

The Biology of Mental Disorders: Progress at Last

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Mental disorders are common, complex, highly morbid conditions for which basic underlying mechanisms are poorly understood. Despite the utility of many existing treatments, there remains vast unmet need for more effective and safer therapeutics. Most current medicines for mental disorders are based on chemical modifications of serendipitously discovered mid-twentieth-century prototypes, and widely used diagnostic manuals remain phenomenological and conceptually confused. After decades of stasis, research on mental disorders has reached an inflection point. Unbiased large-scale genetics provides information that, if interpreted circumspectly and integrated with neurobiology, provides “finding tools” for causal biological mechanisms that can advance discovery of biomarkers, preventive interventions, and better treatments. However, uncritically applied predictive genomic technologies can produce fatalism and exacerbate stigma. Moreover, polygenic risk scores for cognitive ability and risk of mental illness are already being offered commercially for embryo selection with in vitro fertilization, a worrisome resurgence of eugenics hiding in liberal (noncoercive) guise.

Mental disorders are highly prevalent, seriously distressing conditions that disrupt cognition, emotion, behavioral control, and physiologic functions such as sleep, appetite, and energy. Mental disorders are significant causes of disability worldwide, leading risk factors for suicide, and major contributors to other causes of premature death.¹ Mental disorders predominantly begin before age twenty. Thus, their damaging effects on cognition and behavior often interfere with education, social development, and adaptive transitions to adult independence.² The morbidity and suffering associated with mental disorders are often worsened by stigma and marginalization of sufferers, lack of services, exclusion from opportunities, and, for those with the most severe forms of mental illness, a high risk of homelessness and incarceration. Compelling social science research documenting costs and harms of mental illness has not convinced policymakers to implement cost-effective preventive and therapeutic interventions for mental disorders, as has been accomplished for some general medical disorders.³

A variety of psychotherapies, pharmacotherapies, and neuromodulatory interventions are effective for some people with mental disorders. However, even when marshaled appropriately, the efficacy of existing treatments often falls short of need and side effects may prove limiting. Further, the range of symptoms responsive to current therapeutics is too narrow, leaving many people without effective interventions.⁴ The benefits and limitations of current drug treatments can usefully be considered through the lens of antipsychotic drugs and their use in treating schizophrenia. The prototype antipsychotic drug, chlorpromazine, was synthesized in 1951 in France for its antihistaminergic properties: it binds promiscuously to multiple neurotransmitter receptors, including H1 histamine receptors and dopamine D2 receptors. Chlorpromazine was first used clinically as a pre-anesthetic by surgeon Henri Laborit. He was impressed with its physiological and sedating properties and persuaded psychiatric colleagues at La Salpêtrière Hospital to test the drug on their patients. The responses they observed – reduction of psychotic symptoms such as hallucinations and delusions – produced a seismic shift in the treatment of psychotic disorders. Within a few decades, these drugs facilitated the deinstitutionalization of people with severe mental illness. Unfortunately, underinvestment and significant policy failures undercut the promised benefits of deinstitutionalization.

The commercial success of chlorpromazine led pharmaceutical companies to develop many similar antipsychotic drugs, most often by screening for chlorpromazine-like effects on the motor behaviors of laboratory rats. These procedures identified new antipsychotic drugs by replicating in rats the Parkinson's-like side effects they also produced in humans.⁵ During the 1950s, dopamine was not yet recognized as a neurotransmitter, and it was not until 1963 that neuropharmacologist Arvid Carlsson demonstrated that the effects of chlorpromazine resulted from the blockade of dopamine receptors.⁶

There are now scores of antipsychotic drugs that block D2 dopamine receptors, differing largely in their side effects. Clozapine, an antipsychotic drug discovered in 1959, turned out to be more effective than other antipsychotic drugs for reasons that have stubbornly withstood attempts at elucidation. Despite evidence of its efficacy, clozapine was initially abandoned because in a small percentage of patients it caused a potentially fatal decrement in counts of white blood cells that fight infection. Confirmation of its unusual benefits for many otherwise treatment-unresponsive patients was demonstrated in clinical trials in the 1980s, which facilitated restoration of clozapine to clinical use, combined with required weekly blood counts. Attempts to replicate the efficacy of clozapine without its side effects gave rise to “second generation” antipsychotic drugs, now in wide use, though none has approached the efficacy of clozapine.⁷ Several antipsychotic drug candidates that block muscarinic receptors rather than D2 dopamine receptors are currently being considered for regulatory approval.

Antipsychotic drugs are not specific, mechanism-based treatments for schizophrenia; rather, they effectively reduce psychotic symptoms associated with many conditions, including bipolar disorder, depression with psychotic features, Alzheimer's and Parkinson's diseases, and drug-induced psychoses. The blockade of D2 dopamine receptors by antipsychotic drugs represents their initial molecular interaction in the brain. Their full therapeutic mechanism – that is, the steps beyond D2 receptor binding by which they diminish psychotic symptoms – remains unknown. Without deeper understandings of the mechanisms underlying disorders and their symptoms, the pharmaceutical industry must rely on “black box” screens informed by the properties of existing drugs, a process not likely to identify novel treatments. This unfortunate situation contrasts with scientifically more mature fields, such as oncology, in which excisional biopsies have given investigators direct access to diseased tissue. Large collaborative projects have sequenced the genomes of many cancer cells (which are replete with acquired mutations) obtained from biopsies, yielding knowledge of “driver” mutations that play causal roles in many types of cancers.⁸ This knowledge has made it increasingly possible to replace broadly cytotoxic chemotherapies with monoclonal antibodies targeted at protein products of the mutated genes. In contrast to studies of cancer and other organ pathologies, psychiatry lacks access to living brain tissue for both ethical and medical reasons.

