; Zanos et al., 2016). A recent structural study has also revealed the structural basis of ketamine's action on the human NMDAR (Zhang et al., 2021). Given the homogenous expression of glutamate system throughout the entire brain, it remains unclear why systemic administration of ketamine is effective in treating depression. Therefore, it is crucial to gain a deeper understanding of the specific alterations in glutamatergic transmission in depression, including region-specific release patterns. To achieve this, the development of related tools to monitor glutamate transmission in different brain regions is essential.

Over the past few decades, numerous neuropeptides have been identified and many of them have been linked to the pathophysiology of depressive disorders. Neuropeptides are small polypeptides that are widely expressed in the nervous system and can be secreted upon neuronal activation (Hokfelt et al., 2000). When neuropeptides bind to their corresponding receptors, they act as neuromodulators to initiate signaling cascades in postsynaptic cells. Unlike small molecule neurotransmitters, which are stored in small vesicles, neuropeptides are believed to be stored in large dense core vesicles (LDCVs) and exert their functions in a slower and more distinct way (van den Pol, 2012).

The hypothalamic–pituitary–adrenal (HPA) axis plays an essential role in mediating stress-related responses (Smith & Vale, 2006) (Figure 1). Neuropeptides that are enriched in the HPA axis have been extensively studied in relation to anxiety and depressive disorders. Corticotropin-releasing hormone (CRF/CRH) is synthesized and released from neurons in the paraventricular nucleus of the hypothalamus, which further stimulates the synthesis and release of other peptide hormones along the HPA axis, such as adrenocorticotrophic hormone (ACTH) and cortisol (Smith & Vale, 2006). These neuropeptides usually show potent anxiogenic effects in response to stress, which is a major symptom of patients with depressive disorder (Dunn & Berridge, 1990; Stenzel-Poore et al., 1994). Research has reported that patients with chronic depressive disorders often show a higher degree of dysregulation in the HPA axis (Arborelius et al., 1999; Pariante & Lightman, 2008). Besides HPA axis-related neuropeptides, oxytocin, and vasopressin, known as important regulators of social behaviors, are also shown to be involved in the regulation of stress response and the treatment of depressive disorders (van Londe et al., 1997). Neuropeptides that have been found to interact with monoamine systems, such as neurotensin, substance P, and neuropeptide Y, also play important roles in the pathophysiology of depression (Biggins et al., 1983; Kramer et al., 2004; Morales-Medina et al., 2010).

One hypothesis regarding the pathophysiology of depression focuses on neuronal plasticity, a process critical for memory formation. It is suggested that the inability to adapt to negative stimuli observed in patients with depression may be because of the dysfunction in neuronal plasticity (Duman, 2002; Duman et al., 1999). In turn, the therapeutic effect of long-term administration of antidepressants may be attributed to their impact on key neurochemicals involved in neuronal plasticity, particularly cyclic adenosine monophosphate (cAMP) and brain-derived neurotrophic factor (BDNF). Studies have shown that chronic antidepressant treatments can up-regulate the cAMP cascade (Fujita et al., 2016; Thome et al., 2000). Moreover, a study found decreased expression of BDNF in the amygdala, the brain region involved in aversive association (Guilloux et al., 2011). However, it remains uncertain whether these neurochemical systems play a role in specific depressive behavior, largely because of the lack of real-time techniques for monitoring their dynamics.

It is clear that one of the major needs in the field of depressive disorder research is the development of in vivo tools capable of detecting neurochemical changes involved in depression. Based on previous studies, it is likely that diverse symptoms of depressive disorders are mediated by various neurochemicals in the different brain regions. Therefore, an in vivo tool with good temporal and spatial resolution is needed. In the following section, we summarize the current methods used to detect neurochemical dynamics,

including those involved in depression, with an emphasis on the developments and advancements of genetically encoded neurochemical sensors.

2 | CURRENT METHODS TO DETECT NEUROCHEMICALS INVOLVED IN DEPRESSION

Over the past several decades, significant progress has been made in developing methods and tools for monitoring neurochemicals under various conditions. These advancements have greatly contributed to our understanding of neurotransmission. In this section, we will focus on the existing methods utilized for detecting neurochemicals, specifically the ones implicated in depression.

2.1 | Analytical chemistry method

2.1.1 | Microdialysis

Microdialysis, a technique developed in the 1960s (Bito et al., 1966), has become a widely used method for detecting neurochemicals in vivo. This technique involves collecting molecules from a specific region of the brain through a semipermeable membrane with a small aperture. The collected samples can then be analyzed using high-performance liquid chromatography (HPLC) and/or mass spectrometry (MS) to separate and analyze the target molecules (Olson & Justice, 1993). One of the key advantages of microdialysis is its high sensitivity in detecting neurochemicals within the picomolar to nanomolar concentration range. Additionally, microdialysis offers exceptional molecular specificity, allowing for the differentiation of structurally similar NMs, such as DA and NE, which offers a great opportunity to measure different monoamines in depression. Microdialysis enables researchers to determine the absolute concentration of neurochemicals across different brain regions in diverse animal models, covering a range of physiological and pathological conditions. Using microdialysis, a previous study examined 5-HT levels in the hippocampus in a chronic mild stress (CMS) model of depression. The researchers observed a decrease in gamma-aminobutyric acid (GABA) levels in the hippocampus, as well as a lack of correlation between wake and sleep stages and 5-HT levels following exposure to CMS. This suggests that the altered sleep patterns observed in depression may be related to the changes seen in this study (Gronli et al., 2007). However, it is important to note the limitations of microdialysis in terms of its spatial and temporal resolution, particularly when monitoring neurochemicals in vivo. The microprobe used in microdialysis has a diameter of approximately 100 μm, which is much larger than the size of a single cell, making it unable to achieve single-cell resolution. Furthermore, the temporal resolution of microdialysis is limited because of the collection of analytes from the brain, making it difficult to detect the transient release of neurochemicals during physiological conditions.

