Global Journal of Advanced
Research and Reviews
Journal homepage: https://gsjournals.com/gjarr/
ISSN: 2980-423X (Online)

(REVIEW ARTICLE)

Check for updates

THE CHEMISTRY OF MENTAL DISORDERS: NEUROCHEMICAL SYSTEMS, MOLECULAR MECHANISMS, AND TRANSLATIONAL IMPLICATIONS

John Chimerenka Ifenkwe [1,*] and Otiogha Erowo Udogidi [2]

[1] Department of Chemical Pathology, Federal University Otuoke, Bayelsa State, Nigeria.
[2] Department of Medical Laboratory Science, Bayelsa Medical University, Yenagoa, Bayelsa State, Nigeria.
* Corresponding Author

ORCID Details
John Chimerenka Ifenkwe: https://orcid.org/0009-0000-9976-1368

Global Journal of Advanced Research and Reviews, 2026, 04(04), 063–069

Publication history: Received on 24 September 2026; revised on 02 November 2026; accepted on 04 November 2026

Article DOI: https://doi.org/10.58175/gjarr.2026.4.4.0089

Copyright © 2026 Author(s) retain the copyright of this article. This article is published under the terms of the Creative Commons Attribution License 4.0

ABSTRACT

Mental disorders are not attributable to a single chemical imbalance, but they are profoundly shaped by dynamic interactions among neurotransmitters, neuropeptides, neurosteroids, inflammatory mediators, genetic variation, neural circuitry, and environmental experience. This review provides an integrated overview of the chemistry of major psychiatric conditions, including major depressive disorder, bipolar disorder, schizophrenia spectrum disorders, anxiety disorders, post-traumatic stress disorder, substance-use disorders, and neurodevelopmental conditions. It examines monoaminergic, amino-acidergic, cholinergic, endocannabinoid, neuroendocrine, immune, epigenetic, and metabolic mechanisms, while emphasizing that molecular changes must be interpreted within developmental, circuit-level, and psychosocial contexts. Contemporary evidence supports dimensional, transdiagnostic frameworks such as the National Institute of Mental Health Research Domain Criteria (RDoC), which integrate molecular, cellular, circuit, behavioral, and environmental levels of analysis.

Keywords: Neurochemistry, Mental disorder, Depression, Schizophrenia, Bipolar disorder, Anxiety

1 INTRODUCTION

The phrase chemical imbalance has been widely used to explain mental illness, particularly depression, but it is scientifically incomplete and potentially misleading. Mental disorders arise from complex, interacting influences that include genetic vulnerability, early-life adversity, stress, infection and inflammation, substance exposure, sleep disruption, social context, and neural plasticity. Chemistry is central to these processes, but no single neurotransmitter abnormality explains depression, psychosis, anxiety, or addiction.

Modern psychiatric neuroscience instead asks how molecular systems regulate perception, emotion, motivation, learning, memory, stress responsiveness, and social behavior and how disruptions contribute to psychopathology. This perspective aligns with dimensional frameworks such as the NIMH Research Domain Criteria (RDoC), which proposes

studying mental health across multiple units of analysis, from genes to self-report, rather than assuming diagnostic categories represent distinct biological entities (Insel et al., 2010; Kozak and Cuthbert, 2016). Genetic studies indicate that psychiatric diagnoses do not map neatly onto distinct pathogenic entities and often share genetic influences (Gandal et al., 2018; Anttila et al., 2018).

2 HISTORICAL AND CONCEPTUAL FOUNDATIONS

The idea that internal bodily states shape mental life is ancient. Early humoral theories, though scientifically outdated, introduced the concept that mood and thought are sensitive to the body's biochemical environment. A decisive shift occurred in the mid-20th century with the introduction of psychotropic agents whose clinical effects demanded mechanistic explanations.

Chlorpromazine, first observed to calm psychotic agitation in the early 1950s, became the foundation for understanding dopamine signaling in psychosis. Concurrently, observations that reserpine could lower mood while monoamine oxidase inhibitors and tricyclic compounds could elevate it led to the formulation of monoamine-based theories of depression. The anxiolytic properties of benzodiazepines later pointed to the importance of inhibitory GABAergic signaling.

