

Review

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Review

From Monoamines to Systems Psychiatry: Rewiring Depression Science and Care (1960s–2025)

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Abstract

Major depressive disorder was, until recently, framed as a single entity arising from a linear stress–monoamine–hypothalamic–pituitary–adrenal (HPA) axis cascade, modeled by forced swim and learned helplessness tests and evaluated by brief Hamilton Depression Rating Scale (HAM-D)/Montgomery–Åsberg Depression Rating Scale (MADRS) symptom trials. This “unitary cascade” view has been dismantled by imaging, immune–metabolic and sleep profiling, and plasticity markers, which reveal divergent circuit, inflammatory, and chronobiological patterns across anxious, pain-laden, and cognitively weighted depression, with non-response and relapse common. Translationally, face-valid rodent assays that equated immobility with despair have yielded limited bedside benefit, whereas cross-species bridges—electroencephalography (EEG) motifs, rapid eye movement (REM) architecture, effort-based reward tasks, and inflammatory/metabolic panels—are beginning to provide mechanistically grounded, clinically actionable readouts. In current practice, depression care is shifting toward systems psychiatry: inflammation-high and metabolic-high archetypes, anhedonia- and circadian-dominant subgroups, formal treatment-resistant depression (TRD) staging, connectivity-guided neuromodulation, esketamine, selected pharmacogenomic panels, and early digital phenotyping, as endpoints broaden to functioning and durability. A central gap is that heterogeneity is acknowledged but rarely built into trial design or implementation. This perspective advances a plasticity-centered systems psychiatry in which a testable prediction is that manipulating defined prefrontal–striatal and prefrontal–limbic circuits in sex-balanced, chronic-stress models will reproduce human network-defined biotypes and treatment response, and proposes hybrid effectiveness–implementation platforms that embed immune–metabolic and sleep panels, circuit-sensitive tasks, and digital monitoring under a shared, preregistered data standard.

Keywords: major depressive disorder (MDD); neurocircuitry; synaptic plasticity; neuroimmune interactions; metabolic syndrome; treatment-resistant depression (TRD); neuromodulation; biomarkers; kynurenine; precision medicine

1. Framing the Journey—Prompts

Major depressive disorder has long been framed through a monoamine-centric lens, a narrative that catalyzed pharmacotherapy yet left substantial non-response and relapse [1]. Historical reassessments of the monoamine hypothesis and contemporary work on clinical, neurobiological, and treatment advances now converge on a simple conclusion: incremental refinements of the same model are no longer sufficient [2,3]. In an era of high dimensional neuroimaging, immune profiling, and digital phenotyping, revisiting the trajectory from 1960s monoamine theories to emerging systems psychiatry is therefore a strategic necessity [4,5](Figure 1). (4 refs)

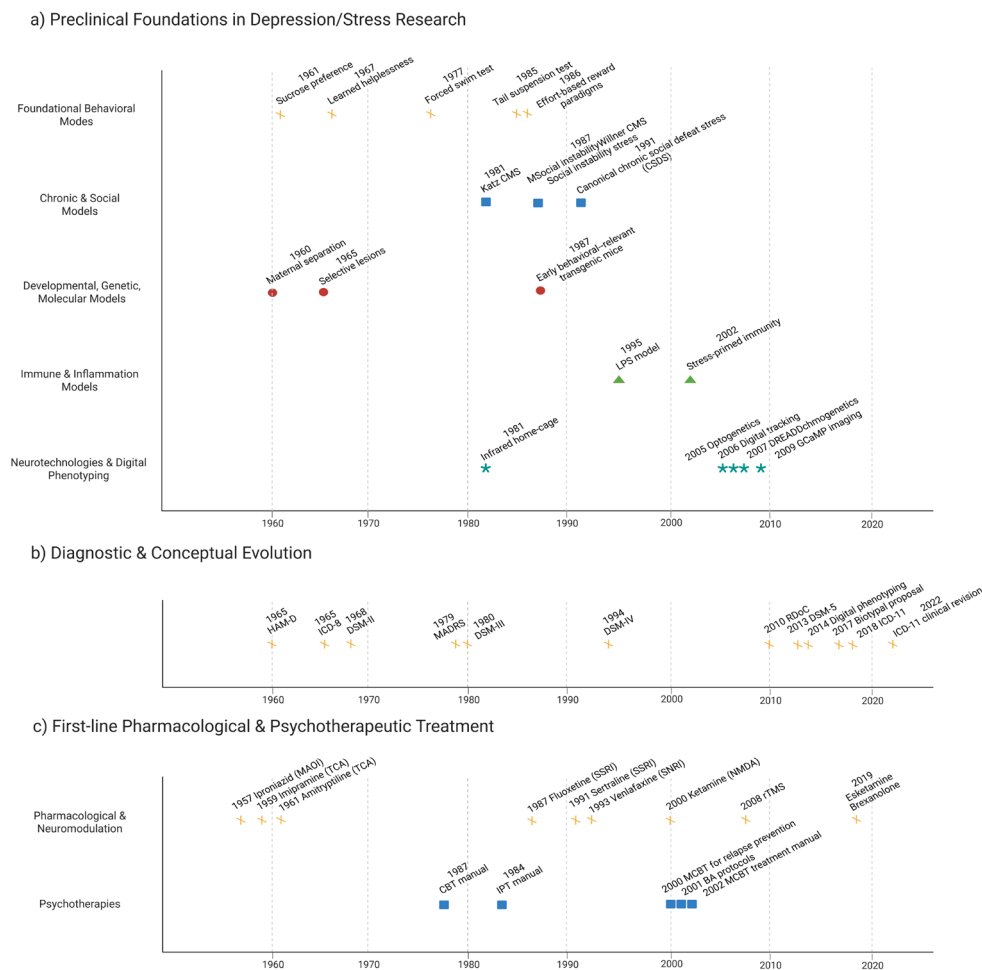


Figure 1. Translational timeline strip linking preclinical models, diagnostic milestones, and first-line depression treatments. Stylized timeline strip spanning the mid-20th century to the present, organized in three horizontal bands: (top) preclinical depression-relevant models, (middle) diagnostic milestones, and (bottom) first-line pharmacological and psychotherapeutic treatments. Each band highlights when core tools entered the field (e.g., forced-swim and learned helplessness assays, Diagnostic and Statistical Manual of Mental Disorders (DSM)-III formalization of major depressive disorder, the SSRI era, evidence-based psychotherapies, and rapid-acting agents such as ketamine/esketamine), emphasizing where innovation in models, nosology, and frontline care has been synchronized—or strikingly decoupled. Arrows and shaded zones indicate potential “bridgeable gaps” where contemporary preclinical assays could be explicitly linked to diagnostic refinements and treatment decisions in next-generation clinical trial designs.

This perspective views major depressive disorder as a nexus condition with dense cross talk to anxiety, chronic pain, and dementia, where shared and distinct pathways blur categorical boundaries [6]. Large scale cohort and imaging studies reveal common yet dissociable alterations in prefrontal and limbic circuitry across depression, anxiety, post-traumatic stress disorder, and pain, while mechanistic work highlights bidirectional links with cardiometabolic and neurodegenerative disease [7–9]. Within this landscape, anxious, pain enriched, and cognitively loaded depression exemplify how comorbidity patterns reshape prognosis, treatment response, and trial outcomes [10,11]. (5 refs)

Our central thread traces the shift from neurotransmitter first thinking toward an integrated immune, metabolic, and circuit-based framework that can anchor precision care [12]. This perspective synthesizes evidence on central–peripheral immune interactions, network-level biotypes, and model-driven subtypes of brain organization, and outlines how these advances should inform next-

generation therapeutics and trial design [13–15]. Rather than another unitary model of depression, this perspective advances frameworks that treat heterogeneity as signal, not noise, enabling stratified, personalized interventions across intertwined spectra of mood, anxiety, pain, and cognitive decline [16]. (4 refs)

Box A—Key Terms

A *biomarker* is an objective biological signal that indexes state, risk, or treatment response. An *endophenotype* reflects a heritable, mechanistic intermediate—closer to circuitry than symptoms. *Anhedonia* captures reduced reward sensitivity or effort, a core transdiagnostic deficit. *Treatment-resistant* denotes limited response after adequate therapeutic trials. *Rapid-acting* refers to interventions producing meaningful change within hours to days. A *network target* is a circuit-defined node guiding drug or device precision. A *digital endpoint* leverages passive or task-based sensors to quantify behavior in real time.

2. Early Paradigms & Assumptions (1960s–1990s)

Early paradigms of depression research crystallized around stress, monoamines, and the hypothalamic pituitary adrenal axis as the primary translators of adversity into “behavioral despair” [2,17]. Forced swim and learned helplessness tests, later complemented by chronic stress paradigms in rodents and primates, operationalized immobility, withdrawal, and subdued exploration as proxies for hopelessness [18,19]. These models were highly sensitive to monoaminergic and hypothalamic–pituitary–adrenal axis (HPA) modulating drugs and, for a time, appeared to bridge synapse and symptom [20,21]. Parallel work on glucocorticoid feedback, neurosteroids, and early immune and gut brain signals refined this picture, yet still treated depression largely as a unitary endpoint of a relatively linear stress monoamine HPA cascade [22,23].

On the clinical side, the introduction of DSM III and DSM III R reconfigured nosology around symptom checklists, while Hamilton Depression Rating Scale (HAM-D) and later Montgomery–Åsberg Depression Rating Scale (MADRS) scores became the dominant trial endpoints [24,25]. Response and remission were quantified by cutoffs on these scales, and short, fixed duration trials with single primary mood outcomes became the gold standard for regulatory sensitive evidence [26,27]. Placebo run in phases, designed to screen out early improvers and sharpen drug signal, further shaped effect sizes and sample composition, often at the cost of ecological validity [26,28]. Translation across trials relied on scale equivalence rather than deeper phenotyping or mechanistic anchors [29,30].

Within this framework, crucial sources of heterogeneity were marginalized [31]. Sex and age dependent profiles of mood, anxiety, and somatic symptoms were rarely modeled explicitly in either preclinical or clinical research, despite emerging data on sex specific monoamine and HPA signatures [32–35]. Ancestry, social context, chronic pain, and subthreshold anxiety were treated as noise, not structure [36]. Endpoint myopia, focused on short term mood change in narrowly defined samples, left longer term trajectories, functional outcomes, and comorbidity patterns largely uncharted, planting many of the seeds for the replication, generalization, and treatment resistance challenges that later decades would confront [37–39].

3. Pivot Suite (10 Mini-Cards)

This Pivot Suite condenses ten mechanistic “mini-cards” that reorient depression from a monoamine-shortage model toward a multiscale systems disorder. Each card anchors a specific lever—plasticity and circuit dynamics, reward and stress alignment, immune–metabolic and genomic milieu, or multi-point intervention logic—and links it to concrete translational readouts. Together, these pivots outline how synapses, circuits, body-wide signals, and trial architectures can be jointly tuned to redesign treatment-resistant depression (TRD) as a tractable, stratified systems problem.

3.1. Plasticity & Circuit Control of Depressive States

Across these cards, depression science shifts from monoamine scarcity toward dynamic systems. Each mini-anchor foregrounds mechanisms, actionable readouts, and clinically tractable targets that scaffold next-generation translational trial designs.

3.1.1. Synaptic Plasticity & Intrinsic Excitability

- Synaptic plasticity and intrinsic excitability reframe depression as a disorder of experience-dependent wiring rather than transmitter shortage [40,41].
- Long-term potentiation and depression, α -amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid (AMPA) receptor throughput, and evoked excitatory postsynaptic potentials (eEPSPs) index rapid remodeling, while neurogenesis and extracellular signal-regulated kinase (ERK)-sensitive priming by ketamine extend effects [42–45].
- Early electroencephalography (EEG), local field potential (LFP), resting-state functional magnetic resonance imaging (rsfMRI) plasticity markers and AMPA-forward assays become core translational readouts [46,47].

