Chapter 1

What Causes Mental Illness?

Unanswered Question #1: ***What causes mental illness, and what is the role of evolutionary forces, genes, neurobiology, life experiences, and social stressors?***

1.1 A Historical Perspective

Since the birth of psychiatry as a medical specialty, clinicians and researchers have been searching for the causes of mental illness. A century later, we still don't know. We can identify risk factors for illness but cannot predict who will fall ill. Even so, we treat patients with reasonable success: Most psychiatric treatments are as effective as those in internal medicine (Leucht et al., 2012).

One of the puzzling aspects of psychopathology is how many patients who develop disabling symptoms have been well functioning in the past. Some mental disorders have prodromal symptoms that begin in childhood, and some patients have a family history of psychopathology. In those cases, we can describe statistical risks but cannot make firm predictions. Moreover, most severe mental illnesses become clinically apparent in adolescence or youth (Jones, 2013). But the onset of a mental disorder can come as a nasty surprise.

Several theories have been proposed to explain the time of onset of mental illness. The contenders include a hypothesis that adolescence is a time when synapses in the brain are heavily pruned (Germann et al., 2021), when there are notable changes in hormone levels (Graber, 2013), and when psychosocial stressors make relationships more difficult (Grant et al., 2014). But none of these risks explains why some are afflicted while others are not.

Consider, for example, this personal anecdote. In my first year at university, I lived in a dormitory. I was 16 years old, away from home for the first time, and in need of guidance. A senior student, then in his early twenties, was responsible for helping everyone living on the floor. I was shocked when he suddenly developed a severe mental illness – found in his room, naked and delusional, attempting to paint the walls. He then went on to receive a diagnosis of schizophrenia at a prominent psychiatric hospital. As far as I knew, this young man had never been previously ill. What could have caused this breakdown? Seventy years later, psychiatrists still have only a general idea as to what lies behind the disorders they treat.

A year later, I observed a mental hospital as it then was. Some might have been horrified by what they saw there. But I could not help being fascinated with this world of

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madness. I soon learned that clinicians who treat mentally ill patients were also struggling to find explanations for severe psychopathology. Some thought that abnormal neurotransmitters could be responsible. Another idea, often the view of psychoanalysts, was that mental illness was due to bad parenting. A few therapists were even emboldened to treat psychoses with psychotherapy, but they had no success, often making patients worse (Dolnick, 1998).

Psychiatry has always had a large gap between theory and practice. That is still the case. Some of its greatest breakthroughs in biological treatment have occurred by accident (Healy, 2004). The use of antipsychotic drugs began when a new antihistamine was found to calm psychotic patients. These new medications turned out to be one of the most dramatic discoveries in the history of medicine. Within a few years, when prescribed these drugs, most psychotic patients could be discharged after brief admissions. Large mental hospitals ended up being demolished (including the one near my undergraduate university, which once had 4,000 patients), or converted into research labs (as happened in Canada, where I studied psychiatry). It is true that medications tend to leave patients only partially remitted, and that inadequate funding of treatment in the community has often left them seriously adrift (Frances, 2013). But no one claims that long hospital admissions are still needed.

1.2 There Is More to Psychiatry than Psychosis

Most patients have disorders that are painful but not incapacitating. The most frequent condition in outpatient practice is what diagnostic manuals call a "major depressive episode." But major depression is not a single condition (Parker, 2005). It is a heterogenous mix of symptoms that varies from brief experiences of low mood to extended and disabling psychopathology (Spoelma et al., 2023). A minority of patients need to be hospitalized, but the vast majority have episodes that are much less severe (Cohen and DeRubeis, 2018). This variability raises questions about whether it is possible to find a single pathway to depression.

The Diagnostic and Statistical Manual of Mental Disorders, 5th edition, text revision or DSM-5-TR (American Psychiatric Association, 2022) advises us to make this diagnosis if depression lasts for at least two weeks. But that is a very short time span, uncomfortably close to normal reactions to losses. Variability in severity makes it unclear as to whether all "major" depressions are the same, and whether they are really major. Research has questioned whether all depressions are part of a single spectrum (Parker, 2005).

There are notable sex differences in the prevalence of depression, with a strong predominance in women. These differences are more broadly seen in internalizing disorders, including anxiety disorders and post-traumatic stress disorder (PTSD), while men have higher rates of externalizing behaviors such as substance use and crime. We do not know the reason, but women score higher in the personality trait of neuroticism (see Chapter 4).

