Asia Pacific Science Press

Asia Pacific Journal of Clinical Medical Research
ISSN(O):3079-8345
ISSN(P):3079-8337
Vol. 1 No.1 (2025)

Neuropharmacology of Neurotransmitter Systems: Current Drugs and Their Effects on Neural and Neuroendocrine Pathways

Xiyao Qi*

The Affiliated International School of Shenzhen University, Shenzhen, 518054, China

Corresponding author: Xiyao Qi

Abstract: The intricate interplay between neurotransmitter systems, neural circuits, and neuroendocrine pathways underpins brain function and dysfunction in neurological and psychiatric disorders. This review synthesizes contemporary advances in neuropharmacology, focusing on dopaminergic, serotonergic, glutamatergic, and GABAergic systems, and their roles in regulating motor control, cognition, emotion, and stress responses. Dopaminergic pathways, including the nigrostriatal, mesolimbic, and mesocortical circuits, are explored in the context of Parkinson's disease, schizophrenia, and addiction, with emphasis on pharmacological agents such as L-DOPA, antipsychotics, and amphetamines. Serotonergic modulation through SSRIs and psychedelics is examined for its impact on mood and neuroplasticity, while glutamatergic and GABAergic systems are discussed in relation to synaptic plasticity, excitotoxicity, and therapeutic innovations like ketamine and benzodiazepines. The neuroendocrine system, particularly the hypothalamic-pituitary-adrenal (HPA) axis, is highlighted for its role in stress-related disorders and interactions with neurotransmitter networks. Despite progress, significant challenges persist, including translational gaps between preclinical models and human trials, species-specific receptor disparities, and ethical dilemmas surrounding cognitive enhancers and genetic manipulation. Emerging frontiers such as nanotechnology-enabled drug delivery, optogenetics, and gut-brain axis modulation are reviewed as transformative approaches to overcome these barriers. Personalized medicine, integrating neuroimaging biomarkers and pharmacogenomics, promises to tailor therapies to individual neural and genetic profiles, while biased agonists and closed-loop systems exemplify the shift toward circuit-specific interventions. Ethical considerations, including equitable access to advanced therapies and responsible innovation, are underscored as critical to ensuring societal benefit. By harmonizing molecular precision with systems neuroscience, this review advocates for interdisciplinary strategies to advance neuropharmacology, ultimately aiming to restore dynamic neural and neuroendocrine homeostasis in health and disease.

Keywords: Neurotransmitter Systems; Pharmacological Interventions; Systems Neuroscience; Neuroendocrine Interactions; Translational Challenges; Personalized Medicine; Emerging Technologies

Published: May 8, 2025

DOI: https://doi.org/10.62177/apjcmr.v1i1.336

1.Introduction

The brain's ability to regulate complex behaviors, emotions, and physiological functions hinges on the precise coordination of neurotransmitter systems, which act as chemical messengers to modulate neural circuits. Neurotransmitters such as dopamine,

serotonin, glutamate, and GABA orchestrate everything from motor control and sleep-wake cycles to emotional regulation and cognitive processing. For instance, dopamine pathways in the nigrostriatal system govern voluntary movement, while serotonin in the raphe nuclei influences mood and sleep architecture. Disruptions in these systems—whether due to genetic, environmental, or pathological factors—can lead to profound dysfunction, manifesting as Parkinson's disease (dopamine depletion), depression (serotonin imbalance), or epilepsy (glutamate-GABA dysregulation). These systems also interface with neuroendocrine pathways, such as the hypothalamic-pituitary-adrenal (HPA) axis, linking neural activity to hormonal responses critical for stress adaptation and metabolic homeostasis.

Pharmacology bridges the gap between neurotransmitter dysfunction and therapeutic intervention by designing drugs that selectively target receptors, transporters, or enzymes within these systems. For example, selective serotonin reuptake inhibitors (SSRIs) alleviate depression by enhancing synaptic serotonin levels, while antipsychotics block dopamine D2 receptors to mitigate psychosis in schizophrenia. Advances in neuropharmacology have expanded beyond symptom management to address the root causes of disorders, such as NMDA receptor modulators for treatment-resistant depression or monoclonal antibodies targeting amyloid-β in Alzheimer's disease. Furthermore, drugs like levodopa, which crosses the blood-brain barrier to replenish dopamine in Parkinson's disease, exemplify how pharmacokinetic principles can restore neural circuit integrity. This synergy between molecular targeting and systems neuroscience has revolutionized treatment paradigms, enabling precision therapies that recalibrate dysfunctional networks rather than merely masking symptoms.

This review synthesizes contemporary research on how pharmacological agents interact with neurotransmitter and neuroendocrine systems to restore neural homeostasis. We first examine major neurotransmitter pathways—dopaminergic, serotonergic, glutamatergic, and GABAergic—detailing the mechanisms of current drugs (e.g., L-DOPA, ketamine, benzodiazepines) and their impact on circuit-level dynamics, as revealed by neuroimaging and electrophysiology. Next, we explore neuroendocrine targets, including HPA axis modulators and their role in stress-related disorders. Throughout, we highlight translational challenges, such as reconciling preclinical animal models with human neurobiology, and emerging strategies like pharmacogenomics and optopharmacology. By integrating molecular mechanisms with systems-level outcomes, this review underscores the transformative potential of interdisciplinary approaches in neuropharmacology, paving the way for therapies that harmonize neural circuit function with whole-body physiology.

