CHAPTER 18

The Chemical Imbalance That Wasn't

> ***Central question:*** *If mental illness is biological, does that mean it is fundamentally chemical?*

18.1 the Attraction of Simple Explanations

Few explanations are more satisfying than a simple one. A complicated experience becomes easier to bear when it can be linked to a clear mechanism: a gland fails, a hormone falls, an infection enters the body, a molecule is missing. The explanation gives the problem a name, places it inside biology and suggests a route toward treatment. Psychiatry has always had strong reasons to want explanations of this kind.

The appeal is especially powerful because mental illness can feel mysterious. Depression changes motivation, sleep, appetite, attention and the sense of the future. Psychosis can alter what seems real. Anxiety can make an imagined danger feel physically immediate. When symptoms reach into thought and identity, a biological explanation can be reassuring. It says that the experience is not merely weakness, bad character or lack of willpower. Something in the nervous system is genuinely different.

The language of chemistry seemed ideally suited to this task. Neurotransmitters are real molecules. Receptors can be measured. Drugs can raise or lower signalling. The chain from molecule to synapse to behaviour appears concrete in a way that broad concepts such as stress, personality or social environment may not. Once antidepressants became associated with serotonin and antipsychotics with dopamine, the temptation to convert treatment mechanisms into disease explanations became enormous.

Simple stories also travel well. ’Depression involves many interacting developmental, circuit, cognitive and social processes’ is scientifically defensible but difficult to communicate. ’Depression is caused by low serotonin’ can fit in a sentence. It can be remembered, repeated and placed on a diagram. Patients, clinicians, journalists and pharmaceutical marketing all had reasons to prefer the shorter version, even when the evidence was less tidy.

But usefulness in communication is not the same as truth in mechanism. A map can be useful because it leaves details out. Trouble begins when the map is mistaken for the territory. The chemical-imbalance idea performed an important cultural function by emphasizing that mental illness has biological dimensions, but it also encouraged the belief that one could understand a disorder by identifying the transmitter that was supposedly too high or too low.

The chapters so far have shown why that expectation fails. Acetylcholine can contract muscle, slow the heart and modulate memory. Dopamine can influence movement, learning, motivation and psychosis. Serotonin participates in mood, anxiety, patience, sleep and perception. The same molecule acquires different meanings in different circuits. If neurotransmitters themselves do not have one psychological function, psychiatric disorders are unlikely to map neatly onto one neurotransmitter each.

The attraction of simple explanations is therefore understandable. The mistake is not wanting biology. The mistake is assuming that biology must be simple.

18.2 One Disorder, One Neurotransmitter

During the rise of modern psychopharmacology, a convenient set of associations began to form. Depression became linked with serotonin and noradrenaline. Schizophrenia became linked with dopamine. Anxiety was associated with GABA and serotonin. ADHD became connected with dopamine and noradrenaline. These pairings were not invented from nothing. They emerged from genuine pharmacological observations.

Monoamine oxidase inhibitors and tricyclic antidepressants increased monoaminergic signalling and could improve depression. SSRIs acted more selectively on serotonin transport. Antipsychotic potency correlated strongly with D2 receptor blockade. Benzodiazepines enhanced GABAergic inhibition and rapidly reduced anxiety. Stimulants altered catecholamine signalling and improved attention in many people with ADHD. Each treatment pointed toward a chemical system that mattered.

The problem arose when ’matters for treatment’ quietly became ’causes the disorder.’ A medicine that changes one transmitter can alter the operation of a much larger network. The fact that this intervention improves symptoms does not imply that the original illness began as a simple excess or deficiency of that transmitter. Pharmacology gives us a powerful handle on a system, but the handle is not the whole machine.

The one-disorder, one-transmitter model also struggles with overlap. Serotonin-targeting drugs are used not only for depression but for anxiety disorders, obsessive-compulsive disorder and other conditions. Dopamine-blocking drugs can treat psychosis arising in different diagnoses. Stimulants influence attention, motivation and arousal rather than one disease-specific process. If a transmitter belonged to only one disorder, this clinical cross-over would be difficult to explain.

