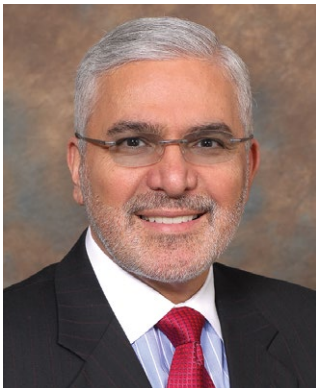
Depression and schizophrenia: Many biological and clinical similarities



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doi: 10.12788/cp.0331

Clinicians generally regard major depressive disorder (MDD) and schizophrenia as 2 separate and distinct psychiatric brain disorders. However, despite some differences, those 2 psychiatric syndromes have numerous similarities across clinical features and neurobiologic parameters.

Biological similarities

Both disorders share the following variables:

- Highly genetic in etiology but with environmental influences and epigenetics
- Associated with childhood maltreatment, abuse, or neglect
- Disrupted neuroplasticity, especially shrinkage in hippocampal volume
- Significant drop in brain-derived neurotrophic factor resulting in decreased neurogenesis
- Extensive white matter pathology across interhemispheric and intrahemispheric bundles
- Increased levels of serum cortisol, a stress hormone and inflammatory biomarker
- Hypofrontal cerebral blood flow during acute episodes of both MDD and schizophrenia
- Reduced dendritic spines (in number and size) and impaired experiential neuroplasticity
- Neuroinflammation (eg, cytokines, tumor necrosis factor-alpha, C-reactive protein) during acute episodes
- Elevated oxidative stress biomarkers, indicating an increase in free radicals
- Overactive default mode network associated with ruminations in MDD and "daydreaming" in schizophrenia
- Decrease in gamma-aminobutyric acid (GABA) and its inhibitory activity, translating into dysregulation of glutamatergic pathways and other neurotransmitters
- Immune dysregulation and comorbid autoimmune disorders

Clinical similarities

- Psychotic symptoms, especially delusional thinking such as paranoia in schizophrenia and severe self-deprecation in MDD
- Significantly elevated lifetime suicide risk
- Cognitive impairment (more severe in schizophrenia across several cognitive functions)
- Similarity of depressive and negative symptoms (especially anhedonia, apathy, restricted facial expression, social withdrawal)

continued

The overlap is consistent with the emerging transdiagnostic model of psychopathology

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• Antidepressant medications improve depressive and negative symptoms (though not completely in the case of negative symptoms of schizophrenia)
• Both have treatment-resistant subtypes that fail to respond to standard therapies
• Both are associated with comorbid generalized anxiety disorder
• Both are associated with comorbid obsessive-compulsive disorder
• Both are associated with serious alcohol and drug use
• Early mortality from general medical conditions, especially cardiovascular risks due to obesity, diabetes, hypertension, dyslipidemia
• Elevated risk of dementia with aging compared to the unaffected general population
• Opioids improve MDD and psychosis (buprenorphine in MDD and morphine in schizophrenia)
• Several second-generation antipsychotic medications are approved for both MDD and schizophrenia
• Electroconvulsive therapy is effective when pharmacotherapy fails in both MDD and schizophrenia

Biological differences

• Glutamate *N*-methyl-D-aspartate receptor antagonists (eg, ketamine) improve MDD but worsen schizophrenia
• Muscarinic agonists improve psychosis but worsen depression
• High pain threshold in schizophrenia (pain insensitivity) and low threshold in MDD (in which pain is a common comorbidity)
• Cortical thinning more severe in schizophrenia
• Hippocampal atrophy is reversible with successful treatment in MDD but not in schizophrenia
• Hypofrontality is reversible with remission in MDD but not in schizophrenia