What does treatment tell us about the nature of depression? Not as much as one might think. Antidepressants were discovered by accident (Healy, 2004), and the tricyclic group was originally thought to be another set of antipsychotics. It was only when specific serotonin reuptake inhibitors (SSRIs) came on the market that we had anything like "designer drugs."

Antidepressants are useful tools, especially when depression is severe (Parker, 2005). But they are being overprescribed to people who would do as well, if not better, with a

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course of psychotherapy (Cuijpers et al., 2020). Since talking therapy is not well insured, physicians (not only psychiatrists) offer antidepressants routinely to patients with almost any clinical features of low mood. But psychiatry has no cure for unhappiness (Horwitz and Wakefield, 2007).

Anxiety disorders, as a group, have a similarly high prevalence. Fear is even more prevalent than sadness (Horwitz and Wakefield, 2012). Anxious symptoms such as excessive worry or panic attacks can also accompany depressive episodes. This overlap is mainly due to the fact that our diagnoses are imprecise. Most have massive "comorbidity," that is, they overlap with other categories (Pincus et al., 2004). These fuzzy boundaries are an artifact of the DSM system, which lists similar criteria for different diagnoses. It does not mean that patients have two separate disorders.

We often treat patients with problems that are close to normality. One of our subspecialties is addiction psychiatry. Another is eating disorders. My own domain of personality disorders concerns a group of diagnoses that describe long-term problems in finding a direction in life and establishing meaningful relationships (Paris, 2015a). All these conditions are common, and respond best to psychotherapy, while medications are much less useful. But as long as talking therapies are difficult to access, the gap will be filled by prescriptions.

1.3 Does Neuroscience Account for Mental Disorders?

Physicians treat many illnesses with success and have greatly increased the human lifespan. Scientists send rockets and telescopes into orbit. So why can't we cure mental disorders? The answer is that the brain is much more complex than planets, stars, or space itself.

Yes, neuroscience is currently on a roll. We know much more about which brain functions are localized and which are not. But the regions devoted to thinking and consciousness are widely distributed and operate at a higher level of interaction (Fornito et al., 2017). Understanding neural connectivity is (and will continue to be) an uphill climb. I recently heard a brain scientist on a podcast state that he felt he was climbing Mount Everest but remained in its foothills.

Dynamic complexity systems are nonlinear and lead to emergent properties (Rust, 2025). This is a model that best fits brain disorders. Such processes cannot just be mapped as a "connectome." You could measure the activity of every synapse and still not have a clue what the brain is doing. The reason is that the environment usually determines what most neurons do. As long as researchers delude themselves with the assumption that psychiatry is nothing but an application of neuroscience (Insel and Quirion, 2005), we will never solve these mysteries.

Psychiatry, therefore, also is unwise to reinvent itself as a branch of neurology, as it originally was. I know how neurologists see patients (I have been one myself, very briefly). They are certainly experts in diseases in which (unlike psychiatry) one can measure change in specific brain regions. They order scans and tests to confirm diagnoses, even when they are unlikely to show anything new. But neurologists do not always have the skills in managing behavior, emotions, and cognitions that psychiatrists have. We are limited by the symptoms that patients report but are trained in skills that help us to talk to people in trouble.

Psychiatry is also different because it concerns the mind, not just the brain. I am not advocating dualism; that is a long-debunked idea. But the mind, although totally

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dependent on brain activity, is an *emergent* construct, whose properties exist at a different level. This makes psychiatry a unique discipline in medicine. Due to ethical considerations, psychiatry cannot be an experimental science. So it has had to depend almost entirely on systematic observations.

We do not know how the brain produces consciousness. But what is crucial to psychiatry that we have the capacity to make choices. Thus, in spite of claims to the contrary, minds have free will (Baumeister, 2008). This is because our species could not have survived without a cognitive capacity for agency when the environment presents conflicting choices (Mitchell, 2023). Those who claim that the laws of physics mean that determinism rules human behavior are applying the wrong model, one that sees the mind as a machine. Moreover, other animals have a degree of consciousness and free will (Baumeister, 2024). Even bacteria choose to approach food and to avoid danger.

Given the complexity of our brains, there have been no useful animal models of mental illness. Some of the attempts to create them have been dubious, such as mouse models of schizophrenia (Ang et al., 2021) or of autism (Silverman et al., 2022). Animals have emotions and thoughts, but live in the present, and do not have the mental disorders that humans do. The more complex the brain, the more it is at risk of malfunctioning.