The reverse is equally important. A single disorder can respond to drugs that act through very different mechanisms. Depression may improve with SSRIs,

psychotherapy, electroconvulsive therapy, ketamine or other interventions. Bipolar disorder can respond to lithium, anticonvulsants and certain antipsychotics. The existence of multiple therapeutic routes suggests that symptoms can be changed from several entry points into the same distributed system.

This is not a weakness of biological psychiatry. It is what one should expect from a complex nervous system. A network can be pushed toward a healthier state by altering several different components. The route taken by the treatment need not identify the unique cause of the original instability.

The one-disorder, one-transmitter scheme was attractive because it resembled the clean logic of deficiency diseases. But psychiatric syndromes are not usually like scurvy, in which one missing nutrient provides a dominant explanation. They are patterns emerging from interacting genes, circuits, experiences and environments. Neurotransmitters remain central, but they are participants in these patterns rather than labels attached one-to-one to diagnoses.

18.3 How the Chemical-Imbalance Metaphor Arose

The phrase chemical imbalance sounds like the conclusion of a precise experiment: measure the chemicals, discover the imbalance, correct it. Historically, the path was much less direct. The metaphor grew gradually from the early successes of psychopharmacology, when drugs transformed psychiatry faster than theories could explain why they worked.

Reserpine could deplete monoamines and sometimes produce behavioural changes resembling aspects of depression. Monoamine oxidase inhibitors and tricyclic antidepressants increased monoaminergic signalling and could relieve depressive symptoms. These findings helped generate monoamine hypotheses of depression. In psychosis, the success of dopamine-receptor-blocking drugs and the psychotic effects that could follow high-dose stimulant use supported dopamine-based models. The original hypotheses were attempts to connect pharmacological clues with disease biology.

These scientific proposals were already more nuanced than the slogans they later became. Researchers debated receptor sensitivity, downstream adaptation, multiple transmitters and the anatomical location of abnormalities. Yet the public version increasingly condensed the argument into an intuitive metaphor: mental illness results from chemicals being out of balance, and medication restores balance.

The metaphor had several advantages. It made psychiatry sound mechanistically grounded at a time when biological explanations were often uncertain. It could reduce moral blame by presenting mental disorders as illnesses of the brain. It also gave patients a reason to persist with medication: the drug was not merely changing how they felt but correcting an underlying biological problem. Pharmaceutical promotion sometimes amplified this language because a simple deficiency-and-replacement story made the purpose of treatment easy to understand.

But 'chemical imbalance' was never one coherent, experimentally established theory applying across psychiatric disorders. It was a family of simplified interpretations layered over several different scientific hypotheses. Some concerned transmitter synthesis, others receptor function, transporter activity, release, downstream signalling or circuit-level regulation. Translating all of these into a single image of a chemical scale being restored to equilibrium erased the very mechanisms researchers were trying to distinguish.

There was another problem. Neurotransmission is not organised around a universal normal concentration. Dopamine should not be equally high in every pathway. Serotonin should not be fixed at one ideal level across all states. Transmitter release changes from moment to moment with sleep, stress, learning, movement and context. A healthy brain is chemically dynamic. The relevant question is not whether a molecule is globally balanced but whether signalling is appropriate in a particular circuit at a particular time.

The chemical-imbalance metaphor therefore arose from real discoveries but outgrew the evidence that gave birth to it. It converted useful pharmacological clues into an overly literal disease model. Understanding why requires separating two questions that are often confused: what a treatment does, and what caused the disorder in the first place.