For people with schizophrenia, antipsychotic drugs typically produce good responses when administered during a person's first few psychotic episodes, but over time, the benefits typically wane, leaving many individuals with chronic schizophrenia suffering residual psychotic symptoms and significant relapses despite treatment. Notwithstanding such limitations, there is good evidence that appropriately administered antipsychotic drugs improve outcomes.⁹

But the side effects of antipsychotic drugs are often severe. Motor side effects caused by blockade of dopamine D2 receptors are distressing and impairing; tardive dyskinesia, a form of abnormal involuntary movements associated with long-term dopamine D2 receptor blockade, is persistent and may be irreversible. Other side effects, especially associated with second generation antipsychotic drugs, include significant weight gain and metabolic derangements including hyperglycemia and hyperlipidemia. Overall, the poor tolerability of antipsychotic drugs leads many people to stop taking them, often at the cost of relapse.¹⁰

Most important, antipsychotic drugs offer no benefit for the progressive cognitive impairments and negative (deficit) symptoms that represent the foremost causes of disability in schizophrenia. Cognitive and negative symptoms typically begin during teen years, generally antedate the onset of psychotic symptoms by months or years, progressively worsen over time, and are strongly associated with poor outcomes.¹¹ A highly compelling need exists for treatments that would prevent or at least significantly ameliorate the cognitive and negative symptoms

of schizophrenia, but to date, all attempts at discovery have failed. While such a hoped-for intervention would likely involve a medication or neuromodulatory therapy administered to the “right” patients identified by biomarkers, full efficacy might be expected to require a companion psychotherapy aimed at producing adaptive neural plasticity to support cognitive remediation.¹² A similarly pressing need exists for better treatments for bipolar disorder, depressive and anxiety disorders, obsessive-compulsive disorder, anorexia nervosa, and other mental disorders.

The pharmaceutical industry long profited by making incremental modifications to compounds descended from the serendipitously discovered prototype antipsychotic and antidepressant drugs. The resulting medications are often safer and more tolerable than earlier compounds or, in the case of antipsychotic drugs, offer different side effect profiles. However, the newer drugs do not deliver material improvements in efficacy.¹³ Certainly, no second-generation antipsychotic drug matches the efficacy of clozapine. This incremental pattern is illustrated by the selective serotonin reuptake inhibitors (SSRIs), of which the first approved was fluoxetine (1987 in the United States). The SSRIs and related serotonin-norepinephrine reuptake inhibitors (SNRIs) rapidly displaced the older, more toxic, and less tolerable tricyclic antidepressants and monoamine oxidase inhibitors in high-income countries. However, the newer drugs offered no advance in efficacy or speed of onset.¹⁴ Recently, an older anesthetic drug, ketamine, an NMDA (N-methyl-D-aspartate) glutamate receptor blocker, has been repurposed as a rapidly acting antidepressant and gained FDA approval. Over time, governments and insurers have begun to resist paying for new, expensive, and heavily marketed drugs that have no demonstrable advantages in effectiveness over less costly generic drugs. Unfortunately, a clear scientific path to discovery of more effective antidepressants has not been charted. Further, for lack of biomarkers and mechanistic insight, psychiatric drug candidates have the highest failure rates of any drugs in the large, expensive late-stage clinical trials that are required for regulatory approval. Thus, despite recognition of the high prevalence and vast unmet need for better treatments, the industry has, for the last two decades, deprioritized discovery efforts in psychiatry, investing instead in cancer, autoimmunity, and metabolism research, where more mature science affords greater opportunity for success.¹⁵

Given the pressing need for better therapies, we must ask why progress has been so slow. The most significant impediments are the staggering complexity of human brains, their profound heterogeneity, and their general inviolability with respect to obtaining tissue in life. Because of significant inter-individual differences at every level of brain organization – ranging from patterns of

gene expression in neurons and glial cells to synaptic networks to patterns of computation underlying cognition and behavior – identification of illness-associated pathology is often masked by normal background variation. The heterogeneity of human brains reflects the variability of human genomes, which contain tens of millions of differences in their nucleotide sequences, the diversity of environmental exposures, and the many stochastic events that affect brain development, maturation, and adaptation.¹⁶ The resulting heterogeneity of brain structure and function underlies much of the rich temperamental, cognitive, and behavioral diversity of human beings – and differential susceptibilities to mental disorders. Because psychiatric diagnoses are based on phenomenology, such brain differences portend clinically significant differences among individuals who appear to be suffering from the same disorders. The lack of well-supported biomarkers means that patient-oriented studies, ranging from neuroimaging to clinical trials, unwittingly contain participants who are similar in surface characteristics but not in underlying causal mechanisms. As a result, even when large sample sizes are employed, many clinical studies yield modest effects that fail to translate to the clinic. Many studies simply fail to replicate.

While the complexity and heterogeneity of genomes, exposomes, and brains create high hurdles for research on mental disorders, human efforts at diagnostic classification have made a difficult situation worse. Diagnostic classification matters for research because disorder definitions determine who is included in study cohorts for genetics, imaging, and clinical research. Diagnoses matter for classification of biological samples, including brains used in postmortem studies, and even for assessment of putative animal models.¹⁷

The current, widely used diagnostic classification developed by the American Psychiatric Association, the *Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition, Text Revision* (DSM-5-TR), reflects historical decisions made in the paradigm-setting third edition, DSM-III.¹⁸ DSM-III, published in 1980, prioritized inter-rater agreement (reliability) in diagnosis despite the contemporaneously understood impossibility of scientifically validating those diagnoses at the time.¹⁹ Scientifically premature promulgation of a shared diagnostic language has had the perverse effect of guiding clinicians and researchers to rely on a classification grounded in the science of the 1960s and 1970s: that is, prior to the advent of molecular biology, modern human genetics, the coalescence of neurobiology as a field, or such technologies as magnetic resonance imaging (MRI).