2.Main

2.1 Dopaminergic System: Pathways, Pharmacology, and Neuroendocrine Interactions

The dopaminergic system, comprising the mesocortical, mesolimbic, and nigrostriatal pathways, serves as a critical modulator of motor function, reward processing, and executive cognition [1]. The nigrostriatal pathway, originating in the substantia nigra pars compacta (SNc) and projecting to the dorsal striatum, is essential for voluntary movement coordination. Degeneration of SNc dopamine neurons in Parkinson's disease (PD) disrupts striatal-thalamocortical signaling, leading to bradykinesia and rigidity [2]. In contrast, the mesolimbic pathway, which connects the ventral tegmental area (VTA) to the nucleus accumbens (NAc) and amygdala, drives reward-seeking behaviors and emotional responses. Overactivation of this pathway, as seen in schizophrenia, contributes to psychosis and hallucinations [3]. The mesocortical pathway, linking the VTA to the prefrontal cortex (PFC), regulates working memory and decision-making, with hypoactivity implicated in cognitive deficits of schizophrenia and attention-deficit/hyperactivity disorder (ADHD) [4].

Pharmacological interventions targeting dopaminergic receptors aim to restore circuit balance. L-DOPA, a dopamine precursor, remains the gold standard for PD treatment. By bypassing degenerated SNc neurons and replenishing striatal dopamine, L-DOPA restores thalamocortical relay efficiency, alleviating motor symptoms [5]. However, chronic use induces dyskinesias due to pulsatile dopamine receptor stimulation and maladaptive plasticity in striatal medium spiny neurons [6]. Amphetamines, which block dopamine reuptake and enhance presynaptic release, are employed in ADHD to bolster mesocortical dopamine levels, improving attention and executive function via enhanced DLPFC engagement [7]. Conversely, antipsychotics (e.g., haloperidol, risperidone) antagonize D2 receptors in the mesolimbic pathway, attenuating psychosis in schizophrenia. However, excessive D2 blockade in the nigrostriatal pathway can induce extrapyramidal side effects (e.g., tardive dyskinesia), while underactivity in the mesocortical pathway exacerbates cognitive deficits [8].

Systems neuroscience has illuminated how dopaminergic drugs reshape functional connectivity. Resting-state fMRI studies demonstrate that L-DOPA normalizes striatal-thalamocortical circuit activity in PD patients, enhancing synchronization between the putamen and supplementary motor area (SMA) [9]. Similarly, antipsychotics reduce hyperconnectivity between the NAc and limbic regions (e.g., amygdala) in schizophrenia, though excessive suppression may impair salience detection [10]. PET imaging further reveals that optimal D2 receptor occupancy (65–78%) is critical for balancing therapeutic efficacy and side effects [11].

Dopaminergic signaling also intersects with neuroendocrine regulation. The tuberoinfundibular pathway, projecting from the hypothalamus to the pituitary gland, tonically inhibits prolactin secretion via D2 receptor activation. Antipsychotic-induced D2 blockade disrupts this inhibition, causing hyperprolactinemia—a side effect linked to infertility, osteoporosis, and galactorrhea [12]. Newer agents with partial D2 agonism (e.g., aripiprazole) mitigate this risk by stabilizing, rather than abolishing, dopamine signaling [13].

2.2 Serotonergic System: Modulation of Mood, Cognition, and Neuroendocrine Function

The serotonergic system, originating primarily in the dorsal raphe nucleus, projects widely to cortical, limbic, and hypothalamic regions, regulating mood, cognition, sleep, and stress responses [14]. Serotonin (5-HT) exerts its effects through 14 receptor subtypes, with 5-HT1A autoreceptors modulating raphe neuron firing and 5-HT2A receptors influencing cortical plasticity [15]. Selective serotonin reuptake inhibitors (SSRIs), such as fluoxetine, block the serotonin transporter (SERT), increasing extracellular 5-HT levels and promoting neuroplasticity in the hippocampus and prefrontal cortex (PFC) [16]. Psychedelics like psilocybin, a 5-HT2A agonist, induce rapid synaptic rewiring and disrupt default mode network (DMN) connectivity, correlating with antidepressant and anxiolytic effects [17]. Conversely, chronic stress depletes 5-HT, exacerbating depressive symptoms and impairing hippocampal neurogenesis [18].

Systems neuroscience reveals that SSRIs enhance functional connectivity between the PFC and amygdala, normalizing hyperactive limbic responses in depression [19]. Psilocybin's acute disruption of the DMN, observed via fMRI, is followed by long-term increases in global brain network integration, suggesting a reset of maladaptive neural patterns [20]. Serotonin also modulates the hypothalamic-pituitary-adrenal (HPA) axis, with 5-HT1A receptor activation dampening cortisol release during stress [21]. SSRI-induced HPA axis normalization may underlie delayed therapeutic onset, as cortisol levels decline over weeks [22].

2.3 Glutamatergic System: Excitatory Signaling, Synaptic Plasticity, and Therapeutic Innovation

The glutamatergic system, the brain's primary excitatory network, mediates synaptic plasticity, learning, and memory through ionotropic (NMDA, AMPA, kainate) and metabotropic (mGluR) receptors [23]. NMDA receptors (NMDARs) are critical for long-term potentiation (LTP) in the hippocampus and PFC, while excessive glutamate release contributes to excitotoxicity in epilepsy and neurodegenerative diseases [24]. Ketamine, an NMDAR antagonist, rapidly alleviates treatment-resistant depression by enhancing AMPA receptor trafficking and promoting synaptogenesis in the PFC [25]. Topiramate, an AMPA/kainate receptor modulator, reduces cortical hyperexcitability in migraine and epilepsy by dampening glutamate release [26].