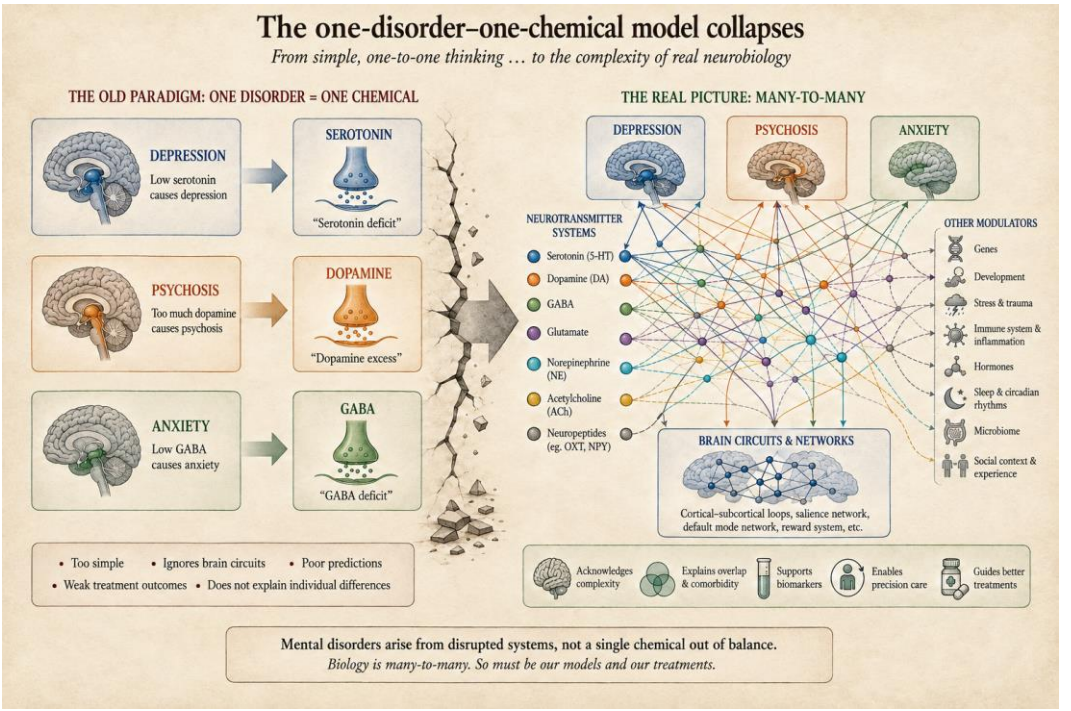

Fig. 18.1 | The one-disorder–one-chemical model breaks down.

18.4 Treatment Mechanism Is Not Necessarily Disease Cause

Suppose a drug improves a symptom by acting on a particular receptor. What have we learned? We have learned that changing that receptor can move the system in a therapeutically useful direction. We have not automatically learned that the disorder was caused by an abnormality in that receptor.

This distinction sounds obvious when stated explicitly, yet much of the chemical-imbalance story depended on forgetting it. SSRIs block the serotonin transporter, so depression was inferred to involve too little serotonin. Antipsychotics block D2 receptors, so schizophrenia was inferred to involve too much dopamine. Benzodiazepines enhance GABA-A receptor signalling, so anxiety could be imagined as a GABA deficiency. Each step moves from an intervention to an origin story.

But complex systems can often be corrected downstream from the event that destabilized them. A fever can be lowered without eliminating the infection that produced it. Pain can be relieved without reversing the tissue injury that generated the nociceptive signals. A heart rhythm can be stabilised by altering ion channels even when the initiating disease lies elsewhere. Medicine routinely intervenes at points that are therapeutically useful rather than causally primary.

The brain makes this distinction even more important because symptoms are emergent properties of circuits. A depressed state may involve sleep disruption, altered reward processing, stress signalling, cognitive biases, inflammatory processes and changes in plasticity. A serotonergic drug can influence several of these networks and gradually shift the system without serotonin having been the unique upstream defect.

The time course of treatment provides an additional clue. SSRIs alter serotonin reuptake quickly, yet mood improvement usually develops more slowly. Antipsychotics occupy D2 receptors rapidly, while some clinical changes unfold over days or weeks. Lithium enters the body immediately, but mood stabilization depends on slower cellular adaptation. The therapeutic mechanism is therefore often a cascade rather than the first molecular action alone.

