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General psychiatric disease: a unifying nosographic framework for psychiatry with applications across psychopathology, pharmacology, psychotherapy, and cognition

Doença psiquiátrica geral: um marco nosográfico unificador para a psiquiatria com aplicações em psicopatologia, farmacologia, psicoterapia e cognição

Enfermedad psiquiátrica general: un marco nosográfico unificador para la psiquiatría con aplicaciones en psicopatología, farmacología, psicoterapia y cognición

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ABSTRACT:
Introduction: Modern psychiatry has been dominated, for over four decades, by the categorical diagnostic model codified in the Diagnostic and Statistical Manual of Mental Disorders (DSM) and the International Classification of Diseases (ICD). **Objective:** To introduce and systematize General Psychiatric Disease (GPD), a unifying nosographic framework proposing that diverse psychiatric conditions represent variable clinical expressions of a common functional-etiopathogenic disturbance, and to evaluate its explanatory capacity across five major clinical domains. Study design: Conceptual review and theoretical synthesis. **Methodology:** Integrative conceptual review of evidence from psychopathology, neuropsychiatry, clinical genetics, pharmacology, and psychotherapy, applied across five clinical domains: the neurodevelopmental spectrum (autism, dysphasia, dyslexia, ADHD), mood disorders, personality disorders, psychotic disorders, and neuropsychiatric syndromes. **Results:** GPD provides a coherent account of: (a) high psychiatric comorbidity rates; (b) symptom migration across the lifespan; (c) pharmacological cross-categoricality, and (d) shared genetic architecture across diagnostic categories. Constitutes the foundational framework from which advances in psychopathology, pharmacology, psychotherapy, and cognition can be systematically derived. **Conclusion:** GPD represents a paradigmatic shift in psychiatric nosography. Without replacing categorical diagnosis, it provides the theoretical substrate for a more integrated and scientifically productive psychiatry, with direct implications for research, clinical practice, training, and drug development.

Keywords: general psychiatric disease, nosography, psychopathology, comorbidity, psychiatric spectrum, transdiagnostic, neuropsychiatry, pharmacology, psychotherapy.

RESUMO:
Introdução: A psiquiatria moderna tem sido dominada, há mais de quatro décadas, pelo modelo diagnóstico categorial codificado no Manual Diagnóstico e Estatístico de Transtornos Mentais (DSM) e na Classificação Internacional de Doenças (CID). **Objetivo:** Introduzir e sistematizar a Doença Psiquiátrica Geral (DPG), um marco nosográfico unificador que propõe que diversas condições psiquiátricas representam expressões clínicas variáveis de um distúrbio funcional-etiopatogênico comum, e avaliar sua capacidade explicativa em cinco grandes domínios clínicos. Desenho do estudo: Revisão conceitual e síntese teórica. **Metodologia:** Revisão conceitual integrativa de evidências da psicopatologia, neuropsiquiatria, genética clínica, farmacologia e psicoterapia, aplicada em cinco domínios clínicos: o espectro neurodesenvolvimentista (autismo, disfasia, dislexia, TDAH), transtornos do humor, transtornos da personalidade, transtornos psicóticos e síndromes neuropsiquiátricas. **Resultados:** A DPG fornece uma explicação coerente de: (a) altas taxas de comorbidade psiquiátrica; (b) migração de sintomas ao longo da vida; (c) cross-categoricalidade farmacológica, e (d) arquitetura genética compartilhada entre categorias diagnósticas. O conceito, constitui o marco fundamental a partir do qual avanços em psicopatologia, farmacologia, psicoterapia e cognição podem ser sistematicamente derivados. **Conclusão:** A DPG representa uma mudança de paradigma na nosografia psiquiátrica. Sem substituir o diagnóstico categórico, fornece o substrato teórico para uma psiquiatria mais integrada e cientificamente produtiva, com implicações diretas para pesquisa, prática clínica, treinamento e desenvolvimento de fármacos.

Palavras-chave: doença psiquiátrica geral, nosografia, psicopatologia, comorbidade, espectro psiquiátrico, transdiagnóstico, neuropsiquiatria, farmacologia, psicoterapia.

RESUMEN:
Introducción: La psiquiatría moderna ha estado dominada, durante más de cuatro décadas, por el modelo diagnóstico categorial codificado en el Manual diagnóstico y estadístico de los trastornos mentales (DSM) y en la Clasificación Internacional de Enfermedades (CIE). **Objectivo:** Introducir y sistematizar la Enfermedad Psiquiátrica General (EPG), un marco nosográfico unificador que propone que diversas condiciones psiquiátricas representan expresiones clínicas variables de un trastorno funcional-etiopatogénico común, y evaluar su capacidad explicativa en cinco grandes

dominios clínicos. Diseño del estudio: Revisión conceptual y síntesis teórica. **Metodología:** Revisión conceptual integrativa de evidencias de psicopatología, neuropsiquiatría, genética clínica, farmacología y psicoterapia, aplicada en cinco dominios clínicos: el espectro neurodesarrollista (autismo, disfasia, dislexia, TDAH), trastornos del humor, trastornos de la personalidad, trastornos psicóticos y síndromes neuropsiquiátricos. **Resultados**: La EPG proporciona una explicación coherente de: (a) altas tasas de comorbilidad psiquiátrica; (b) migración de síntomas a lo largo de la vida; (c) cross-categoricalidad farmacológica, y (d) arquitectura genética compartida entre categorías diagnósticas. El concepto, constituye el marco fundamental a partir del cual los avances en psicopatología, farmacología, psicoterapia y cognición pueden derivarse sistemáticamente. **Conclusión:** La EPG representa un cambio de paradigma en la nosografía psiquiátrica. Sin reemplazar el diagnóstico categórico, proporciona el sustrato teórico para una psiquiatría más integrada y científicamente productiva, con implicaciones directas para investigación, práctica clínica, capacitación y desarrollo de fármacos.