Some psychiatrists hope that technological advances will overcome the limitations of current research. Two scenarios based on technology have recently gathered a fair amount of attention. The first is artificial intelligence (AI). Here the hope is that machine learning could sharpen diagnosis, guide treatment choices, and identify those most at risk for psychopathology (Monteith et al., 2022). The second is personalized psychiatry (Baune, 2019). The hope there is to address "treatment resistance," often seen in depression, by identifying biomarkers or changes in the genome, which could be linked to variations in neural connectivity. These goals remain elusive, at least for now. Psychiatry is too complex to be a servant of any technology, no matter how powerful.

1.4 Mental Disorders Are Complex and Do Not Have Simple Causes

Psychiatry has not benefited from attempts at searching for simple explanations of complex pathways leading to mental disorders. The problem is that our minds are structured to favor *linear* causation. We struggle to see the world as it truly is – an enormously complex set of *interactions*. That is why statistical analyses in research these days usually report multivariate analyses instead of univariate relationships.

The fact that multiple interacting forces shape the development of mental illness supports the need for a broader model. This book will argue that psychopathology is best understood as *biopsychosocial*. While biological vulnerability leads to a *risk* for mental illness, it does not necessarily cause disorders in the absence of environmental risks. Similarly, adverse life experiences do not necessarily lead to mental disorders, unless they interact with heritable risks that have a basis in biology. The environment is not just something that happens to us but reflects the choices we make. Moreover, negative life events do not lead everyone exposed to them to develop mental disorders, but mainly affect a vulnerable minority (Paris, 2022b). Fortunately, those of us born with good genes and who grew up in a supportive environment are more resilient to adversity. Thus, gene-environment interactions are the best way to understand psychopathology (Uher and Zwicker, 2017).

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We can also benefit from considering the role of evolution (Del Giudice and Haltigan, 2023; Gilbert, 1995; Nesse, 2023). Individual differences in vulnerability are in part determined by genes. If these biological variations lead to better ways of managing environments, they will be passed on and become more frequent in a population (Dawkins, 1976). But if the main goal of any organism is to pass on its genes, why are human beings so often afflicted by mental disorders that make reproduction less likely?

The answer to this question is that nature is not necessarily benign or progressive. Natural selection is based as much on competition as cooperation. That is why many social scientists dismiss (or do their best to ignore) evolutionary psychology (Pinker, 2002, 2011). Many of them dislike competition and believe in social change on a road to Utopia.

Another key concept in psychiatry concerns individual differences in risk factors related to heritable traits. *Personality* is the construct that reflects these differences in vulnerability (Paris, 2022b). Trait profiles describe how individuals respond to and process life events, leading to major differences in personality. Some traits are of clear benefit. Others, such as neuroticism, are more problematic. Heritable traits also have different effects in different environments: They can be positive or negative in one set of circumstances but not in another. Temperamental variability remains in the gene pool because environments are not stable.

Genetics and environments interact in several ways. *Passive* gene-environment correlations occur when genes and environment mutually reinforce each other. *Active* gene-environment correlations occur when individuals seek out environments that align with genetic predispositions. *Evocative* gene-environment correlations occur when the environment reacts to genetically influenced behaviors. All these mechanisms amplify the effects of genes but are difficult to disentangle.

In summary, the biological factors in mental disorders carry a risk for psychopathology but are not its only cause. Keep in mind that brain sciences describe statistical risks, but do not fully account for outcomes. While a proverb says that "as the twig is bent, so grows the tree," the most lasting effects in development depend on gene-environment interactions.

1.5 Molecular Genetics

A few decades ago, at the height of excitement about the decoding of the genome, I chaired a committee for the recruitment of an endowed chair in schizophrenia. The donor was the father of a young man who had that illness, but died from complications of his medical treatment. The father, who kept up with media reports on science, had a hope for research to find a gene (or a small number of genes) that causes schizophrenia, and that this knowledge would lead to a cure.

The result of the search led to the hiring of a neurologist who was an expert in complex inheritance but had no expertise in schizophrenia. He continued his previous research for years without touching the problem of psychosis. The neurologist was later replaced by a PhD molecular biologist who also lacked clinical experience but was expert on neurotransmitters in mice. No doubt these recruits contributed to the advancement of neuroscience.

Many years later, I sat on a grant review committee and was told that there were now three or four mouse models of schizophrenia. I found the idea of an animal model for this complex disorder to be absurd. Mice do not suffer from psychoses, and we have no

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access to their thoughts. Not surprisingly, research using these reductionistic models has done little to help patients.

Schizophrenia remains as mysterious as it ever was. While errors in synaptic pruning are our best hypothesis for now, it is far from proven (Johnson and Hyman, 2022).