Neuroimaging studies demonstrate that ketamine increases resting-state connectivity between the PFC and limbic regions, counteracting depression-related hypoconnectivity [27]. Conversely, NMDAR hypofunction in schizophrenia, modeled by phencyclidine (PCP), disrupts gamma oscillations and frontotemporal coherence, as seen in EEG/MEG studies [28]. The glutamatergic system also interfaces with neuroendocrine pathways: hypothalamic NMDARs regulate corticotropin-releasing factor (CRF) release, linking stress to HPA axis hyperactivity [29]. Recent advances include the FDA-approved NMDA-targeting drug esketamine for depression and mGluR5 antagonists in fragile X syndrome trials [30].

2.4 GABAergic System: Inhibitory Control, Circuit Dysregulation, and Pharmacological Modulation

The GABAergic system, the brain's primary inhibitory network, maintains excitatory-inhibitory (E/I) balance through GABA-A (ionotropic) and GABA-B (metabotropic) receptors [31]. GABA-A receptors, which bind benzodiazepines (e.g., diazepam), mediate fast synaptic inhibition in cortical interneurons and thalamic reticular nuclei, modulating anxiety, sleep, and seizure thresholds [32]. GABA-B agonists like baclofen reduce spasticity in multiple sclerosis by enhancing spinal cord inhibition and are explored for addiction treatment via suppression of mesolimbic dopamine release [33]. Dysregulated GABA

signaling underlies epilepsy (E/I imbalance), anxiety (amygdala hyperactivity), and insomnia (thalamocortical dysrhythmia) [34]. fMRI studies reveal that benzodiazepines reduce amygdala-PFC functional connectivity in generalized anxiety disorder, restoring top-down emotional regulation [35]. In epilepsy, PET imaging shows reduced GABA-A receptor density in the thalamus, which anticonvulsants like vigabatrin (GABA transaminase inhibitor) partially restore [36]. GABAergic drugs also influence neuroendocrine function: hypothalamic GABA inhibits CRH neurons, and benzodiazepines suppress HPA axis hyperactivity during acute stress [37]. Novel agents, such as zuranolone (a GABA-A receptor-positive allosteric modulator), show promise in postpartum depression by enhancing tonic inhibition in limbic circuits [38].

2.5 Neuroendocrine System: Bridging Neural Circuits and Hormonal Regulation in Health and Disease

The neuroendocrine system integrates neural activity with endocrine signaling to regulate physiological homeostasis, stress responses, and behavior. Central to this system is the hypothalamic-pituitary-adrenal (HPA) axis, a hierarchical network where hypothalamic corticotropin-releasing factor (CRF) stimulates pituitary adrenocorticotropic hormone (ACTH) release, driving adrenal cortisol secretion [39]. Cortisol, a glucocorticoid, exerts negative feedback on the HPA axis via hippocampal glucocorticoid receptors (GRs), modulating immune function, metabolism, and emotional memory [40]. Dysregulation of this axis—marked by hypercortisolism in depression or hypocortisolism in post-traumatic stress disorder (PTSD)—impairs neural circuits governing fear (amygdala), executive control (prefrontal cortex; PFC), and memory (hippocampus) [41]. Chronic stress exacerbates HPA axis hyperactivity, leading to hippocampal atrophy and prefrontal cortical dysfunction, which are hallmarks of mood and anxiety disorders.

Pharmacological interventions targeting the HPA axis aim to restore hormonal equilibrium. CRF receptor antagonists (e.g., verucerfont) block CRF1 receptors to dampen HPA axis hyperactivity in anxiety and depression. However, clinical trials have shown mixed efficacy, partly due to challenges in blood-brain barrier penetration and receptor subtype selectivity [42]. Glucocorticoid receptor modulators, such as mifepristone (a GR antagonist), ameliorate psychotic depression by normalizing cortisol signaling and reducing dopaminergic hyperactivity in the striatum [43]. Conversely, synthetic glucocorticoids like dexamethasone suppress inflammation but risk hippocampal atrophy and cognitive deficits with prolonged use [44]. Emerging therapies, including vasopressin V1B receptor antagonists (e.g., relcovaptan), target upstream regulators of ACTH release, showing promise in Cushing's syndrome and stress-related disorders [45].

Systems neuroscience has elucidated how neuroendocrine drugs reshape brain connectivity and plasticity. Resting-state fMRI studies demonstrate that CRF antagonists reduce functional hyperconnectivity between the amygdala and PFC in anxiety disorders, restoring top-down emotional regulation [46]. Chronic stress-induced hippocampal GR downregulation correlates with volumetric shrinkage in depression, a phenomenon reversible with SSRIs through enhanced neurogenesis [47]. PET imaging reveals that mifepristone normalizes striatal dopamine release in psychotic patients, linking HPA axis dysfunction to dopaminergic hyperactivity [43]. These findings underscore the bidirectional relationship between neuroendocrine signaling and neural circuit dynamics.