Palabras clave: enfermedad psiquiátrica general, nosografía, psicopatología, comorbilidad, espectro psiquiátrico, transdiagnóstico, neuropsiquiatría, farmacología, psicoterapia.

INTRODUCTION

Modern psychiatry has been dominated, for over four decades, by the categorical diagnostic model codified in the Diagnostic and Statistical Manual of Mental Disorders (DSM) and the International Classification of Diseases (ICD). This model treats each diagnostic category, schizophrenia, bipolar disorder, major depression, autism spectrum disorder (ASD), and dysphasia, among others, as an autonomous entity, defined by discrete criteria, with implied distinct etiology, pathophysiology, and treatment.

Clinical reality, however, systematically contradicts this model. Psychiatric comorbidity is the rule, not the exception: most patients with one psychiatric diagnosis meet criteria for at least one other [1]. Symptom migration, the phenomenon by which the same individual presents different diagnostic pictures at different life stages, is widely documented [2]. Psychopharmacological agents demonstrate efficacy across categorical boundaries: mood stabilizers used in bipolar disorder show efficacy in epilepsy, impulsivity, and certain personality disorders [3], atypical antipsychotics are used in depression, anxiety, autism, and ADHD [4].

These findings suggest that the categorical boundaries of current psychiatric nosography are, to a significant degree, arbitrary, reflecting pragmatic classification conventions rather than genuine natural kinds. They point toward the existence of shared mechanisms across ostensibly distinct conditions.

The concept of General Psychiatric Disease (GPD), also termed General Psychiatric Syndrome, was proposed and systematized by Caixeta et al. to address precisely this explanatory gap [5 – 6]. Its core proposition is that diverse psychiatric conditions represent variable clinical expressions of a common functional-etiopathogenic disturbance, whose phenomenological manifestations differ according to which neural systems, developmental stages, and environmental contexts are most affected.

GPD is positioned as a mechanistic elaboration of dimensional /transdiagnostic frameworks (such as the Hierarchical Taxonomy of Psychopathology [HiTOP] [7] and network psychometrics) and complements clinical staging approaches [8]. Unlike purely descriptive dimensional models, GPD proposes a specific neural substrate (integration/precision-weighting dysfunction) that explains both cross-disorder commonalities and domain-specific variations. This mechanistic grounding enables testable predictions about neuroimaging endophenotypes, genetic architecture, and pharmacological response.

This paper introduces and systematically develops the GPD framework, demonstrates its explanatory capacity across five clinical domains, and outlines its implications for psychopathology, pharmacology, psychotherapy, cognition research, and training.

METHODS

The concept of general psychiatric disease

Historical roots and theoretical positioning

The notion that diverse psychiatric presentations share common mechanisms has deep historical roots, substantially recapitulating the nineteenth-century Einheitspsychose (unitary psychosis) tradition. Griesinger's [9] doctrine held that all mental disorders manifest a single underlying brain disease with phenotypic variation, while Zeller and Neumann articulated parallel positions. More recently, Meehl's schizotaxia model and Claridge's psychoticism spectrum proposed common neural diatheses producing variable phenotypes through environmental modulation [10]. GPD builds upon these historical foundations by

specifying the exact neural integration mechanisms involved and applying them to modern clinical and pharmacological application.

That diverse psychiatric presentations share common mechanisms is not new. Kraepelin's foundational dichotomy between dementia praecox and manic-depressive insanity has been progressively eroded since the mid-twentieth century by findings of clinical continuity, shared genetic architecture, and overlapping neurobiological substrates between psychotic and affective conditions [11].

The Research Domain Criteria (RDoC) initiative of the US National Institute of Mental Health (NIMH), launched in 2010, explicitly proposed organizing psychiatric research around neurobiological dimensions rather than categorical diagnoses [12]. Parallel dimensional frameworks, such as the Hierarchical Taxonomy of Psychopathology (HiTOP) [12]. The "p-factor" model, derived from structural analyses of psychiatric comorbidity, suggests that a single general psychopathological factor underlies diverse diagnostic categories [13]. A decade of subsequent research has refined this construct: Caspi et al. [14] demonstrated through criterion-validation studies that the p-factor performs consistently across different statistical models, reinforcing its status as a robust transdiagnostic index of general psychopathological liability rather than a statistical artifact.

GPD shares the transdiagnostic orientation of these initiatives but differs in critical ways. RDoC and the p-factor are primarily research constructs derived from dimensional analyses. GPD is a clinically grounded nosographic framework, proposed from the integration of clinical observations, neuropsychiatric cases, and the systematic analysis of comorbidity patterns in clinical practice. It does not merely describe dimensional overlap, it proposes a mechanism.

Core propositions of GPD

The GPD framework rests on five interconnected propositions

Psychiatric conditions do not constitute autonomous disease entities with fully distinct etiologies and mechanisms. They represent variable clinical expressions of a common functional disturbance.