Given a lack of objective diagnostic tests – unfortunately still the case – a reasonable, if necessary, choice was made by the “descriptive psychiatrists” of the 1960s to ground diagnosis in patient-reported symptoms, course of illness, and clinical observation. The diagnostic limitations inherent in phenomenology were unfortunately worsened by contingent decisions made in developing DSM-III. With scant evidence and breathtaking arrogance, the DSM-III task force divided

psychopathology into 265 narrowly defined categorical diagnoses – a number that increased in later editions – with each diagnosis conceptualized as being qualitatively discontinuous from health and from each other. The DSM-III developers rejected or ignored substantial contemporaneous evidence that mental disorders might be better understood as quantitative deviations from health in analogy with almost all other chronic noncommunicable diseases like hypertension, type 2 diabetes mellitus, or osteoarthritis. Instead, DSM-III is based on discontinuous categories, as if mental disorders were more like acute infectious diseases such as influenza.²⁰ As a result, in Procrustean fashion, the DSM imposes arbitrary boundaries between illness and health, and between its myriad different disorders. Oddly, the resulting categories are too narrow and too broad at the same time. They are too broad because they group heterogeneous patients together. They are too narrow because, in carving psychopathology into nearly three hundred slices, the DSM imposes unnatural categorical boundaries on broad symptom spectra. This problem is evidenced by the high frequency with which patients receive multiple successive or contemporaneous diagnoses (comorbidity) for the shifting manifestations of what is almost certainly a single underlying pathological process.²¹ Symptoms change over the life course, reflecting brain development, aging, and the accrual of new exposures including life experience.²² The pervasiveness of comorbidity, together with the recent discovery that many DNA sequence variants are shared among putatively distinct DSM disorders, provides evidence that the current nosology is substantially in error and that alternatives are needed.²³ It would be a fool's errand to attempt to discover or validate biological markers using today's fictive DSM categories as a gold standard.

Given limitations on invasive anatomic or physiological studies of human brains, noninvasive tools such as structural and functional magnetic resonance imaging, positron emission tomography, electrophysiology, and magnetoencephalography have been widely used to study mental disorders. The complexity and heterogeneity of brain structure and function, especially when parsed into the unnatural groupings introduced by DSM diagnoses, have defeated attempts to identify robust case-control differences that replicate across patient cohorts and laboratories. Except for excessive cerebral cortical thinning in schizophrenia spectrum disorders (with convergent confirmation from postmortem studies), few if any differences identified by imaging have replicated with adequate effect size to be clinically meaningful. Thus, except when ruling out a neurological disorder, noninvasive neuroimaging has no current role in psychiatric practice, whether for diagnosis or to follow treatment effects. These failures rest to some degree on limitations in the resolution of current technologies. To a greater degree, they reflect the difficulty of determining which differences observed in imaging studies are replicable characteristics of a meaningful patient group dis-

tinct from normal background variation. Task-dependent studies are complicated further by the normal diversity of cognitive and behavioral “strategies” implemented by different human brains.²⁴ Large international consortia have formed to share and meta-analyze imaging data on the premise that greater statistical power, especially with help from machine learning, might overcome multiple sources of heterogeneity.²⁵ Unfortunately, structural and functional brain heterogeneity are so pervasive and diagnoses so poor that even large consortial efforts might still fall short until armed with robust diagnostic biomarkers complementary to the imaging methods used.

Problems with heterogeneity are not limited to psychiatry. Across all areas of medicine, unacceptable variability in treatment response has given rise to an aspirational goal often denoted as “precision medicine.” The goal is to match patients with the treatments that are most likely to help them based on predictive use of genetics and biomarkers. Early intimations of success have come from oncology. Traditional cancer diagnoses based on tissue of origin (such as lung cancer) are giving way to diagnoses based on “driver” somatic mutations and cell types. Large-scale longitudinal cohort studies are underway with the goal of producing knowledge for “precision” approaches across broad domains of medicine. For example, the UK Biobank links the electronic medical records of its half-million participants with their whole genome sequences, biochemical measures, cognitive tests, biological fluid and tissue samples stored in biorepositories, and, for a large subset of participants, imaging studies of their brains, hearts, and abdomens.²⁶ Data can be shared among scientists worldwide in a manner designed to protect individual privacy. Psychiatry shares the aspiration for more effective treatments targeted to appropriate individuals, but notwithstanding occasional overclaiming, meaningful “precision psychiatry” remains a distant goal.

Many basic discoveries about brain and behavior have suggestive relevance to the biology of mental disorders. However, twentieth-century biological psychiatry lacked the tools and technologies necessary to gain significant empirical traction on mental disorders. Thus, neurobiological hypotheses concerning psychiatric disorders were often based on plausibility and speculative inferential leaps rather than ground truth. In this context, intellectually weak constructs such as “face validity” – the extent to which a model plausibly *appears* to reflect characteristics of the disease – were used to justify many putative animal models, but these typically produced phenocopies that, despite appearances, did not capture the human mechanism of illness. Excessive reliance on face validity led psychiatric treatment development into an intellectual cul-de-sac.

Inspired by the discoveries of antipsychotic and antidepressant drugs, biological psychiatry embraced models of brain function and mental disorders based on the reverse engineering of drug actions.²⁷ Thus, many studies nominated mono-

amine or amino acid neurotransmitters, their receptors, or their postreceptor signaling pathways for central roles in pathogenesis of psychiatric disorders. The highly reductive models that resulted foundered on the unrecognized complexity and heterogeneity of human brains, and progress in discovering new treatment mechanisms or improving treatment efficacy stalled. To generate meaningful, testable hypotheses and disease models, what was needed was a transparent and principled method of associating neurobiological findings with mental illness phenotypes. This need was ultimately met by unbiased, large-scale genetics. Increasingly, results from psychiatric genetics can be interpreted in light of relevant multiomic datasets from the neural cells and postmortem brains of people who were affected or unaffected by particular psychiatric disorders. These include epigenomics (which captures the state of chromatin across the genome), transcriptomics (the full catalog of RNAs expressed in any cell type or brain region), and connectomics, among others. Such unbiased large-scale datasets provide insight into neurobiology at the genomic scale needed to interpret genetic associations.

In 1965, psychiatrist Joseph Schildkraut proposed a catecholamine hypothesis of mood disorders based on the pharmacology of noradrenergic antidepressants.²⁸ Schildkraut appropriately noted the absence of key data: evidence for altered catecholamine levels in drug-free individuals as they moved from healthy to depressive states and changes in levels associated with successful treatment. Multiple studies subsequently measured levels of catecholamines and their metabolites in blood, cerebrospinal fluid, and urine, but never found strong, reproducible evidence of changes that correlated with mood states. Following the introduction of SSRIs, a focus on serotonin, another monoamine, crowded out work on norepinephrine, but the evidence for serotonergic mechanisms of mood disorders was no better. Despite later recognition that the efficacy of monoaminergic antidepressants is rather modest, monoamine theories of mood disorders have retained currency in biological psychiatry.²⁹ Undeterred by the lack of evidence, pharmaceutical companies popularized the impoverished idea of depression as a chemical imbalance among neurotransmitters to be rectified by their products.