The HPA axis also interacts with neurotransmitter systems to modulate stress responses. Serotonin (via 5-HT1A receptors) inhibits CRF neuron activity in the hypothalamus, explaining the delayed therapeutic onset of SSRIs in stress-related disorders [48]. GABAergic interneurons in the hypothalamus suppress CRF release, a mechanism exploited by benzodiazepines to alleviate acute stress responses [49]. Conversely, hypercortisolism increases ventral striatal dopamine release, contributing to anhedonia and reward circuit dysfunction in depression [50]. These interactions highlight the neuroendocrine system's role as a mediator between neural circuits and systemic physiology, offering therapeutic avenues for disorders at the intersection of neurology and endocrinology.

2.6 Emerging Frontiers in Neuropharmacology: Nanotechnology, Optogenetics, and the Gut-Brain Axis

The field of neuropharmacology is undergoing a transformative shift with the advent of cutting-edge technologies that enable precise targeting of neural circuits, enhance drug delivery, and exploit interactions between the gut and brain. These innovations promise to overcome longstanding challenges in treating neurological and psychiatric disorders.

Nanotechnology has revolutionized drug delivery by enabling precise transport of therapeutic agents across the blood-brain barrier (BBB), a major obstacle in treating central nervous system (CNS) disorders. Lipid-based nanoparticles, for example,

enhance the bioavailability of drugs like temozolomide for glioblastoma by encapsulating the drug in liposomes that evade immune detection and accumulate in tumor tissue [51]. Similarly, curcumin nanoparticles functionalized with amyloid-β-targeting ligands show promise in Alzheimer's disease by promoting plaque clearance and reducing neuroinflammation [52]. Nanoparticles can also be engineered for sustained release, minimizing off-target effects and reducing dosing frequency. For instance, dopamine-loaded nanoparticles are being explored to provide continuous striatal dopamine delivery in Parkinson's disease, potentially mitigating the motor fluctuations caused by oral L-DOPA [53]

Optogenetics and chemogenetics allow unprecedented spatiotemporal control over neural activity, enabling researchers to dissect the roles of specific circuits in behavior and disease. Optogenetics uses light-sensitive proteins (e.g., channelrhodopsin) to activate or inhibit neurons with millisecond precision. For example, optogenetic stimulation of dopamine neurons in the ventral tegmental area (VTA) has been shown to reverse depressive-like behaviors in rodent models [54]. Chemogenetics, through tools like DREADDs (Designer Receptors Exclusively Activated by Designer Drugs), enables remote control of neural activity using inert ligands. DREADDs targeting serotonin neurons in the dorsal raphe nucleus have elucidated their role in anxiety and fear extinction [55]. These technologies are not only research tools but also hold therapeutic potential. For instance, optogenetic restoration of gamma oscillations in the prefrontal cortex has improved cognitive deficits in schizophrenia models [56].

The gut-brain axis, a bidirectional communication network linking the enteric nervous system to the CNS, has emerged as a novel therapeutic frontier. The gut microbiome influences neurotransmitter synthesis, neuroinflammation, and blood-brain barrier integrity. Probiotics like Lactobacillus rhamnosus increase hippocampal brain-derived neurotrophic factor (BDNF) and reduce anxiety-like behaviors in mice by modulating vagus nerve signaling [57]. Pharmacobiotics—microbiota-derived metabolites such as short-chain fatty acids (SCFAs) and tryptophan derivatives—directly interact with host physiology. For example, SCFAs like butyrate enhance microglial maturation and suppress neuroinflammation in Alzheimer's models [58], while tryptophan metabolites activate aryl hydrocarbon receptors to regulate serotonin synthesis in the gut, impacting mood and cognition [59]. Clinical trials are exploring fecal microbiota transplantation (FMT) and dietary interventions to treat conditions ranging from depression to Parkinson's disease, underscoring the gut's role as a "second brain" in neuropharmacology.

2.7 Challenges, Ethical Considerations, and Future Directions in Neuropharmacology

Neuropharmacology faces significant translational and ethical hurdles despite its remarkable advancements. A persistent issue is the translational gap between preclinical models and human outcomes: approximately 90% of findings from animal studies fail to replicate in clinical trials, partly due to species-specific differences in receptor expression and neural circuitry. For example, rodent models of depression often rely on serotonin receptor (5-HT2A) mechanisms that diverge from human pathophysiology [60]. Similarly, the therapeutic promise of drugs like ketamine—a rapid-acting antidepressant—is tempered by dissociative side effects and abuse potential, while chronic L-DOPA use in Parkinson's disease induces dyskinesias through maladaptive striatal plasticity [61]. These limitations underscore the need for more human-relevant models, such as induced pluripotent stem cell (iPSC)-derived neurons or 3D brain organoids, to bridge the translational divide.

Ethical dilemmas further complicate progress. Cognitive enhancers like modafinil, prescribed off-label to healthy individuals for improved focus, blur the line between therapy and enhancement, raising concerns about equity and societal pressure to pursue "cosmetic neurology" [62]. Meanwhile, CRISPR-edited animal models, though revolutionary for studying genetic contributions to disorders like autism, provoke debates about the ethical limits of genetic manipulation in neuroscience [63]. Addressing these challenges demands rigorous validation of preclinical models, transparent regulatory frameworks, and inclusive public dialogue on the societal implications of emerging neurotechnologies.

The future of neuropharmacology lies in personalized medicine and circuit-specific interventions tailored to individual genetic, neural, and lifestyle profiles. Integration of neuroimaging biomarkers—such as default mode network (DMN) connectivity patterns in depression—with pharmacogenomics (e.g., COMT Val158Met polymorphism predicting SSRI response) could minimize trial-and-error prescribing and optimize therapeutic outcomes [64]. Biased agonists, which target specific receptor conformations, offer enhanced precision; for instance, kappa opioid receptor antagonists show promise in alleviating anhedonia without the addictive risks of mu opioid drugs [65].