While transformative, these therapeutic breakthroughs inadvertently promoted reductionist narratives. Framing depression as a simple deficit in serotonin, or psychosis as an excess of dopamine, offered intuitive appeal but failed to capture the distributed nature of brain function. Current models view symptoms as arising from dysregulation in large-scale networks, where neurochemical systems act as modulators that tune the gain, timing, and plasticity of information processing rather than acting as singular causes.

3 CORE NEUROCHEMICAL SYSTEMS

Monoamine systems function as diffuse neuromodulators that set the gain on arousal, affective tone, motivation, reward learning, attentional control, and motor output through broadly distributed projections.

Dopamine is synthesized from tyrosine, with tyrosine hydroxylase serving as the rate-limiting step. It acts via two major receptor families: D1-like receptors (D1, D5) that generally increase cellular excitability, and D2-like receptors (D2, D3, D4) that mediate inhibitory signaling. Howes and Kapur (2009) reformulated psychosis in a Version III dopamine model, proposing that heterogeneous genetic and environmental risk factors converge to produce a sensitized presynaptic dopamine phenotype, particularly in associative striatum. Under this model, dysregulated phasic dopamine release confers aberrant salience to otherwise neutral stimuli, providing a mechanistic substrate for delusions and hallucinations. D2 receptor antagonism largely accounts for antipsychotic efficacy against positive symptoms, with limited impact on negative and cognitive domains. In substance-use research, dopamine is more accurately conceptualized as encoding reward prediction errors and incentive salience rather than hedonic pleasure per se, with chronic drug exposure associated with downregulation of striatal D2 availability and progressive recruitment of stress-related circuitry (Koob and Volkow, 2016).

Serotonin (5-hydroxytryptamine) is derived from tryptophan and originates predominantly from dorsal and median raphe nuclei. Its actions are diversified across 14 receptor subtypes organized into seven families (5-HT1 to 5-HT7), enabling regulation of mood, sleep-wake architecture, appetite, and impulse control. While selective serotonin reuptake inhibitors elevate synaptic serotonin by blocking the serotonin transporter, therapeutic effects emerge with a delay of weeks, indicating that benefit depends on downstream adaptations in neuroplasticity and emotional information processing rather than acute transporter blockade alone (Artigas, 2013; Harmer et al., 2017).

Norepinephrine is produced from dopamine via dopamine beta-hydroxylase within locus coeruleus neurons. As a key regulator of vigilance, arousal, and autonomic responsiveness, its dysregulation has been implicated across depressive, attentional, anxiety, and trauma-related phenotypes.

Glutamate represents the principal excitatory neurotransmitter in the central nervous system, signaling through ionotropic receptors (NMDA, AMPA, kainate) and metabotropic receptors (mGluR1-8). A prominent model of schizophrenia posits attenuated NMDA receptor function on fast-spiking parvalbumin-expressing interneurons, leading to disinhibition of cortical pyramidal cells, disruption of excitation-inhibition balance, and impaired gamma-band synchrony. The observation that subanesthetic ketamine, an NMDA receptor antagonist, can produce rapid antidepressant effects in treatment-resistant depression has further underscored the role of glutamatergic plasticity in mood regulation (Zarate et al., 2006; Krystal et al., 2019).

GABA, the principal inhibitory transmitter, is synthesized from glutamate by glutamic acid decarboxylase (GAD). Inhibition is mediated by GABA-A receptors, which are ligand-gated chloride channels, and by G-protein-coupled GABA-B receptors. Positive allosteric modulation of GABA-A receptors underlies the anxiolytic actions of benzodiazepines, whereas reduced cortical inhibitory tone has been reported across anxiety, depression, schizophrenia, and autism.

Acetylcholine acts via nicotinic ionotropic and muscarinic metabotropic receptors to regulate attention, learning, memory consolidation, and REM sleep architecture. The alpha-7 nicotinic acetylcholine receptor has garnered interest as a target for sensory gating deficits observed in schizophrenia.