Can modern genetics untie this Gordian knot? The decoding of the human genome early in this century encouraged some people to expect that to happen, but this hope turned into another disappointment. Again, the obstacle to progress in understanding mental disorders lies in the complexity of the brain. Human beings have about 20,000 genes, fewer than many plants or animals. Most of their effects on heredity are not linear but arise from interactions with many other genes. The mistake was to believe that each gene has a specific function, or is "for" one outcome, such as physical or mental disorders. But that is only true for a small minority of Mendelian traits. (Even Mendel could not replicate his findings on peas when working on other plants.) It was eventually realized that almost all traits are shaped by large numbers of interacting genes.

For years, researchers searched for linkages on chromosomes and "candidate genes" that could be associated with specific forms of psychopathology (Farrell et al., 2015). That scientific program was a failure, and this line of research has now been largely abandoned (Turkheimer, 2024).

With this setback in mind, researchers adopted a different method called Genome-Wide Association Studies (GWAS). Here the idea was to read the entire genome in a large sample, searching for small variations at sites called single nucleotide polymorphisms. The results showed that innate differences are shaped by complex interactions between very large numbers of alleles. Thus, while almost all categories of mental illness have a notable degree of heritability, outcomes reflect interactions between hundreds of sites in the genome. Thus, genes work in teams, each carrying some aspects of the heritability of traits.

GWAS findings, by themselves, have not been strongly linked to any trait or mental disorder. A *polygenic risk score* can be calculated from GWAS data by adding up all associations with outcomes. But that procedure still only accounts for about 5% of the total variance (Plomin et al., 2022). Thus, the heritability gap does not disappear.

GWAS may turn out to be another failed research strategy. Turkheimer (2024) concludes that genes and environment are so closely intertwined that measuring them separately is impossible. How could it be otherwise in a science that aims to account for phenomena as complex as human behavior?

Research using GWAS also undermines the idea of offering patients "personalized medicine" based on their genome. You can pay companies to conduct analyses that claim to identify risks for various illnesses. But these relationships are purely statistical and not in any way reliable. Using such measures plays little role in uncovering the secrets of psychopathology.

The moral of this story, once again, is that innate differences are not direct outcomes of genes but are shaped by large numbers of interactions between them and with the environment. To understand mental disorders, we need to give up the hope for simple solutions and embrace complexity. Psychiatry is not near to doing so.

1.6 Behavioral Genetics

At this point, the best way to measure the heritability of psychopathology comes from *behavioral genetics*, that is, studies comparing the concordance of traits in identical and

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fraternal twins. These differences allow us to calculate heritability as a percentage in a population. The precise amount of variance that is genetic can still vary from one person to another. These findings have been consistently supported by another (but less common) method, adoption studies that compare traits in biological and adoptive parents (Kendler et al., 2018).

Turkheimer (2000) has proposed three "laws" of behavior genetics. The first is that all human behavioral traits are partially heritable, the second is that the influence of genes on human behavior is greater than the family environment, and the third is that a significant number of behavioral traits cannot be explained by either genes or the environment. When people are more similar because of being raised in the same family, one can speak of a "*shared environment*." But the last two laws suggest that an "*unshared environment*" (outside families) is more important than growing up in a particular family.

So much for psychiatry's unfortunate history of blaming parents for every problem in their children! To put it another way, parents with one child believe in the primacy of the environment but change their minds once they have a second child. While the unshared environment can also include differences in experiences inside a family, siblings are generally quite different from each other (Harris, 1998).

Behavior genetics shows that all mental illnesses are under some degree of genetic influence (Giangrande et al., 2022). Some social scientists are skeptical about these conclusions, but they are biased against data that contradicts their own model. Uncertainty only lies in the level of variance under genetic influence. In the most *T* mental disorders (schizophrenia and bipolar-I), heritability can be as high as 80%. In common mental disorders (anxiety and nonpsychotic depression), the heritable influence is closer to 40% (Jang, 2005). Similar findings have been found in substance use disorder (Deak and Johnson, 2021), and a similar level applies to personality disorders (Jang, 2005).

Nonetheless, the heritability of these disorders has major clinical significance. Note that genes also have major effects on the personality traits that lie behind the symptoms of mental disorders (Turkheimer et al., 2014). These traits are risk factors for psychopathology, but do not necessarily predict the emergence of mental disorders (Smoller et al., 2019).

In summary, genes play a major role in all forms of psychopathology, but do not reliably determine its development. *This is also the case for schizophrenia*. Moreover, none of the illnesses we treat are related to just a few genes, but to very large numbers of them, each with a small effect. Finally, genetic risk factors cannot properly be understood without considering how they interact with the environment.