2.1.2 | Fast-scan cyclic voltammetry

Fast-scan cyclic voltammetry (FSCV) using a carbon-fiber microelectrode is a widely used real-time method for detecting neurochemicals, particularly those that are prone to oxidation, such as DA and 5-HT (Robinson et al., 2003). FSCV involves rapidly ramping the potential from a holding potential to a switching potential and back in a triangular wave pattern, with a scan rate around a range of 100–1000 V/s (Venton & Cao, 2020). This technique allows for the oxidation and reduction cycles of neurochemicals within the appropriate potential range, offering high temporal resolution in the millisecond time scale. By refining the size of the carbon-fiber electrode to approximately 10 microns, FSCV exhibits decent spatial resolution. It has been successfully used to detect 5-HT and DA in vivo (Jackson et al., 1995; Phillips et al., 2003; Stuber et al., 2008). Researchers have utilized FSCV to detect 5-HT dynamics changes following the administration of acute SSRI. This study may potentially shed light on the underlying mechanisms that contribute to the exacerbation of depression after the onset of SSRI treatment (Wood & Hashemi, 2013). The great temporal and spatial resolution of FSCV makes it a powerful tool for detecting neurochemicals in real time within living organisms. Furthermore, FSCV's applicability to human studies makes it particularly advantageous for investigating the dynamics of neurochemical dynamics in patients with depression (Bang et al., 2020; Kishida et al., 2016). However, this technique does have several limitations. Firstly, it is difficult to use FSCV to detect neuropeptides that are not electroactive. Additionally, FSCV faces challenges in differentiating analytes with similar oxidation and reduction potentials, such as DA and NE, which is a drawback when used in depression studies. Furthermore, FSCV lacks the ability to provide detailed spatial information, which is crucial in depression research.

2.1.3 | Nanotube-based sensor

Near-infrared (NIR) fluorescent single-walled carbon nanotubes (SWCNTs) have been developed as a detection method for neurochemicals. These nanomaterial-based probes consist of semiconducting NIR SWCNTs combined with single-stranded DNAs (ssDNAs) through noncovalent conjugation. The molecular specificity of these probes is dependent on the ssDNAs. Through high-throughput screening of the ssDNAs, researchers have successfully developed specific SWCNT-based probes, nIRCat and nIRHT, for the detection of catecholamines and 5-HT respectively. These nanomaterial-based sensors offer promising spatial and temporal resolution for studying the dynamics of neurochemicals. They also demonstrate good photostability and compatibility with drugs targeted 5-HT receptors. Additionally, the fluorescence of SWCNTs resides in the NIR window (1000 to 1300 nm), enabling deeper in vivo imaging and minimizing background interference and photon scattering. However, it is important to acknowledge that nanotube-based sensors do have limitations in terms of molecular specificity.

For instance, current nIRCat sensor is quite challenging to differentiate between DA and NE, making it less useful when used in depression studies.

2.2 | Downstream coupling-based reporting assay

2.2.1 | Tango assay

The Tango assay, developed by Barnea et al. (2008), utilizes the interaction between two chimeric proteins to initiate the expression of a downstream reporter gene (Barnea et al., 2008). In this assay, a fusion of a transcription factor (TF) with a membrane-tethered receptor is created, with a viral protease cleavage site acting as the linker between them. When neurochemicals specifically activate their corresponding receptors, particularly G-protein-coupled receptors (GPCRs), β-arrestin fused with TEV protease is recruited to interact with the GPCR and cleave the TEV cleavage site, resulting in the release of tTA and subsequent expression of the reporter gene. Tango assay has been used to in vitro screen potential antidepressants that target the 5-HT1A receptor (Partyka et al., 2020). However, the Tango system has some limitations. It exhibits high background signals and the ligand-induced expression of the reporter gene is irreversible, making it less suitable for in vivo applications. To mitigate the background signals, iTango and iTango2 were developed by incorporating the light-sensitive AsLOV2 domain into the system. iTango2, for instance, has been utilized to label and manipulate DA-positive neurons in mice. Although improvements have been made to the signal-to-noise ratio (SNR) by reducing background signals, temporal resolution remains a challenge because of the expression of the reporter protein.

2.2.2 | CNiFERs

Cell-based neurotransmitter fluorescent-engineered reporters (CNiFERs) were developed to monitor the release of specific neurochemicals (Muller et al., 2014). This assay involves culturing cells that express the corresponding GPCR for the Neurochemical of interest. Activation of the GPCR leads to downstream signaling, resulting in an increase in cytosolic calcium levels. Calcium indicators are utilized to detect changes in intracellular calcium concentrations, providing a readout for Neurochemical release. CNiFERs aim to achieve high specificity and sensitivity by utilizing endogenous binding modules and amplified downstream signals. DA D2 receptor-based D2-CNiFERs and NE α1A receptor-based α1A-CNiFERs have been developed and utilized to monitor DA and NE dynamics in vivo (Foo et al., 2021; Muller et al., 2014). Despite these advantages, the implantation of cultured cells into the animal brain is a complex procedure that may lead to immunological rejection. Consequently, this assay may not be suitable for long-term in vivo imaging because of these challenges.