Neuropeptide systems - including corticotropin-releasing factor (CRF), oxytocin, vasopressin, neuropeptide Y, substance P, endogenous opioid peptides, and orexin/hypocretin - operate on slower temporal scales and coordinate integrated responses related to stress reactivity, social affiliation, appetitive behavior, nociception, arousal, and reward.

4 STRESS CHEMISTRY AND THE HYPOTHALAMIC-PITUITARY-ADRENAL (HPA) AXIS

Psychological and physiological stress activates a hierarchical neuroendocrine cascade: paraventricular hypothalamic neurons release corticotropin-releasing hormone (CRH) and vasopressin, which stimulate corticotrophs in the anterior pituitary to secrete adrenocorticotropic hormone (ACTH), which in turn drives cortisol release from the adrenal cortex. This response is adaptive acutely but deleterious when sustained, leading to impaired hippocampal inhibitory feedback and potentiated amygdala reactivity.

HPA phenotypes are heterogeneous across disorders. Hypercortisolemia with impaired feedback sensitivity is observed in a subset of melancholic and psychotic depression, whereas blunted cortisol reactivity and altered diurnal rhythmicity are more characteristic of trauma-related and atypical presentations. The hippocampus provides essential negative-feedback inhibition of the axis and is itself vulnerable to prolonged glucocorticoid exposure.

Developmentally, early-life adversity — encompassing abuse, neglect, and deprivation — is associated with enduring recalibration of HPA axis set-points, in part via epigenetic mechanisms such as increased methylation of the glucocorticoid receptor gene NR3C1 and reduced hippocampal receptor expression. These programming effects are probabilistic, not deterministic, and reflect altered developmental trajectories rather than fixed damage. The trajectory retains plasticity and can be buffered by stable supportive relationships and evidence-based psychosocial and pharmacological interventions.

5 INFLAMMATION, IMMUNITY, AND THE BRAIN

Immune-to-brain communication is critically mediated by pro-inflammatory cytokines, including IL-1β, IL-6, and TNF-α, via vagal afferent signaling and increased blood-brain barrier permeability. This signaling induces sickness behavior - marked by profound fatigue, anhedonia, and social withdrawal - which phenotypically mirrors major depressive symptomatology. Crucially, a distinct and replicable subgroup of patients with major depressive disorder (MDD) exhibits significantly elevated peripheral inflammatory markers (Miller & Raison, 2016). Anti-inflammatory interventions remain experimental and have not demonstrated efficacy as universal or standalone antidepressants. In schizophrenia, epidemiological associations with prenatal infection and autoimmunity have been reported, with convergent mechanisms implicating microglial activation and complement-mediated synaptic pruning; however, inflammation is neither necessary nor sufficient to account for the disorder. Similarly, the gut microbiome is proposed to influence brain function via microbial metabolites, modulation of tryptophan metabolism, and vagal signaling pathways. To date, human findings remain largely correlational and are substantially confounded by diet, BMI, and psychotropic medication. Consequently, probiotic and microbiome-targeted interventions remain adjunctive and experimental, and do not replace evidence-based care.

6 GENETICS, EPIGENETICS, AND GENE-ENVIRONMENT INTERPLAY

Psychiatric disorders exhibit a highly polygenic architecture, arising from the cumulative impact of many common variants of small individual effect and a smaller burden of rare variants of larger effect. Significant cross-disorder overlap is evident, with schizophrenia, bipolar disorder, depression, autism, and Attention-Deficit/Hyperactivity Disorder (ADHD) sharing substantial genetic liability, reflecting pleiotropy rather than discrete genetic boundaries.

Risk variants converge on proteins governing neurotransmitter synthesis and signaling, receptor function, synaptic architecture and plasticity, ion channel activity, immune signaling, and neurodevelopmental processes. However, the phenotypic expression of this genetic liability is contingent on developmental timing, cellular context, and environmental exposure.