Genes are not only related to pathology; heritability is found in normal traits. These individual differences are described as *temperament* (in children) or as *personality* (in adults). Thus, personality emerges from an amalgam of genes and life experiences (Rutter, 2005). Some traits are beneficial, while others have little or no benefit. Even so, the same traits could have been functional in a different environment. Gene-environment interactions leading to feedback loops are what make traits problematic. This is why people at genetic risk may not consistently develop mental disorders.

1.7 Brain Imaging

Brain scans, particularly Functional Magnetic Resonance Imaging (fMRI), are a technology showing that different regions "light up" (i.e., are more metabolically active) when

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carrying out specific mental tasks. This kind of research is very expensive, and many publications using fMRI have been based on very small samples (Button et al., 2013), with results that fail to replicate (Turner et al., 2018). Moreover, given that connections are widespread across the brain, we may not really understand what we observe when a single region lights up on a scan.

When I trained in psychiatry, our ability to measure what goes on in the brain was limited to skull x-rays and electroencephalography. Imaging technology seemed at first to be a major breakthrough. Its methods began with computed axial tomography, later replaced by measures of blood flow and receptor binding to brain regions or positron emission tomography. The most common current method is fMRI. This method, focusing on specific brain regions, has been most widely used in research.

Researchers using imaging hoped to shed light on the *connectome*, that is, the way the brain is wired up (Fornito et al., 2017). One of the great questions in neuroscience has been the extent to which the brain functions as a whole, or whether specific regions carry out specific tasks. The answer is both. We know that some regions have particular functions, such as the role of the amygdala in fear, and of the hippocampus in memory. There are, of course, specific regions in the cortex that manage perception and movement. But vast regions in the frontal cortex are more related to "higher" functions such as cognition and consciousness. These networks are not necessarily specific but process how we learn from experience. Thus, even when we see a region of the brain lighting up on fMRI, these striking images are not a direct measure of the brain at work.

A psychiatrist specializing in addictions, along with a well-known psychologist, published a book titled *Brainwashed* (Satel and Lilienfeld, 2013) that focused on the hype around fMRI. Its main point was that the findings of brain imaging are at best approximate and do not provide a window to the mind.

Once again, we need not follow the advice of those who see psychiatry as nothing but an application of neuroscience, while downplaying the role of life experiences. A failure to consider interactions between heritable risk and life experiences is what has been called "psychiatry without the psyche" (Parnas, 2014). As for researchers who see psychiatry as a branch of neurology, their optimism is unjustified. These experts might be more cautious in their conclusions if they had more experience treating patients.

Brain imaging is a beginning. But we need better methods of measuring what goes on inside the "black box" under the skull. Perhaps future technologies will tell us more. In the meantime, we must be patient. Every few years, researchers tell us that we are on the cusp of a major breakthrough, but that has not yet happened. We remain on the cusp and may have to stay there for decades to come.

1.8 Neurotransmitters

Research in neuroscience has not solved the problems of psychiatry but it has revolutionized the biology of the brain. I can remember when this domain was in its infancy. When I was a student, models of how the brain works were illuminated by a theory of "cell assemblies" (Hebb, 1949), in which neuronal circuits followed the rule that "what fires together wires together." But the way these circuits (i.e., the connectome) function was not understood in any detail.

Serious attempts have been made by researchers to show that neurotransmitters malfunction at synapses in severe mental disorders. A Swedish scientist won a Nobel

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Prize for his work in this domain (Carlsson, 2001). But these findings did little for the treatment of psychiatric patients. This line of inquiry has drawn criticism for being reductionistic and lacking a capacity to make predictions (Moncrieff et al., 2023).

The upshot is that while we still prescribe antipsychotics, antidepressants, and antimanic drugs, and have theories about their mechanism of action, we do not really know how they work in the brain. A lack of precise knowledge is not unusual in medicine (consider that we long lacked explanations for why aspirin reduces pain), but it is pervasive in psychiatry.

We need not be discouraged – just humble. Again, consider that the human brain is the most complex structure in the known universe. It is worth restating that it has circuits involving 86 billion neurons (and even more glial cells), all linked by trillions of synapses. While some parts of the brain are specific to certain functions, much of its circuitry is spread over different regions that work together.