2.3 | Genetically encoded neurochemical sensors

The genetically encoded calcium indicators (GECIs) have undergone significant development, characterization, improvement, and application in studying neuronal activity under various conditions (Chen et al., 2013; Dana et al., 2019; Palmer & Tsien, 2006; Tian et al., 2009). GECIs consist of two main modules: the analyte binding domain and the reporter module. The reporter part usually consists of either a pair of fluorescent proteins (FPs) with spectral overlap in emission and excitation or a single FP. Ligand binding induces conformational changes in the analyte binding domain, which in turn leads to changes in fluorescence intensity in single FP-based reporters or facilitates fluorescence resonance energy transfer (FRET) between the FP pairs. Following a similar concept, a number of genetically encoded neurochemical sensors have been developed. Based on the binding domain, these sensors can be categorized into two groups: periplasmic binding protein (PBP)-based sensors and G-protein-coupled receptor (GPCR)-based sensors (Table 1).

2.3.1 | PBP-based genetically encoded neurochemical sensor

PBPs are a family of receptors found in bacteria that recognize small molecules and transport them into the cytoplasm. The first PBP-based NT sensor, FLIP-E, was developed to monitor glutamate (Glu) by utilizing the ybeJ domain for Glu sensing and two FPs for FRET (Okumoto et al., 2005). The further improvements in dynamic range and response led to the development of a single fluorophore-based Glu sensor called iGluSnFR, which employs a circularly permuted green fluorescent protein (cpGFP) sensitive to conformational changes (Marvin et al., 2013). iGluSnFR demonstrates superior SNR compared to previous FRET-based sensors and is well-suited for in vivo detection of Glu release. Furthermore, single FP-based sensors require only one excitation wavelength, enabling multicolor imaging in circumstances involving the co-release of neurochemicals. Building on this principle, more PBP-based sensors have been developed, including the ones that are capable of detecting 5-HT.

As a result of the lack of a specific 5-HT binding protein in PBPs, researchers have redesigned the ligand binding pocket of an acetylcholine (ACh) sensor and employed machine learning-based algorithms to develop the specific 5-HT sensor, iSeroSnFR (Unger et al., 2020). The iSeroSnFR demonstrates moderate affinity to 5-HT in the hundreds of micromolar range and exhibits significant fluorescence increase upon 5-HT binding while eliminating ACh or choline-binding. This sensor has been successfully used to monitor 5-HT release during fear conditioning and sleep–wake cycles in freely behaving mice. However, the sensor's affinity to 5-HT is relatively low compared to endogenous 5-HT receptors, which operate in the nanomolar to micromolar range. Consequently, the iSeroSnFR may not be suited for conditions with moderate changes in 5-HT levels.

TABLE 1 Characteristics of genetically encoded neurochemical sensors.

Neurochemical sensor	Backbone	EC50 (nM) in vitro	$\Delta F/F_0$ max in vitro	On/off rate (s) in vitro	Reference
Dopamine					
$GRAB_{DA1h}$	D2R	10	0.9	0.14/2.5	Sun et al. (2018)
$GRAB_{DA1m}$	D2R	130	0.9	0.06/0.7	Sun et al. (2018)
$GRAB_{DA2h}$	D2R	7	2.8	0.05/7.3	Sun et al. (2020)
$GRAB_{DA2m}$	D2R	90	3.4	0.04/1.3	Sun et al. (2020)
$GRAB_{DA3h}$	D1R	22	12.4	0.05/1.85	Zhuo et al. (2023)
$GRAB_{DA3m}$	D1R	89	10	0.07/0.56	Zhuo et al. (2023)
$rGRAB_{DA1h}$	D2R	4	1.0	0.06/2.15	Sun et al. (2020)
$rGRAB_{DA1m}$	D2R	95	1.5	0.08/0.77	Sun et al. (2020)
$rGRAB_{DA2h}$	D2R	9.8	2.4	0.05/3.35	Zhuo et al. (2023)
$rGRAB_{DA2m}$	D2R	210	5.3	0.05/2.24	Zhuo et al. (2023)
$rGRAB_{DA3h}$	D1R	22	14.2	0.06/3.6	Zhuo et al. (2023)
$rGRAB_{DA3m}$	D1R	140	14.6	0.06/0.61	Zhuo et al. (2023)
dLight1.1	D1R	330	2.3	0.01/0.1	Patriarchi et al. (2018)
dLight1.2	D1R	770	3.4	0.01/0.09	Patriarchi et al. (2018)
dLight1.3b	D1R	1.6	9.3	NA	Patriarchi et al. (2018)
dLight1.4	D4R	4	1.7	NA	Patriarchi et al. (2018)
RdLight1	D1R	859	2.5	14.1/398	Patriarchi et al. (2020)
YdLight1	D1R	1630	3.06	NA	Patriarchi et al. (2020)
Serotonin					
$GRAB_{5HT1.0}$	HTR2	22	2.5	0.16/2.81	Wan et al. (2021)
$GRAB_{5HT3.0}$	HTR4	150	13	0.25/1.39	Deng et al. (2023)
$rGRAB_{5HT1.0}$	HTR4	790	3.3	0.06/0.68	Deng et al. (2023)
PsychLight	HTR2A	26	0.8	NA/5.4	Dong et al. (2021)
iSeroSnFR	iAChSnFR	310	17	0.0005/5 (fast) 0.01/18 (slow)	Unger et al. (2020)
sDarken	HTR1A	127	−0.64	0.04/0.32	Kubitschke et al. (2022)
Norepinephrine					
$GRAB_{NE1h}$	α2AR	83	1.3	0.04/1.89	Feng et al. (2019)
$GRAB_{NE1m}$	α2AR	930	2.3	0.07/0.68	Feng et al. (2019)
$GRAB_{NE2h}$	α2AR	78	4.2	0.09/1.93	Feng et al. (2023)
$GRAB_{NE2m}$	α2AR	320	3.8	0.12/1.72	Feng et al. (2023)
nLightG	α1AR	755	10	0.02/0.19	Kagiampaki et al. (2023)
nLightR	α1AR	654	1.3	NA	Kagiampaki et al. (2023)
Glutamate					
iGluSnFR	GltI	4 (μM)	4.5	0.01/0.09	Marvin et al. (2013)
SF-iGluSnFR series	GltI	7–40 (μM)	2–4	0.6–6/25–108	Marvin et al. (2018)
iGluSnFR3 series	GltI	1.8–9.6 (mM)	13.1–54	~0.02/NA	Aggarwal et al. (2023)