3.1.2. Glutamate/ γ -Aminobutyric Acid (GABA) Microcircuit Control

- Glutamate and γ -aminobutyric acid (GABA) microcircuits position excitation/inhibition balance, shaped by somatostatin and parvalbumin interneurons, as a tunable affective set point [48–51].
- N-methyl-D-aspartate (NMDA) and metabotropic glutamate receptor modulation, inhibitory postsynaptic potentials, and layer-specific oscillations provide mechanistic levers [52–54].
- Oscillation-anchored endpoints, task-locked transcranial magnetic stimulation–electroencephalography (TMS-EEG), and interneuron-specific *in silico* or animal models link inhibition deficits to scalable EEG and behavioral signatures [55,56].

3.1.3. Circuit-Level Nodes (Drugs & Devices)

- Circuit-level nodes highlight how drugs and devices now target networks connecting habenula, subcallosal cingulate, and ventromedial prefrontal cortex.
- Deep brain, vagus nerve, and transcranial magnetic stimulation, including accelerated theta-burst protocols, are steered by connectivity-guided targeting and TMS-EEG physiology.
- Proof of target engagement, intensified dosing schedules, and responder enrichment by baseline network topology redefine how device parameters map onto durable outcomes [57].

3.2. Reward, Motivation & Stress Systems

The pivot pair tracks how stress reshapes reward pursuit and timekeeping, linking mesolimbic opioid tone and HPA plus circadian drift to anhedonia and fatigue.

3.2.1. Reward, motivation, and stress–opioid tone

- Anhedonia is reframed as a mesolimbic dialogue where dopamine driven reward signaling is gated by dynorphin and kappa (κ)-opioid stress tone [58,59].
- Effort based choice behavior, ventral striatal activity, and inflammatory status jointly index motivational collapse [60–63].
- Selective κ -opioid antagonists and κ -opioid-active antidepressants invite augmentation trials that separate hedonic liking, motivated effort, and stress challenge responses [64,65].

3.2.2. HPA–Circadian–Stress Axis

- The HPA and circadian system form a coupled stress axis in which glucocorticoid receptor (GR) sensitivity, cortisol rhythms, and sleep architecture tune mood regulation [66–69].

- Delayed dim light melatonin onset, altered actigraphy, and a dysregulated cortisol awakening response signal internal misalignment [70–72].
- Chronotype aware protocols, sleep linked endpoints, and GR assays operationalize this chronobiological vulnerability in real patients [73,74].

3.3. Immune–Metabolic–Genomic Modifiers of Risk and Treatment Response

This pivot gathers immune, metabolic, and genomic modifiers that quietly bias risk, symptom expression, and durability of response, turning background milieu into explicit treatment design variables.

3.3.1. Tryptophan (Trp)–kynurenine (KYN) steering

Tryptophan (Trp)-kynurenine (KYN) steering links immune activation to serotonin scarcity and neurotoxic load [75]. indoleamine 2,3-dioxygenase (IDO) and tryptophan 2,3-dioxygenase (TDO) divert Trp into KYN, tuning kynurenic acid (KYNA) versus quinolinic acid (QA) and aryl hydrocarbon receptor (AhR) signaling [76]. Peripheral C-reactive protein (CRP), KYN/Trp ratios, and microglia astrocyte metabolism align with cognitive, affective, and somatic symptom clusters, inviting inflammation stratified, longitudinal KYN panels in back translation [77–87].

3.3.2. Neuroimmune and glia

- Neuroimmune and glial modifiers position microglia, astrocytes, complement, and colony-stimulating factor 1 receptor (CSF1R) or purinergic P2X7 receptor signaling as active sculptors of synaptic strength and network tone [88–90].
- Positron emission tomography (PET) ligands, cerebrospinal cytokine panels, and EEG complexity provide convergent signatures of immune engagement [91–94].
- Trials should treat sex, inflammatory state, and electroconvulsive or stimulation induced immune shifts as designable dimensions for precision psychiatry [95].

3.3.3. Metabolic–endocrine crosstalk

- Metabolic endocrine crosstalk highlights insulin resistance, adiposity, and glucagon-like peptide-1 (GLP-1) signaling as levers that couple energy allocation to mood, cognition, and treatment response.
- Metabolic syndrome phenotypes and type 2 diabetes (T2D) comorbidity flag patients in whom antidepressant efficacy, tolerability, and neuromodulation outcomes hinge on brain insulin signaling.
- Pragmatic trials should embed metabolic stratification and functional endpoints.

3.3.4. Epigenetic/transcriptional gating

- Epigenetic and transcriptional gating captures how histone deacetylases (HDACs), bromodomain, lysine-specific demethylase 1 (LSD1), and DNA methyltransferases (DNMTs) stabilize or relax depressive states and treatment induced remissions [96,97].
- Cell type resolved assay for transposase-accessible chromatin (ATAC) and ribonucleic acid (RNA) sequencing, combined with peripheral chromatin marks, chart medication and neuromodulation trajectories [98–100].
- Future trials should incorporate durability endpoints and convergent multi omic panels that track chromatin state ladders clinically [97,99,100].

3.4. Multi-Point Precision Strategies & Emerging Targets

The pivot turns from single levers to integrated playbooks, treating TRD as a heterogeneous systems problem that demands multiscale, multi-point intervention logic frameworks.

3.4.1. Multi-point strategies and next-wave targets

- Multi point strategies view TRD as overlapping biotypes that require coordinated pharmacology, psychedelics, neuromodulation, and psychotherapeutic or digital tools [101–104].
- Biomarker informed sequencing, pharmacogenomics, and biotype specific combinations replace linear trials of single agents [101,105–107].
- Adaptive platform and N-of-1 designs, coupled to digital phenotyping and recovery focused endpoints, orient care toward precision and durability [102–104,107].

4. Divergence → Reconnection

As monoamine and stress-based models began to fray, a new translational strategy sought bridges that could genuinely scale across species rather than rely on face validity alone [108]. Electrophysiological motifs, such as frontal alpha asymmetry and reward related event related potentials, emerged as candidate intermediate phenotypes that can be measured in rodents and humans using homologous paradigms [109–111]. Sleep architecture, particularly REM density and slow wave fragmentation, offered another shared metric, mirrored by alterations in stress exposed animals and patients with melancholic or TRD [112–114]. In parallel, probabilistic reward tasks and cognitive control batteries were adapted across rodents, non-human primates, and humans, while longitudinal inflammatory and endocrine panels were integrated into both preclinical and clinical protocols, enabling richer cross species modeling of reward inflammation coupling [115,116].

Yet the field also accumulated clear failures to learn from earlier missteps [117]. The assumption that immobility equals despair persisted long after it became evident that forced swim behavior reflects a narrow coping style, not the multidimensional construct of depression [118,119]. Short duration trials and brief stress paradigms continued to dominate despite growing evidence that synaptic, circuit, and immune remodeling unfold over weeks to months [120,121]. Single endpoint thinking, usually centered on global depression scores or single behavioral tests, repeatedly obscured domain specific gains and masked heterogeneity in trajectories [122,123].

The most promising advances have come from deliberate back translation [124,125]. Symptom clusters and rating scale factors are first decomposed into Research Domain Criteria (RdoC) like domains of negative valence, reward processing, arousal, and cognition, then re instantiated as tractable tasks and physiological readouts in animals [125,126]. Multimodal biomarker programs now use human defined phenotypes to guide the design of cross species EEG batteries, reward and cognitive paradigms, and peripheral immune signatures [127,128]. In doing so, they begin to reconnect bench and bedside around shared dimensions rather than diagnostic labels alone [129,130].

Table 1. Cross-species bridge map for depression-relevant constructs and translatable assays. Cross-species bridge map linking human constructs to preclinical assays, quantitative readouts, and clinical analogs that can be implemented in contemporary trials. “Status” summarizes translational maturity (routine, emerging, or exploratory), while “Design tip” highlights one concrete way to embed each bridge into mechanistically anchored, heterogeneity-aware study designs.

Human construct	Preclinical assay	Readout	Clinical analog	Status	Design tip
Anhedonia/ motivational deficit	Effort-based decision tasks (progressive ratio, T-maze barrier, operant sucrose)	Breakpoint, lever presses, willingness to work under stress or inflammation	Probabilistic reward tasks, EEfRT, ventral striatal BOLD,	Emerging biomarker	Separate hedonic “liking” from motivational “wanting”; include stress/inflam

				anhedonia scales		mation challenge blocks.
Negative affect/threat bias	Fear and chronic defeat conditioning and social	Freezing/avoidance, extinction curves, startle, social withdrawal	Fear-learning and extinction tasks, startle paradigms, threat-bias tasks in anxious/MD D subgroups	Robust basic science; limited clinical use	Use as domain-specific endpoint in anxious and trauma-loaded depression; pair behavior with EEG/fMRI.	
Cognitive control/executive dysfunction	Attentional set-shifting, 5-CSRTT, reversal learning	Errors, omissions, reaction times, perseveration indexes	Set-shifting (e.g., CANTAB), n-back, Stroop, Trail Making, DLPFC activation	Secondary endpoint in several trials	Pre-stratify “cognitively loaded” depression; link change to functioning and return-to-work outcomes.	
Sleep and circadian disruption	Rodent EEG/EMG with chronic stress or light-cycle shift; REM-deprivation models	REM latency/density, NREM slow-wave power, activity rhythms, phase shifts	Polysomnography, actigraphy, DLMO, sleep/circadian questionnaire	Strong observational; emerging endpoints	Align dosing and assessments with chronotype; treat sleep/circadian metrics as primary modifiable targets.	
HPA axis and stress reactivity	Chronic stress, social challenges; mild restraint; defeat; Dex/CRH	Corticosterone profiles, GR sensitivity, coping style, stress-induced behavioral shift	Cortisol awakening response, DST, lab stress tests, hair cortisol	Mixed but promising for subtyping	Sample across diurnal cycle; co-model stress markers with symptom domains (anergy,	

Inflammation-KYN steering	LPS/IFN- α stress-sensitized immune activation; Trp-KYN pathway assays	or KYN/Trp ratio, QA/KYNA balance, microglial activation, cytokine panels	CRP, IL-6/TNF panels, plasma KYN/Trp, symptom clusters (anergia, anhedonia, psychomotor slowing)	High translational interest	Pre-specify “inflammation-high” strata; collect longitudinal KYN panels and align with treatment response.
Metabolic-endocrine load	High-fat diet, genetic obesity, insulin-resistance models	Glucose tolerance, insulin signaling, adiposity, spontaneous activity	BMI, waist-to-hip ratio, HOMA-IR, HbA1c, metabolic-syndrome indices	Growing but underused in trials	Embed metabolic panels into TRD studies; design dedicated obesity/T2D depression trials with functional endpoints.
Synaptic plasticity / rapid-acting response	Ketamine/psychogenic paradigms; LTP/LTD, in vivo spine imaging, AMPA-forward assays	Spine density, AMPA/NMDA ratio, LTP/LTD magnitude, early oscillatory changes	Early EEG/MEG plasticity markers, TMS-LTP readouts, 24-72 h symptom and cognition shifts	Strong mechanistic, clinical for ketamine	Build in early (24-72 h) windows and plasticity markers as key secondary endpoints in rapid-acting trials.
Network-level connectivity biotypes	Chemogenetic/optogenetic PFC-striatal/limbic manipulation; rodent rsfMRI/EEG	Resting-state connectivity, oscillatory coupling, causal node influence, behavior	rsfMRI biotypes, TMS-EEG connectivity, SCC/vmPFC network markers for	Emerging targeting tool	Require “target engagement” thresholds for drugs/devices; enrich samples by baseline

			under circuit	neuromodula		network
			control	tion targeting		topology.
Digital	Home-cage	Continuous	Smartphone-	Early	Predefine	
behavior	automated	activity,	based	explorato	digital	
and passive	monitoring	of sleep-wake	mobility,	ry	endpoints	
monitoring	movement,	sleep,	structure,	call/text	(e.g., mobility,	
	and	social	social	patterns,	social	
	interaction		proximity,	speech and	withdrawal)	
			exploration	behavior	and link them	
			patterns	passively	to functional	
				captured by	and relapse	
				sensors	outcomes.	