This does not make receptor pharmacology superficial. The first molecular action matters because it starts the cascade. But identifying the first domino touched by the drug is not the same as identifying the first domino that fell in the disease. Those may be different parts of the system altogether.

Once this distinction is clear, many apparent contradictions disappear. A serotonin-targeting drug can help depression without depression being a serotonin-deficiency disease. A dopamine-blocking drug can reduce psychosis without schizophrenia being a global dopamine-excess disorder. Treatment mechanisms reveal leverage points. Disease mechanisms require a broader causal explanation.

18.5 the Aspirin-Deficiency Fallacy

A useful analogy is sometimes called the aspirin-deficiency fallacy. Aspirin can relieve a headache, but we would not conclude that the headache was caused by an aspirin

deficiency. The treatment works because it changes biochemical processes that contribute to pain. The absence of the medicine was not the origin of the symptom.

The analogy is deliberately simple, but it captures an important error in reasoning. If a treatment reverses a state, we are tempted to imagine that the untreated state represented a deficiency of whatever the treatment supplied or enhanced. L-DOPA makes this reasoning especially seductive because in Parkinson's disease there really is a major loss of dopaminergic neurons and a corresponding deficit in striatal dopamine. Replacement is therefore unusually close to the pathology.

Psychiatric treatment often does not have that structure. An SSRI does not simply replace missing serotonin. It changes the duration and distribution of serotonergic signalling and then triggers adaptation in receptors, gene expression and networks. Ketamine can produce antidepressant effects through glutamatergic mechanisms without implying that depression is fundamentally a ketamine-sensitive glutamate deficiency. Psychotherapy can alter symptoms without implying that the illness was caused by a psychotherapy shortage.

The fallacy matters because it shapes expectations. If depression is described as low serotonin, then an SSRI can sound like insulin for diabetes: the correct substance is being restored. When the drug does not work, the patient may conclude that the diagnosis was wrong, the biology is hopeless or the treatment has somehow failed to correct the presumed chemical defect. In reality, non-response may simply reflect the heterogeneity of the syndrome and the fact that the chosen intervention did not reach the most relevant mechanism for that person.

The same error can also make side effects seem puzzling. If a drug merely restores a deficient chemical, why should it produce nausea, sexual dysfunction, sleep disturbance or emotional blunting? These effects make more sense when the drug is understood as perturbing a transmitter system that serves many normal functions throughout the brain and body.

A better therapeutic model is to think in terms of leverage. Drugs act at sites where a modest molecular intervention can shift network dynamics. Some leverage points are highly effective, some modest, some useful only for certain patients. Their usefulness tells us something about the organisation of the system, but it does not automatically reveal the original cause of the disorder.

The aspirin analogy therefore does not diminish pharmacology. It protects pharmacology from being asked to prove more than it can. A successful medicine demonstrates that a biological pathway can be used to change illness. It does not, by itself, tell us that illness began as a defect in that pathway.