2.3.2 | GPCR-based genetically encoded neurochemical sensor

Nature has evolved a superfamily of cell surface receptors, predominantly GPCRs, that are capable of sensing corresponding neurochemicals. Cryo-electron microscopy studies have revealed a conserved large conformational change, particularly in transmembrane helices 5 and 6, induced by ligand binding across different GPCRs (Manglik et al., 2015). Leveraging this conformational change, several independent groups have developed sensors for neurochemicals. This platform offers sensors with high sensitivity, molecular specificity, fast kinetics, and high spatial resolution. Besides, these sensors were specifically designed to lose the ability to initiate downstream signals, and instead, only

detect neurochemical release. This design can eliminate the potential effect of sensor expression on normal cell physiology. By combining ligand-induced conformational changes in GPCRs with the structure-sensitive cpGFP, various GPCR-activation-based sensors have been developed (Figure 2), including $GRAB_{DA}$ based on the DA D2 and D1 receptor (Sun et al., 2018, 2020; Zhuo et al., 2023), dLight based on the DA D1 receptor (Patriarchi et al., 2018, 2020), $GRAB_{NE}$ based on the NE α2A receptor (Feng et al., 2019, 2023), nLight based on the α1A adrenergic receptor (Kagiampaki et al., 2023), $GRAB_{5\text{-}HT}$ based on the 5-HT2C receptor (Wan et al., 2021), PsychLight based on the 5-HT2A receptor (Dong et al., 2021), and sDarken based on the 5-HT1A receptor (Kubitschke et al., 2022).

To illustrate the detailed development strategy and applications of GPCR-based sensors, we will take the 5-HT sensor as an example, which holds significant relevance in the field of depression research. By inserting cpGFP into the third intracellular loop (ICL3) of the 5-HT2C receptor, where it can efficiently couple ligand-induced conformational changes to the FP, the $GRAB_{5\text{-}HT1.0}$ sensor was developed with an EC50 of approximately 20 nM, similar to the wild-type 5-HT2C receptor. The $GRAB_{5\text{-}HT1.0}$ sensor exhibits a 300% fluorescence increase ($\Delta F/F_0$) at saturated 5-HT concentrations, with subsecond on-kinetics and minimal effects on downstream signaling. This sensor provides high spatial resolution and has been successfully expressed in a single neuron to detect 5-HT dynamics during the learning and memory process in Drosophila (Wan et al., 2021). Moreover, the $GRAB_{5\text{-}HT1.0}$ sensor has revealed a global modulation of 5-HT release during spontaneous sleep–wake cycles by simultaneously monitoring 5-HT levels in multiple brain regions of freely moving mice. Using two-photon imaging, the long-lasting effects of addictive drugs, such as MDMA, on extracellular 5-HT levels were observed in the prefrontal cortex (PFC) of mice (Wan et al., 2021). Through systematic screening of scaffolds, insertion sites in ICL3, linkers between cpGFP and the receptor backbone, and key sites in cpGFP and GPCR, a new version of the green 5-HT sensor, $GRAB_{5\text{-}HT3.0}$, was developed with higher SNR and a larger dynamic range compared to $GRAB_{5\text{-}HT1.0}$ (Deng et al., 2023). With a similar strategy, other groups have independently developed PsychLight, based on the 5-HT2A receptor, with an 80% fluorescence increase (Dong et al., 2021), and sDarken based on the 5-HT1A receptor, with a 60% fluorescence decrease (Kubitschke et al., 2022).