The clinical heterogeneity of psychiatric presentations reflects individual differences in **(a)** which neural systems are most intensely affected; **(b)** which developmental stage the disturbance occurs at; **(c)** which compensatory mechanisms develop, and **(d)** which environmental factors modulate expression.

The boundaries between categorical diagnoses are not natural kinds but clinical approximations. A patient diagnosed with dysphasia may share etiopathogenic mechanisms with a patient diagnosed with autism or ADHD.

Within the same family or genetic lineage, different members may manifest clinically distinct expressions of the same underlying vulnerability, just as family members sharing bipolar vulnerability may present with classic bipolar disorder, recurrent depression, fibromyalgia, or impulse control disorders.

The common mechanism underlying GPD involves disturbances in neural integration systems, a distributed architecture comprising the action-observation network (fronto-temporo-parietal regions supporting motor simulation), thalamocortical circuits (gating and filtering of sensory/cognitive information), and default mode network interactions (self-referential processing and mentalizing). These systems mediate social cognition, causal learning, self-other differentiation, and symbolic development. Expected neurophysiological signatures of this dysfunction include altered EEG/MEG mu suppression, aberrant effective connectivity patterns, and atypical task-based fMRI contrasts in mentalizing regions.

GPD and categorical diagnosis: complementary, not opposed
GPD does not propose the abolition of categorical diagnosis. Categories remain essential for clinical communication, epidemiological research, treatment protocols, and administrative purposes. What GPD proposes is that categorical labels be understood as phenomenological cross-sections of a dimensional and processual underlying reality, not as entities in themselves.

This is analogous to the relationship between categorical definitions of hypertension, diabetes, and hypercholesterolemia, and the understanding that all three reflect disturbances in overlapping metabolic-vascular regulatory systems, share risk factors and pathways, and often respond to the same therapeutic interventions. (Figure 1)

Falsifiable predictions of the GPD framework
To distinguish GPD from purely descriptive models, the framework generates specific, falsifiable predictions that can be empirically tested:

Common vs. Domain-Specific Deficits: Individuals across autism, ADHD, mood disorders, and psychosis should demonstrate shared, directionally specific deficits in neural integration (specifically, reduced mu suppression

during action observation relative to neurotypical controls, and decreased top-down effective connectivity from prefrontal to sensorimotor regions during social tasks). Domain-specific symptoms correlate with secondary compensatory network recruitment. This prediction is falsifiable if cross-diagnostic cohorts show enhanced rather than reduced mu suppression, or intact top-down connectivity.

Stage-Dependent Markers: Rather than a strict motor-to-mentalizing dichotomy, early neurodevelopmental conditions (e.g., ASD) may present with both sensorimotor and mentalizing deficits depending on which specific node of the integration network is primarily affected. However, across a defined neurodevelopmental-to-adulthood continuum (excluding primary neurodegenerative motor circuit pathologies), early environmental insults will disproportionately affect basic integration scaffolding, while later psychosocial stressors will modulate higher-order affective and psychotic expressions.

Treatment Response Moderators: Medications enhancing glutamatergic or dopaminergic signaling (implicated in precision weighting) should predict cross-diagnostic response specifically in patients showing baseline neural integration deficits, rather than across all patients with a given categorical diagnosis. This can be tested through mechanism-stratified randomized controlled trials.

RESULTS

Evidence base for GPD

Comorbidity Patterns

Epidemiological data consistently demonstrate that psychiatric comorbidity is the rule rather than the exception. Population-based studies estimate that over 50% of individuals with one DSM diagnosis meet criteria for at least one additional diagnosis [1]. The National Comorbidity Survey Replication found that 27.7% of individuals in the United States had three or more lifetime mental disorders [15].

Under the categorical model, comorbidity requires explanation for of distinct entities. Under GPD, comorbidity is expected: it reflects the natural tendency of a common underlying disturbance to manifest across multiple phenomenological dimensions simultaneously.

We acknowledge that high comorbidity rates are also elegantly explained by Network Theory [16], which posits that symptoms causally influence each other (e.g., sleep disturbance → fatigue → concentration failure)

without requiring a shared latent substrate. To distinguish GPD from Network Theory, GPD generates differential predictions by condition pair: comorbidity rates should be highest between conditions sharing the same primary network deficit (e.g., ASD and ADHD via the action-observation network) and lower between conditions with non-overlapping primary network involvement (e.g., specific phobia and schizophrenia). Network theory, conversely, predicts comorbidity based strictly on symptom adjacency cascades rather than underlying neural network overlap.

Genetic architecture

Genome-wide association studies (GWAS) have consistently documented extensive genetic overlap across psychiatric diagnostic categories. The Cross-Disorder Group of the Psychiatric Genomics Consortium demonstrated significant genetic correlations between schizophrenia, bipolar disorder, major depression, ASD, and ADHD [17]. Polygenic risk scores for one condition confer risk across others. Some identified loci, including genes related to calcium channel signaling (CACNA1C) and neuronal connectivity, are associated with multiple psychiatric phenotypes simultaneously [18].

More recently, a protein–protein interaction network analysis by Guillen-Burgos et al. [19] confirmed that severe psychiatric disorders, including schizophrenia, bipolar disorder, major depressive disorder, and PTSD, share common biological pathways related to neuroinflammation, dopaminergic and glutamatergic transmission, and synaptic plasticity, with approximately 75% of genetic loci shared across at least two disorders. These findings offer converging systems-biology support for the shared neural vulnerability that GPD proposes as its mechanistic core.