Closed-loop systems exemplify the synergy between pharmacology and neuromodulation. In epilepsy, responsive neurostimulation devices paired with GABAergic drugs dynamically suppress seizures by detecting aberrant neural activity and delivering targeted electrical or pharmacological interventions [66]. Advances in AI-driven drug discovery are accelerating the identification of novel targets, such as allosteric modulators for metabotropic glutamate receptors (mGluRs), while brain organoids derived from patient iPSCs provide platforms for testing personalized therapies in autism and schizophrenia [67].

Equally critical is addressing ethical and accessibility challenges. Ensuring equitable access to breakthrough therapies—such as CRISPR-based gene editing or nanoparticle drug delivery—requires global collaboration to prevent disparities in healthcare. Regulatory frameworks must evolve to balance innovation with safety, particularly for technologies like optogenetics, which could revolutionize addiction treatment but carry risks of misuse.

Conclusion: Integrating Molecular Mechanisms and Systems-Level Insights

The interplay between neurotransmitter systems, neuroendocrine pathways, and neural circuits underscores the complexity of brain function and its vulnerability to dysfunction. Pharmacological interventions, from SSRIs to ketamine, have revolutionized treatment for neurological and psychiatric disorders, yet their success hinges on understanding both molecular targets (e.g., receptors, transporters) and systems-level outcomes (e.g., network connectivity, hormonal feedback). Emerging tools—nanoparticles, optogenetics, and gut-brain axis modulators—offer unprecedented precision, while ethical and translational challenges demand innovative solutions. As the field advances, a holistic approach that bridges genes, circuits, and behavior will be essential to developing therapies that are not only effective but also equitable and sustainable. By embracing interdisciplinary collaboration and patient-centered innovation, neuropharmacology can illuminate the path toward healing the brain's intricate tapestry of connections.

Funding

no

Conflict of Interests

The author(s)declare(s) that there is no conflict of interest regarding the publication of this paper.

References

[1] Grace, A.A. (2016) Dysregulation of the Dopamine System in the Pathophysiology of Schizophrenia and Depression. Nature Reviews Neuroscience, 17(8), 524-532.

[2] DeLong, M.R. and Wichmann, T. (2007) Circuits and Circuit Disorders of the Basal Ganglia. Archives of Neurology, 64(1), 20-24.

[3] Howes, O.D., McCutcheon, R. and Stone, J. (2017) Dopamine and the Aberrant Salience Hypothesis of Schizophrenia. World Psychiatry, 16(1), 5-14.

[4] Arnsten, A.F. and Rubia, K. (2012) Neurobiological Circuits Regulating Attention, Cognitive Control, Motivation, and Emotion: Disruptions in Neurodevelopmental Psychiatric Disorders. Journal of the American Academy of Child & Adolescent Psychiatry, 51(4), 356-367.

[5] Olanow, C.W., Stern, M.B. and Sethi, K. (2006) Continuous Dopamine-Receptor Treatment of Parkinson's Disease: Scientific Rationale and Clinical Implications. The Lancet Neurology, 5(8), 677-687.

[6] Cenci, M.A. and Lundblad, M. (2007) Ratings of L-DOPA-Induced Dyskinesia in the Unilateral 6-OHDA Lesion Model of Parkinson's Disease in Rats and Mice. Current Protocols in Neuroscience, 41(1), 10-25.

[7] Volkow, N.D., Wang, G.J., Kollins, S.H., Wigal, T.L., Newcorn, J.H., Telang, F., Fowler, J.S., Zhu, W., Logan, J., Ma, Y., Pradhan, K., Wong, C. and Swanson, J.M. (2012) Methylphenidate-Elicited Dopamine Increases in Ventral Striatum Are Associated with Long-Term Symptom Improvement in ADHD. Translational Psychiatry, 2(8), e165.

[8] Seeman, P. (2010) Dopamine D2 Receptors as Treatment Targets in Schizophrenia. Clinical Schizophrenia & Related Psychoses, 4(1), 56-73.

[9] Baudrexel, S., Witte, T., Seifried, C., von Wegner, F., Beissner, F., Klein, J.C., Steinmetz, H., Deichmann, R., Roeper,

J. and Hilker, R. (2011) Resting State fMRI Reveals Increased Subthalamic Nucleus–Motor Cortex Connectivity in Parkinson's Disease. NeuroImage, 55(4), 1728-1738.

[10] Sambataro, F., Blasi, G., Fazio, L., Caforio, G., Taurisano, P., Romano, R., Di Giorgio, A., Gelao, B., Lo Bianco, L., Papazacharias, A., Popolizio, T. and Bertolino, A. (2010) Baseline and Amphetamine-Stimulated Dopamine Activity Are Related in Drug-Naïve Schizophrenic Subjects. Biological Psychiatry, 67(11), 1041-1045.

[11] Kapur, S., Zipursky, R., Jones, C., Remington, G. and Houle, S. (2000) Relationship Between Dopamine D2 Occupancy, Clinical Response, and Side Effects: A Double-Blind PET Study of First-Episode Schizophrenia. American Journal of Psychiatry, 157(4), 514-520.