A similarly naive belief held that the molecular basis of mental disorders would rest on a handful of familiar genes – many inferred from pharmacology – although these represented only a small fraction of the human genome. This belief led many researchers in the 1990s to apply “candidate gene” approaches to psychiatric disorders. In this statistically infirm methodology, a single polymorphism within a candidate gene would be tested for association with a chosen phenotype. In the face of failure, related phenotypes were often exchanged for each other in a search for nominal statistical significance, typically without recognizing the need to correct for multiple testing procedures. This approach was thought by its proponents to be an efficient way to shortcut the large, unbiased genetic studies that ultimately proved necessary. Even though the candidate-gene and the close-

ly related candidate-gene-by-candidate-environment approaches have been thoroughly discredited, many of their false claims of discovery persist in psychiatry and psychology textbooks.³⁰

By the late 1990s, clear-eyed observers recognized that for psychiatry, hypothesis-driven attempts to discover causal associations between mental disorders and biologically selected candidate genes had failed because we simply did not know enough. Psychiatry shared with all medical disciplines a need for a robust methodology to identify causal connections between disease phenotypes and biological mechanisms that did not rely on existing biological knowledge. As noted above, the answer lay in unbiased, large-scale genetics.

Genetics has a unique place in biology because it yields causal information. DNA sequences are fixed at fertilization, prior to any developmental processes or exposures. As a result, a statistically rigorous association of a trait with a specific DNA variant (an allele) can be inferred to be causal rather than caused. All other biological associations with a disease or other trait might represent causes, effects, adaptations, or, for diseases, treatment effects. However, it is important to interpret genetics results circumspectly. For example, an early study of lung cancer genetics found what appeared to be an association with the gene encoding the alpha5 subunit of nicotinic acetylcholine receptors. In this case, it was clear that confounding had occurred because of the high prevalence of nicotine dependent smokers in the lung cancer cohort. The alpha5 subunit gene did play a causal role, but for the risk of smoking, not molecular mechanisms of carcinogenesis.³¹ Sources of confounding in human genetics are often far less obvious.

The genetic basis of almost all cognitive and behavioral traits, including the vast preponderance of risk for psychiatric disorders, reflects the additive effects of many alleles of small effect. Among affected individuals, the genetic component of risk results from the chance inheritance of a small subset from among the thousands of common risk-associated variants segregating in populations. For a tiny fraction of people with schizophrenia, bipolar disorder, and perhaps other psychiatric disorders (likely <1 percent), ultrarare variants of large effect, albeit not fully penetrant, significantly increase risk. To discover the genes that contribute to risk of psychiatric disorders, it was necessary to detect many small signals against the noisy background of human genomic variability. This only became possible with the arrival of technologies and computational tools developed in association with the Human Genome Project (1990–2003). These technologies permitted the efficient and financially affordable study of the very large samples (thousands to tens of thousands of affected and unaffected individuals) needed for the unfavorable signal-to-noise relationship of psychiatric genetics. The detection of ultrarare variants had to wait longer for improvement in the efficiency and cost of DNA sequencing. Since the second decade of the twenty-first century, human genetics researchers have discovered many thousands of DNA sequence variants associated

with diverse traits, including risk of psychiatric disorders using case-control association studies. These include genome-wide association studies (GWAS) calibrated to detect common variants of small effect, as well as whole-exome (sequencing of all protein-coding genes) and whole-genome sequencing studies needed to identify ultrarare variants. Genome-wide association studies have proven extremely successful for many diseases and traits across all medical and population genetics, including psychiatric genetics.³² I will focus the discussion that follows on schizophrenia as an exemplary disorder seen through the lens of modern genetics and select areas of neurobiology.

In 2009, the International Schizophrenia Consortium (ISC), a forerunner of the Psychiatric Genomics Consortium (PGC), performed a genome-wide association study on what was thought to be a large genetic sample: 3,322 individuals affected by schizophrenia and 3,587 controls.³³ The sample turned out to be far too small to identify genome-wide significant associations, although it did implicate a locus on chromosome 6 in schizophrenia, a finding later confirmed by larger studies.³⁴ This locus was subsequently found to harbor a gene encoding complement factor 4A (C4A), with significant implications for the direction of schizophrenia research.³⁵ The ISC study reported that genetic risk for schizophrenia and bipolar disorder overlapped, which proved to be a harbinger of widespread sharing of risk alleles across psychiatric disorders.³⁶ The study also formally demonstrated that genetic risk for both schizophrenia and bipolar disorder is highly polygenic (resulting from the additive effects of many genetic variants), and introduced polygenic risk scores to human genetics.³⁷

The most recent schizophrenia GWAS conducted by the PGC analyzed DNA samples from 76,755 individuals affected by schizophrenia and 243,649 unaffected control subjects. With more advanced technology, better computational resources, and the ability – based on collaboration – to study and meta-analyze data from multiple cohorts, this study found more than 250 independent genome-wide significant loci associated with schizophrenia, and presumptively implicated 120 genes in schizophrenia pathogenesis.³⁸ A significant fraction of the implicated genes indicates an important role in schizophrenia for the structure, development, and plasticity of synapses, albeit with many remaining unknowns that will require additional discoveries and advances in computational modeling across multiple scales in the brain.³⁹ Genome-wide association studies for bipolar disorder, major depressive disorder, autism spectrum disorders, and many other mental disorders are also yielding new biological insights.⁴⁰

As noted, a small minority of people affected by schizophrenia and bipolar disorder have genetic loading not only for common variants of small effect but also for ultrarare variants within protein-coding regions of the genome. All the ultrarare variants associated with schizophrenia and bipolar disorder discovered

to date exert their large effects on disease risk by disrupting the synthesis of a vital protein. Whole exome sequencing of 24,248 individuals with schizophrenia and 97,322 unaffected individuals identified ten such ultrarare protein disrupting variants.⁴¹ The ultrarare variants associated with schizophrenia cause loss of function (LoF) of one of the two copies of the affected gene that each person carries. An additional ultrarare LoF variant, AKAP11, was discovered in a large study of bipolar disorder.⁴² Consistent with genetic sharing across disorder phenotypes, AKAP11 was found to be associated with schizophrenia in other individuals.