Epigenetic mechanisms - including DNA methylation, histone modification, and non-coding RNA regulation - provide a plausible interface between environmental factors such as stress, trauma, and substance exposure and gene expression, though interpretation in humans remains limited by tissue specificity and cellular heterogeneity. Critically, gene-environment interaction dictates that genetic vulnerability is expressed conditionally upon exposure context. Thus, biological risk is probabilistic and modifiable, not deterministic; biology is not destiny.

7 CHEMISTRY OF MAJOR DISORDERS

Major Depressive Disorder (MDD) is neurobiologically heterogeneous. No single neurotransmitter deficiency accounts for MDD. Convergent evidence implicates: (i) monoaminergic dysregulation; (ii) glutamatergic dysfunction and impaired neuroplasticity via Brain-Derived Neurotrophic Factor (BDNF) and AMPA receptor-mediated signaling; (iii) HPA axis dysregulation driven by CRH hypersecretion; (iv) low-grade inflammation that shunts tryptophan metabolism away from serotonin toward the kynurenine pathway; and (v) reward circuit dysfunction and circadian disruption. Depression thus represents a systems-level failure of plasticity, stress regulation, and reward processing.

Bipolar Disorder involves dysregulation of mood stability, bioenergetics, and circadian biology. Pathophysiology converges on intracellular signaling, mitochondrial energy metabolism, and circadian clock mechanisms. Lithium, a prototypical mood stabilizer, inhibits inositol monophosphatase and glycogen synthase kinase-3 beta (GSK-3β), thereby modulating neurotrophic signaling, synaptic plasticity, and circadian rhythmicity. Dopaminergic hyperactivity is strongly implicated in the pathophysiology of mania and aberrant salience.

Schizophrenia reflects interacting dopamine, glutamate, and GABA abnormalities within a neurodevelopmental framework. The disorder is characterized by (i) presynaptic striatal dopamine excess underlying positive symptoms and aberrant salience attribution; (ii) NMDA receptor hypofunction and parvalbumin-positive GABAergic interneuron dysfunction contributing to cognitive deficits and negative symptoms; and (iii) aberrant developmental synaptic pruning and large-scale connectivity disruption. No single transmitter system is sufficient.

Anxiety Disorders and PTSD involve a dysregulated threat-detection network. Key nodes include the amygdala, hippocampus, ventromedial prefrontal cortex, insula, and bed nucleus of the stria terminalis (BNST). Norepinephrine and CRH promote hypervigilance and autonomic arousal, while GABAergic and endocannabinoid signaling provide critical inhibitory restraint of fear. Glutamatergic signaling mediates fear extinction learning. PTSD is specifically characterized by impaired extinction retention and noradrenergic hyperactivity. SSRIs and SNRIs remain first-line pharmacotherapies; prazosin for trauma-related nightmares has shown mixed evidence.

Substance Use Disorders involve distinct primary targets but converge on a common final pathway. While addictive substances act on discrete initial targets — mu-opioid receptors, monoamine transporters, GABA-A potentiation, NMDA receptor inhibition, nicotinic acetylcholine receptors, and CB1 receptors — chronic use produces a common shift toward reduced striatal dopamine D2 receptor availability, recruitment of stress-related CRH circuitry, and sensitization of craving and habit circuits.

Neurodevelopmental Disorders reflect circuit-level excitation-inhibition imbalance. ADHD is characterized by frontostriatal dysregulation of dopamine and norepinephrine signaling underlying executive dysfunction and reward processing. Autism Spectrum Disorder is etiologically heterogeneous, with convergent evidence for excitation-inhibition imbalance involving GABAergic, glutamatergic, and serotonergic systems, including serotonin transporter dysregulation, as well as modulatory systems such as oxytocin signaling.

In sum, major psychiatric conditions are not single-chemical disorders but distributed disorders of synaptic signaling, plasticity, and circuit regulation shaped by polygenic risk and environmental context.