Also, gene-environment (G×E) interactions play a crucial role in determining which specific phenotype emerges from this shared genetic vulnerability. While G×E main effects are strong, interaction magnitudes can be modest and developmentally specific. Under GPD, early environmental stressors (e.g., obstetric complications, early trauma) tend to modulate neurodevelopmental expressions, while later psychosocial stressors (e.g., social rejection, occupational stress) modulate affective and psychotic expressions. This developmental specificity of G×E interactions represents a key prediction of GPD that warrants systematic investigation.

Pharmacological cross-categoricality

Atypical antipsychotics are now utilized transdiagnostically, functioning as augmentation agents in treatment-resistant depression [20 - 21], as primary interventions for ASD-associated irritability based on pivotal regulatory trials, and across various anxiety and psychotic spectrum presentations [4].

This pharmacological cross-categoricality is coherently explained by GPD: medications that modulate shared neural mechanisms, dopaminergic, serotonergic, glutamatergic, GABAergic systems, will naturally demonstrate efficacy across diagnostic categories. Importantly, GPD argues this is not merely due to nonspecific sedative or anxiolytic effects, but reflects mechanism-level overlap in neural integration dysfunction. For instance, glutamatergic modulators should demonstrate prospective, mechanism-stratified efficacy across diagnoses when patients are selected based on integration metrics rather than categorical labels. This prediction can be tested through pharmacogenomic studies examining whether integration-based biomarkers predict treatment response more robustly than categorical diagnosis.

Symptom migration and longitudinal polymorphism

Symptom migration, the tendency of individual patients to manifest different diagnostic pictures at different life stages, is poorly explained by the categorical model. Longitudinal studies demonstrate that children with ASD diagnoses may present with attentional, mood, and anxiety features in adolescence, individuals diagnosed with ADHD in childhood frequently develop mood or personality disorder features in adulthood [2].

Under GPD, symptom migration is expected: it reflects the intersection of a stable underlying vulnerability with changing developmental-environmental demands across the lifespan. The underlying disturbance remains constant, its phenomenological expression varies as neural systems mature and environmental contexts shift.

GPD across clinical domains

As illustrated in Figure 2 below, each of the five clinical domains examined in this section represents a distinct phenotypic arena in which the common disturbance of GPD manifests. The solid bidirectional arrows in Figure 2 indicate shared neural mechanisms between each domain and the common substrate, the dashed arcs reflect the well-documented cross-domain comorbidity and symptom migration that the categorical model struggles to explain.

Child and adolescent psychiatry: the neurodevelopmental spectrum

The clearest clinical manifestation of GPD is arguably visible in child psychiatry, where the boundaries between autism, dysphasia, dyslexia, and ADHD are notoriously porous. Rapin documented a spectrum-continuum between dysphasia and autism [22]. Baker and Cantwell [23] demonstrated high comorbidity between language disorders and diverse psychiatric conditions. Gérard [24] described transition forms between dysphasia, hyperactivity, and autism.

Notably, the 'broken mirror' hypothesis of ASD remains empirically contested, studies utilizing simultaneous EEG and fMRI have sometimes failed to find significant differences in mu suppression between ASD and neurotypical participants [25]. As a result, GPD frames mirror neuron dysfunction not as an established, isolated cause, but as one highly relevant candidate substrate within a much broader, distributed integration network.

Under GPD, these conditions share a common etiopathogenic substrate, prominently, disturbances in mirror neuron systems that mediate causal learning, social cognition, and symbolic development. The specific clinical presentation in each patient depends on which aspects of this substrate are most intensely affected: pragmatic processing, phonological formulation, attentional regulation, rhythmic-motor integration, or self-other differentiation.

This framework explains the clinical observation documented by Caixeta et al. [5 – 6], that a child may present with severe apraxic dysphasia clinically indistinguishable from Kanner autism, without meeting criteria for autism itself. The two conditions share a mechanism, they differ in the scope and pattern of neural involvement. As illustrated in Figure 1, when objectalization bypasses normal causal integration, the result is symbols with absent or fragile meaning, a pattern observable across the entire neurodevelopmental spectrum.

Mood disorders

Mood disorders illustrate GPD's proposition regarding symptom migration and familial heterogeneity with particular clarity. It is well documented in family studies that families with high loading of bipolar disorder include members who present with: classic bipolar I disorder, bipolar II disorder, recurrent unipolar depression, cyclothymia, dysthymia, and what Akiskal and Pinto [26] termed "bipolar spectrum" conditions, including individuals

with predominantly somatic presentations, fibromyalgia, chronic pain syndromes, migraine, who never develop overt affective episodes.

This shared vulnerability supports neuroimaging evidence. Resting-state fMRI studies in both unipolar and bipolar depression consistently demonstrate connectivity abnormalities within the default mode network and altered cross-network integration with the central executive network, providing the mechanistic substrate for the affective dysregulation observed across these phenotypes.

Under the categorical model, these diverse presentations require complex explanations involving multiple distinct entities with coincidentally high familial clustering. Under GPD, they represent variable phenomenological expressions, differing in severity, predominant symptom cluster, and compensatory capacity, of a shared affective dysregulation vulnerability. The family itself becomes a natural experiment in phenotypic variability under a common genetic substrate.