A popular theory that has had a long sway over psychiatry, and is still supported by some experts, has been that many patients suffer from a "chemical imbalance." The most common neurotransmitters in the brain are glutamate, which is excitatory, and gamma-aminobutyric acid (GABA), which is inhibitory. But the most widely researched transmitters (serotonin, dopamine, acetylcholine, and norepinephrine) are neuromodulators that act as regulators across many regions. The largest body of research has focused on serotonin and dopamine, which are active in all parts of the brain.

However, consistent relationships between neurotransmitters and psychopathology remain unclear. Moncrieff et al. (2022), in an influential review, documented the lack of evidence for chemical imbalances in mental disorders, especially for serotonin. Initial findings told a story of high expectations that led to dead ends. While millions have been spent on this line of research, it has failed to find these chemical imbalances and has also failed to replicate findings that made this claim. This is why I always taught students not to rely on any single research paper. They need to wait until there is a meta-analysis combining results from multiple research groups. (Even then, the conclusions of meta-analyses can change when further studies appear.)

Do *interactions* between neurotransmitter activity and the environment do a better job at predicting psychopathology? For example, two much quoted papers over two decades ago found that a history of childhood adversity combined with low serotonin levels can be a risk factor for depression (Caspi et al., 2002), and that low levels of a mono-amine oxidase inhibitor can increase the risk for antisocial behavior (Caspi et al., 2003). These reports have been widely cited because, unlike most biological research, they seriously attempted to measure gene-environment interactions. However, these findings have been difficult to replicate, and the strength of these relationships remains controversial (Munafò et al., 2009). One major limitation of this line of research was that it examined single alleles, and not the genome as a whole.

In a famous paper titled "Why Most Research Findings are False," IoannIdis (2005) pointed out that *most* research in medicine fails to replicate. Often no one bothers to attempt replications. Medical journals may reject submissions that show when previous findings fail to do so. When replications have been carried out, some of the most cited research turns out to be false.

There are several reasons for this problem. One is that since scientific journals prefer to publish positive findings, negative results may never be submitted for publication but may end up in a file drawer. Another is that medical research is too often limited by

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sample sizes that are too small to prove anything. Still another is that samples in clinical research, even if they have adequate power, usually consist of volunteers for clinical trials who are not representative of clinical populations. Some of these problems can be dealt with by meta-analyses. But we need to realize that if even some of the most quoted findings in medicine and psychology are false, we can truly speak of a "replication crisis" (Ioannidis, 2012). That is why combining the results of many studies is so crucial.

1.9 Trauma and Adverse Life Experiences

I was taught by psychiatrists who took it for granted that the origins of mental disorders lie in an unhappy childhood. Even today, many clinicians (and their patients) continue to believe that early life experiences are the main cause of psychopathology. This idea, now folded into incorrect interpretations about the effects of trauma, retains a strong influence on psychiatry and clinical psychology. It does not consider that when the environment of childhood is problematic, it tends to stay that way, leading to cumulative effects from multiple exposures.

These ideas were even more extreme in the past. Early adversity was offered as an explanation for *severe* mental illnesses, even including schizophrenia (Pietrek et al., 2013). The assumption was that the earlier the trauma, the more severe must be the disorder. Actually, there is no evidence to support that idea, and quite a bit of evidence that contradicts it (Rutter et al., 2007). Moreover, the findings that have been quoted to support this hypothesis are only *correlations* that fail to distinguish between genetic and environmental risk factors.

In any case, explaining mental disorders as the result of single risk factors is almost always wrong. As research on the effects of life events on later functioning has consistently shown (Rutter, 2013), multiple hits have cumulative effects, while single events, even the most serious adversities, do not necessarily cause disorders.

1.10 Trauma and Psychopathology

Ideas about the purely psychological origins of psychopathology are less popular today. But they live on in the construct of PTSD. I am not questioning the validity of this diagnosis, even if its boundaries are not well defined (McNally, 2003). But I am concerned about the overdiagnosis of PTSD and the overuse of childhood trauma as an explanation for mental disorders. In the absence of longitudinal follow-up data, these attributions tend to be glib and mistaken.

The effects of trauma are by no means predictable. The vast majority of those who suffer traumatic experiences (at least 90%) will not develop PTSD or any other mental disorder (Paris, 2022c). This reflects the ubiquity of resilience in both community and clinical populations. The precise percentages of PTSD vary greatly depending on the nature of the trauma, with rape having the highest rate of 20% (Scott et al., 2018), while exposure to combat in war has a prevalence of about 15% (Stein et al., 2002; True et al., 1993).