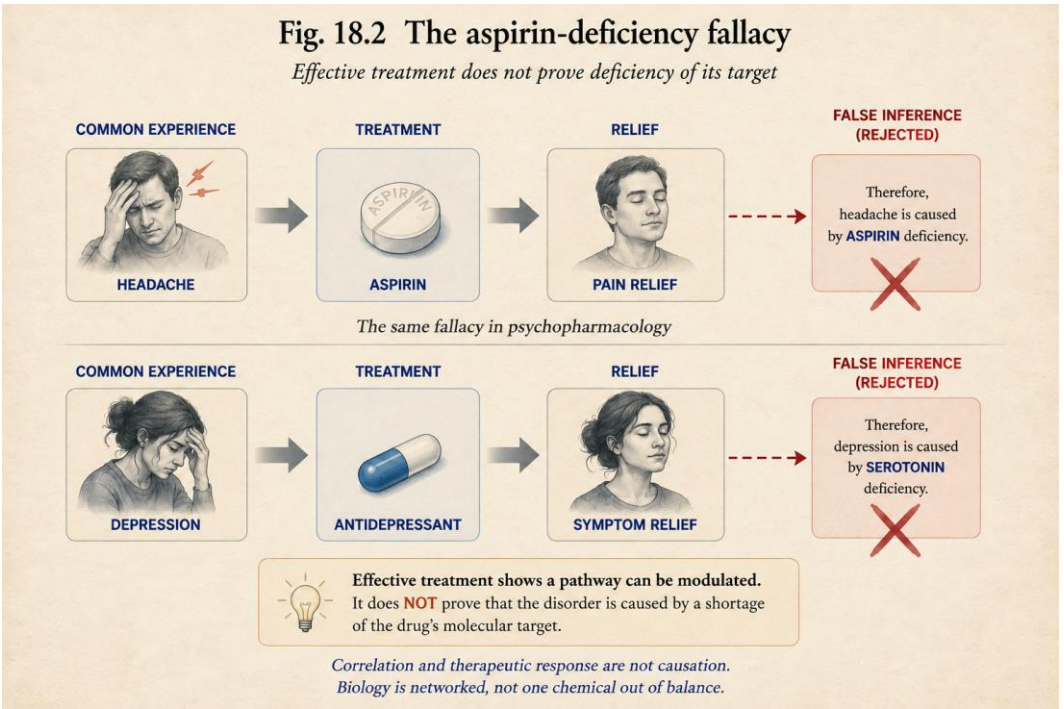

Fig. 18.2 | The aspirin-deficiency fallacy.

18.6 Psychiatric Diagnoses Are Heterogeneous

The chemical-imbalance model becomes even harder to sustain when we examine what psychiatric diagnoses actually contain. A diagnosis such as major depression is not defined by one biological test. It is defined by a pattern of symptoms, and different people can meet the diagnostic criteria through different combinations of those symptoms.

One person may sleep excessively, gain weight and feel physically slowed. Another may sleep very little, lose appetite and become agitated. One may describe profound sadness; another may emphasize loss of pleasure, fatigue or inability to think. Both can receive the same diagnosis. The label is clinically useful because the patterns overlap enough to guide communication and treatment, but biological uniformity cannot be assumed from the shared name.

The same issue appears elsewhere. ADHD can involve different mixtures of inattention, impulsivity and hyperactivity. Schizophrenia encompasses varying degrees of hallucinations, delusions, cognitive impairment, motivational change and social dysfunction. Anxiety disorders share threat-related processes but differ in triggers, avoidance patterns and bodily symptoms. A diagnostic category is therefore often a family resemblance rather than a single mechanistic entity.

This heterogeneity matters enormously for neurochemistry. If two patients arrive at a similar clinical state through different pathways, one transmitter abnormality is unlikely to explain both. A person whose depression follows chronic inflammatory illness may not have the same dominant mechanisms as someone whose depression

emerges after prolonged social loss, disrupted sleep or a strong familial vulnerability. Their symptoms can converge while their causal histories differ.

Heterogeneity also helps explain why treatment response varies. A drug can perform well on average while being transformative for some patients, modestly useful for others and ineffective for another group. This is not necessarily random noise around one disease mechanism. It may reflect several partially distinct biological routes grouped under the same diagnostic umbrella.

The implication is not that diagnoses are useless. Clinicians still need syndromic categories to recognise patterns, estimate risk and select interventions. But diagnosis is the beginning of mechanistic inquiry, not its end. We should resist treating a label as though it identifies one hidden chemical lesion.

Once we accept heterogeneity, the next question becomes unavoidable: can the same symptom itself arise from different mechanisms? In many cases, the answer is clearly yes.

18.7 Similar Symptoms, Different Mechanisms

Consider insomnia. A person may be unable to sleep because of anxiety, pain, stimulant use, mania, circadian disruption, sleep apnoea, grief or an irregular work schedule. The surface symptom is the same: sleep is poor. The biological route into that symptom can be very different.