Personality disorders

The personality disorders as classified in DSM-5 present one of the most documented challenges to categorical nosography: their high internal comorbidity, dimensional relationship with Axis I conditions, and inconsistency over time have been widely criticized [27].

GPD reframes personality disorders as habitual and relatively stabilized modes of expressing an underlying functional disturbance, modes that, under stress, decompensate into what are categorically classified as Axis I conditions. Borderline personality disorder (BPD), for instance, shares neurobiological features with PTSD, affective disorders, and impulse control disorders [28], and is effectively treated by agents and psychotherapeutic approaches whose mechanisms operate across these categorical boundaries [29]. This cross-categorical therapeutic efficacy is precisely what GPD predicts: interventions targeting the shared substrate will benefit patients across the diagnostic spectrum.

Psychotic disorders

The categorical boundary between schizophrenia and bipolar disorder, one of Kraepelin's founding dichotomies, has been progressively eroded by genetic, neuroimaging, and clinical evidence [11]. The existence of schizoaffective disorder as a recognized diagnostic category reflects clinical reality's resistance to the categorical segregation of psychotic and affective symptoms.

GPD accommodates this reality by treating psychotic phenomenology, delusional thinking, hallucinations, formal thought disorder, as particular modes of expression of the common underlying disturbance, rather than pathognomonic features of a distinct disease entity. The dimensional relationship between subclinical psychotic experiences in the general population and clinical psychosis, documented by van Os et al. [30], is consistent with this view: psychosis is not a categorically distinct state but a point on a continuum that the entire population inhabits at varying distance from threshold.

Neuropsychiatric syndromes

A distinctive contribution of the GPD framework is the systematic attention to neuropsychiatric syndromes at the intersection of neurology and psychiatry: frontal syndromes, thalamic syndromes, basal ganglia-related behavioral disturbances, and neuropsychiatric manifestations of neurodegenerative conditions. These have been historically assigned to either neurology or psychiatry based on whether a structural lesion is demonstrable, a distinction GPD considers arbitrary.

Behavioral and psychiatric symptoms in Parkinson's disease, Huntington's disease, Wilson's disease, and the dementias are not merely "secondary" complications of "primary" neurological conditions: they are manifestations of the same disturbance in neural integration systems that underlies "primary" psychiatric conditions. The mechanism is shared, the etiological trigger differs. This reframing justifies the use of the same psychopharmacological and psychotherapeutic approaches across neurological and psychiatric presentations, and supports integrated neuropsychiatric training.

As illustrated in Figure 2 below, each of the five clinical domains examined in this section represents a distinct phenotypic arena in which the common disturbance of GPD manifests. The solid bidirectional arrows in Figure 2 indicate shared neural mechanisms between each domain and the common substrate, the dashed arcs reflect the well-documented cross-domain comorbidity and symptom migration that the categorical model struggles to explain.

As illustrated in Figure 2 below, each of the five clinical domains examined in this section represents a distinct phenotypic arena in which the common disturbance of GPD manifests. The solid bidirectional arrows in Figure 2 indicate shared neural mechanisms between each domain and the common substrate, the dashed arcs reflect the well-documented cross-domain

comorbidity and symptom migration that the categorical model struggles to explain.

Table 1 summarizes the transdiagnostic implications of GPD across seven disciplinary domains, each with its corresponding practical consequences for clinical practice, research, and training.

DISCUSSION

GPD and existing transdiagnostic frameworks

GPD shares its transdiagnostic orientation with several existing frameworks but differs fundamentally in scope, grounding, and clinical ambition. The RDoC initiative [12] proposes research organization around neurobiological dimensions, but remains primarily a research taxonomy without clinical application guidelines and without a unifying mechanistic narrative. The p-factor model [13 – 14] provides compelling psychometric evidence for a general psychopathological factor and has been shown to be statistically robust across different modeling approaches, however, it remains descriptive, it does not propose a mechanistic explanation for why such covariation exists, nor does it translate into clinical practice guidance. Unified Protocol approaches in psychotherapy [29] operationalize transdiagnostic treatment without a comprehensive nosographic rationale, limiting their integration with biological and pharmacological perspectives.

GPD offers what these frameworks do not: a clinically grounded, mechanistically explicit nosographic concept that can simultaneously guide research, clinical practice, pharmacological development, and psychotherapeutic application. Its roots in clinical observation, including detailed neuropsychiatric case studies and systematic analysis of comorbidity patterns in clinical practice, give it ecological validity that purely data-derived dimensional models may lack. Importantly, GPD is not merely a descriptive overlap model: it proposes that shared neural integration dysfunction, mediated prominently by the mirror neuron system and related circuits, constitutes the substrate from which diverse phenotypes emerge through developmental, genetic, and environmental modulation.

The mechanistic core: neural integration and shared vulnerability

The mechanistic core of GPD, disturbances in neural integration systems, with the mirror neuron system as a prominent but not exclusive substrate, supports converging lines of evidence. Rizzolatti and Craighero [31] established that the mirror neuron system mediates the mapping of observed actions onto motor representations, providing the neural basis

for social cognition, imitation, empathy, and causal learning. Disruptions to this system have been implicated in the social deficits of ASD, the impaired mentalization in borderline personality disorder, and the self-other boundary disturbances in psychosis.