8 NEUROSTEROIDS, SLEEP, AND CIRCADIAN CHEMISTRY

Neurosteroids provide a critical link between endocrine status and inhibitory neurotransmission. Allopregnanolone, a progesterone-derived metabolite, is a potent positive allosteric modulator of the GABA-A receptor, producing rapid anxiolytic and sedative effects. Fluctuations in allopregnanolone are implicated in premenstrual dysphoric disorder (PMDD) and postpartum depression (PPD), conditions characterized by abrupt neurosteroid withdrawal.

This mechanism has been therapeutically validated. Brexanolone, an intravenous formulation of allopregnanolone, was FDA-approved in 2019 for PPD. Due to risks of excessive sedation and sudden loss of consciousness, its use is restricted under a Risk Evaluation and Mitigation Strategy (REMS) and requires continuous monitoring in a certified healthcare facility. Zuranolone, a synthetic oral analogue with improved bioavailability, was FDA-approved in 2023 for PPD, offering a more accessible neurosteroid-based intervention.

Sleep is not a passive state but an active, highly regulated neurochemical process governed by the accumulation of adenosine promoting sleep pressure, melatonin signaling circadian night, hypocretin/orexin stabilizing wakefulness, and the circadian nadir of cortisol. It is essential for synaptic homeostasis and memory consolidation. Circadian disruption — including phase advance/delay, amplitude blunting, and sleep fragmentation — is a core pathophysiological feature and modifiable risk factor for bipolar disorder, major depression, and psychosis.

9 PHARMACOLOGY AND TREATMENT MECHANISMS

Antidepressants: Mechanistically diverse. Selective serotonin reuptake inhibitors (SSRIs) block the serotonin transporter (SERT); serotonin-norepinephrine reuptake inhibitors (SNRIs) block SERT and the norepinephrine transporter (NET); tricyclic antidepressants (TCAs) inhibit multiple monoamine transporters with additional antihistaminergic and anticholinergic activity; monoamine oxidase inhibitors (MAOIs) reduce enzymatic degradation of monoamines; and atypical agents act via distinct mechanisms including melatonergic agonism (agomelatine) and glutamatergic modulation (e.g., ketamine via NMDA receptor antagonism). The characteristic delay of weeks to clinical effect despite immediate target engagement suggests that therapeutic efficacy depends on downstream neuroplasticity mechanisms, including BDNF upregulation and restoration of prefrontal-hippocampal connectivity, rather than acute monoamine elevation alone.

Antipsychotics: First-generation agents exert therapeutic effects primarily through high-affinity D2 receptor antagonism, effective for positive symptoms but associated with dose-dependent extrapyramidal symptoms and hyperprolactinemia. Second-generation agents exhibit broader receptor occupancy, including 5-HT2A antagonism and variable affinity for histaminergic, muscarinic, and adrenergic receptors, conferring a lower risk of motor side effects but an increased liability for metabolic syndrome. Clozapine remains uniquely effective for treatment-resistant schizophrenia, likely due to its complex polypharmacology and preferential modulation of cortical circuits.

Mood Stabilizers: Lithium inhibits inositol monophosphatase and glycogen synthase kinase-3 beta (GSK-3β), enhancing neurotrophic signaling, promoting synaptic resilience, and stabilizing circadian molecular clocks. Valproate enhances GABAergic transmission, blocks voltage-gated sodium channels, and acts as a histone deacetylase (HDAC) inhibitor, thereby influencing epigenetic regulation.

Anxiolytics and Psychotherapy: Benzodiazepines produce rapid anxiolysis via positive allosteric modulation of GABA-A receptors but are limited by tolerance, dependence, sedation, increased risk of falls and cognitive impairment, and lack of long-term efficacy for core anxiety disorders; SSRIs/SNRIs are therefore preferred for chronic management. Importantly, evidence-based psychotherapies are biologically active: exposure-based therapies, cognitive-behavioral therapy (CBT), and trauma-focused interventions produce measurable changes in fear extinction learning, ventromedial prefrontal regulation of the amygdala, HPA axis reactivity, and large-scale network connectivity.