Many of the ultrarare variants discovered so far converge with small-effect common variants on the same biological processes.⁴³ The importance of such convergence for biological experiments can be illustrated by the schizophrenia-associated gene GRIN2A, which encodes a subunit NMDA glutamate receptor. Ultrarare LoF variants affecting GRIN2A increase the risk of schizophrenia by approximately twenty-fold, whereas a common variant affecting GRIN2A increases the risk of schizophrenia by only 1.07-fold. The ultrarare variant leads to a marked reduction in the amount of receptor subunit protein in the nervous system. The common variant is found within the noncoding genome, like approximately 90 percent of GWAS associations across all of biology. The best-known function of the noncoding genome is to regulate the expression of RNAs and proteins. Thus, the common variant presumably regulates expression of the GRIN2A gene and has a far more modest effect on NMDA receptors in the brain than the ultrarare LoF variant.

From an experimental point of view, ultrarare variants have the benefit of providing better tools or studying disease mechanisms than common variants that exert small effects on gene regulation. Effects of LoF variants can be modeled by knocking out one of the two copies of the gene in a mouse or other model organism or in genetically diverse human induced pluripotent stem cell (iPSC) lines. Alternatively, iPSC lines can be obtained from individuals with schizophrenia or unaffected individuals who carry ultrarare variants of interest. iPSCs can readily be reprogrammed into many different types of neurons, glial cells, or other cells. They can be grown alone or be mixed with other cells to study cell-cell interactions including synapse formation. Alternatively, they can be coaxed to develop over months into self-organizing brain organoids that contain hundreds of different neural cell types.⁴⁴ Human cellular models are scientifically critical because they permit genetic variants of interest to be studied against diverse human genetic backgrounds derived from individuals with and without the illness under study. This is important because single-variants – even high-impact LoF mutations – do not, by themselves, cause schizophrenia or bipolar disorder.

With appropriate informed consent procedures and privacy protections, pluripotent stem cell lines can be linked to a person's medical and other records and thus studied in the context of their disease status and treatment responses. Mod-

ern cohort studies like the UK Biobank permit participants to be recontacted, thus facilitating new rounds of phenotyping as new hypotheses are formulated.⁴⁵ Studies using iPSC cell lines from individuals in such cohorts can identify genetic variants that modify the effects of strong-effect alleles like the GRIN2A LoF variant, including alleles that are protective.

What have we learned about schizophrenia and other mental disorders in the fifteen years since the advent of modern psychiatric genetics and new, relevant technologies?⁴⁶ How might such discoveries lead to better diagnostics and better treatments? One illustrative place to begin is the discovery that the gene encoding complement factor C4A is associated with schizophrenia.⁴⁷ An important caveat is that schizophrenia, like all psychiatric disorders, is highly polygenic. This means that many alleles contribute to risk, along with nongenetic risk factors, and that no one gene is either necessary or sufficient for illness. That means no one gene can be diagnostic on its own. Thus, individuals may suffer from schizophrenia despite carrying low-risk alleles of C4A, while some others are unaffected despite carrying high-risk alleles. Such unaffected individuals may lack much additional loading for genetic risk or may have protective alleles or benefit from protective nongenetic factors. In the search for biological insight, genetics serves as an unbiased “finding tool” for causal associations of a disease (or other trait) with biology, such as certain molecules, molecular pathways, cell types, or mechanisms. When used as a tool to associate a trait with biology, the effect size of the allele on the ultimate phenotype does not matter. (As noted, however, effect size is important for the design of experiments, such as the construction of cellular or genetically engineered animal models.) Similarly, what makes a gene product a good drug target is not the effect size of the associated allele, but its overall role in biology. The importance of LDL cholesterol as a risk for coronary artery disease was initially learned epidemiologically from the Framingham heart study.⁴⁸ Genetic studies that implicated the LDL cholesterol receptor in atherosclerotic heart disease served to focus attention on the cholesterol biosynthetic pathway. Once a pathway is shown to play a causal role, it can be exploited for biomarkers (such as serum LDL cholesterol levels) and therapeutic targets for drugs, antibodies, or other modalities. The rate-limiting enzyme in the cholesterol biosynthetic pathway, HMG-CoA reductase, is the target of the highly effective statin drugs because of its biochemical role in the pathway. It does not matter that the gene that encodes HMG-CoA reductase is linked to a common SNP with a vanishingly small effect on overall risk of coronary artery disease. What matters is that convergent evidence from epidemiology and genetics identified a causal pathway that could be exploited for effective therapies.

C4A acts within the classical complement cascade, a component of the innate immune system, which is the body’s first line of defense against infectious agents

and abnormal cells. Prior to the discovery of a genetic association with schizophrenia, the complement cascade was not suspected to play a role in mental illness. The association of the C4A gene with schizophrenia illustrates the benefit of unbiased discovery science in that it permits surprises and thus opens new avenues of investigation. Complement proteins were known to mark bacteria, virally infected cells, and cancer cells for destruction by cells such as macrophages, components of the immune system that remove unwanted cells and substances by engulfing them (phagocytosis). In the brain, the classical complement pathway has been shown to mark weak synapses for elimination (pruning) by microglia (the major phagocytic cells of the central nervous system) during brain development, experience-dependent plasticity, and neurodegenerative disorders.⁴⁹ Thus, the association of C4A with schizophrenia raised the possibility that synapse elimination might be involved in pathogenesis.