By and large, exposure to trauma leads to PTSD in about 5–10% of cases. These relationships have also been documented in longitudinal research, following people who are most exposed to trauma, such as police, firefighters, or soldiers (McNally, 2003). Those who do develop PTSD are genetically vulnerable, either by personality traits associated with anxiety and depression such as high baseline traits of neuroticism

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(increased sensitivity to adverse life events). Notably, *all* the individual criteria in the DSM manual that define PTSD have a heritable component (Stein et al., 2002).

The studies that have examined people whose occupations put them at risk for exposure to traumatic events also has the advantage that follow-up begins prior to exposure and does not depend on memory. Most findings show that most exposed individuals never develop PTSD, but that those who do, have high levels of trait neuroticism and/or a history of mental disorder (McNally, 2003).

Similarly, several large-scale studies that followed children exposed to abuse into adulthood support a similar conclusion: Only a small percentage of long-term outcomes are related to childhood trauma (Fergusson et al., 2008; Paris, 2022c). Thus, the idea that trauma, by itself, can cause PTSD or related disorders is seriously misleading.

A better explanation lies in a trait called *differential sensitivity to the environment* that applies to most, if not all, life experiences (Belsky and Pluess, 2009). A similar concept is that of a "sensitive child" (Aron et al., 2012). It is worth noting that differential sensitivity also makes people benefit more from positive live experiences.

The personality trait that is most consistently related to PTSD is neuroticism. Moreover, those who develop PTSD may also have traits that make them more likely to be exposed to stressors, such as risk-taking (Stein et al., 2002).

The idea that early adversities are more pathogenic for children than for adults is based on the assumption that children are more emotionally dependent. But research has not found differences in levels of resilience to adversity between children and adults (Rutter, 2013).

In assessing trauma during childhood, consider that the way we remember the past is shaped by how we function in the present. Unfortunately, therapists who believe in the primacy of trauma are all too quick to encourage patients to report adverse early experiences and to explain their current difficulties on that basis. It would be hard to find anyone who has never had serious difficulty at some point during childhood. Some traumatic events, like sexual abuse by a caretaker, are much more pathogenic, but even children with the most severe life adversities do not necessarily develop mental disorders as adults (Fergusson et al., 2008; Rutter et al., 2007).

Failure to understand these relationships has led to serious overestimates of the prevalence of what is called "trauma," broadly defined to include adversities of all kinds (McNally, 2005). This is an example of *concept creep*, that is, how constructs in psychology tend to expand over time (Jones and McNally, 2022). For example, childhood emotional neglect is more common in clinical populations, and is not the same thing as abuse or trauma. I am not talking about families that do not offer even a minimum of care, but those in which the emotions of children are dismissed without providing support (Linehan, 1993).

An excessive focus on traumatic life events has led to false conclusions about its role in adult psychopathology. More longitudinal research is needed here. What it shows thus far is that resilience, not pathology, is the usual outcome of adversity. Most children, even when they grow up in a problematic environment, can still function well in adulthood. Those who do not have traits that make them more sensitive to their environment are relatively protected from developing psychopathology.

Thus, much of the research on trauma and life adversity is biased and misleading. As a clinician, I have seen thousands of patients with major histories of childhood adversity. But studies of community populations put these clinical observations into a

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different perspective. Trauma has a context, which includes everything from genes and brain systems to families and neighborhoods. Once again, we always need to consider the importance of gene-environment interactions. This is not to say that we should not work with patients with trauma histories, or fail to understand how adversity affects them, but that we should not attribute all aspects of mental dysfunction as related to adverse life experiences.

Unfortunately, an exclusive focus on trauma, associated with the prescription of "trauma-informed" therapy, has been adopted by some therapists and their patients. These methods, focusing on the processing of traumatic events, have not been shown to be superior to standard therapy for PTSD (Paris, 2022c). Trauma is a popular idea because it implies that psychological symptoms are someone else's fault, a point of view that can reduce stigma. But a focus on trauma leads to another set of conclusions that are mistaken. One best-selling book claims that trauma is somehow remembered in the human body (van der Kolk, 2015). Evidently many patients are searching for answers to problems, and trauma sells, in this case in an attractive package of pseudoscience.

In short, well-meaning therapists treating people with childhood adversity are making the same mistake as biologically based clinicians who see psychiatry as an application of neuroscience. They are searching for single causes of mental disorders instead of framing them within a biopsychosocial model. This bias leads to treatment choices that are less than optimal.

1.11 A Different Way of Looking at Environmental Effects

A large body of research has found that life adversities of all kinds, early in life or currently, are associated with mental disorders, both in adults and in children (Rutter, 2006). But these are statistical relationships in populations, not in individual patients. For this reason, we need to consider these findings in the context of a biopsychosocial model. Adverse life events cause mental disorders when there is also a prior biological vulnerability and/or stressful experiences that are multiple, long-standing, and cumulative.