10 BIOMARKERS AND PRECISION PSYCHIATRY

A clinically useful biomarker must be reliable, reproducible, specific to a mechanistic subgroup, predictive of treatment response, and actionable. At present, few psychiatric biomarkers satisfy all criteria. Promising domains under investigation include polygenic risk scores, multimodal neuroimaging, quantitative EEG, peripheral inflammatory markers (e.g., CRP, IL-6), HPA axis indices, metabolomics, objective sleep and circadian phenotyping, and digital phenotypes derived from behavioral sensing.

The objective of precision psychiatry is not to replace diagnostic categories but to identify transdiagnostic mechanistic subgroups — for example, inflammatory versus reward-dysfunction subtypes of depression — to guide stratified intervention. Current DSM/ICD categories remain essential for clinical communication and service delivery but must be supplemented by dimensional measures of pathophysiology.

11 ETHICAL, SOCIAL, AND CLINICAL IMPLICATIONS

Biological explanations have complex psychosocial effects. While they can reduce moral blame and self-stigmatization by framing psychiatric conditions as medical conditions, deterministic framing can inadvertently foster therapeutic fatalism and pessimism about recovery. A scientifically accurate formulation is that vulnerability is probabilistic, developmentally embedded, and modifiable.

Stigma persists independently of etiological attribution. A constructive, non-reductionist message emphasizes that psychiatric disorders involve real, measurable processes in the brain and body, which are profoundly shaped by social determinants and are responsive to intervention. Poverty, discrimination, exposure to violence, and housing insecurity

are not merely psychosocial stressors but become biologically embedded through chronic HPA activation, systemic inflammation, circadian disruption, and impaired sleep.

12 FUTURE DIRECTIONS

Progress will require a shift from cross-sectional associations to longitudinal studies linking molecular and circuit-level mechanisms to symptom trajectories. Priority areas include: (i) cell-type and circuit-specific interrogation of disease mechanisms; (ii) integration of multi-omics with neuroimaging and continuous digital phenotyping; (iii) development and validation of biomarkers predictive of treatment response; (iv) inclusion of ancestrally and socially diverse populations; (v) ethical governance of genetic and predictive data; and (vi) systematic evaluation of integrated interventions combining pharmacology, evidence-based psychotherapy, sleep and circadian stabilization, physical activity, nutritional support, and social interventions.

The future of psychiatry lies not in identifying a single chemical cause, but in mapping multiple convergent and divergent pathways that link biological, psychological, and social factors - to deliver more precise, effective, and humane care.

13 CONCLUSION

This review shows that mental disorders are not caused by a single chemical imbalance, but by dynamic interactions among neurotransmitters, hormones, immune signals, genetic vulnerability, brain circuits, development, and environmental experience. Across depression, bipolar disorder, schizophrenia, anxiety, trauma-related disorders, substance-use disorders, and neurodevelopmental conditions, the strongest evidence points to distributed problems in synaptic signaling, stress regulation, plasticity, and circuit function rather than isolated defects in one molecule. This integrated view can help society move beyond blame and oversimplified explanations toward earlier recognition, more precise treatment, reduced stigma, and care that combines pharmacological, psychological, sleep, lifestyle, and social interventions, while future research should prioritize longitudinal, diverse, and mechanism-guided studies that translate neurochemical insight into safer and more effective care.

STATEMENTS ON COMPLIANCE WITH ETHICAL STANDARDS

Disclosure of conflict of interest

The authors declare no conflicts of interest regarding this manuscript.