Inappropriate and excessive synaptic pruning had been hypothesized to be a potential mechanism of schizophrenia pathogenesis by Dr. Irwin Feinberg in 1982, but the idea gained little traction and his paper was rarely cited.⁵⁰ Feinberg noted that schizophrenia typically begins during adolescence, a period during which brain maturation produces a characteristic wave of synaptic reorganization and synapse elimination in the prefrontal and temporal cerebral cortex. Feinberg was aware of a postmortem study of infants and children in the 1970s that showed net synaptogenesis in the cerebral cortex in early childhood, reaching a maximum at about age ten, followed by net synapse loss.⁵¹ Brain development involves such waves of experience-dependent synaptic plasticity that results in fewer, stronger synapses, and reorganized, more-efficient synaptic networks. The refinement of synaptic networks begins in the first years of life in occipital regions of the cerebral cortex, where it results in binocular vision, the process through which the brain combines the complex mix of input signals from both eyes to create one image of the world. A key mechanism of synapse elimination involves the marking of weak synapses by complement proteins, leading to engulfment by microglia and other glial cell types. Following the discovery that the C4A gene is associated with schizophrenia, researchers found that postmortem brain tissue from people diagnosed with schizophrenia have higher average levels of C4 messenger RNA than unaffected individuals.⁵² In living people with schizophrenia, a subset has elevated levels of C4 protein in the cerebrospinal fluid compared with unaffected control subjects. It is hypothesized that in association with other risk factors such as variations in synaptic proteins, as suggested by schizophrenia genetics, elevated levels of complement proteins might contribute to excessive and inappropriate synaptic pruning.

Because normal brain maturation results in net synapse elimination, longitudinal studies of typically developing adolescents reveal reductions in cortical thickness. However, individuals who develop schizophrenia show more rapid

and severe patterns of cortical thinning.⁵³ Such findings from structural neuroimaging, which have been corroborated by postmortem studies, converge on the conclusion that people affected by schizophrenia have greater net reductions in synapse numbers and the dendritic spines that bear them than unaffected individuals. The pattern of cognitive deficits observed in schizophrenia, such as prominent impairments of working memory and executive function, map to the prefrontal cortex where cortical thinning is most severe.⁵⁴ It is further hypothesized that psychosis is a downstream result of excessive synapse loss and synaptic dysfunction that leave the brain unable to process information and of abnormal reorganization of remaining synaptic networks. If this is correct, the psychotic symptoms of schizophrenia would have a similar basis to the psychotic symptoms that occur in Alzheimer's and other neurodegenerative disorders, in which synapse loss is a proximate cause of cognitive decline that occurs well before the cell death that is characteristic of neurodegeneration but not schizophrenia.

The proposed cascade from genes to synapse elimination as a mechanism of schizophrenia pathogenesis is, of course, no more than a hypothesis with many outstanding questions. Grounded as it is in genetics and neurobiology, it is now being investigated and its predictions tested in patient samples, patient-derived iPSC lines, and transgenic animals carrying strong-effect variants associated with schizophrenia and bipolar disorder. Using new technologies, studies of gene expression (based on mRNA sequencing) and epigenomics are being performed by multiple laboratories using postmortem brains from affected and unaffected individuals.⁵⁵ Genetically informed attempts to discover biomarkers, critical for future clinical trials and early detection, are underway in young adults diagnosed with the clinical high-risk state for schizophrenia and in people recently diagnosed with a schizophrenia spectrum disorder. A critical goal of such investigations is to identify pathogenic mechanisms in detail and to precisely identify molecular pathways that can be modified to intervene in disease processes, with the goal of prevention and treatment. For all therapeutics development, mechanistic insights are also central to the discovery of biomarkers to match affected individuals with treatments, and to monitor disease progression, drug action, and treatment response. For schizophrenia prevention or early intervention, biomarkers are critical: the risks inherent in altering trajectories of brain development are such that accurate, contemporaneous biological monitoring will be very important.

Genetics plays a critical role in associating traits – here, schizophrenia – with biological hypotheses. Given associations based on well-powered and unbiased human genetics, funding agencies and laboratories, many outside of psychiatry departments, are willing to invest in substantial efforts at hypothesis testing. Genetics and neurobiological hypothesis testing are still in their early stages – any claims of scientifically durable findings would be premature. Yet, unlike the early decades of biological psychiatry, in which needed tools and knowledge did not yet

exist, this is not likely a false dawn. No longer a laggard, the strongest components of psychiatric research are collaborating closely with other fields of medicine and biology. Indeed, some of the cutting-edge technology in wide use was developed in laboratories focused on psychiatric disorders.

Genetics is not only a critical discovery tool for biology but also for risk prediction. Genetic risk prediction is widely familiar when it comes to fully dominant or recessive (Mendelian) traits such as Huntington's disease (dominant) or cystic fibrosis (recessive). However, even potentially harmful mutations of single genes often produce significant complexities for interpretation. For example, mutations in the cancer suppressor gene *BRCA1* are associated with elevated risk of breast and ovarian cancer; however, the degree of risk, if any, for a particular person depends on the precise mutations in *BRCA1* and on modifier genes in the person's polygenic background. Mental disorders are far more complex: they are polygenic, even when a person carries an ultrarare strong-effect variant. The causal relationship of individual common-risk variants to cognitive, behavioral, and psychopathology-related traits are, for the most part, indirect, dependent on complex gene networks, and still poorly understood. Complicating matters further, many alleles contribute to multiple different traits (pleiotropy) by acting within different gene networks in different cell types, although at least some apparent pleiotropy results from DSM-based diagnostic misclassification.

For polygenic traits such as mental disorders, genetic contribution to an individual's risk arises probabilistically from the person's genetic loading for risk alleles. These are a stochastic "grab bag" drawn from among the thousands of risk alleles segregating in the population and resulting from the shuffling and distribution of alleles from the genomes of both parents during meiosis. Ultimately, the genetic component of risk interacts with stochastic developmental effects and environmental exposures to determine phenotype. Risk prediction from individual alleles is not possible for mental disorders: the connections of alleles to traits are too complex and indirect, and the odds ratios conferred by individual variants do not add up to fate. It is, however, possible to make statistical predictions of risk based on the sum of all known trait-associated variants of small effects and calculated as polygenic scores (PGS). A PGS is derived from a person's genotypes across the entire genome and represents the sum of the effects of trait-associated SNPs, each weighted for its effect size.⁵⁶ A PGS is not only probabilistic, but as it is based on GWAS and thus, as now constructed, does not capture rare genetic variants, it is also at best a partial predictor of genetic contributions to a trait. In addition, for most traits and most human populations, the best available GWAS is still relatively small – if existent at all. As a result of these limitations, PGS are not accurate independent risk predictors for individuals. A PGS can be used to show where a person's risk for a trait – including a disease trait – stands with respect to an appro-

appropriate comparator population matched for ancestry. A person's relative risk in the population is often displayed as a percentile, which represents pseudoprecision at present. It is, however, possible to determine whether a person is at slightly or significantly greater or lower risk than average for their population. Because most studies of medical genetics have been performed in European populations based on convenient, well-documented registries, PGS for non-Europeans are currently less predictive than for Europeans.⁵⁷ Especially as clinical use of PGS is being proposed in some areas, such as coronary artery disease risk, the lack of population diversity in medical genetics represents a new source of health disparities that urgently needs to be addressed.⁵⁸