Clinical differences

• Auditory and visual hallucinations are more common in schizophrenia than in MDD
• Anosognosia is common in schizophrenia but not in MDD
• Implausible delusions are more common in schizophrenia than in MDD
• Mood-congruent delusions are more common in MDD than in schizophrenia
• Sadness, crying, pessimism, and self-deprecation are common in MDD but not in schizophrenia
• Achieving full remission is more common in MDD than in schizophrenia
• Long-acting injectable medications are available for schizophrenia but not for MDD
• Evidence-based psychotherapy, without pharmacotherapy, is more likely to be effective in MDD than in schizophrenia

A transdiagnostic model of psychopathology

The significant overlap between MDD and schizophrenia should not be surprising. They are both generated by the same organ, the human brain, with disrupted neurochemical and physiological circuits in the brain.

The overlap is also consistent with the emerging transdiagnostic model of psychopathology.[1-9] This model proposes that there is a "core" genetic risk for psychopathology with different iterations. The transdiagnostic model is in stark contrast to the prevailing DSM-5, which categorizes psychiatric disorders in "silos," as if they are completely independent from each other despite many shared features. This is highly debatable according to the substantial evidence that multiple psychiatric disorders share many genes that influence brain development in utero and predispose individuals to a variety of clinical

symptoms in adolescence and young adulthood.

The origin of mental illness is being disentangled by emerging research, which is identifying the common links among the various disorders currently listed in DSM-5.[10] However, the evolution of psychiatric diagnosis has come full circle from a single entity before DSM, to multiple entities with DSM, and now back to a unified transdiagnostic model that is rapidly emerging.[11] This has implications for the FDA's persistent dogma that clinical trials for new drugs must be targeted for 1 of the DSM-5 categories, a flawed and narrow assumption. Given the accelerating body of evidence for a unified, transdiagnostic model, it makes much more sense for the FDA to approve medications that target a psychiatric *symptom* that is shared by multiple psychiatric conditions within a transdiagnostic clinical system. When medications are approved for a symptom regardless of a DSM diagnosis, the term "off-label" and its "stigma" will then fade into history, along with the malignant preauthorization racket that was invented by greedy insurance companies that exploit the off-label use of medications (even when an FDA-approved medication for the patient's condition does not yet exist) simply to deny coverage, lower their expenses, and fatten their profits.

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The evolution of psychiatric diagnosis has come full circle, back to a unified transdiagnostic model

References

1. Goodkind M, Eickhoff SB, Oathes DJ, et al. Identification of a common neurobiological substrate for mental illness. JAMA Psychiatry. 2015;72(4):305-315.
2. Caspi A, Moffitt TE. All for one and one for all: mental disorders in one dimension. Am J Psychiatry. 2018;175(9):831-844.
3. Krueger RF, Easton NR. Transdiagnostic factors in mental disorders. World Psychiatry. 2015;14(1):27-29.
4. Hyman SE. New evidence for shared risk architecture for mental disorders. JAMA Psychiatry. 2019;76(3):235-236.
5. Selzam S, Coleman JRI, Caspi A, et al. A polygenic p factor for major psychiatric disorders. Translational Psychiatry. 2018;8(1):205.
6. Barch DM. What it means to be transdiagnostic and how do we know? Am J Psychiatry. 2020;177(5):370-372.
7. Nasrallah HA. Is there only 1 neurobiologic psychiatric disorder with different clinical expressions? Current Psychiatry. 2015;14(7):10-12.
8. Nasrallah HA. Pleiotropy of psychiatric disorders will reinvent DSM. Current Psychiatry. 2013;12(4):6-7.
9. Nasrallah HA. Beyond DSM-5: clinical and biological features shared by major psychiatric syndromes. Current Psychiatry. 2017;16(10):4-7.
10. Marshall M. Roots of mental illness: researchers are beginning to untangle the common biology that links supposedly distinct psychiatric conditions. Nature. 2020;581:19-21.
11. Kendler KS. From many to one to many--the search for causes of psychiatric illness. JAMA Psychiatry. 2019;76(10):1085-1091.