To support this argument, I am drawing on the seminal work of Michael Rutter, a British child psychiatrist who conducted large-scale research programs and wrote influential reviews about gene-environment interactions in development (Rutter, 2006). He was also known for studies of the mechanisms, both biological and psychosocial, that drive resilience (Rutter, 2013). Moreover, he carried out with longitudinal research projects on children, including a landmark study of Romanian orphans who suffered severe neglect in infancy, but did well when adopted into British families (Rutter et al., 2007).

Rutter helped to define child psychiatry in the UK and was unique in an ability to straddle the gaps between genes and environment. Let me summarize his overall conclusions about the role of the environment in mental disorders (Rutter, 2005):

(1) Environmentally mediated risks have been demonstrated for the family rearing environment, peer groups, schools, and community.
(2) However, children have effects on parents, just as parents have effects on children.
(3) Associations with disorders can derive from the effects of a difficult child on family functioning.

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(4) Individual differences in response to adversity are partly based on strengthening (or weakening) experiences prior to exposure, protective influences, and positive turning-point experiences.
(5) Behavioral genetic studies show that the unshared environment has more impact than the shared environment, but that does not mean that families have no impact.
(6) The main risk for antisocial behavior associated with "broken homes" is a function of family discord and conflict, rather than family breakup.
(7) The risks for depressive disorders in adult life are a function of impaired parenting, rather than of parental loss.
(8) Shared environmental effects are more prominent causes of antisocial behavior than for depression.

Rutter was a role model for me, although his eminence and originality far exceeded my own accomplishments. He followed children into adulthood to see what happened to them, and found that when the environment changed, so did children who had mental symptoms. He showed that resilience is ubiquitous, but that larger numbers of adversities have the capacity to overwhelm the "psychological immune system."

Rutter was not alone. Jerome Kagan was an American developmental psychologist who made a long scientific journey from psychodynamic theory to the biology of temperament (Kagan, 1998). His research showed how temperamental extremes, observable in infancy, shape traits in adolescence, and most likely in adulthood as well. Rutter and Kagan were part of a larger group of researchers pioneering a new paradigm called developmental psychopathology to build a bridge between biology, psychology, and the social context (Cicchetti, 2023).

In a systematic review of this research literature, Pine and Fox (2015) concluded that while the majority of mental disorders begin in childhood, they are not due to trauma alone but also due to interactions between heritable traits and environmental risks. They found that neurodevelopmental and psychotic disorders are most strongly associated with genetic variations due to temperamental variability, while gene-environment interactions create pathways that most strongly affect emotional disorders such as anxiety and depression.

These conclusions have not been changed by more recent findings. An interactive point of view makes it possible to think about genes and environment as a single system. You just need to stretch your mind.

1.12 Prospects for Understanding the Causes of Mental Disorders

The less that was known about the causes of mental disorders, the more theories there have been, with a tendency for explanations to multiply over time. Many advances in pharmacological treatment have occurred without understanding the etiology of the mental disorders for which they are used. But in view of the current lengthy hiatus in this domain of research (see Chapter 6), we probably need to know much more about causation.

The greatest triumphs of modern medicine have occurred in understanding acute illness, with the best examples being infectious diseases. The germ theory of disease was the breakthrough that eventually allowed treatments that can be managed by antibiotics or prevented by vaccination.

Chronic illnesses are a problem for physicians in all specialties. These conditions can be controlled, but tend to be resistant to cure. That is the situation for most of the

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problems that bring people to psychiatrists. But chronicity is usually a sign of complexity. No simple theory of causality is sufficient to understand the pathways to mental disorders.

To sort out these complex factors, we need longitudinal studies of children and adults in large samples, applying valid measures of biological risk and environmental risks. One way of doing this is to follow cohorts of monozygotic and dizygotic twins, and/or a birth cohort. Researchers in the UK (Fisher et al., 2015) and in New Zealand (Belsky et al., 2020) have been doing this for some time. But the problem of measuring the impact of genes and environment and their interactions is too complex to yield a clear verdict any time soon.

Answer to Unanswered Question #1
Mental disorders are complex and have multiple causes. Most are related to heritable vulnerabilities that are amplified by adverse life events. The biological aspects of this vulnerability are not currently explicable by specific changes in genetic makeup or in brain functioning. We lack a model that can accurately predict why people develop mental illness.

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