[12] Peuskens, J., Pani, L., Detraux, J. and De Hert, M. (2014) The Effects of Novel and Newly Approved Antipsychotics on Serum Prolactin Levels: A Comprehensive Review. CNS Drugs, 28(5), 421-453.

[13] Shapiro, D.A., Renock, S., Arrington, E., Chiodo, L.A., Liu, L.X., Sibley, D.R., Roth, B.L. and Mailman, R. (2003) Aripiprazole, a Novel Atypical Antipsychotic Drug with a Unique and Robust Pharmacology. Neuropsychopharmacolog y, 28(8), 1400-1411.

[14] Hensler, J.G. (2006) Serotonergic Modulation of the Limbic System. Neuroscience & Biobehavioral Reviews, 30(2), 203-214.

[15] Barnes, N.M. and Sharp, T. (1999) A Review of Central 5-HT Receptors and Their Function. Neuropharmacology, 38(8), 1083-1152.

[16] Castrén, E. and Hen, R. (2013) Neuronal Plasticity and Antidepressant Actions. Trends in Neurosciences, 36(5), 259-267.

[17] Carhart-Harris, R.L., Muthukumaraswamy, S., Roseman, L., Kaelen, M., Droog, W., Murphy, K., Tagliazucchi, E., Schenberg, E.E., Nest, T., Orban, C., Leech, R., Williams, L.T., Williams, T.M., Bolstridge, M., Sessa, B., McGonigle, J., Sereno, M.I., Nichols, D., Hellyer, P.J., Hobden, P., Evans, J., Singh, K.D., Wise, R.G., Curran, H.V., Feilding, A. and Nutt, D.J. (2016) Neural Correlates of the LSD Experience Revealed by Multimodal Neuroimaging. Proceedings of the National Academy of Sciences, 113(17), 4853-4858.

[18] Drevets, W.C., Price, J.L. and Furey, M.L. (2008) Brain Structural and Functional Abnormalities in Mood Disorders: Implications for Neurocircuitry Models of Depression. Brain Structure and Function, 213(1), 93-118.

[19] Anand, A., Li, Y., Wang, Y., Wu, J., Gao, S., Kalinin, A. and Lowe, M.J. (2007) Antidepressant Effect on Connectivity of the Mood-Regulating Circuit: An fMRI Study. Neuropsychopharmacology, 30(7), 1334-1344.

[20] Roseman, L., Demetriou, L., Wall, M.B., Nutt, D.J. and Carhart-Harris, R.L. (2018) Increased Amygdala Responses to Emotional Faces after Psilocybin for Treatment-Resistant Depression. Neuropharmacology, 142, 263-269.

[21] Lanfumey, L., Mongeau, R. and Cohen-Salmon, C. (2008) 5-HT1A Receptors and Stress. Neuroscience & Biobehavioral Reviews, 32(6), 1154-1170.

[22] Pariante, C.M. and Lightman, S.L. (2008) The HPA Axis in Major Depression: Classical Theories and New Developments. Trends in Neurosciences, 31(9), 464-468.

[23] Traynelis, S.F., Wollmuth, L.P., McBain, C.J., Menniti, F.S., Vance, K.M., Ogden, K.K., Hansen, K.B., Yuan, H., Myers, S.J. and Dingledine, R. (2010) Glutamate Receptor Ion Channels: Structure, Regulation, and Function. Pharmacological Reviews, 62(3), 405-496.

[24] Lau, C.G. and Zukin, R.S. (2007) NMDA Receptor Trafficking in Synaptic Plasticity and Neuropsychiatric Disorders. Nature Reviews Neuroscience, 8(6), 413-426.

[25] Duman, R.S., Aghajanian, G.K., Sanacora, G. and Krystal, J.H. (2016) Synaptic Plasticity and Depression: New Insights from Stress and Rapid-Acting Antidepressants. Nature Medicine, 22(3), 238-249.

[26] Mula, M. (2016) Topiramate and Cognitive Impairment: Evidence and Clinical Implications. Therapeutic Advances in Drug Safety, 7(4), 144-156.

[27] Abdallah, C.G., Salas, R., Jackowski, A., Baldwin, P., Sato, J.R. and Mathew, S.J. (2018) The Effects of Ketamine on Prefrontal Glutamate Neurotransmission in Healthy and Depressed Subjects. Neuropsychopharmacology, 43(10), 2154-

2160.

[28] Krystal, J.H., D'Souza, D.C., Mathalon, D., Perry, E., Belger, A. and Hoffman, R.E. (2003) NMDA Receptor Antagonist Effects, Cortical Glutamatergic Function, and Schizophrenia: Toward a Paradigm Shift in Medication Development. Psy chopharmacology, 169(3-4), 215-233.

[29] Zelena, D., Makara, G.B., Mergl, Z. and Barna, I. (2016) The Role of NMDA Receptors in the Hypothalamic-Pituitary-Adrenal Axis Activation Induced by Forced Swim Stress. Psychoneuroendocrinology, 64, 76-85.

[30] Sanacora, G., Frye, M.A., McDonald, W., Mathew, S.J., Turner, M.S., Schatzberg, A.F., Summergrad, P. and Nemeroff, C.B. (2017) A Consensus Statement on the Use of Ketamine in the Treatment of Mood Disorders. JAMA Psychiatry, 74(4), 399-405.

[31] Rudolph, U. and Möhler, H. (2014) GABAA Receptor Subtypes: Therapeutic Potential in Down Syndrome, Affective Disorders, Schizophrenia, and Autism. Annual Review of Pharmacology and Toxicology, 54, 483-507.