5-CSRTT, five-choice serial reaction time task; BMI, body mass index; AMPA, α -amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid; BOLD, blood-oxygen-level-dependent; CANTAB, Cambridge Neuropsychological Test Automated Battery; Dex/CRH, dexamethasone/corticotropin-releasing hormone; DLPFC, dorsolateral prefrontal cortex; DLMO, dim light melatonin onset; DST, dexamethasone suppression test; EefRT, Effort Expenditure for Rewards Task, EEG, electroencephalograph; EMG, electromyography; fMRI, functional magnetic resonance imaging; GR, HbA1c, glycated hemoglobin; glucocorticoid receptor; HOMA-IR, homeostatic model assessment of insulin resistance; HPA, hypothalamic-pituitary-adrenal; IFN- α interferon-alpha; IL-6, interleukin-6; KYN, kynurenine; LTD, long-term depression; LPS, lipopolysaccharide; LTP, long-term potentiation; MEG, magnetoencephalography; MMD, major depressive disorder; NMDA, N-methyl-D-aspartate; NREM, non-rapid eye movement; PFC, prefrontal cortex; QA, quinolinic acid; REM, rapid eye movement; rsfMRI, resting-state functional magnetic resonance imaging; SCC, subcallosal cingulate; T2D, type 2 diabetes; TMS, transcranial magnetic stimulation; TNF, tumor necrosis factor; TRD, treatment-resistant depression; Trp, tryptophan; vmPFC, ventromedial prefrontal cortex.

5. Clinical Applications Today

Clinical applications of systems psychiatry are moving beyond one-size-fits-all algorithms toward stratified care grounded in biology and behavior [131]. Depression is increasingly parsed into inflammation high, metabolically burdened, anhedonia dominant, and sleep or circadian disrupted profiles, overlaid on formal staging of treatment resistance [132,133]. Elevated CRP altered neutrophil to lymphocyte ratios, and immune metabolic gene signatures delineate patients whose symptoms cluster around anergia and anhedonia, while sleep fragmentation and circadian misalignment identify another modifiable axis that cuts across stages of non-response [134]. Parallel work on pharmacogenomics, circuit-based biotypes, and age specific EEG signatures is entering specialist clinics and early phase trials [13,135,136].

A clear distinction now separates tools that are clinically ready from those that are almost ready [137]. Structured TRD staging, esketamine, neuromodulation devices, and several pharmacogenomic panels have achieved regulatory approval and are supported by comparative effectiveness data [106,138,139]. By contrast, multiplex inflammatory and metabolic panels, task based cognitive emotional biomarkers, and digital phenotyping batteries remain largely in the candidate domain, often validated in carefully selected cohorts but not yet embedded in stepped care pathways [128,140].

Translating these advances into everyday practice faces substantial hurdles [141]. Access to neuromodulation, ketamine-based interventions, and genomic testing is uneven, constrained by cost, infrastructure, and workforce training [142]. Regulatory frameworks still privilege drug over device and algorithm, and reimbursement rarely rewards stratified assessment [143]. Without deliberate attention to equity, biologically enriched care risks deepening disparities, as populations with higher

inflammatory burden, multimorbidity, and limited digital access may be the least likely to receive precision guided interventions [144–146].

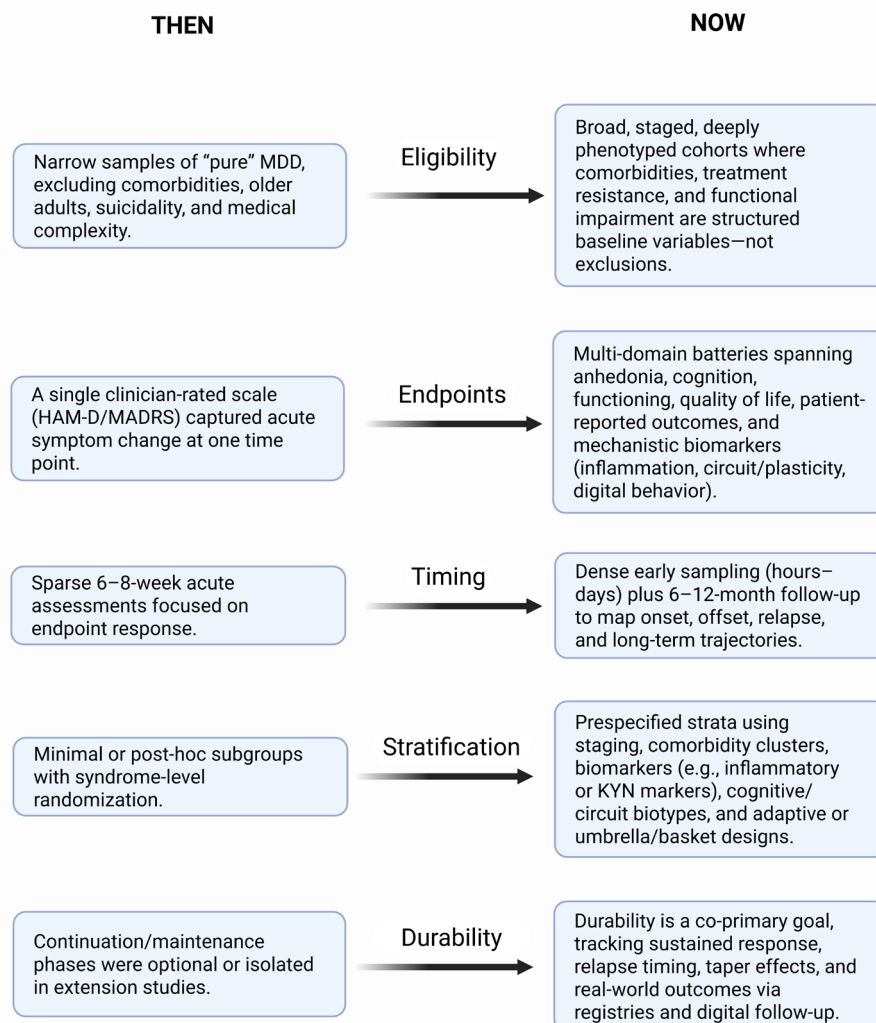


Figure 2. Evolution of depression trial design across eligibility, endpoints, timing, stratification and durability. The schematic contrasts conventional antidepressant trials (**Then**, left) with emerging systems-psychiatry-informed designs (**Now**, right). **Eligibility.** Earlier trials typically enrolled narrowly defined adults with “pure” major depressive disorder, excluding common comorbidities, older age, suicidality and medical complexity; contemporary designs move toward staged, better-characterized and more inclusive samples, with comorbidities, treatment resistance and functional impairment captured as structured baseline variables rather than automatic exclusions. **Endpoints.** Traditional studies relied on a single clinician-rated symptom scale (for example, HAM-D or MADRS) at one acute time point; modern trials incorporate multi-domain outcome batteries, including anhedonia and cognition, functioning and quality of life, patient-reported outcomes, and mechanistic readouts (for example, inflammatory markers, circuit or plasticity measures, digital behavior). **Timing.** Classic trials emphasized 6–8-week acute response with relatively sparse visits; new designs layer dense early sampling windows (hours to days for rapid-acting agents) onto longer follow-up to 6–12 months, enabling characterization of onset, offset and relapse dynamics. **Stratification.** Earlier studies used minimal or post-hoc subgrouping (for example, melancholic versus atypical) and randomization only at the syndrome level; contemporary designs prespecify strata and enrichment rules based on clinical staging, comorbidity clusters, biomarkers (such as inflammation or KYN metrics), cognitive or circuit biotypes, and sometimes deploy adaptive or umbrella/basket architectures. **Durability.** Historically, continuation and maintenance phases were

optional or handled in separate extension studies; current trials increasingly embed durability as a co-primary objective, tracking time to relapse, sustained response, taper/discontinuation effects and real-world effectiveness via registries or digital follow-up, thereby aligning trial design with the long-term course of depressive illness. HAM-D, Hamilton Depression Rating Scale; KYN, kynurenine; MADRS, Montgomery–Åsberg Depression Rating Scale; MDD, major depressive disorder.

6. What We Got Wrong/Right

Many of the field's "failures" now look like solvable design problems rather than fatal errors [147,148]. Trial and error prescribing, short term symptom focused trials, and inflated remission estimates exposed what happens when heterogeneity is ignored and protocols drift [147,149,150]. The corrective principles are clearer now: implement decision support and data driven personalization, redesign trials to prioritize long term functioning and real-world effectiveness and adhere strictly to pre specified protocols with transparent reporting [151–153]. The concept of difficult to treat depression and consensus definitions of TRD are direct products of these lessons [104,154,155].

A second cluster of mistakes involved what and whom we chose to measure [156,157]. Overbroad diagnostic criteria without biomarkers, unclear psychotherapy "active ingredients," late recognition of comorbidity, and neglect of patient preference and digital engagement all narrowed impact [147,158–160]. The responses are already reshaping practice [161]. Biomarker informed and endophenotype based frameworks, component focused psychotherapy trials, integrated care models, shared decision tools, guided digital and blended interventions, and Delphi based TRD guidelines collectively represent durable gains and a more realistic architecture for precision psychiatry [104,155,159,162].

7. Outlook

The next decade will be judged by whether it can turn systems psychiatry from an attractive narrative into falsifiable science [163,164]. Two preclinical predictions are within reach. First, that manipulating specific prefrontal–striatal and prefrontal–limbic circuits in sex balanced, chronic stress models will yield biotypes that map onto human imaging defined network patterns and differential treatment response [165–167]. Second, that patient derived cellular systems combined with multi-omic profiling will prospectively predict which immune and metabolic perturbations in animals reproduce anhedonia dominant, inflammation high phenotypes observed in humans [134,168].

On the clinical side, trial design must shift in two concrete ways. Large, multivariate, cross trial prediction studies should be powered not only to detect average effects but to learn stable individual level treatment rules [169–171]. In parallel, factorial and adaptive designs need to dissect psychotherapy and combined treatment "active ingredients" rather than testing monolithic packages [172–175].

A viable implementation pathway is hybrid effectiveness implementation research embedded in integrated care, where stratification tools, targeted pharmacotherapy, and digital monitoring are co designed with health systems [176]. Underpinning all of this should be a shared data standard that harmonizes symptom networks, EEG and imaging markers, and trial metadata, with preregistered analytic pipelines and mandatory external validation [177,178].

8. Conclusions

In this perspectives review, I propose plasticity centered systems psychiatry as the key lens through which both model building and bedside decisions can be restructured. Synaptic remodeling, circuit dynamics, immune metabolic context, and sleep dependent homeostasis become explicit levers for intervention rather than diffuse background. A concrete practice change is to implement structured, plasticity informed care pathways that link symptom profiles to simple circuit sensitive indices such as reward tasks, sleep and circadian metrics, and low burden immune or metabolic panels. A parallel research change is to develop adaptive, multimodal platforms in which the ten

subsequent papers systematically interrogate promising synaptic, microcircuit, network, immune, and chronobiological targets for depression treatment.