The same is true of reduced motivation. It may appear in depression, Parkinson's disease, schizophrenia, chronic inflammatory states, severe sleep deprivation or the aftermath of prolonged stress. In one case dopaminergic motor circuits may be central; in another, reward valuation, fatigue, cortical control or negative expectation may dominate. Calling all of these states 'low motivation' does not make them chemically equivalent.

Hallucinations provide another example. They can occur in schizophrenia, severe mood disorders, neurological illness, drug intoxication, sleep-related states or sensory deprivation. The experience may look similar at the level of description while arising from different combinations of sensory processing, prediction, attention and neuromodulation. A symptom is an endpoint produced by a system, and complex systems can reach the same endpoint by different paths.

This phenomenon is sometimes described as equifinality: different causes converge on a similar outcome. It is common throughout biology. Different genetic mutations can produce similar physiological syndromes. Different injuries can impair the same function. Different perturbations of a network can push it into the same unstable state.

For psychiatry, equifinality is especially important because the symptoms themselves are often the variables used to define the diagnosis. If those symptoms are mechanistically many-to-one, the diagnostic category inherits that heterogeneity. Searching for one transmitter abnormality across the entire group may therefore dilute several genuine subtypes into one weak average effect.

This also changes how we should interpret biomarkers. A useful biomarker may not identify every person with a diagnosis. It may identify a mechanistic subgroup: patients whose symptoms involve a particular inflammatory profile, reward-processing pattern, sleep disturbance or circuit abnormality. Precision may come from dividing broad syndromes into biologically meaningful pathways rather than finding one universal marker.

The chemical-imbalance idea assumed a relatively direct mapping from diagnosis to molecule. The reality may be closer to a network of routes, with several causes converging on similar symptoms. But biology contains the opposite pattern as well: one biological alteration can produce different outcomes in different people.

18.8 One Biological Alteration, Different Outcomes

If different mechanisms can produce the same symptom, the reverse is also true. A similar biological perturbation can lead to different psychological or clinical outcomes depending on the rest of the system in which it occurs.

Stress provides a familiar example. Prolonged activation of stress-related physiology can affect sleep, immune signalling, memory, appetite and emotional regulation. Yet people exposed to similar stressors do not all develop the same disorder. One may become depressed, another anxious, another develop substance misuse, while another remains relatively resilient. The stress biology matters, but its outcome depends on prior vulnerability, coping, social support, developmental history and many other variables.

Genetics shows the same pattern. Most common psychiatric disorders are influenced by many genetic variants, each contributing only a small amount of risk. The same variant can sometimes be associated with more than one diagnostic outcome, and different combinations of variants can contribute to the same disorder. Genes influence developmental pathways and cellular processes; they do not usually encode a diagnosis in a one-to-one fashion.

Even a change in one neurotransmitter system can have divergent consequences. Increased dopaminergic signalling in one circuit may alter reward pursuit, in another it may affect cognitive control, and in another it may contribute to psychotic salience. The outcome depends on projection target, receptor distribution, timing and the state of the network receiving the signal.

This many-outcomes-from-one-cause pattern is sometimes called multifinality. Together with equifinality, it undermines the expectation that psychiatric biology should form a simple lookup table: one disorder, one lesion; one lesion, one disorder. Developmental systems are conditional. The effect of a perturbation depends on when it occurs, where it occurs and what else is happening at the same time.

The concept of resilience also belongs here. A biological risk factor is not destiny. Networks can compensate. Alternative strategies can be learned. Supportive environments can reduce the impact of vulnerability. Conversely, repeated stress, sleep disruption or substance exposure can amplify a modest vulnerability until

symptoms emerge. The final phenotype is produced by interactions rather than by a single isolated cause.