At the genetic level, the protein–protein interaction analyses by Guillen-Burgos et al. [19] revealed that shared genetic loci across schizophrenia, bipolar disorder, MDD, and PTSD converge on pathways related to dopaminergic and glutamatergic transmission, cytokine signaling, and synaptic vesicle cycling, all components of the neural integration disturbance GPD proposes. The CACNA1C locus, identified as a pleiotropic risk variant across multiple psychiatric phenotypes [18], encodes a calcium channel subunit that regulates synaptic plasticity and neural connectivity, precisely the type of molecular mechanism GPD would predict as part of its common substrate. These converging genetic data suggest that GPD is not merely a clinical observation but may be grounded in a molecular biology of shared vulnerability.

Clinical implications: from category to mechanism

The clinical implications of GPD extend across the full spectrum of psychiatric practice. In pharmacology, the GPD framework provides a principled theoretical basis for what has until now been empirically observed without adequate explanation: the cross-categorical efficacy of psychopharmacological agents. Rather than treating this as anomalous off-label use, GPD reframes it as the expected consequence of medications that modulate shared pathophysiological substrates. This has direct implications for drug development: rather than designing agents for categorical diagnoses, future pharmacology should target shared mechanisms: glutamatergic modulation, neuroinflammatory pathways, synaptic plasticity, with transdiagnostic indications.

In psychotherapy, the GPD framework provides the nosographic rationale for transdiagnostic interventions that Unified Protocol approaches [29] have operationalized clinically. Mechanisms such as emotion regulation, mentalization, and cognitive flexibility, targeted by DBT, MBT, and ACT respectively, are not disorder-specific competencies but transdiagnostic capacities whose impairment reflects the common underlying vulnerability. This means that developing and disseminating these approaches benefits a far larger patient population than disorder-specific protocols would reach.

In clinical training, GPD argues for a fundamental shift in how psychiatric residents and medical students are educated. Training focused exclusively

on categorical diagnosis, learning DSM criteria for each disorder in isolation, produces clinicians poorly equipped to understand the transdiagnostic reality of their patients' presentations, to recognize symptom migration, to explain familial heterogeneity, or to justify cross-categorical pharmacological interventions. Integration of the GPD framework into residency curricula would produce clinicians with a more coherent, mechanism-oriented understanding of psychiatric illness.

Limitations and research agenda

Several limitations of the current presentation must be acknowledged. First, GPD as presented here is a conceptual framework derived from clinical observation and theoretical integration, not from prospective empirical study. Validation studies examining whether GPD-consistent predictions hold in longitudinal cohorts are needed. Specifically, studies should test whether individuals with high GPD substrate vulnerability (identified by polygenic risk scores, mirror neuron function measures, or neural integration indices) show the predicted cross-diagnostic symptom profiles and migration patterns over time.

Second, the identification of the mirror neuron system as the primary shared mechanism reflects an emerging and still controversial literature. Hickok [32] identified significant problems with the mirror neuron theory of action understanding, noting that the system's function in humans is substantially more complex and less anatomically discrete than in the macaque model from which the concept was originally derived. More precision in mechanistic specification is needed, the mirror neuron system is best understood as one node in a broader neural integration network rather than the sole substrate of GPD.

Third, not all psychiatric comorbidity reflects shared mechanisms: some comorbidity patterns reflect causal relationships, iatrogenic effects, or statistical artifact from criterion overlap. Distinguishing genuine GPD-type transdiagnostic overlap from these other comorbidity sources requires systematic research using methods capable of separating pleiotropic genetic effects from other forms of association.

Fourth, practical implementation of GPD in clinical settings requires development of assessment tools capable of capturing the dimensional, mechanistic profile of individual patients. Progress in computational psychiatry, digital phenotyping, and machine learning-based clinical decision support may provide the methodological infrastructure for this next generation of GPD-informed assessment.

Validation roadmap: from concept to empirical testing

To move from conceptual synthesis to empirical validation, a concrete research program is required. The following roadmap outlines the necessary steps across three time horizons:

Short Term (1-2 years): Formal scoping reviews with quantitative summaries are needed, including meta-analyses of cross-disorder genetic correlations, effect sizes for pharmacologic cross-efficacy, and systematic documentation of comorbidity patterns across diagnostic categories. These syntheses will establish the empirical foundation upon which GPD rests.

Medium Term (2-5 years): Longitudinal cohorts must assess whether multimodal integration indices (EEG connectivity entropy, fMRI effective connectivity within action-observation and default mode networks, DTI measures of white matter organization) prospectively predict cross-diagnostic symptom profiles and symptom migration. Also, genetic triangulation using Mendelian randomization should test whether putative integration endophenotypes mediate the path from genetic liability to symptom dimensions. Mechanism-stratified clinical trials (e.g., testing glutamatergic modulators across diagnoses based on integration metrics) will provide direct evidence for GPD's clinical utility.

Long Term (5+ years): Prospective prediction of symptom migration using baseline integration metrics will validate GPD's developmental predictions. Biomarker-based patient stratification for precision psychiatry, selecting treatments based on integration metrics rather than categorical diagnosis, will demonstrate clinical utility. Integration-informed treatment guidelines and training curricula will embed GPD into psychiatric practice and education.

CONCLUSION

General Psychiatric Disease represents a significant mechanistic elaboration of the unitary psychosis tradition. Rather than a wholly unprecedented paradigm shift, it provides the specific neurobiological substrate (integration/precision-weighting dysfunction) required to translate historical unitary concepts into testable modern hypotheses.