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Abbreviations

The following abbreviations are used in this manuscript:

5-CSRTT	five-choice serial reaction time task
AhR	aryl hydrocarbon receptor
AMPA	α -amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid
ATAC	assay for transposase-accessible chromatin
BMI	body mass index
BOLD	blood-oxygen-level-dependent
CANTAB	Cambridge Neuropsychological Test Automated Battery
CRP	C-reactive protein
CSF1R	colony-stimulating factor 1 receptor
Dex/CRH	dexamethasone/corticotropin-releasing hormone
DLMO	dim light melatonin onset
DLPFC	dorsolateral prefrontal cortex
DNMTs	DNA methyltransferases
DSM	Diagnostic and Statistical Manual of Mental Disorders
EEG	electroencephalography
EefRT	Effort Expenditure for Rewards Task
eEPSPs	evoked excitatory postsynaptic potentials
ERK	extracellular signal-regulated kinase
EMG	electromyography
fMRI	functional magnetic resonance imaging
GABA	γ -aminobutyric acid
GLP-1	glucagon-like peptide-1
GR	glucocorticoid receptor
HAM-D	Hamilton Depression Rating Scale
HbA1c	glycated hemoglobin
HDACs	histone deacetylases
HOMA-IR	homeostatic model assessment of insulin resistance
HPA	hypothalamic–pituitary–adrenal axis
IDO	indoleamine 2,3-dioxygenase

IFN- α	interferon-alpha
IL-6	interleukin-6
IPSPs	inhibitory postsynaptic potentials
κ	kappa
KYN	kynurenine
KYNA	kynurenic acid
LFP	local field potential
LPS	lipopolysaccharide
LSD1	lysine-specific demethylase 1
LTD	long-term depression
LTP	long-term potentiation
MADRS	Montgomery-Åsberg Depression Rating Scale
MDD	major depressive disorder
MEG	magnetoencephalography
NMDA	N-methyl-D-aspartate
PET	positron emission tomography
PFC	prefrontal cortex
QA	quinolinic acid
RDoC	Research Domain Criteria
REM	rapid eye movement
RNA	ribonucleic acid
rsfMRI	resting-state functional magnetic resonance imaging
SCC	subcallosal cingulate cortex
T2D	type 2 diabetes
TDO	tryptophan 2,3-dioxygenase
TMS	transcranial magnetic stimulation
TMS-EEG	transcranial magnetic stimulation-electroencephalography
TNF	tumor necrosis factor
TRD	treatment-resistant depression
Trp	tryptophan
vmPFC	ventromedial prefrontal cortex
VNS	vagus nerve stimulation

References

1. Hirschfeld, R.M. History and evolution of the monoamine hypothesis of depression. *J Clin Psychiatry* **2000**, *61 Suppl 6*, 4-6.
2. Boku, S.; Nakagawa, S.; Toda, H.; Hishimoto, A. Neural basis of major depressive disorder: Beyond monoamine hypothesis. *Psychiatry Clin Neurosci* **2018**, *72*, 3-12, doi:10.1111/pcn.12604.
3. Liu, B.; Liu, J.; Wang, M.; Zhang, Y.; Li, L. From Serotonin to Neuroplasticity: Evolvement of Theories for Major Depressive Disorder. *Front Cell Neurosci* **2017**, *11*, 305, doi:10.3389/fncel.2017.00305.
4. Spellman, T.; Liston, C. Toward Circuit Mechanisms of Pathophysiology in Depression. *Am J Psychiatry* **2020**, *177*, 381-390, doi:10.1176/appi.ajp.2020.20030280.
5. Fries, G.R.; Saldana, V.A.; Finnstein, J.; Rein, T. Molecular pathways of major depressive disorder converge on the synapse. *Mol Psychiatry* **2023**, *28*, 284-297, doi:10.1038/s41380-022-01806-1.
6. Brandl, F.; Weise, B.; Mulej Bratec, S.; Jassim, N.; Hoffmann Ayala, D.; Bertram, T.; Ploner, M.; Sorg, C. Common and specific large-scale brain changes in major depressive disorder, anxiety disorders, and chronic pain: a transdiagnostic multimodal meta-analysis of structural and functional MRI studies. *Neuropsychopharmacology* **2022**, *47*, 1071-1080, doi:10.1038/s41386-022-01271-y.
7. Sindermann, L.; Redlich, R.; Opel, N.; Böhnlein, J.; Dannlowski, U.; Lehr, E.J. Systematic transdiagnostic review of magnetic-resonance imaging results: Depression, anxiety disorders and their co-occurrence. *J Psychiatr Res* **2021**, *142*, 226-239, doi:10.1016/j.jpsychires.2021.07.022.
8. Arnaud, A.M.; Brister, T.S.; Duckworth, K.; Foxworth, P.; Fulwider, T.; Suthoff, E.D.; Werneburg, B.; Aleksanderek, I.; Reinhart, M.L. Impact of Major Depressive Disorder on Comorbidities: A Systematic Literature Review. *J Clin Psychiatry* **2022**, *83*, doi:10.4088/JCP.21r14328.
9. Tanaka, M.; Battaglia, S.; Liloia, D. Navigating Neurodegeneration: Integrating Biomarkers, Neuroinflammation, and Imaging in Parkinson's, Alzheimer's, and Motor Neuron Disorders. *Biomedicines* **2025**, *13*, doi:10.3390/biomedicines13051045.
10. Berk, M.; Köhler-Forsberg, O.; Turner, M.; Penninx, B.; Wrobel, A.; Firth, J.; Loughman, A.; Reavley, N.J.; McGrath, J.J.; Momen, N.C.; et al. Comorbidity between major depressive disorder and physical diseases: a comprehensive review of epidemiology, mechanisms and management. *World Psychiatry* **2023**, *22*, 366-387, doi:10.1002/wps.21110.
11. Tanaka, M.; Battaglia, S. From Biomarkers to Behavior: Mapping the Neuroimmune Web of Pain, Mood, and Memory. *Biomedicines* **2025**, *13*, doi:10.3390/biomedicines13092226.
12. Bottaccioli, A.G.; Bologna, M.; Bottaccioli, F. Rethinking Depression-Beyond Neurotransmitters: An Integrated Psychoneuroendocrineimmunology Framework for Depression's Pathophysiology and Tailored Treatment. *Int J Mol Sci* **2025**, *26*, doi:10.3390/ijms26062759.
13. Tozzi, L.; Zhang, X.; Pines, A.; Olmsted, A.M.; Zhai, E.S.; Anene, E.T.; Chesnut, M.; Holt-Gosselin, B.; Chang, S.; Stetz, P.C.; et al. Personalized brain circuit scores identify clinically distinct biotypes in depression and anxiety. *Nat Med* **2024**, *30*, 2076-2087, doi:10.1038/s41591-024-03057-9.
14. Jiao, W.; Lin, J.; Deng, Y.; Ji, Y.; Liang, C.; Wei, S.; Jing, X.; Yan, F. The immunological perspective of major depressive disorder: unveiling the interactions between central and peripheral immune mechanisms. *J Neuroinflammation* **2025**, *22*, 10, doi:10.1186/s12974-024-03312-3.
15. Tanaka, M.; Battaglia, S. Dualistic Dynamics in Neuropsychiatry: From Monoaminergic Modulators to Multiscale Biomarker Maps. *Biomedicines* **2025**, *13*, doi:10.3390/biomedicines13061456.
16. Drevets, W.C.; Wittenberg, G.M.; Bullmore, E.T.; Manji, H.K. Immune targets for therapeutic development in depression: towards precision medicine. *Nat Rev Drug Discov* **2022**, *21*, 224-244, doi:10.1038/s41573-021-00368-1.
17. Tafet, G.E.; Nemeroff, C.B. The Links Between Stress and Depression: Psychoneuroendocrinological, Genetic, and Environmental Interactions. *J Neuropsychiatry Clin Neurosci* **2016**, *28*, 77-88, doi:10.1176/appi.neuropsych.15030053.
18. Yankelevitch-Yahav, R.; Franko, M.; Huly, A.; Doron, R. The forced swim test as a model of depressive-like behavior. *J Vis Exp* **2015**, doi:10.3791/52587.
19. Yan, H.C.; Cao, X.; Das, M.; Zhu, X.H.; Gao, T.M. Behavioral animal models of depression. *Neurosci Bull* **2010**, *26*, 327-337, doi:10.1007/s12264-010-0323-7.

20. Dale, E.; Bang-Andersen, B.; Sánchez, C. Emerging mechanisms and treatments for depression beyond SSRIs and SNRIs. *Biochem Pharmacol* **2015**, *95*, 81-97, doi:10.1016/j.bcp.2015.03.011.
21. Abelaira, H.M.; Réus, G.Z.; Quevedo, J. Animal models as tools to study the pathophysiology of depression. *Braz J Psychiatry* **2013**, *35 Suppl 2*, S112-120, doi:10.1590/1516-4446-2013-1098.
22. Sharma, S.; Chawla, S.; Kumar, P.; Ahmad, R.; Kumar Verma, P. The chronic unpredictable mild stress (CUMS) Paradigm: Bridging the gap in depression research from bench to bedside. *Brain Res* **2024**, *1843*, 149123, doi:10.1016/j.brainres.2024.149123.
23. Ji, N.; Lei, M.; Chen, Y.; Tian, S.; Li, C.; Zhang, B. How Oxidative Stress Induces Depression? *ASN Neuro* **2023**, *15*, 17590914231181037, doi:10.1177/17590914231181037.
24. Bech, P. Modern psychometrics in clinimetrics: impact on clinical trials of antidepressants. *Psychother Psychosom* **2004**, *73*, 134-138, doi:10.1159/000076448.
25. Regier, D.A.; Narrow, W.E.; Kuhl, E.A.; Kupfer, D.J. The conceptual development of DSM-V. *Am J Psychiatry* **2009**, *166*, 645-650, doi:10.1176/appi.ajp.2009.09020279.
26. Hengartner, M.P.; Jakobsen, J.C.; Sørensen, A.; Plöderl, M. Efficacy of new-generation antidepressants assessed with the Montgomery-Asberg Depression Rating Scale, the gold standard clinician rating scale: A meta-analysis of randomised placebo-controlled trials. *PLoS One* **2020**, *15*, e0229381, doi:10.1371/journal.pone.0229381.
27. Khan, A.; Khan, S.R.; Shankles, E.B.; Polissar, N.L. Relative sensitivity of the Montgomery-Asberg Depression Rating Scale, the Hamilton Depression rating scale and the Clinical Global Impressions rating scale in antidepressant clinical trials. *Int Clin Psychopharmacol* **2002**, *17*, 281-285, doi:10.1097/00004850-200211000-00003.
28. Guizzaro, L.; Morgan, D.D.V.; Falco, A.; Gallo, C. Hamilton scale and MADRS are interchangeable in meta-analyses but can disagree at trial level. *J Clin Epidemiol* **2020**, *124*, 106-117, doi:10.1016/j.jclinepi.2020.04.022.
29. Leucht, S.; Fennema, H.; Engel, R.R.; Kaspers-Janssen, M.; Szegedi, A. Translating the HAM-D into the MADRS and vice versa with equipercentile linking. *J Affect Disord* **2018**, *226*, 326-331, doi:10.1016/j.jad.2017.09.042.
30. Santi, N.S.; Biswal, S.B.; Naik, B.N.; Sahoo, J.P.; Rath, B. Comparison of Hamilton Depression Rating Scale and Montgomery-Åsberg Depression Rating Scale: Baked Straight From a Randomized Study. *Cureus* **2023**, *15*, e45098, doi:10.7759/cureus.45098.
31. Ratheesh, A.; Berk, M.; Schmaal, L. Can we overcome the heterogeneity of mood disorders in clinical trials? *Aust N Z J Psychiatry* **2023**, *57*, 309-311, doi:10.1177/00048674231158266.
32. Su, Z.; Yang, X.; Hou, J.; Liu, S.; Wang, Y.; Chen, Z. Gender differences in the co-occurrence of anxiety and depressive symptoms among early adolescents: A network approach. *J Psychiatr Res* **2024**, *179*, 300-305, doi:10.1016/j.jpsychires.2024.09.024.
33. Vasiliadis, H.M.; Desjardins, F.; Roberge, P.; Grenier, S. Sex Differences in Anxiety Disorders in Older Adults. *Curr Psychiatry Rep* **2020**, *22*, 75, doi:10.1007/s11920-020-01203-x.
34. Thompson, K.N.; Hübel, C.; Cheesman, R.; Adey, B.N.; Armour, C.; Davies, M.R.; Hotopf, M.; Jones, I.R.; Kalsi, G.; McIntosh, A.M.; et al. Age and sex-related variability in the presentation of generalized anxiety and depression symptoms. *Depress Anxiety* **2021**, *38*, 1054-1065, doi:10.1002/da.23213.
35. Pavlidi, P.; Kokras, N.; Dalla, C. Sex Differences in Depression and Anxiety. *Curr Top Behav Neurosci* **2023**, *62*, 103-132, doi:10.1007/7854_2022_375.
36. Kuper, P.; Miguel, C.; Cuijpers, P.; Apfelbacher, C.; Buntrock, C.; Karyotaki, E.; Sprenger, A.A.; Harrer, M. Sample size and geographical region predict effect heterogeneity in psychotherapy research for depression: a meta-epidemiological study. *J Clin Epidemiol* **2025**, *183*, 111779, doi:10.1016/j.jclinepi.2025.111779.
37. Cai, N.; Choi, K.W.; Fried, E.I. Reviewing the genetics of heterogeneity in depression: operationalizations, manifestations and etiologies. *Hum Mol Genet* **2020**, *29*, R10-r18, doi:10.1093/hmg/ddaa115.
38. Hickie, I.B.; Berk, M.; Scott, J.; Crouse, J.; Scott, E.; Wray, N.; Iorfino, F. What are the best strategies for stratification of clinical cohorts with depression and other mood disorders? *Research Directions: Depression* **2024**, *1*, e18.