Somatic gene therapy, including gene editing and base editing, are becoming a reality, with many gene therapies either approved by regulatory authorities (such as for spinal muscular atrophy) or in development. In contrast, heritable germ-line gene therapy is explicitly forbidden in most countries: its safety and effectiveness remain to be established and, more important, the ethical and policy concerns raised by making heritable changes in the human gene pool deserve extensive reflection and discussion. However, embryo selection based on pre-implantation genetic diagnosis (PGD) is already approved and widely practiced in association with *in vitro* fertilization. *In vitro* fertilization (IVF) generally produces multiple viable embryos; PGD can be used to avoid implanting an embryo with a severe genetic or chromosomal abnormality, including one that might have been introduced during the fertilization process. Families carrying mutations for severe monogenic disorders such as Huntington's disease or familial forms of amyotrophic lateral sclerosis (ALS) may use IVF with PGD precisely to avoid passing these severe lethal diseases to the next generation.

In addition to these generally accepted applications of PGD, several companies have begun to offer embryo selection for complex traits in collaboration with IVF clinics. This form of risk prediction relies on polygenic scores derived from GWAS of embryonic DNA sometimes supported by GWAS results from the parents.⁵⁹ Risk prediction has already been offered for a variety of genetically complex conditions, such as coronary artery disease, idiopathic short stature, type 2 diabetes, and schizophrenia. Through their websites, these companies have also offered to customers PGS-based selection for educational attainment (prediction of probable years of schooling) and cognitive ability, with the potentially disingenuous claim of preventing intellectual disability. Different services have appeared and disappeared on different company websites, but once GWAS results from an embryo are known, they can be used to derive a PGS for any traits for which a large enough GWAS has been performed in the relevant population. Several technical concerns limit the true (not advertised) utility of embryo selection based on polygenic scores.⁶⁰ These include the lower expected genetic diversity of embryos derived from two parents compared with broad population estimates, the important

problem of pleiotropy, and the dearth of information to guide choices currently in non-European populations. Because of poorly understood pleiotropy, selection against several mental disorders, such as bipolar disorder, obsessive compulsive disorder, anorexia nervosa, and autism spectrum conditions, may also select against creativity, cognitive abilities, academic attainment, and academic achievement (measured using grades in college).⁶¹ Conversely, selecting for cognitive ability and academic attainment may also select for some of these conditions. What is important is that these traits share alleles; the identity of the shared alleles is currently unknown; and the possibility of getting results opposite to what is desired cannot be judged at present. Even if we imagine a time when such technical issues can be managed, familial and broader societal risk of embryo selections for complex traits remains. Most worrisome, perhaps, is the creeping normalization of eugenics in liberal (noncoercive) form. That risk warrants extensive discussion within civil society and among health care professionals and policymakers. What is the concern? Advertised and actual selection against misunderstood or disfavored traits can worsen stigma and prejudice, for example, against autistic, ADHD-like, or certain depressive traits that can, for people with those traits, be associated not only with distress and some impairments, but also with some talents or other advantages and with a positive sense of individual or group identity. Some selections can also exacerbate racism, such as by selecting against certain appearances or skin tones (one of the “conditions” that has disappeared from one of the corporate websites, for now). I do not argue unequivocally against the use of polygenic scores in embryo selection for complex disease risks, but proceeding without far fuller consideration of the technical, ethical, and policy concerns would be a mistake.

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ENDNOTES

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Schizophrenia spectrum disorders and other severe mental disorders are associated with significant reductions in lifespan. Because death certificates only record proximate causes of mortality—often chronic noncommunicable diseases related, *inter alia*, to such risk factors as smoking, poor health care, and poor nutrition—the role of mental illness is not typically recognized. See Carsten Hjorthøj, Anne Emilie Stürup, John J. McGrath, and Merete Nordentoft, “Years of Potential Life Lost and Life Expectancy in Schizophrenia: A Systematic Review and Meta-Analysis,” *The Lancet Psychiatry* 4 (4) (2017): 295–301, [https://doi.org/10.1016/S2215-0366\(17\)30078-0](https://doi.org/10.1016/S2215-0366(17)30078-0).

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which carries high mortality risk, treatment is typically limited to behavioral interventions that may require hospitalization.

- ⁵ Thomas A. Ban, “Fifty Years Chlorpromazine: A Historical Perspective,” *Neuropsychiatric Disease and Treatment* 3 (4) (2007): 495–500. Interestingly, one apparently failed antipsychotic drug, imipramine, was recognized to have antidepressant properties by Roland Kuhn in 1957 and became the prototype tricyclic antidepressant. See Francisco López-Muñoz and Cecilio Alamo, “Monoaminergic Neurotransmission: The History of the Discovery of Antidepressants from 1950s until Today,” *Current Pharmaceutical Design* 15 (14) (2009): 1563–1586, <https://doi.org/10.2174/138161209788168001>.

Serendipity should not be confused with luck, as the former requires an observer with a “prepared mind” and the ability to act on the observation. Alexander Fleming’s famously serendipitous discovery of penicillin was based on his observation of patches of clearing in the bacterial lawns on Petrie dishes he had inadvertently allowed to grow moldy. He correctly attributed the bacterial killing to a substance secreted by the *Penicillium* mold. Microbiologists could switch the types of bacteria and molds grown within this paradigm and were thus able to discover antibiotics that could kill diverse bacteria. In contrast, the serendipitous discovery of the antipsychotic properties of chlorpromazine lacked similar downstream possibilities. Unlike microbiologists’ observation of bacterial killing, psychopharmacologists lacked any line of sight into the actions of antipsychotic drugs in patient brains. Thus, they were left to inject drugs that differed only incrementally from the chlorpromazine prototype into laboratory rodents and look for chlorpromazine-like effects. The result was repeatedly rediscovering drugs that blocked dopamine D2 receptors or acted similarly in the brain.