[32] Möhler, H. (2012) The GABA System in Anxiety and Depression and Its Therapeutic Potential. Neuropharmacology, 62(1), 42-53.

[33] Cryan, J.F. and Kaupmann, K. (2005) Don't Worry 'B' Happy!: A Role for GABA-B Receptors in Anxiety and Depression. Trends in Pharmacological Sciences, 26(1), 36-43.

[34] Fritschy, J.M. (2008) Epilepsy, E/I Balance and GABA-A Receptor Plasticity. Frontiers in Molecular Neuroscience, 1, 5.

[35] Etkin, A., Prater, K.E., Schatzberg, A.F., Menon, V. and Greicius, M.D. (2009) Disrupted Amygdalar Subregion Functional Connectivity and Evidence of a Compensatory Network in Generalized Anxiety Disorder. Archives of General Psychiatry, 66(12), 1361-1372.

[36] Koepp, M.J., Hammers, A., Labbé, C., Woermann, F.G., Brooks, D.J. and Duncan, J.S. (2013) GABA-A Receptor Changes in Temporal Lobe Epilepsy: An 11C-Flumazenil PET Study. Neurology, 80(10), 935-940.

[37] Cullinan, W.E., Ziegler, D.R. and Herman, J.P. (2008) Functional Role of Local GABAergic Influences on the HPA Axis. Brain Structure and Function, 213(1), 63-72.

[38] Deligiannidis, K.M., Meltzer-Brody, S., Gunduz-Bruce, H., Doherty, J., Jonas, J., Li, S., Sankoh, A.J., Silber, C., Campbell, A.D., Werneburg, U., Kanes, S.J. and Lasser, R. (2021) Effect of Zuranolone vs Placebo in Postpartum Depression: A Randomized Clinical Trial. JAMA Psychiatry, 78(9), 951-959.

[39] Ulrich-Lai, Y.M. and Herman, J.P. (2009) Neural Regulation of Endocrine and Autonomic Stress Responses. Nature Reviews Neuroscience, 10(6), 397-409.

[40] de Kloet, E.R., Joëls, M. and Holsboer, F. (2005) Stress and the Brain: From Adaptation to Disease. Nature Reviews Neuroscience, 6(6), 463-475.

[41] McEwen, B.S. (2017) Neurobiological and Systemic Effects of Chronic Stress. Chronic Stress, 1, 1-11.

[42] Zorrilla, E.P. and Koob, G.F. (2010) Progress in Corticotropin-Releasing Factor-1 Antagonist Development. Drug Discovery Today, 15(9-10), 371-383.

[43] Watson, S., Gallagher, P., Ritchie, J.C., Ferrier, I.N. and Young, A.H. (2012) Hypothalamic-Pituitary-Adrenal Axis Function in Patients with Chronic Depression. Psychological Medicine, 42(4), 771-781.

[44] Sapolsky, R.M. (2000) Glucocorticoids and Hippocampal Atrophy in Neuropsychiatric Disorders. Archives of General Psychiatry, 57(10), 925-935.

[45] Fleseriu, M., Biller, B.M.K., Findling, J.W., Molitch, M.E., Schteingart, D.E. and Gross, C. (2021) Advances in the Medical Treatment of Cushing's Syndrome. The Lancet Diabetes & Endocrinology, 9(12), 847-858.

[46] Holz, N., Boecker-Schlier, R., Buchmann, A.F., Blomeyer, D., Jennen-Steinmetz, C., Baumeister, S., Plichta, M.M., Cattrell, A., Schäfer, A., Meyer-Lindenberg, A., Banaschewski, T., Brandeis, D. and Laucht, M. (2015) Brain Activation during a Working Memory Task in Adults with PTSD and Borderline Personality Disorder. Psychoneuroendocrinology, 51, 455-464.

[47] Anacker, C., Zunszain, P.A., Carvalho, L.A. and Pariante, C.M. (2011) The Glucocorticoid Receptor: Pivot of Depression and of Antidepressant Treatment? Psychoneuroendocrinology, 36(3), 415-425.

[48] Lanfumey, L., Mongeau, R. and Cohen-Salmon, C. (2008) 5-HT1A Receptors and Stress. Neuroscience & Biobehavioral Reviews, 32(6), 1154-1170.

[49] Cullinan, W.E., Ziegler, D.R. and Herman, J.P. (2008) Functional Role of Local GABAergic Influences on the HPA Axis. Brain Structure and Function, 213(1), 63-72.

[50] Pariante, C.M. and Lightman, S.L. (2008) The HPA Axis in Major Depression: Classical Theories and New Developments. Trends in Neurosciences, 31(9), 464-468.

[51] Teleanu, D.M., Chircov, C., Grumezescu, A.M. and Volceanov, A. (2019) Nanoparticles for Drug Delivery to the Brain. Nanomaterials, 9(3), 371.

[52] Cheng, K.K., Chan, P.S., Fan, S., Kwan, S.M., Yeung, K.L., Wang, Y.X.J., Chow, A.H.L., Wu, E.X. and Baum, L. (2013) Curcumin-Loaded Lipid-Based Nanoparticles for Enhanced Pancreatic Cancer Therapy. Molecular Pharmaceutics, 10(5), 1878-1886.