This shift enriches clinical psychiatry. It provides a rational basis for understanding why patients rarely fit neatly into single diagnostic categories, why psychiatric symptoms migrate across the lifespan, why the same drug works across ostensibly distinct conditions, why psychotherapeutic mechanisms of change transcend diagnostic categories,

and why family members sharing genetic vulnerability manifest strikingly different clinical pictures.

Most critically, GPD provides psychiatry with a coherent scientific foundation, a framework that connects clinical observation, neurobiology, genetics, and therapeutic intervention within a unified conceptual architecture. The concept was originally published in Caixeta et al. [5 – 6] and constitutes the foundational axis from which the research group's program in psychopathology, neuropsychiatry, cognition, and child psychiatry proceeds.

Future research should pursue: **(a)** prospective longitudinal validation of GPD-consistent predictions; **(b)** neurobiological specification of shared mechanisms; **(c)** development of GPD-aligned clinical assessment instruments; **(d)** clinical trials of transdiagnostic interventions explicitly designed from the GPD framework, and **(e)** integration of GPD into psychiatric education at undergraduate and postgraduate levels. Psychiatry's greatest challenge in the coming decades may be precisely this: to move from a science of categories to a science of mechanisms. General Psychiatric Disease offers a map for that journey.

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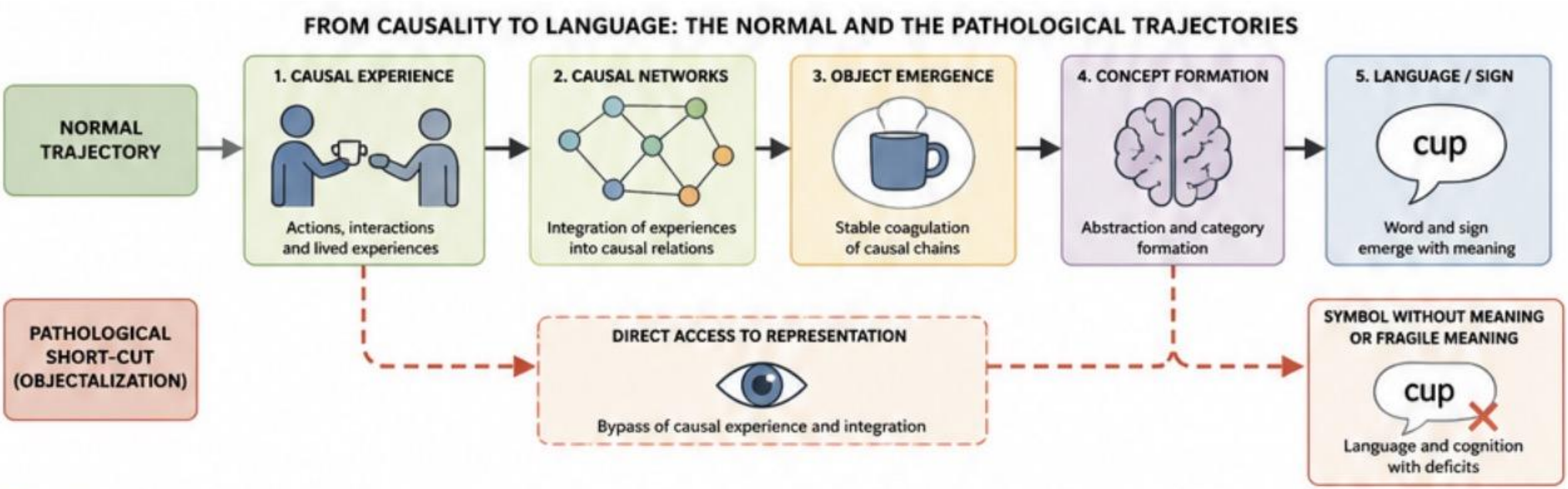

Figure 1. The normal trajectory (upper row) from causality to language versus the pathological shortcut (lower row) characterized by objectalization. This model illustrates how deviations in early causal processing can impair concept formation and language acquisition.

Figure 1. The normal trajectory (upper row) from causality to language versus the pathological shortcut (lower row) characterized by objectalization.

Source: The authors.

Note: This model illustrates how deviations in early causal processing can impair concept formation and language acquisition, a central pathological pathway within the GPD framework. The five-stage normal sequence (causal experience → causal networks → object emergence → concept formation → language/sign) is bypassed when objectalization occurs, resulting in symbols with absent or fragile meaning.