REFERENCES

[1] Anttila, V., Bulik-Sullivan, B., Finucane, H. K., Walters, R. K., Bras, J., Duncan, L., Escott-Price, V., Falcone, G. J., Gormley, P., Malik, R., Patsopoulos, N. A., Ripke, S., Wei, Z., Yu, D., Lee, P. H., Turley, P., Grenier-Boley, B., Chouraki, V., Kamatani, Y., Berr, C., ... Brainstorm Consortium. (2018). Analysis of shared heritability in common disorders of the brain. Science, 360(6395), eaap8757. https://doi.org/10.1126/science.aap8757

[2] Artigas, F. (2013). Serotonin receptors involved in antidepressant effects. Pharmacology & Therapeutics, 137(1), 119–131. https://doi.org/10.1016/j.pharmthera.2012.09.006

[3] Bahji, A., Vazquez, G. H., & Zarate, C. A., Jr. (2021). Comparative efficacy of racemic ketamine and esketamine for depression: A systematic review and meta-analysis. Journal of Affective Disorders, 278, 542–555. https://doi.org/10.1016/j.jad.2020.09.102

[4] Bale, T. L., Baram, T. Z., Brown, A. S., Goldstein, J. M., Insel, T. R., McCarthy, M. M., Nemeroff, C. B., Reyes, T. M., Simerly, R. B., Susser, E. S., & Nestler, E. J. (2010). Early life programming and neurodevelopmental disorders. Biological Psychiatry, 68(4), 314–319. https://doi.org/10.1016/j.biopsych.2010.05.028

[5] Belujon, P., & Grace, A. A. (2017). Dopamine system dysregulation in major depressive disorders. International Journal of Neuropsychopharmacology, 20(12), 1036–1046. https://doi.org/10.1093/ijnp/pyx056

[6] Boksa, P. (2010). Effects of prenatal infection on brain development and behavior: A review of findings from animal models. Brain, Behavior, and Immunity, 24(6), 881–897. https://doi.org/10.1016/j.bbi.2010.03.005

[7] Cryan, J. F., & 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. https://doi.org/10.1016/j.tips.2004.11.004

[8] Cryan, J. F., O'Riordan, K. J., Cowan, C. S. M., Sandhu, K. V., Bastiaanssen, T. F. S., Boehme, M., Codagnone, M. G., Cussotto, S., Fulling, C., Golubeva, A. V., Guzzetta, K. E., Jaggar, M., Long-Smith, C. M., Lyte, J. M., Martin, J. A.,

Molinero-Perez, A., Moloney, G., Morelli, E., Morillas, E., ... Dinan, T. G. (2019). The microbiota-gut-brain axis. Physiological Reviews, 99(4), 1877–2013. https://doi.org/10.1152/physrev.00018.2018

[9] Deligiannidis, K. M., Meltzer-Brody, S., Gunduz-Bruce, H., Doherty, J., Jonas, J., Li, S., Sankoh, A. J., Silber, C., Campbell, A. D., Werneburg, B., Kanes, S. J., & Lasser, R. (2023). Effect of zuranolone vs placebo in postpartum depression: A randomized clinical trial. JAMA Psychiatry, 80(7), 708–719. https://doi.org/10.1001/jamapsychiatry.2023.1552

[10] Duman, R. S., & Aghajanian, G. K. (2012). Synaptic dysfunction in depression: Potential therapeutic targets. Science, 338(6103), 68–72. https://doi.org/10.1126/science.1222939

[11] Gandal, M. J., Haney, J. R., Parikshak, N. N., Leppa, V., Ramaswami, G., Hartl, C., Schork, A. J., Appadurai, V., Buil, A., Werge, T. M., Liu, C., White, K. P., Horvath, S., & Geschwind, D. H. (2018). Shared molecular neuropathology across major psychiatric disorders parallels polygenic overlap. Science, 359(6376), 693–697. https://doi.org/10.1126/science.aad6469

[12] Harmer, C. J., Duman, R. S., & Cowen, P. J. (2017). How do antidepressants work? New perspectives for refining future treatment approaches. Lancet Psychiatry, 4(5), 409–418. https://doi.org/10.1016/S2215-0366(17)30015-9

[13] Howes, O. D., & Kapur, S. (2009). The dopamine hypothesis of schizophrenia: Version III—The final common pathway. Schizophrenia Bulletin, 35(3), 549–562. https://doi.org/10.1093/schbul/sbp006