To expand the spectrum of 5-HT sensors, a red 5-HT sensor was developed by replacing cpGFP with the red fluorescent protein (RFP), cpmApple, named $rGRAB_{5\text{-}HT1.0}$ (Deng et al., 2023). $rGRAB_{5\text{-}HT1.0}$ is based on the 5-HT4 receptor and exhibits over 300% response to 5-HT with an EC50 of approximately 800 nM. The $rGRAB_{5\text{-}HT1.0}$ sensor has been successfully employed to monitor optogenetically elicited endogenous 5-HT release in the basal forebrain (BF) and during the sleep–wake cycle of freely moving mice. Notably, simultaneous imaging of $rGRAB_{5\text{-}HT1.0}$ and $GRAB_{eCB2.0}$ revealed a wave of 5-HT release in the mouse dorsal cortex followed by endocannabinoid waves during seizure conditions (Deng et al., 2023). The red 5-HT sensor can be effectively combined with other green neurochemical sensors in various conditions, such as under depression-related behaviors. Additionally, RFP exhibits superior performance to GFP in-depth imaging because of its low background and decreased scattering properties. As these neurochemical sensors are developed based on the native neurochemical receptors, they should inherit the pharmacological profile of the corresponding receptor and could be affected by genetic manipulation targeting the native receptor. Thus, users should carefully consider the pharmacological profiles of these sensors and be aware of the direct effect of certain drugs on the sensors (Table 1).

In summary, these neurochemical sensors have revolutionized the field of studying neurotransmission, providing unprecedented opportunities to enhance our understanding of neuronal mechanisms in both health and disease conditions. In the following section, we will discuss recent studies that have utilized these genetically encoded sensors to better understand depressive-like behaviors.

3 | APPLICATIONS OF GENETICALLY ENCODED SENSORS IN DEPRESSIVE DISORDER STUDIES

Since the development of genetically encoded sensors for monoamines, they have been utilized in various studies investigating depressive disorders. In this section, we highlight some of the research that aims to elucidate the specific roles of neurochemicals in specific depression-related behaviors (Figure 2).

To facilitate the development of new therapeutics targeting multiple monoaminergic systems, studies have developed and utilized genetically encoded sensors to monitor the real-time dynamics of monoamines during relevant animal behaviors. The 5-HT2A receptor, which is targeted by classical hallucinogens, atypical antipsychotics, and psychoplastogens, plays a crucial role in the field of depression research (Celada et al., 2004; Kim et al., 2020). Therefore, the development of an assay capable of reporting the conformational changes of the 5-HT2A receptor is essential for screening compounds that bind to the receptor without inducing hallucinogenic effects. One such sensor is the PsychLight sensor, derived from the 5-HT2A receptor, which has proven effective in predicting the hallucinogenic behavioral effects of compounds. Using PsychLight, researchers identified a new compound that acts as a ligand of the 5-HT2A receptor, exhibiting antidepressant effects without inducing hallucinations (Dong et al., 2021). Another study reports the identification of drugs that preferentially target the 5-HT reuptake transporter (SERT) over the DA reupdate transporter (DAT), and confirms the increase in extracellular 5-HT without affecting DA (DA) levels using genetically encoded sensors, presenting valuable information about the role of 5-HT elevation in the symptoms of depression (Mayer et al., 2022).

Anxiety-like behaviors are common symptoms exhibited by patients with depressive disorders. DA is hypothesized to modulate anxiety, although the precise mechanisms are not well understood