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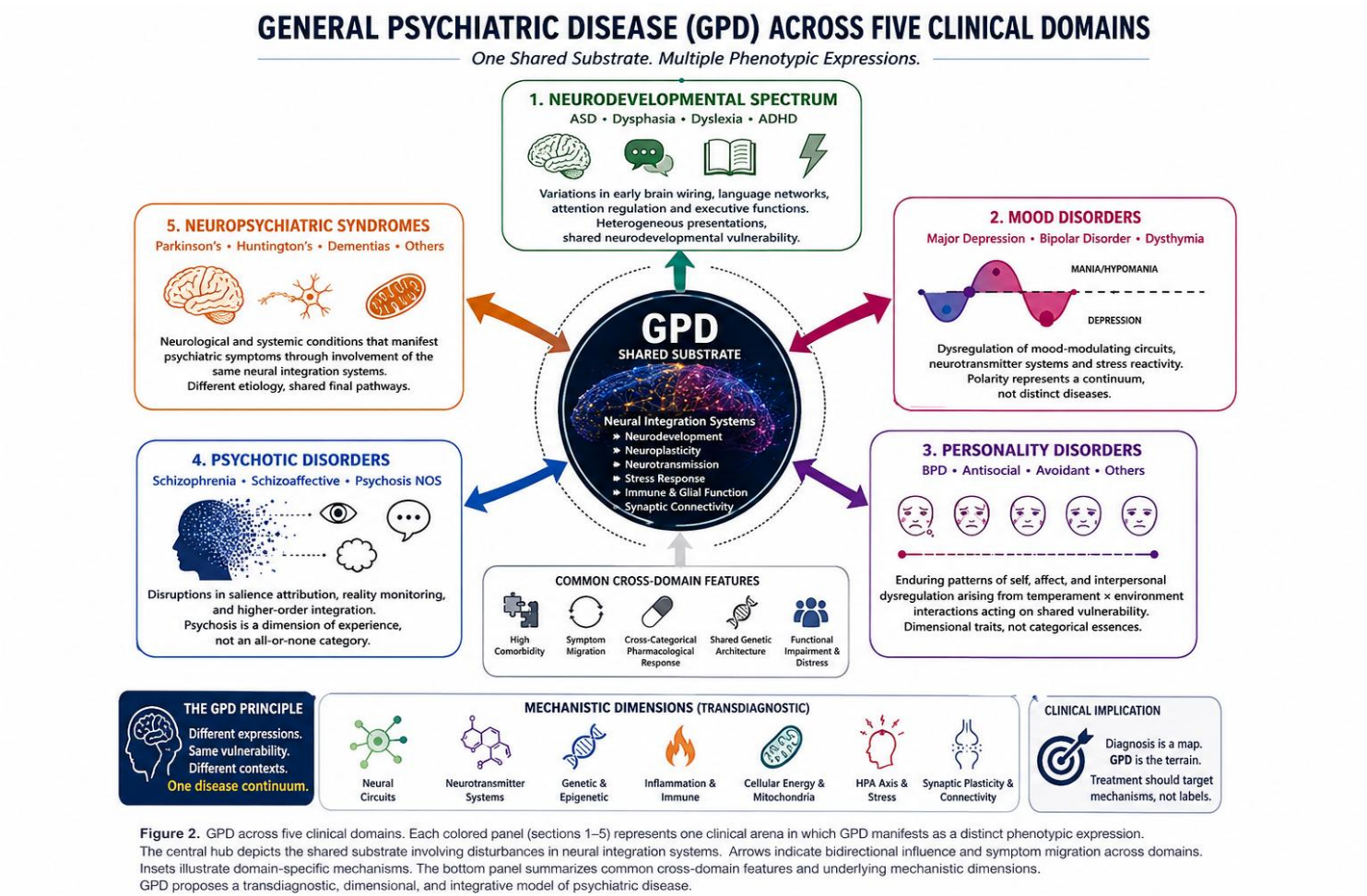

Figure 2. GPD across five clinical domains. Each colored panel (sections 1–5) represents one clinical arena in which GPD manifests as a distinct phenotypic expression. The central hub depicts the shared substrate involving disturbances in neural integration systems. Arrows indicate bidirectional influence and symptom migration across domains. Insets illustrate domain-specific mechanisms. The bottom panel summarizes common cross-domain features and underlying mechanistic dimensions. GPD proposes a transdiagnostic, dimensional, and integrative model of psychiatric disease.

Figure 2. GPO across five clinical domais
Source: The authors.

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Table 1. Transdiagnostic implications of GPD across disciplinary domains

Domain	Implication of GPD	Practical Consequence
Psychopathology	Symptoms are not disease-specific; they reflect common mechanism + contextual modulation	Dimensional symptom assessment; cross-diagnostic psychopathological research
Pharmacology	Agents modulating shared mechanisms will show cross-categorical efficacy; drug repurposing is theoretically grounded	Rational basis for off-label use; targeted development of agents on shared pathways (glutamate, neuroinflammation)
Psychotherapy	Transdiagnostic therapeutic mechanisms explain efficacy of unified protocols across diagnoses	Development of transdiagnostic protocols (UP, DBT, ACT, MBT); reduced need for disorder-specific manuals
Cognition Research	Cognitive alterations are transdiagnostic and should be primary research targets	Cognitive remediation applicable across diagnoses; cognitive outcome measures in clinical trials
Education/Pedagogy	Learning disorders, behavioral difficulties, and social cognition deficits share mechanisms with clinical psychiatric conditions	Integrated school-based early intervention; causal-cognitive stimulation over symptom management
Genetics	Genetic architecture is shared across categorical boundaries; polygenic risk confers transdiagnostic vulnerability	Pleiotropic gene discovery; familial risk counseling across diagnostic spectra
Clinical Training	Training limited to categorical diagnoses produces clinicians ill-equipped for transdiagnostic reality	Integration of GPD into residency curricula; case formulation emphasizing mechanism over category

Souce: The authors
Note: UP: Unified Protocol; **DBT:** dialectical behavior therapy; **ACT:** acceptance and commitment therapy; **MBT:** mentalization-based therapy.

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