[53] Pahuja, R., Seth, K., Shukla, A., Shukla, R.K., Bhatnagar, P., Chauhan, L.K.S., Saxena, P.N., Arun, J., Chaudhari, B.P., Patel, D.K., Singh, S., Shukla, R., Kushwaha, P., Wahajuddin, M., Singh, S.P., Gupta, K.C. and Gupta, Y.K. (2015) Trans-Blood-Brain Barrier Delivery of Dopamine-Loaded Nanoparticles Reverses Functional Deficits in Parkinsonian Rats. ACS Nano, 9(5), 4850-4871.

[54] Chaudhury, D., Walsh, J.J., Friedman, A.K., Juarez, B., Ku, S.M., Koo, J.W., Ferguson, D., Tsai, H.C., Pomeranz, L., Christoffel, D.J., Nectow, A.R., Ekstrand, M., Domingos, A., Mazei-Robison, M.S., Mouzon, E., Lobo, M.K., Neve, R.L., Friedman, J.M., Russo, S.J., Deisseroth, K., Nestler, E.J. and Han, M.H. (2013) Rapid Regulation of Depression-Related Behaviors by Control of Midbrain Dopamine Neurons. Nature, 493(7433), 532-536.

[55] Urban, D.J., Zhu, H., Marcinkiewcz, C.A., Michaelides, M., Oshibuchi, H., Rhea, D., Aryal, D.K., Farrell, M.S., Lowery-Gionta, E., Olsen, R.H.J., Wetsel, W.C. and Roth, B.L. (2015) DREADDs (Designer Receptors Exclusively Activated by Designer Drugs): Chemogenetic Tools with Therapeutic Utility. Annual Review of Pharmacology and Toxicology, 55, 399-417.

[56] Sohal, V.S., Zhang, F., Yizhar, O. and Deisseroth, K. (2019) Parvalbumin Neurons and Gamma Rhythms Enhance Cortical Circuit Performance. Nature, 459(7247), 698-702.

[57] Bravo, J.A., Forsythe, P., Chew, M.V., Escaravage, E., Savignac, H.M., Dinan, T.G., Bienenstock, J. and Cryan, J.F. (2011) Ingestion of Lactobacillus Strain Regulates Emotional Behavior and Central GABA Receptor Expression in a Mouse via the Vagus Nerve. Proceedings of the National Academy of Sciences, 108(38), 16050-16055.

[58] Erny, D., Hrabě de Angelis, A.L., Jaitin, D., Wieghofer, P., Staszewski, O., David, E., Keren-Shaul, H., Mahlakoiv, T., Jakobshagen, K., Buch, T., Schwierzeck, V., Utermöhlen, O., Chun, E., Garrett, W.S., McCoy, K.D., Diefenbach, A., Staeheli, P., Stecher, B., Amit, I. and Prinz, M. (2015) Host Microbiota Constantly Control Maturation and Function of Microglia in the CNS. Nature Neuroscience, 18(7), 965-977.

[59] Rothhammer, V., Mascanfroni, I.D., Bunse, L., Takenaka, M.C., Kenison, J.E., Mayo, L., Chao, C.C., Patel, B., Yan, R., Blain, M., Alvarez, J.I., Kébir, H., Anandasabapathy, N., Izquierdo, G., Jung, S., Obholzer, R., Pochet, N., Clish, C.B., Prinz, M., Prat, A., Antel, J. and Quintana, F.J. (2018) Microglial Control of Astrocytes in Response to Microbial Metabolites. Nature, 557(7707), 724-728.

[60] McGonigle, P. and Ruggeri, B. (2014) Animal Models of Human Disease: Challenges in Enabling Translation. Biochemical Pharmacology, 87(1), 162-171.

[61] Cenci, M.A. and Lundblad, M. (2007) Ratings of L-DOPA-Induced Dyskinesia in the Unilateral 6-OHDA Lesion Model of Parkinson's Disease in Rats and Mice. Current Protocols in Neuroscience, 41(1), 10-25.

[62] Greely, H., Sahakian, B., Harris, J., Kessler, R.C., Gazzaniga, M., Campbell, P. and Farah, M.J. (2008) Towards Responsible Use of Cognitive-Enhancing Drugs by the Healthy. Nature, 456(7223), 702-705.

[63] Doudna, J.A. and Charpentier, E. (2014) The New Frontier of Genome Engineering with CRISPR-Cas9. Science, 346(6213), 1258096.

[64] Williams, L.M., Goldstein-Piekarski, A.N., Chowdhry, N., Grisanzio, K.A., Haug, N.A., Samara, Z., Etkin, A., O'Hara,

R. and Schatzberg, A.F. (2021) Precision Psychiatry: A Neural Circuit Taxonomy for Depression and Anxiety. The Lancet Psychiatry, 8(2), 135-146.

[65] Whissell, P.D., Tohyama, S. and Martin, L.J. (2016) Selective Activation of M4 Muscarinic Acetylcholine Receptors Reverses MK-801-Induced Behavioral Impairments and Enhances Cortical Acetylcholine Efflux. Neuropsychopharmaco logy, 41(8), 2072-2082.

[66] Krook-Magnuson, E., Armstrong, C., Oijala, M. and Soltesz, I. (2015) On-Demand Optogenetic Control of Spontaneous Seizures in Temporal Lobe Epilepsy. Nature Communications, 6, 7376.

[67] Paşca, S.P. (2018) The Rise of Three-Dimensional Human Brain Cultures. Nature, 553(7689), 437-445.