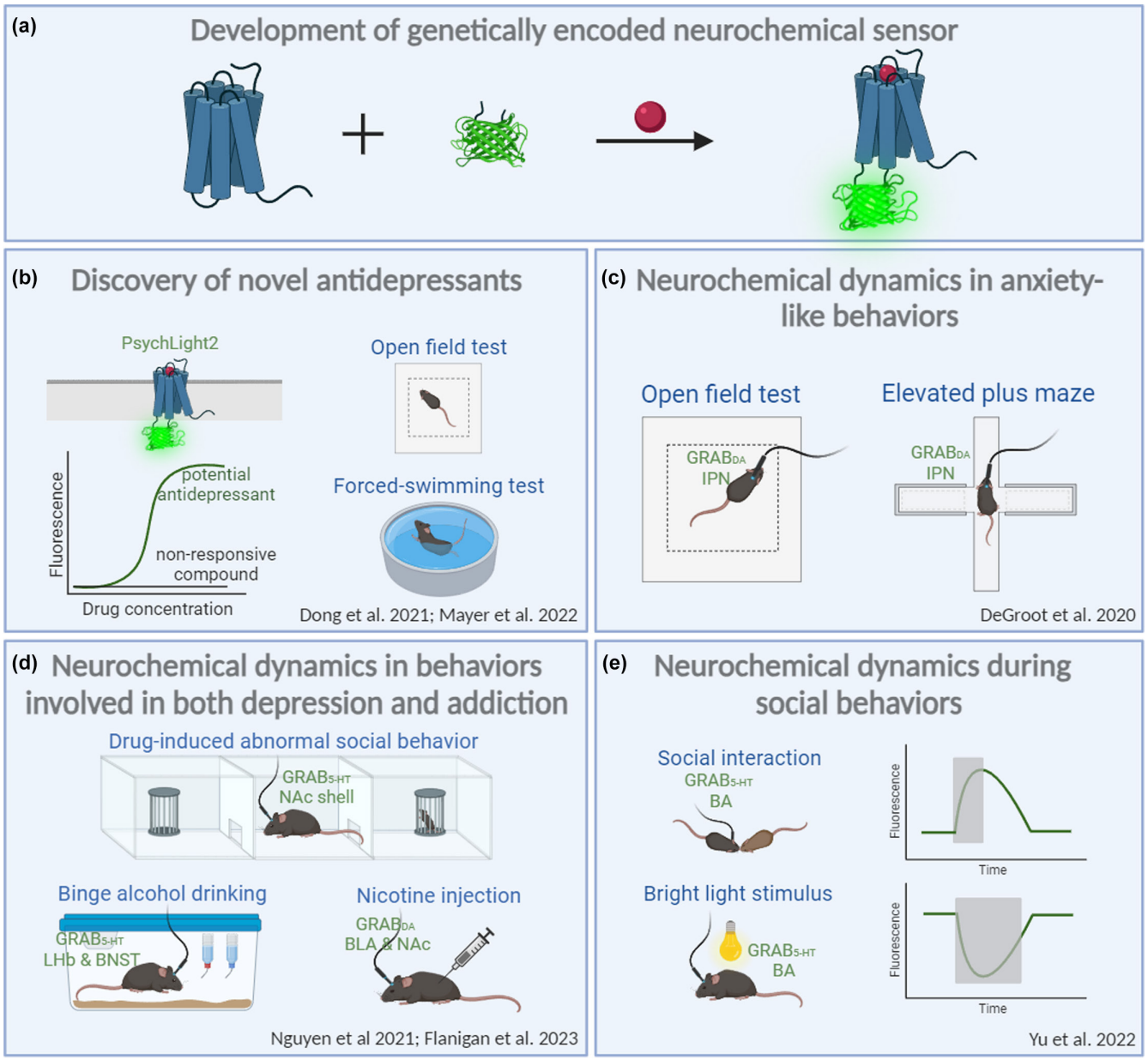

FIGURE 2 Development and applications of genetically encoded neurochemical sensors. This figure illustrates the principle underlying G-protein-coupled receptor-based neurochemical sensors (a). These neurochemical sensors have been utilized in the screening of novel antidepressants (b). Recent studies utilizing these genetically encoded neurochemical sensors have provided insights into the neurochemical dynamics during anxiety-like behaviors (c), the behaviors implicated in both depression and addiction (d), as well as in social behaviors (e). Figure prepared in Biorender.com.

(Calhoon & Tye, 2015; Zweifel et al., 2011). In a recent study using the $GRAB_{DA}$ sensor, researchers identified DA release in the interpeduncular nucleus (IPN), a brain region that receives VTA dopaminergic projections. They demonstrated that the perfusion of amphetamine on IPN-containing brain slices resulted in a $GRAB_{DA}$ signal, which could be blocked by a D2 receptor antagonist. To further investigate the role of this circuit on anxiety-like behaviors, researchers conducted optogenetic manipulations and observed animal behaviors in the elevated plus maze test and open field test. Their findings revealed that optogenetic inhibition of VTA-IPN dopaminergic projections promoted anxiety-like behaviors, and the opposite was true when these projections were activated. Additional pharmacological manipulations revealed that DA mediates anxiety-like behaviors through the modulation of the specific subpopulations of IPN neurons (DeGroot et al., 2020).

The comorbidity of depression and substance abuse is well-documented, with approximately 50% of patients with substance use disorders also being diagnosed with major depression (Abraham & Fava, 1999). This poses a challenge in treating depression in patients with substance dependence. Since monoamine systems are also involved in addiction (Russo & Nestler, 2013), several studies have measured monoamine dynamics during drug-related

behaviors using genetically encoded sensors. Using the $GRAB_{5\text{-}HT}$ sensor, researchers have identified that the release of 5-HT in response to prosocial behaviors is suppressed by the activation of kappa opioid receptors during opioid withdrawal. This suppression of 5-HT release may contribute to the risk of relapse (Pomrenze et al., 2022). Another study combined a fiber photometry recording system with a genetically encoded $GRAB_{DA}$ sensor to study the underlying mechanism of nicotine-induced anxiety (Nguyen et al., 2021). The findings showed that intraperitoneal injection of nicotine elicited a $GRAB_{DA}$ fluorescence increase in the nucleus accumbens (NAc) and a contrasting fluorescence change in the amygdala, indicating activation of two distinct groups of VTA DA neurons with anatomically segregated projections. These results may explain the complex effects of nicotine on both reinforcing and anxiogenic behaviors. Depressive disorders are prevalent in individuals with alcohol use disorders, such as binge alcohol drinking (Castillo-Carniglia et al., 2019). Dysregulation of serotonergic system has been implicated in the pathophysiology of alcohol drinking disorders (Nordquist & Oreland, 2010). To characterize 5-HT dynamics during binge alcohol drinking, researchers expressed the $GRAB_{5\text{-}HT}$ sensor in brain regions implicated in the negative behavioral outcomes of binge alcohol consumption. Surprisingly, they found sex- and region-specific differences in 5-HT dynamics, which highly correlated with disrupted social recognition in females and potentiated arousal in males upon binge alcohol consumption (Flanigan et al., 2023). These findings may contribute to the development of sex-specific therapeutics for depression symptoms and alcohol use disorders. Although these sensors could provide valuable information regarding neurochemical dynamics in addiction, researchers need to consider the effect of pH change induced by drug application on the sensor signal. Studies have shown that the application of addictive drugs, such as cocaine, often leads to acidic pH in the brain (Heien et al., 2005). Like other fluorescence protein-based sensors, genetically encoded neurochemical sensors may experience pH-dependent signal change (Zhao et al., 2011). Researchers should be aware of the sudden change in sensor signals caused by acidic pH, as this could potentially affect the accuracy of measurements. To further calibrate this type of signal, users can choose a mutant sensor as a control, which is available for most genetically encoded neurochemical sensors (Feng et al., 2019; Sun et al., 2018, 2020; Wan et al., 2021).