39. Dunlop, K.; Grosenick, L.; Downar, J.; Vila-Rodriguez, F.; Gunning, F.M.; Daskalakis, Z.J.; Blumberger, D.M.; Liston, C. Dimensional and categorical solutions to parsing depression heterogeneity in a large single-site sample. *Biological Psychiatry* **2024**, *96*, 422-434.
40. Marsden, W.N. Synaptic plasticity in depression: molecular, cellular and functional correlates. *Prog Neuropsychopharmacol Biol Psychiatry* **2013**, *43*, 168-184, doi:10.1016/j.pnpbp.2012.12.012.
41. Shenoy, S.; Ibrahim, S. Perinatal Depression and the Role of Synaptic Plasticity in Its Pathogenesis and Treatment. *Behav Sci (Basel)* **2023**, *13*, doi:10.3390/bs13110942.
42. Brown, J.C.; Higgins, E.S.; George, M.S. Synaptic Plasticity 101: The Story of the AMPA Receptor for the Brain Stimulation Practitioner. *Neuromodulation* **2022**, *25*, 1289-1298, doi:10.1016/j.neurom.2021.09.003.
43. He, J.G.; Zhou, H.Y.; Wang, F.; Chen, J.G. Dysfunction of Glutamatergic Synaptic Transmission in Depression: Focus on AMPA Receptor Trafficking. *Biol Psychiatry Glob Open Sci* **2023**, *3*, 187-196, doi:10.1016/j.bpsgos.2022.02.007.
44. Brager, D.H.; Johnston, D. Plasticity of intrinsic excitability during long-term depression is mediated through mGluR-dependent changes in I(h) in hippocampal CA1 pyramidal neurons. *J Neurosci* **2007**, *27*, 13926-13937, doi:10.1523/jneurosci.3520-07.2007.
45. Cavalleri, L.; Merlo Pich, E.; Millan, M.J.; Chiamulera, C.; Kunath, T.; Spano, P.F.; Collo, G. Ketamine enhances structural plasticity in mouse mesencephalic and human iPSC-derived dopaminergic neurons via AMPAR-driven BDNF and mTOR signaling. *Mol Psychiatry* **2018**, *23*, 812-823, doi:10.1038/mp.2017.241.
46. Appelbaum, L.G.; Shenasa, M.A.; Stolz, L.; Daskalakis, Z. Synaptic plasticity and mental health: methods, challenges and opportunities. *Neuropsychopharmacology* **2023**, *48*, 113-120, doi:10.1038/s41386-022-01370-w.
47. Cantone, M.; Bramanti, A.; Lanza, G.; Pennisi, M.; Bramanti, P.; Pennisi, G.; Bella, R. Cortical Plasticity in Depression. *ASN Neuro* **2017**, *9*, 1759091417711512, doi:10.1177/1759091417711512.
48. Hu, Y.T.; Tan, Z.L.; Hirjak, D.; Northoff, G. Brain-wide changes in excitation-inhibition balance of major depressive disorder: a systematic review of topographic patterns of GABA- and glutamatergic alterations. *Mol Psychiatry* **2023**, *28*, 3257-3266, doi:10.1038/s41380-023-02193-x.
49. Fee, C.; Banasr, M.; Sibille, E. Somatostatin-Positive Gamma-Aminobutyric Acid Interneuron Deficits in Depression: Cortical Microcircuit and Therapeutic Perspectives. *Biol Psychiatry* **2017**, *82*, 549-559, doi:10.1016/j.biopsych.2017.05.024.
50. Kuki, T.; Fujihara, K.; Miwa, H.; Tamamaki, N.; Yanagawa, Y.; Mushiake, H. Contribution of parvalbumin and somatostatin-expressing GABAergic neurons to slow oscillations and the balance in beta-gamma oscillations across cortical layers. *Front Neural Circuits* **2015**, *9*, 6, doi:10.3389/fncir.2015.00006.
51. Chen, G.; Zhang, Y.; Li, X.; Zhao, X.; Ye, Q.; Lin, Y.; Tao, H.W.; Rasch, M.J.; Zhang, X. Distinct Inhibitory Circuits Orchestrate Cortical beta and gamma Band Oscillations. *Neuron* **2017**, *96*, 1403-1418.e1406, doi:10.1016/j.neuron.2017.11.033.
52. Tsuboi, D.; Nagai, T.; Yoshimoto, J.; Kaibuchi, K. Neuromodulator regulation and emotions: insights from the crosstalk of cell signaling. *Front Mol Neurosci* **2024**, *17*, 1376762, doi:10.3389/fnmol.2024.1376762.
53. Wagatsuma, N.; Nobukawa, S.; Fukai, T. A microcircuit model involving parvalbumin, somatostatin, and vasoactive intestinal polypeptide inhibitory interneurons for the modulation of neuronal oscillation during visual processing. *Cereb Cortex* **2023**, *33*, 4459-4477, doi:10.1093/cercor/bhac355.
54. Tahvili, F.; Vinck, M.; di Volo, M. PV and SOM cells play distinct causal roles in controlling network oscillations and stability. *Cell Rep* **2025**, *44*, 116131, doi:10.1016/j.celrep.2025.116131.
55. Mazza, F.; Guet-McCreight, A.; Valiante, T.A.; Griffiths, J.D.; Hay, E. In-silico EEG biomarkers of reduced inhibition in human cortical microcircuits in depression. *PLoS Comput Biol* **2023**, *19*, e1010986, doi:10.1371/journal.pcbi.1010986.
56. Rademacher, J.; Grent-'t-Jong, T.; Rivolta, D.; Sauer, A.; Scheller, B.; Gonzalez-Burgos, G.; Metzner, C.; Uhlhaas, P.J. Computational modeling of ketamine-induced changes in gamma-band oscillations: The contribution of parvalbumin and somatostatin interneurons. *PLoS Comput Biol* **2025**, *21*, e1013118, doi:10.1371/journal.pcbi.1013118.
57. Tanaka, M.; He, Z.; Han, S.; Battaglia, S. Editorial: Noninvasive brain stimulation: a promising approach to study and improve emotion regulation. *Front Behav Neurosci* **2025**, *19*, 1633936, doi:10.3389/fnbeh.2025.1633936.

58. Bruijnzeel, A.W. kappa-Opioid receptor signaling and brain reward function. *Brain Res Rev* **2009**, *62*, 127-146, doi:10.1016/j.brainresrev.2009.09.008.
59. Wallace, C.W.; Holleran, K.M.; Slinkard, C.Y.; Centanni, S.W.; Lapish, C.C.; Jones, S.R. Kappa opioid receptors diminish spontaneous dopamine signals in awake mice through multiple mechanisms. *Neuropharmacology* **2025**, *273*, 110458, doi:10.1016/j.neuropharm.2025.110458.
60. Bekhbat, M.; Li, Z.; Dunlop, B.W.; Treadway, M.T.; Mehta, N.D.; Revill, K.P.; Lucido, M.J.; Hong, C.; Ashchi, A.; Wommack, E.C.; et al. Sustained effects of repeated levodopa (L-DOPA) administration on reward circuitry, effort-based motivation, and anhedonia in depressed patients with higher inflammation. *Brain Behav Immun* **2025**, *125*, 240-248, doi:10.1016/j.bbi.2024.12.026.
61. Treadway, M.; Etuk, S.; Cooper, J.; Hossein, S.; Hahn, E.; Betters, S.; Liu, S.; Arulpragasam, A.; DeVries, B.; Irfan, N.; et al. A randomized proof-of-mechanism trial of TNF antagonism for motivational anhedonia and related corticostriatal circuitry in depressed patients with high inflammation. *Res Sq* **2024**, doi:10.21203/rs.3.rs-3957252/v1.
62. Felger, J.C.; Treadway, M.T. Inflammation Effects on Motivation and Motor Activity: Role of Dopamine. *Neuropsychopharmacology* **2017**, *42*, 216-241, doi:10.1038/npp.2016.143.
63. Lucido, M.J.; Bekhbat, M.; Goldsmith, D.R.; Treadway, M.T.; Haroon, E.; Felger, J.C.; Miller, A.H. Aiding and Abetting Anhedonia: Impact of Inflammation on the Brain and Pharmacological Implications. *Pharmacol Rev* **2021**, *73*, 1084-1117, doi:10.1124/pharmrev.120.000043.
64. Hasbi, A.; Madras, B.K.; George, S.R. Daily $\Delta(9)$ -Tetrahydrocannabinol and Withdrawal Increase Dopamine D(1)-D(2) Receptor Heteromer to Mediate Anhedonia- and Anxiogenic-like Behavior Through a Dynorphin and Kappa Opioid Receptor Mechanism. *Biol Psychiatry Glob Open Sci* **2023**, *3*, 550-566, doi:10.1016/j.bpsgos.2022.07.003.
65. Thomas, C.S.; Mohammadkhani, A.; Rana, M.; Qiao, M.; Baimel, C.; Borgland, S.L. Optogenetic stimulation of lateral hypothalamic orexin/dynorphin inputs in the ventral tegmental area potentiates mesolimbic dopamine neurotransmission and promotes reward-seeking behaviours. *Neuropsychopharmacology* **2022**, *47*, 728-740, doi:10.1038/s41386-021-01196-y.
66. Albrecht, U. Molecular Mechanisms in Mood Regulation Involving the Circadian Clock. *Front Neurol* **2017**, *8*, 30, doi:10.3389/fneur.2017.00030.
67. Focke, C.M.B.; Iremonger, K.J. Rhythmicity matters: Circadian and ultradian patterns of HPA axis activity. *Mol Cell Endocrinol* **2020**, *501*, 110652, doi:10.1016/j.mce.2019.110652.
68. Nader, N.; Chrousos, G.P.; Kino, T. Interactions of the circadian CLOCK system and the HPA axis. *Trends Endocrinol Metab* **2010**, *21*, 277-286, doi:10.1016/j.tem.2009.12.011.
69. Lightman, S.L.; Birnie, M.T.; Conway-Campbell, B.L. Dynamics of ACTH and Cortisol Secretion and Implications for Disease. *Endocr Rev* **2020**, *41*, doi:10.1210/endrev/bnaa002.
70. Carpenter, J.S.; Crouse, J.J.; Shin, M.; Tonini, E.; Hindmarsh, G.; de Haan, Z.; Iorfino, F.; Robillard, R.; Naismith, S.; Scott, E.M.; et al. Evidence for Internal Misalignment of Circadian Rhythms in Youth With Emerging Mood Disorders. *J Biol Rhythms* **2025**, *40*, 424-440, doi:10.1177/07487304251349408.
71. Skubic, C.; Zevnik, U.; Nahtigal, K.; Dolenc Grošelj, L.; Rozman, D. Circadian Biomarkers in Humans: Methodological Insights into the Detection of Melatonin and Cortisol. *Biomolecules* **2025**, *15*, doi:10.3390/biom15071006.
72. Schrire, Z.M.; Naismith, S.L.; Pye, J.; Duffy, S.L.; Gordon, C.J.; Lewis, S.J.; Hoyos, C.M. Circadian rhythms and misalignment in older adults and those 'at risk' for dementia: A study examining correlates of dim-light melatonin onset: Biomarkers (non-neuroimaging)/Prognostic utility. *Alzheimer's & Dementia* **2020**, *16*, e045525.
73. Scott, M.R.; McClung, C.A. Circadian Rhythms in Mood Disorders. *Adv Exp Med Biol* **2021**, *1344*, 153-168, doi:10.1007/978-3-030-81147-1_9.
74. Johnson, C.; Brzezynski, J.; Bair, A.; Smieszek, S.; Bai, H.; Polymeropoulos, C.; Birznieks, G.; Polymeropoulos, M. 0879 Dim Light Melatonin Onset in a Delayed Sleep-Wake Phase Disorder Cohort: Ongoing Clinical Trial Update. *Sleep* **2025**, *48*, A382-A382.