[14] Insel, T., Cuthbert, B., Garvey, M., Heinssen, R., Pine, D. S., Quinn, K., Sanislow, C., & Wang, P. (2010). Research domain criteria (RDoC): Toward a new classification framework for research on mental disorders. American Journal of Psychiatry, 167(7), 748–751. https://doi.org/10.1176/appi.ajp.2010.09091379

[15] Koob, G. F., & Volkow, N. D. (2016). Neurobiology of addiction: A neurocircuitry analysis. Lancet Psychiatry, 3(8), 760–773. https://doi.org/10.1016/S2215-0366(16)00104-8

[16] Kozak, M. J., & Cuthbert, B. N. (2016). The NIMH research domain criteria initiative: Background, issues, and pragmatics. Psychophysiology, 53(3), 286–297. https://doi.org/10.1111/psyp.12518

[17] Krystal, J. H., Abdallah, C. G., Sanacora, G., Charney, D. S., & Duman, R. S. (2019). Ketamine: A paradigm shift for depression research and treatment. Neuron, 101(5), 774–778. https://doi.org/10.1016/j.neuron.2019.02.033

[18] Lupien, S. J., McEwen, B. S., Gunnar, M. R., & Heim, C. (2009). Effects of stress throughout the lifespan on the brain, behaviour and cognition. Nature Reviews Neuroscience, 10(6), 434–445. https://doi.org/10.1038/nrn2639

[19] McEwen, B. S. (2007). Physiology and neurobiology of stress and adaptation: Central role of the brain. Physiological Reviews, 87(3), 873–904. https://doi.org/10.1152/physrev.00041.2006

[20] Miller, A. H., & Raison, C. L. (2016). The role of inflammation in depression: From evolutionary imperative to modern treatment target. Nature Reviews Immunology, 16(1), 22–34. https://doi.org/10.1038/nri.2015.5

[21] Nestler, E. J., & Hyman, S. E. (2010). Animal models of neuropsychiatric disorders. Nature Neuroscience, 13(10), 1161–1169. https://doi.org/10.1038/nn.2647

[22] Ressler, K. J., & Mayberg, H. S. (2007). Targeting abnormal neural circuits in mood and anxiety disorders: From the laboratory to the clinic. Nature Neuroscience, 10(9), 1116–1124. https://doi.org/10.1038/nn1944

[23] Roth, T. L., Lubin, F. D., Funk, A. J., & Sweatt, J. D. (2009). Lasting epigenetic influence of early-life adversity on the BDNF gene. Biological Psychiatry, 65(9), 760–769. https://doi.org/10.1016/j.biopsych.2008.11.028

[24] Sanacora, G., Treccani, G., & Popoli, M. (2012). Towards a glutamate hypothesis of depression: An emerging frontier of neuropsychopharmacology for mood disorders. Neuropharmacology, 62(1), 63–77. https://doi.org/10.1016/j.neuropharm.2011.07.036

[25] Stahl, S. M. (2013). Stahl's essential psychopharmacology: Neuroscientific basis and practical applications (4th ed.). Cambridge University Press.

[26] Volkow, N. D., Koob, G. F., & McLellan, A. T. (2016). Neurobiologic advances from the brain disease model of addiction. New England Journal of Medicine, 374(4), 363–371. https://doi.org/10.1056/NEJMra1511480

[27] Yehuda, R., Hoge, C. W., McFarlane, A. C., Vermetten, E., Lanius, R. A., Nievergelt, C. M., Hobfoll, S. E., Koenen, K. C., Neylan, T. C., & Hyman, S. E. (2015). Post-traumatic stress disorder. Nature Reviews Disease Primers, 1, 15057. https://doi.org/10.1038/nrdp.2015.57

[28] Zarate, C. A., Jr., Singh, J., Carlson, P. J., Brutsche, N. E., Ameli, R., Luckenbaugh, D. A., Charney, D. S., & Manji, H. K. (2006). A randomized trial of an N-methyl-D-aspartate antagonist in treatment-resistant major depression. Archives of General Psychiatry, 63(8), 856–864. https://doi.org/10.1001/archpsyc.63.8.856