Depressive patients often show impaired social abilities, including low levels of prosocial behavior (Neumann & Landgraf, 2012). Researchers recently investigated the dynamics of 5-HT in relation to social interaction and anxiety. Using the $GRAB_{5\text{-}HT}$ sensor, they observed that 5-HT levels increased during social interactions and decreased during anxiogenic situations in the basal amygdala (BA). By utilizing optogenetics and single-cell sequencing techniques, they identified two distinct populations of $vGluT3^{+}$ 5-HT neurons in the dorsal raphe nucleus (DRN), that project to the BA, each with distinct functions. Activation of the DRN 5-HT neuronal projections to BA PV^{+} neurons resulted in social avoidance mediated by the $GABA_B$ receptor, while activation of the DRN 5-HT neuronal projections to BA pyramidal neurons led to both social avoidance and aversion to brightly lit spaces (Yu et al., 2022). Social isolation has been shown to increase the risk of developing depressive disorders (Matthews, Danese, et al., 2016; Taylor et al., 2016). In animal models, chronic social isolation (CSI) induces changes in social behaviors (Matthews, Nieh, et al., 2016). However, the specific brain circuits related to these changes have not been thoroughly studied. By expressing the $GRAB_{5\text{-}HT}$ sensor in the mice medial prefrontal cortex (mPFC), researchers were able to observe significantly higher levels of 5-HT signal in response to social events in group-housed animals compared to isolated animals. Additionally, through chemogenetic manipulations of the brain circuits identified with the in vivo recording of 5-HT dynamics, researchers found that 5-HT projections from the DR to the mPFC are likely involved in the behavior deficits induced by CSI (Lv et al., 2022). These findings provide valuable insights into the neurobiological underpinnings of social behaviors and their relevance to depressive disorders.

4 | CONCLUSIONS AND PERSPECTIVES

Although the development of genetically encoded sensors has contributed to the recent discoveries related to the mechanisms and treatments of depressive disorders, there are several directions that future studies can take to further optimize these sensors.

4.1 | Quantitative detection of monoamines

In order to better understand the involvement of monoamines in depression, ways to correlate the release levels of monoamines with the behavioral states are needed. Currently available genetically encoded sensors can monitor relative changes in monoamine levels, but they are very challenging to provide quantitative measurements. Therefore, the development of sensors capable of detecting absolute concentrations of monoamines becomes crucial. Ratiometric sensors, which offer the ability to quantify biomolecule concentrations, can be categorized into emission ratiometric sensors and excitation ratiometric sensors. Emission ratiometric sensors are relatively simple to develop by fusing a spectrum separating FP into the existing sensors, usually an orange FP or a red FP (Ast et al., 2017; Kim et al., 2022). This spectrum-separated FP maintains a relatively stable fluorescence intensity independent of the target biomolecule, which can serve as the reference signal. By calculating the ratio between the sensor's signal and the reference FP's signal, these ratiometric sensors provide more accurate and reliable measurements. These sensors play a pivotal role in mitigating the influence of environmental factors or fluctuations that could similarly affect both signals, thereby significantly enhancing the precision of the sensor. However, the use of an additional channel in emission ratiometric sensors may limit the multiplex imaging, and factors like maturation rate, pH effects, and wavelength-dependent light scattering of different fluorophores can affect the accuracy of

quantification. Excitation ratiometric sensors, on the other hand, do not require fusion with another FP, thereby overcoming certain limitations (Kim et al., 2022; Zhao et al., 2011). However, they do place higher demands on the FP utilized in sensor development. These sensors should comprise an excitation channel that directly responds to the target molecules and another excitation channel that either exhibits no response or demonstrates an opposite response to the target molecules. By comparing changes in these two excitation signals—usually by calculating their ratio—excitation ratiometric sensors can accurately measure the concentration of target molecule. However, they face challenges with wavelength-dependent light scattering, usually because of the shorter wavelengths they employ.

An optimal approach for quantifying neurochemicals is to utilize the excited state fluorescence lifetime of a fluorescence molecule, mainly determined by the fluorescence molecule's intrinsic properties, thereby largely eliminating intensity-related artifacts (Becker, 2012; Yasuda, 2006). This method has been successfully employed to quantify calcium and cAMP (Massengill et al., 2022; Zheng et al., 2015). Currently, the neurochemical sensors, show minimal fluorescence lifetime changes, despite a high contrast in intensity change. Therefore, an urgent need exists to develop neurochemical sensors based on fluorescence lifetime changes to enable accurate quantification of neurochemicals under various conditions.