75. Tanaka, M.; Tóth, F.; Polyák, H.; Szabó, Á.; Mándi, Y.; Vécsei, L. Immune Influencers in Action: Metabolites and Enzymes of the Tryptophan-Kynurenine Metabolic Pathway. *Biomedicines* **2021**, *9*, doi:10.3390/biomedicines9070734.
76. Badawy, A.A. Kynurenine Pathway of Tryptophan Metabolism: Regulatory and Functional Aspects. *Int J Tryptophan Res* **2017**, *10*, 1178646917691938, doi:10.1177/1178646917691938.
77. Salminen, A. Role of indoleamine 2,3-dioxygenase 1 (IDO1) and kynurenine pathway in the regulation of the aging process. *Ageing Res Rev* **2022**, *75*, 101573, doi:10.1016/j.arr.2022.101573.
78. Stone, T.W.; Williams, R.O. Tryptophan metabolism as a 'reflex' feature of neuroimmune communication: Sensor and effector functions for the indoleamine-2, 3-dioxygenase kynurenine pathway. *J Neurochem* **2024**, *168*, 3333-3357, doi:10.1111/jnc.16015.
79. MacDowell, K.S.; Munarriz-Cuevra, E.; Meana, J.J.; Leza, J.C.; Ortega, J.E. Paliperidone Reversion of Maternal Immune Activation-Induced Changes on Brain Serotonin and Kynurenine Pathways. *Front Pharmacol* **2021**, *12*, 682602, doi:10.3389/fphar.2021.682602.
80. Pathak, S.; Nadar, R.; Kim, S.; Liu, K.; Govindarajulu, M.; Cook, P.; Watts Alexander, C.S.; Dhanasekaran, M.; Moore, T. The Influence of Kynurenine Metabolites on Neurodegenerative Pathologies. *Int J Mol Sci* **2024**, *25*, doi:10.3390/ijms25020853.
81. Schröcksnadel, K.; Wirleitner, B.; Winkler, C.; Fuchs, D. Monitoring tryptophan metabolism in chronic immune activation. *Clin Chim Acta* **2006**, *364*, 82-90, doi:10.1016/j.cca.2005.06.013.
82. Alfaro-Rodríguez, A.; Reyes-Long, S.; Roldan-Valadez, E.; González-Torres, M.; Bonilla-Jaime, H.; Bandala, C.; Avila-Luna, A.; Bueno-Nava, A.; Cabrera-Ruiz, E.; Sanchez-Aparicio, P.; et al. Association of the Serotonin and Kynurenine Pathways as Possible Therapeutic Targets to Modulate Pain in Patients with Fibromyalgia. *Pharmaceuticals (Basel)* **2024**, *17*, doi:10.3390/ph17091205.
83. Szabó, Á.; Galla, Z.; Spekker, E.; Martos, D.; Szűcs, M.; Fejes-Szabó, A.; Fehér, Á.; Takeda, K.; Ozaki, K.; Inoue, H.; et al. Behavioral Balance in Tryptophan Turmoil: Regional Metabolic Rewiring in Kynurenine Aminotransferase II Knockout Mice. *Cells* **2025**, *14*, doi:10.3390/cells14211711.
84. Tanaka, M.; Vécsei, L. From Microbial Switches to Metabolic Sensors: Rewiring the Gut-Brain Kynurenine Circuit. *Biomedicines* **2025**, *13*, doi:10.3390/biomedicines13082020.
85. Martos, D.; Lőrinczi, B.; Szatmári, I.; Vécsei, L.; Tanaka, M. Decoupling Behavioral Domains via Kynurenic Acid Analog Optimization: Implications for Schizophrenia and Parkinson's Disease Therapeutics. *Cells* **2025**, *14*, doi:10.3390/cells14130973.
86. Juhász, L.; Spisák, K.; Szolnoki, B.Z.; Nászai, A.; Szabó, Á.; Rutai, A.; Tallósy, S.P.; Szabó, A.; Toldi, J.; Tanaka, M.; et al. The Power Struggle: Kynurenine Pathway Enzyme Knockouts and Brain Mitochondrial Respiration. *J Neurochem* **2025**, *169*, e70075, doi:10.1111/jnc.70075.
87. Tanaka, M.; Szatmári, I.; Vécsei, L. Quinoline Quest: Kynurenic Acid Strategies for Next-Generation Therapeutics via Rational Drug Design. *Pharmaceuticals (Basel)* **2025**, *18*, doi:10.3390/ph18050607.
88. Naffaa, M.M. Mechanisms of astrocytic and microglial purinergic signaling in homeostatic regulation and implications for neurological disease. *Exploration of Neuroscience* **2025**, *4*, 100676.
89. Bedetta, M.; Pizzo, P.; Lia, A. The Multifaceted Role of P2X7R in Microglia and Astrocytes. *Neurochem Res* **2025**, *50*, 239, doi:10.1007/s11064-025-04502-y.
90. Batista, A.F.; Khan, K.A.; Papaverigi, M.T.; Lemere, C.A. The Importance of Complement-Mediated Immune Signaling in Alzheimer's Disease Pathogenesis. *Int J Mol Sci* **2024**, *25*, doi:10.3390/ijms25020817.
91. Liu, Y.D.; Chang, Y.H.; Xie, X.T.; Wang, X.Y.; Ma, H.Y.; Liu, M.C.; Zhang, H.M. PET Imaging Unveils Neuroinflammatory Mechanisms in Psychiatric Disorders: From Microglial Activation to Therapeutic Innovation. *Mol Neurobiol* **2025**, *62*, 15318-15335, doi:10.1007/s12035-025-05177-w.
92. Werry, E.L.; Bright, F.M.; Piguet, O.; Ittner, L.M.; Halliday, G.M.; Hodges, J.R.; Kiernan, M.C.; Loy, C.T.; Kril, J.J.; Kassiou, M. Recent Developments in TSPO PET Imaging as A Biomarker of Neuroinflammation in Neurodegenerative Disorders. *Int J Mol Sci* **2019**, *20*, doi:10.3390/ijms20133161.
93. Enache, D.; Pariante, C.M.; Mondelli, V. Markers of central inflammation in major depressive disorder: A systematic review and meta-analysis of studies examining cerebrospinal fluid, positron emission tomography and post-mortem brain tissue. *Brain Behav Immun* **2019**, *81*, 24-40, doi:10.1016/j.bbi.2019.06.015.

94. Dupont, A.C.; Largeau, B.; Santiago Ribeiro, M.J.; Guilloteau, D.; Tronel, C.; Arlicot, N. Translocator Protein-18 kDa (TSPO) Positron Emission Tomography (PET) Imaging and Its Clinical Impact in Neurodegenerative Diseases. *Int J Mol Sci* **2017**, *18*, doi:10.3390/ijms18040785.
95. Meyer, J.H.; Cervenka, S.; Kim, M.J.; Kreisl, W.C.; Henter, I.D.; Innis, R.B. Neuroinflammation in psychiatric disorders: PET imaging and promising new targets. *Lancet Psychiatry* **2020**, *7*, 1064-1074, doi:10.1016/s2215-0366(20)30255-8.
96. Baek, S.Y.; Lee, J.; Kim, T.; Lee, H.; Choi, H.S.; Park, H.; Koh, M.; Kim, E.; Jung, M.E.; Iliopoulos, D.; et al. Development of a novel histone deacetylase inhibitor unveils the role of HDAC11 in alleviating depression by inhibition of microglial activation. *Biomed Pharmacother* **2023**, *166*, 115312, doi:10.1016/j.biopha.2023.115312.
97. Du, J.; Liu, R.; Ma, L.; Liu, Y.; Wei, W.; Liu, N.; Cao, Q.; Yu, J. Novel histone deacetylase-5 inhibitor T2943 exerts an anti-depressive effect in mice by enhancing GRID1 expression. *Sci Rep* **2025**, *15*, 4522, doi:10.1038/s41598-025-88670-5.
98. Sun, Z.; Zhang, B.; Zhou, J.; Luo, Y.; Zhu, X.; Wang, Y.; He, Y.; Zheng, P.; Zhang, L.; Yang, J.; et al. Integrated Single-Cell RNA-seq and ATAC-seq Reveals Heterogeneous Differentiation of CD4(+) Naive T Cell Subsets is Associated with Response to Antidepressant Treatment in Major Depressive Disorder. *Adv Sci (Weinh)* **2024**, *11*, e2308393, doi:10.1002/advs.202308393.
99. Taavitsainen, S.; Engedal, N.; Cao, S.; Handle, F.; Erickson, A.; Prekovic, S.; Wetterskog, D.; Tolonen, T.; Vuorinen, E.M.; Kiviahho, A.; et al. Single-cell ATAC and RNA sequencing reveal pre-existing and persistent cells associated with prostate cancer relapse. *Nat Commun* **2021**, *12*, 5307, doi:10.1038/s41467-021-25624-1.
100. Grandi, F.C.; Modi, H.; Kampman, L.; Corces, M.R. Chromatin accessibility profiling by ATAC-seq. *Nat Protoc* **2022**, *17*, 1518-1552, doi:10.1038/s41596-022-00692-9.
101. Kajumba, M.M.; Kakooza-Mwesige, A.; Nakasujja, N.; Koltai, D.; Canli, T. Treatment-resistant depression: molecular mechanisms and management. *Mol Biomed* **2024**, *5*, 43, doi:10.1186/s43556-024-00205-y.
102. Daeli, J.I.D.; Soemara, A. How Do Combined Pharmacological And Psychotherapeutic Interventions Impact Treatment Outcomes For Patients With Treatment-Resistant Major Depressive Disorder?: A Systematic Review. *The International Journal of Medical Science and Health Research* **2025**, *12*, 49-99.
103. Ruberto, V.L.; Jha, M.K.; Murrough, J.W. Pharmacological Treatments for Patients with Treatment-Resistant Depression. *Pharmaceuticals (Basel)* **2020**, *13*, doi:10.3390/ph13060116.
104. McIntyre, R.S.; Alsuwaidan, M.; Baune, B.T.; Berk, M.; Demyttenaere, K.; Goldberg, J.F.; Gorwood, P.; Ho, R.; Kasper, S.; Kennedy, S.H.; et al. Treatment-resistant depression: definition, prevalence, detection, management, and investigational interventions. *World Psychiatry* **2023**, *22*, 394-412, doi:10.1002/wps.21120.
105. Amasi-Hartoonian, N.; Pariante, C.M.; Cattaneo, A.; Sforzini, L. Understanding treatment-resistant depression using "omics" techniques: A systematic review. *J Affect Disord* **2022**, *318*, 423-455, doi:10.1016/j.jad.2022.09.011.
106. Garcia, G.; Cotner, C.; Spano, R. Precision medicine in psychiatry: Case series on pharmacogenomic solutions for treatment-resistant depression. *J Am Assoc Nurse Pract* **2025**, *37*, 471-476, doi:10.1097/jxx.0000000000001158.
107. Baum, M.L.; Widge, A.S.; Carpenter, L.L.; McDonald, W.M.; Cohen, B.M.; Nemeroff, C.B. Pharmacogenomic Clinical Support Tools for the Treatment of Depression. *Am J Psychiatry* **2024**, *181*, 591-607, doi:10.1176/appi.ajp.20230657.
108. Young, J.W. Development of cross-species translational paradigms for psychiatric research in the Research Domain Criteria era. *Neurosci Biobehav Rev* **2023**, *148*, 105119, doi:10.1016/j.neubiorev.2023.105119.
109. Iturra-Mena, A.M.; Kangas, B.D.; Luc, O.T.; Potter, D.; Pizzagalli, D.A. Electrophysiological signatures of reward learning in the rodent touchscreen-based Probabilistic Reward Task. *Neuropsychopharmacology* **2023**, *48*, 700-709, doi:10.1038/s41386-023-01532-4.
110. Cavanagh, J.F.; Olguin, S.L.; Talledo, J.A.; Kotz, J.E.; Roberts, B.Z.; Nungaray, J.A.; Sprock, J.; Gregg, D.; Bhakta, S.G.; Light, G.A.; et al. Amphetamine alters an EEG marker of reward processing in humans and mice. *Psychopharmacology (Berl)* **2022**, *239*, 923-933, doi:10.1007/s00213-022-06082-z.