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- ⁹ Taishiro Kishimoto, Katsuhiko Hagi, Shunya Kurokawa, et al., “Long-Acting Injectable Versus Oral Antipsychotics for the Maintenance Treatment of Schizophrenia: A Systematic Review and Comparative Meta-Analysis of Randomized, Cohort, and Pre-Post Studies,” *The Lancet Psychiatry* 8 (5) (2021): 387–404, [https://doi.org/10.1016/S2215-0366\(21\)00039-0](https://doi.org/10.1016/S2215-0366(21)00039-0).
- ¹⁰ Kane, Honigfeld, Singer, et al., “Clozapine for the Treatment-Resistant Schizophrenia”; and Lieberman, Stroup, McEvoy, et al., “Effectiveness of Antipsychotic Drugs in Patients with Chronic Schizophrenia.”

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- ¹² Melissa Fisher, Alexander Herman, Dustin B. Stephens, and Sophia Vinogradov, “Neuroscience-Informed Computer-Assisted Cognitive Training in Schizophrenia,” *Annals of the New York Academy of Sciences* 1366 (1) (2016): 90–114, <https://doi.org/10.1111/nyas.13042>.
- ¹³ Ban, “Fifty Years Chlorpromazine: A Historical Perspective”; and López-Muñoz and Alamo, “Monoaminergic Neurotransmission.” Controversy over the efficacy of current antidepressant drugs seems reasonably settled by newly released data from the FDA, described in Marc B. Stone, Zimri S. Yaseen, Brian J. Miller, et al., “Response to Acute Monotherapy for Major Depressive Disorder in Randomized, Placebo Controlled Trials Submitted to the U.S. Food and Drug Administration: Individual Participant Data Analysis,” *The BMJ* 378 (283) (2022): e067606, <http://dx.doi.org/10.1136/bmj-2021-067606>. They report that approximately 15 percent of clinical-trial participants, skewed toward those with the greatest baseline severity of depression, gained substantial benefits from the active drug over the placebo. A larger group had middling, nonspecific responses that could reflect the active drug, regression to the mean, or the placebo, and for another fraction of participants, the active drug was no better than the placebo. This work highlights the need for biomarkers to predict meaningful responses as well as more effective drugs or other interventions. See also Erick H. Turner, Andreas Cipriani, Toshi A. Furukawa, et al., “Selective Publication of Antidepressant Trials and Its Influence on Apparent Efficacy: Updated Comparisons and Meta-Analysis of Newer Versus Older Trials,” *PLOS Medicine* 19 (1) (2022): e1003886, <https://doi.org/10.1371/journal.pmed.1003886>.
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are best understood as variants or polymorphisms, not as mutations that diverge from an ideal DNA sequence. In aggregate, common SNPs contribute the largest fraction of heritability to risk of mental illnesses, to all common cognitive and behavioral traits, and indeed to most human traits.

Rare sequence variants that range in size from a single base to millions of bases also contribute to risk of mental illness. Rare variants are predominantly recent in origin and thus have been less subject to natural selection; some are not transmitted from the parents but occur *de novo*. Thus, rare variants can occasionally exert very large effects associated with disorders. Both common and rare DNA sequence variants have been well documented to be associated with autism, schizophrenia, and bipolar disorder. For discussion relevant to allele frequency, see Eugene J. Gardner, Matthew D. C. Neville, Kaitlin E. Samocha, et al., “Reduced Reproductive Success Is Associated with Selective Constraint on Human Genes,” *Nature* 603 (7903) (2022): 858–863, <https://doi.org/10.1038/s41586-022-04549-9>.

Despite vast sequence variation, the human genome is a finite object of investigation for which the necessary tools exist. In contrast, identification of relevant environmental factors for psychiatric disorders (the exposome) and their effect on pathogenesis is far more difficult. For example, there does not appear to be bounds on the types or number of factors that influence risk. Current efforts point to the need for trans-diagnostic longitudinal cohorts in which exposures can be measured and their effects interpreted against differences in susceptibility based on genotypes and susceptibility biomarkers yet to be discovered. For an example of a current attempt to apply a quantitative exposome measure to risk in schizophrenia spectrum disorders, see Laura Fusar-Poli, Thanavadee Prachason, Gamze Erzin, et al., “Examining the Association between Exposome Score for Schizophrenia and Cognition in Schizophrenia, Siblings, and Healthy Controls: Results from the EUGEI Study,” *Psychiatry Research* 323 (2023), <https://doi.org/10.1016/j.psychres.2023.115184>.

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- ²¹ *Ibid.*; Ronald C. Kessler, Johan Ormel, Maria Petukhova, et al., “Development of Lifetime Comorbidity in the World Health Organization World Mental Health Surveys,” *Archives of General Psychiatry* 68 (1) (2011): 90–100, <https://doi.org/10.1001/archgenpsychiatry.2010.180>; and Oleguer Plana-Ripoll, Carsten Bøcker Pederson, Yan Holtz, et al., “Exploring Comorbidity within Mental Disorders among a Danish National

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Inexpensive microarrays (“gene chips”) used for GWAS contain as many as one million DNA sequences—typically SNPs that are common in the population under study are systematically tested for association with a trait. Rigorous statistical procedures are used to determine which SNPs on the microarray are associated with the trait. GWAS is described as unbiased because instead of selecting one or several biological candidate genes to test for disease association, the microarray contains SNPs that index segments of DNA that tile the entire genome. To achieve statistical confidence in GWAS results, very large numbers (often tens of thousands) of affected individuals and unaffected control subjects are tested. Such large numbers are needed to yield statistically significant associations both because of the typically small effects of each of the common SNPs examined—and because of the need to correct for the multiple independent tests conducted in a GWAS reflecting the large number of loci on the microarray. Recognition of the large cohorts needed for GWAS motivated the formation of data-sharing consortia in which psychiatry was an early leader through the Psychiatric Genomics Consortium.

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