4.2 | Detection of other depression-related neurochemicals with GRAB sensors

In addition to monoamine systems, various neuropeptides are also involved in the pathophysiology of depression. Specific genetically encoded sensors to detect neuropeptide dynamics in vivo are necessary to improve our understanding in this area. There have been genetically encoded oxytocin sensors developed by independent groups (Ino et al., 2022; Qian et al., 2023). Both sensors are able to detect oxytocin dynamics that are relevant to social interactions, and these sensors hold potential for use in depression research. A recently published work has developed GRAB neuropeptide sensors that may greatly contribute to the understanding of the neuropeptide dynamics during various depressive symptoms (Wang, Qian, et al., 2023). In this study, researchers successfully monitored CRF dynamics with a $GRAB_{CRF}$ sensor in both the motor cortex and the mPFC in response to stressful stimuli. It has been postulated that neuropeptide release tends to require high neuronal firing rates, which usually happens during disease states, including depression. However, there is still a need for direct evidence showing changes in neuropeptide release during depressive behaviors. Furthermore, in vivo detection tools with high temporal resolution are required to measure neuropeptide dynamics associated with changes in behaving animals. Developing neuropeptide sensors with high spatial–temporal resolution will be especially essential for future studies on the involvement of neuropeptides in depression.

In addition to neuropeptide, recent studies have revealed the implication of adenosine in depressive-like behaviors. It has been shown that A_{2A} receptors in the lateral septum are both necessary and sufficient to trigger depressive phenotypes (Wang, Li, et al., 2023). Another study shows that the levels of ATP in the mPFC play a role in modulating depressive-like behavior (Lin et al., 2022). The recently developed $GRAB_{ATP}$ and $GRAB_{Ado}$ sensors (Peng et al., 2020; Wu et al., 2021; Wu, Cui, et al., 2023) present researchers in the field with valuable opportunities to gain a deeper understanding of the involvement of ATP and adenosine in the pathogenesis of depression.

4.3 | Multiplex imaging

Besides the observation of neuropeptide dynamics during depressive disorders, the genetically encoded neuropeptide sensors may also contribute to understanding the interaction of different neurochemical systems in depression. A growing literature describes that co-transmission of monoamines and neuropeptides is a common occurrence in the brain (Burnstock, 2004; Nusbaum et al., 2017). It is worth exploring the dynamics of different neurochemicals simultaneously during depression-related behaviors. For example, the dysregulation of the HPA axis, which is involved in the stress response and can contribute to depression, has also been found to impact dopaminergic signaling (Mizoguchi et al., 2008). In turn, dual imaging of DA and neuropeptides enriched in the HPA axis during the stress response will provide valuable insights into the underlying mechanisms. Furthermore, the recently developed high-performance cAMP indicator allows for the in vivo detection of cAMP during various behaviors (Wang et al., 2022). Dual imaging of other neurochemicals along with cAMP will further contribute to our understanding of the pathological processes involved in depression. The development of red fluorescence protein-based sensors for monoamines, in combination with the green neuropeptide sensors, will enable dual-color imaging of monoamines and neuropeptides during depressive behaviors. Moreover, in order to measure more than two neurochemicals at the same time, future sensor development should further expand the spectrum, particularly in the range of far-red (650–700 nm) and NIR (>700 nm). Circularly permutated far-red and NIR fluorescence proteins (FPs) have been successfully utilized for calcium and zinc ion sensors (Dalangin et al., 2020; Wu, Kumar, et al., 2023), providing potential fluorescent modules for neurochemical sensors. However, the existing far-red and NIR FPs have low brightness, which can be a challenge for in vivo detection of neurochemicals, especially neuropeptides. A chemigenetic strategy using fluorescent chemical dyes may be a promising alternative for developing far-red and NIR neurochemical sensors. These dyes offer superior brightness and photostability, and some of them can cross the blood–brain barrier for in vivo brain labeling (Abdelfattah et al., 2019, 2023; Kim et al., 2020). Recent advancements have utilized these chemical dyes and circularly permutated HaloTag to develop far-red calcium sensors and voltage sensors (Deo et al., 2021; Wang et al., 2020). This suggests that the

chemigenetic strategy has the potential to facilitate the development of far-red and NIR neurochemical sensors for depression research.

Overall, the incorporation of genetically encoded sensors in depression research will provide valuable insights into the underlying mechanisms of the disorder. These sensors offer great opportunities to study neurochemical dynamics with high spatial and temporal resolution, allowing for a deeper understanding of the changes that occur in the brain during depressive states. By providing a more comprehensive view of neurochemical activity, genetically encoded sensors have the potential to revolutionize the field of depression research and ultimately contribute to the development of more effective treatments for this debilitating disease. However, further advancements in the technology and addressing the limitations are necessary to fully capitalize on the potential of genetically encoded sensors in depression research.

AUTHOR CONTRIBUTIONS

Yulin Zhao: Conceptualization; resources; writing – original draft; writing – review and editing. **Jinxia Wan:** Resources; writing – original draft; writing – review and editing. **Yulong Li:** Conceptualization; supervision; writing – review and editing.

CONFLICT OF INTEREST STATEMENT

Yulong Li is an Editor of the *Journal of Neurochemistry*. None of the authors has a financial conflict of interest to declare.

PEER REVIEW

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DATA AVAILABILITY STATEMENT

Data sharing not applicable—no new data generated, or the article describes entirely theoretical research.

ORCID

Yulong Li https://orcid.org/0000-0002-9166-9919

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