111. Pizzagalli, D.A.; Sherwood, R.J.; Henriques, J.B.; Davidson, R.J. Frontal brain asymmetry and reward responsiveness: a source-localization study. *Psychol Sci* **2005**, *16*, 805-813, doi:10.1111/j.1467-9280.2005.01618.x.
112. Kheirikhah, M.; Duncan, W.C., Jr.; Yuan, Q.; Wang, P.R.; Jamalabadi, H.; Leistriz, L.; Walter, M.; Goldman, D.; Zarate, C.A., Jr.; Hejazi, N.S. REM density predicts rapid antidepressant response to ketamine in individuals with treatment-resistant depression. *Neuropsychopharmacology* **2025**, *50*, 941-946, doi:10.1038/s41386-025-02066-7.
113. Pesonen, A.K.; Gradisar, M.; Kuula, L.; Short, M.; Merikanto, I.; Tark, R.; Räikkönen, K.; Lahti, J. REM sleep fragmentation associated with depressive symptoms and genetic risk for depression in a community-based sample of adolescents. *J Affect Disord* **2019**, *245*, 757-763, doi:10.1016/j.jad.2018.11.077.
114. Lechinger, J.; Koch, J.; Weinhold, S.L.; Seck-Hirschner, M.; Stingele, K.; Kropp-Näf, C.; Braun, M.; Drews, H.J.; Aldenhoff, J.; Huchzermeier, C.; et al. REM density is associated with treatment response in major depression: Antidepressant pharmacotherapy vs. psychotherapy. *J Psychiatr Res* **2021**, *133*, 67-72, doi:10.1016/j.jpsychires.2020.12.009.
115. Luc, O.T.; Kangas, B.D. Validation of a touchscreen probabilistic reward task for mice: A reverse-translated assay with cross-species continuity. *Cogn Affect Behav Neurosci* **2024**, *24*, 281-288, doi:10.3758/s13415-023-01128-x.
116. Palmer, D.; Dumont, J.R.; Dexter, T.D.; Prado, M.A.M.; Finger, E.; Bussey, T.J.; Saksida, L.M. Touchscreen cognitive testing: Cross-species translation and co-clinical trials in neurodegenerative and neuropsychiatric disease. *Neurobiol Learn Mem* **2021**, *182*, 107443, doi:10.1016/j.nlm.2021.107443.
117. Molendijk, M.L.; de Kloet, E.R. Coping with the forced swim stressor: Current state-of-the-art. *Behav Brain Res* **2019**, *364*, 1-10, doi:10.1016/j.bbr.2019.02.005.
118. Commons, K.G.; Cholanians, A.B.; Babb, J.A.; Ehlinger, D.G. The Rodent Forced Swim Test Measures Stress-Coping Strategy, Not Depression-like Behavior. *ACS Chem Neurosci* **2017**, *8*, 955-960, doi:10.1021/acschemneuro.7b00042.
119. Molendijk, M.L.; de Kloet, E.R. Immobility in the forced swim test is adaptive and does not reflect depression. *Psychoneuroendocrinology* **2015**, *62*, 389-391, doi:10.1016/j.psyneuen.2015.08.028.
120. Parekh, P.K.; Johnson, S.B.; Liston, C. Synaptic Mechanisms Regulating Mood State Transitions in Depression. *Annu Rev Neurosci* **2022**, *45*, 581-601, doi:10.1146/annurev-neuro-110920-040422.
121. Aleksandrova, L.R.; Wang, Y.T.; Phillips, A.G. Evaluation of the Wistar-Kyoto rat model of depression and the role of synaptic plasticity in depression and antidepressant response. *Neurosci Biobehav Rev* **2019**, *105*, 1-23, doi:10.1016/j.neubiorev.2019.07.007.
122. Petković, A.; Chaudhury, D. Encore: Behavioural animal models of stress, depression and mood disorders. *Front Behav Neurosci* **2022**, *16*, 931964, doi:10.3389/fnbeh.2022.931964.
123. Della Valle, A.; De Carlo, S.; Sonsini, G.; Pilati, S.; Perali, A.; Ubaldi, M.; Ciccocioppo, R. Machine learning-based model for behavioural analysis in rodents applied to the forced swim test. *Sci Rep* **2025**, *15*, 22314, doi:10.1038/s41598-025-05712-8.
124. Cuthbert, B.N. Research Domain Criteria (RDoC): Progress and Potential. *Curr Dir Psychol Sci* **2022**, *31*, 107-114, doi:10.1177/09637214211051363.
125. Anderzhanova, E.; Kirmeier, T.; Wotjak, C.T. Animal models in psychiatric research: The RDoC system as a new framework for endophenotype-oriented translational neuroscience. *Neurobiol Stress* **2017**, *7*, 47-56, doi:10.1016/j.ynstr.2017.03.003.
126. Nusslock, R.; Alloy, L.B. Reward processing and mood-related symptoms: An RDoC and translational neuroscience perspective. *J Affect Disord* **2017**, *216*, 3-16, doi:10.1016/j.jad.2017.02.001.
127. Cavanagh, J.F.; Gregg, D.; Light, G.A.; Olguin, S.L.; Sharp, R.F.; Bismark, A.W.; Bhakta, S.G.; Swerdlow, N.R.; Brigman, J.L.; Young, J.W. Electrophysiological biomarkers of behavioral dimensions from cross-species paradigms. *Transl Psychiatry* **2021**, *11*, 482, doi:10.1038/s41398-021-01562-w.
128. Fernandes, B.S.; Karmakar, C.; Tamouza, R.; Tran, T.; Yearwood, J.; Hamdani, N.; Laouamri, H.; Richard, J.R.; Yolken, R.; Berk, M.; et al. Precision psychiatry with immunological and cognitive biomarkers: a multi-domain prediction for the diagnosis of bipolar disorder or schizophrenia using machine learning. *Transl Psychiatry* **2020**, *10*, 162, doi:10.1038/s41398-020-0836-4.

129. Sanislow, C.A.; Ferrante, M.; Pacheco, J.; Rudorfer, M.V.; Morris, S.E. Advancing Translational Research Using NIMH Research Domain Criteria and Computational Methods. *Neuron* **2019**, *101*, 779-782, doi:10.1016/j.neuron.2019.02.024.
130. Morris, S.E.; Sanislow, C.A.; Pacheco, J.; Vaidyanathan, U.; Gordon, J.A.; Cuthbert, B.N. Revisiting the seven pillars of RDoC. *BMC Med* **2022**, *20*, 220, doi:10.1186/s12916-022-02414-0.
131. Arns, M.; van Dijk, H.; Luykx, J.J.; van Wingen, G.; Olbrich, S. Stratified psychiatry: Tomorrow's precision psychiatry? *Eur Neuropsychopharmacol* **2022**, *55*, 14-19, doi:10.1016/j.euroneuro.2021.10.863.
132. Milaneschi, Y.; Kappelmann, N.; Ye, Z.; Lamers, F.; Moser, S.; Jones, P.B.; Burgess, S.; Penninx, B.; Khandaker, G.M. Association of inflammation with depression and anxiety: evidence for symptom-specificity and potential causality from UK Biobank and NESDA cohorts. *Mol Psychiatry* **2021**, *26*, 7393-7402, doi:10.1038/s41380-021-01188-w.
133. Tanaka, M. Special Issue "Translating Molecular Psychiatry: From Biomarkers to Personalized Therapies". *Int J Mol Sci* **2025**, *26*, doi:10.3390/ijms262010238.
134. Bekhbat, M.; Treadway, M.T.; Goldsmith, D.R.; Woolwine, B.J.; Haroon, E.; Miller, A.H.; Felger, J.C. Gene signatures in peripheral blood immune cells related to insulin resistance and low tyrosine metabolism define a sub-type of depression with high CRP and anhedonia. *Brain Behav Immun* **2020**, *88*, 161-165, doi:10.1016/j.bbi.2020.03.015.
135. Baune, B.T.; Fromme, S.E.; Aberg, M.; Adli, M.; Afantitis, A.; Akkouh, I.; Andreassen, O.A.; Angulo, C.; Barlati, S.; Brasso, C.; et al. A stratified treatment algorithm in psychiatry: a program on stratified pharmacogenomics in severe mental illness (Psych-STRATA): concept, objectives and methodologies of a multidisciplinary project funded by Horizon Europe. *Eur Arch Psychiatry Clin Neurosci* **2025**, *275*, 1453-1464, doi:10.1007/s00406-024-01944-3.
136. Abi-Dargham, A.; Horga, G. The search for imaging biomarkers in psychiatric disorders. *Nat Med* **2016**, *22*, 1248-1255, doi:10.1038/nm.4190.
137. Guo, Q.; Guo, L.; Wang, Y.; Shang, S. Efficacy and safety of eight enhanced therapies for treatment-resistant depression: A systematic review and network meta-analysis of RCTs. *Psychiatry Res* **2024**, *339*, 116018, doi:10.1016/j.psychres.2024.116018.
138. Łysik, A.; Logoń, K.; Szczygieł, A.; Wołoszczak, J.; Wrześniewska, M.; Leszek, J. Innovative approaches in the treatment-resistant depression: exploring different therapeutic pathways. *Geroscience* **2025**, *47*, 5543-5558, doi:10.1007/s11357-025-01615-8.
139. Salahudeen, M.S.; Wright, C.M.; Peterson, G.M. Esketamine: new hope for the treatment of treatment-resistant depression? A narrative review. *Ther Adv Drug Saf* **2020**, *11*, 2042098620937899, doi:10.1177/2042098620937899.
140. Brietzke, E.; Hawken, E.R.; Idzikowski, M.; Pong, J.; Kennedy, S.H.; Soares, C.N. Integrating digital phenotyping in clinical characterization of individuals with mood disorders. *Neurosci Biobehav Rev* **2019**, *104*, 223-230, doi:10.1016/j.neubiorev.2019.07.009.
141. Baldwin, H.; Loebel-Davidsohn, L.; Oliver, D.; Salazar de Pablo, G.; Stahl, D.; Riper, H.; Fusar-Poli, P. Real-World Implementation of Precision Psychiatry: A Systematic Review of Barriers and Facilitators. *Brain Sci* **2022**, *12*, doi:10.3390/brainsci12070934.
142. Dhieb, D.; Bastaki, K. Pharmaco-Multiomics: A New Frontier in Precision Psychiatry. *Int J Mol Sci* **2025**, *26*, doi:10.3390/ijms26031082.
143. Zanardi, R.; Prestifilippo, D.; Fabbri, C.; Colombo, C.; Maron, E.; Serretti, A. Precision psychiatry in clinical practice. *Int J Psychiatry Clin Pract* **2021**, *25*, 19-27, doi:10.1080/13651501.2020.1809680.
144. Fusar-Poli, P.; Manchia, M.; Koutsouleris, N.; Leslie, D.; Woopen, C.; Calkins, M.E.; Dunn, M.; Tourneau, C.L.; Mannikko, M.; Mollema, T.; et al. Ethical considerations for precision psychiatry: A roadmap for research and clinical practice. *Eur Neuropsychopharmacol* **2022**, *63*, 17-34, doi:10.1016/j.euroneuro.2022.08.001.
145. Brown, J.E.H.; Young, J.L.; Martinez-Martin, N. Psychiatric genomics, mental health equity, and intersectionality: A framework for research and practice. *Front Psychiatry* **2022**, *13*, 1061705, doi:10.3389/fpsy.2022.1061705.

146. Giusti-Rodríguez, P.; Okewole, N.; Jain, S.; Montalvo-Ortiz, J.L.; Peterson, R.E. Diversifying Psychiatric Genomics: Globally Inclusive Strategies Toward Health Equity. *Psychiatr Clin North Am* **2025**, *48*, 241-256, doi:10.1016/j.psc.2025.01.003.
147. Blackburn, T.P. Depressive disorders: Treatment failures and poor prognosis over the last 50 years. *Pharmacol Res Perspect* **2019**, *7*, e00472, doi:10.1002/prp2.472.
148. Oasi, O.; Critchfield, K.L.; Werbart, A. Editorial: Rethinking unsuccessful psychotherapies: when and how do treatments fail? *Front Psychol* **2024**, *15*, 1514654, doi:10.3389/fpsyg.2024.1514654.
149. Petter, J.; Schumacher, L.; Echterhoff, J.; Klein, J.P.; Schramm, E.; Härter, M.; Hautzinger, M.; Kriston, L. Heterogeneity of Treatment Outcomes Across Therapists and Sites in a Randomized Multicentre Psychotherapy Trial. *Clin Psychol Psychother* **2025**, *32*, e70087, doi:10.1002/cpp.70087.
150. Huneke, N.T.M.; Fusetto Veronesi, G.; Garner, M.; Baldwin, D.S.; Cortese, S. Expectancy Effects, Failure of Blinding Integrity, and Placebo Response in Trials of Treatments for Psychiatric Disorders: A Narrative Review. *JAMA Psychiatry* **2025**, *82*, 531-538, doi:10.1001/jamapsychiatry.2025.0085.
151. Bjurner, P.; Isacson, N.H.; Abdesslem, F.B.; Boman, M.; Forsell, E.; Kaldo, V. Study protocol for a triple-blind randomised controlled trial evaluating a machine learning-based predictive clinical decision support tool for internet-delivered cognitive behaviour therapy (ICBT) for depression and anxiety. *Internet Interv* **2025**, *40*, 100816, doi:10.1016/j.invent.2025.100816.
152. Lutz, W.; Deisenhofer, A.K.; Rubel, J.; Bennemann, B.; Giesemann, J.; Poster, K.; Schwartz, B. Prospective evaluation of a clinical decision support system in psychological therapy. *J Consult Clin Psychol* **2022**, *90*, 90-106, doi:10.1037/ccp0000642.
153. Kwan, J.L.; Lo, L.; Ferguson, J.; Goldberg, H.; Diaz-Martinez, J.P.; Tomlinson, G.; Grimshaw, J.M.; Shojania, K.G. Computerised clinical decision support systems and absolute improvements in care: meta-analysis of controlled clinical trials. *Bmj* **2020**, *370*, m3216, doi:10.1136/bmj.m3216.
154. Rybak, Y.E.; Lai, K.S.P.; Ramasubbu, R.; Vila-Rodriguez, F.; Blumberger, D.M.; Chan, P.; Delva, N.; Giacobbe, P.; Gosselin, C.; Kennedy, S.H.; et al. Treatment-resistant major depressive disorder: Canadian expert consensus on definition and assessment. *Depress Anxiety* **2021**, *38*, 456-467, doi:10.1002/da.23135.
155. Mora, F.; Ramos-Quiroga, J.A.; Baca-García, E.; Crespo, J.M.; Gutiérrez-Rojas, L.; Madrazo, A.; Pérez Costillas, L.; Saiz, P.A.; Tordera, V.; Vieta, E. Treatment-resistant depression and intranasal esketamine: Spanish consensus on theoretical aspects. *Front Psychiatry* **2025**, *16*, 1623659, doi:10.3389/fpsyg.2025.1623659.
156. Ivarsson, M.; Danielsson, H.; Imms, C. Measurement issues in longitudinal studies of mental health problems in children with neurodevelopmental disorders. *BMC Psychol* **2025**, *13*, 267, doi:10.1186/s40359-025-02450-4.
157. Lee, W.; Bindman, J.; Ford, T.; Glozier, N.; Moran, P.; Stewart, R.; Hotopf, M. Bias in psychiatric case-control studies: literature survey. *Br J Psychiatry* **2007**, *190*, 204-209, doi:10.1192/bjp.bp.106.027250.
158. Abbaz Yazdian, F.; Khodabakhshi-Koolae, A. Exploring the Counselors and Psychotherapists Perceptions of Therapeutic Errors in the Treatment Room. *SAGE Open* **2024**, *14*, 21582440241257320.
159. Hayes, S.C.; Hofmann, S.G. "Third-wave" cognitive and behavioral therapies and the emergence of a process-based approach to intervention in psychiatry. *World Psychiatry* **2021**, *20*, 363-375, doi:10.1002/wps.20884.
160. Tanaka, M. Parkinson's Disease: Bridging Gaps, Building Biomarkers, and Reimagining Clinical Translation. *Cells* **2025**, *14*, doi:10.3390/cells14151161.
161. Meehan, A.J.; Lewis, S.J.; Fazel, S.; Fusar-Poli, P.; Steyerberg, E.W.; Stahl, D.; Danese, A. Clinical prediction models in psychiatry: a systematic review of two decades of progress and challenges. *Mol Psychiatry* **2022**, *27*, 2700-2708, doi:10.1038/s41380-022-01528-4.
162. Figueiredo Godoy, A.C.; Frota, F.F.; Araújo, L.P.; Valenti, V.E.; Pereira, E.; Detregiachi, C.R.P.; Galhardi, C.M.; Caracio, F.C.; Haber, R.S.A.; Fornari Laurindo, L.; et al. Neuroinflammation and Natural Antidepressants: Balancing Fire with Flora. *Biomedicines* **2025**, *13*, doi:10.3390/biomedicines13051129.
163. Haslbeck, J.; Ryan, O.; Robinaugh, D.J.; Waldorp, L.J.; Borsboom, D. Modeling psychopathology: From data models to formal theories. *Psychological Methods* **2022**, *27*, 930.

164. Halassa, M.M.; Frank, M.J.; Garety, P.; Ongur, D.; Airan, R.D.; Sanacora, G.; Dzirasa, K.; Suresh, S.; Fitzpatrick, S.M.; Rothman, D.L. Developing algorithmic psychiatry via multi-level spanning computational models. *Cell Rep Med* **2025**, *6*, 102094, doi:10.1016/j.xcrm.2025.102094.
165. Tan, T.; Wang, W.; Liu, T.; Zhong, P.; Conrow-Graham, M.; Tian, X.; Yan, Z. Neural circuits and activity dynamics underlying sex-specific effects of chronic social isolation stress. *Cell Rep* **2021**, *34*, 108874, doi:10.1016/j.celrep.2021.108874.
166. Bowman, R.; Frankfurt, M.; Luine, V. Sex differences in anxiety and depression: insights from adult rodent models of chronic stress and neural plasticity. *Front Behav Neurosci* **2025**, *19*, 1591973, doi:10.3389/fnbeh.2025.1591973.
167. Mingardi, J.; Giovenzana, M.; Nicosia, N.; Misztak, P.; Ieraci, A.; Musazzi, L. Sex and Circadian Rhythm Dependent Behavioral Effects of Chronic Stress in Mice and Modulation of Clock Genes in the Prefrontal Cortex. *Int J Mol Sci* **2025**, *26*, doi:10.3390/ijms26136410.
168. Bekhbat, M.; Ulukaya, G.B.; Bhasin, M.K.; Felger, J.C.; Miller, A.H. Cellular and immunometabolic mechanisms of inflammation in depression: Preliminary findings from single cell RNA sequencing and a tribute to Bruce McEwen. *Neurobiol Stress* **2022**, *19*, 100462, doi:10.1016/j.ynstr.2022.100462.
169. Koppe, G.; Meyer-Lindenberg, A.; Durstewitz, D. Deep learning for small and big data in psychiatry. *Neuropsychopharmacology* **2021**, *46*, 176-190, doi:10.1038/s41386-020-0767-z.
170. Driessen, E.; Efthimiou, O.; Wienicke, F.J.; Breunese, J.; Cuijpers, P.; Debray, T.P.A.; Fisher, D.J.; Fokkema, M.; Furukawa, T.A.; Hollon, S.D.; et al. Developing a multivariable prediction model to support personalized selection among five major empirically-supported treatments for adult depression. Study protocol of a systematic review and individual participant data network meta-analysis. *PLoS One* **2025**, *20*, e0322124, doi:10.1371/journal.pone.0322124.
171. Luedtke, A.; Sadikova, E.; Kessler, R.C. Sample size requirements for multivariate models to predict between-patient differences in best treatments of major depressive disorder. *Clinical Psychological Science* **2019**, *7*, 445-461.
172. Watkins, E.R.; Newbold, A. Factorial Designs Help to Understand How Psychological Therapy Works. *Front Psychiatry* **2020**, *11*, 429, doi:10.3389/fpsy.2020.00429.
173. Ciolino, J.D.; Scholtens, D.M.; Bonner, L.B. Factorial Clinical Trial Designs. *Jama* **2025**, *333*, 532-533, doi:10.1001/jama.2024.25374.
174. Watkins, E.; Newbold, A.; Tester-Jones, M.; Javaid, M.; Cadman, J.; Collins, L.M.; Graham, J.; Mostazir, M. Implementing multifactorial psychotherapy research in online virtual environments (IMPROVE-2): study protocol for a phase III trial of the MOST randomized component selection method for internet cognitive-behavioural therapy for depression. *BMC Psychiatry* **2016**, *16*, 345, doi:10.1186/s12888-016-1054-8.
175. Kotecha, G.; Ventz, S.; Fortini, S.; Trippa, L. Uncertainty directed factorial clinical trials. *Biostatistics* **2024**, *25*, 833-851, doi:10.1093/biostatistics/kxad036.
176. Victor, T.A.; Khalsa, S.S.; Simmons, W.K.; Feinstein, J.S.; Savitz, J.; Aupperle, R.L.; Yeh, H.W.; Bodurka, J.; Paulus, M.P. Tulsa 1000: a naturalistic study protocol for multilevel assessment and outcome prediction in a large psychiatric sample. *BMJ Open* **2018**, *8*, e016620, doi:10.1136/bmjopen-2017-016620.
177. Nelson, B.; McGorry, P.D.; Wichers, M.; Wigman, J.T.W.; Hartmann, J.A. Moving From Static to Dynamic Models of the Onset of Mental Disorder: A Review. *JAMA Psychiatry* **2017**, *74*, 528-534, doi:10.1001/jamapsychiatry.2017.0001.
178. Harkness, A.R.; Reynolds, S.M.; Lilienfeld, S.O. A review of systems for psychology and psychiatry: adaptive systems, personality psychopathology five (PSY-5), and the DSM-5. *J Pers Assess* **2014**, *96*, 121-139, doi:10.1080/00223891.2013.823438.

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