This is why average biological differences between diagnostic groups must be interpreted carefully. A group effect can be real without describing every individual in the group. What matters clinically is the configuration of mechanisms in a particular person. And to understand those mechanisms, neurotransmitters must be placed back into the circuits through which they act.

18.9 Neurotransmitters Act Through Circuits

The easiest way to escape the chemical-imbalance metaphor is not to abandon neurotransmitters but to put them in their anatomical context. A neurotransmitter never acts in the abstract. It is released by particular cells, reaches particular targets, binds to particular receptors and changes the behaviour of a circuit that is already doing something.

Dopamine provides the clearest example. Loss of nigrostriatal dopamine impairs movement in Parkinson's disease. Dopamine in mesolimbic circuits contributes to reward learning and motivation. Prefrontal dopamine influences working memory and cognitive control. Tuberoinfundibular dopamine regulates prolactin. There is no single psychological meaning of 'dopamine level.' The pathway determines the consequence.

Serotonin is similarly distributed across raphe projections influencing cortical, limbic, hypothalamic and brainstem systems. GABAergic inhibition shapes local computation throughout the brain. Glutamate carries much of the excitatory traffic but also participates in plasticity and excitotoxicity. A chemical name identifies a signalling mechanism, not a mental state.

Circuit context also explains why the same drug can produce both benefit and side effects. An antipsychotic may reduce psychosis by blocking D2 receptors in one set of circuits while producing parkinsonian motor effects by blocking the same receptor family in another. A cholinergic drug intended to influence cognition can affect the gut. Molecular selectivity is therefore not the same as functional selectivity.

Psychiatric symptoms themselves are circuit-level phenomena. Attention requires coordinated activity across prefrontal, parietal, thalamic and neuromodulatory systems. Fear involves amygdala, hippocampal, cortical and brainstem components. Reward depends on interactions among basal ganglia, midbrain and cortical networks. A transmitter changes the operating conditions of these circuits; it does not perform the psychological function by itself.

This perspective transforms the idea of imbalance. The relevant abnormality may not be too much or too little transmitter globally. It may be an inappropriate pattern of signalling within a particular pathway, altered receptor sensitivity, abnormal timing, excessive coupling between regions or a failure of one circuit to regulate another. The language shifts from quantity alone to organisation.

But even circuits are not fixed machines assembled once and left unchanged. They are products of development. Their connectivity, receptor expression and plasticity

change across childhood, adolescence and adulthood. To understand why the same biological perturbation affects people differently, we must therefore add time to the picture.

18.10 Circuits Develop

A circuit diagram can make the brain look static. Boxes are connected by arrows, as though the adult network had always existed in that form. In reality, neural circuits are built gradually. Genes guide early development, but activity, hormones, learning and experience continuously shape the emerging architecture.

Development changes the meaning of a chemical signal. The density of receptors can shift with age. Long-range connections mature at different rates. Myelination changes communication speed. Inhibitory networks develop over time. Prefrontal systems involved in cognitive control continue maturing through adolescence, while reward and emotional systems follow their own trajectories. A perturbation at age seven is therefore not necessarily equivalent to the same perturbation at age thirty-seven.

Sensitive periods make timing especially important. During some stages of development, particular kinds of experience have unusually strong effects on circuit formation. Sensory systems provide classic examples, but emotional and cognitive networks also pass through periods of heightened plasticity. Early stress, deprivation or instability can influence the later calibration of threat and stress-response systems without determining a single inevitable outcome.

Adolescence illustrates the principle well. It is a period of major changes in reward sensitivity, social motivation, sleep timing and prefrontal control. Many psychiatric disorders first become clinically apparent during adolescence or early adulthood. This does not mean that adolescence itself causes them. It means that developmental transitions can reveal vulnerabilities that were less visible when the network operated in an earlier state.

Development also complicates drug effects. A medicine interacts with a nervous system whose receptors, circuits and compensatory mechanisms depend on age. The same dose cannot be understood purely as a molecular event detached from developmental context. This is one reason paediatric psychopharmacology cannot simply be adult psychopharmacology scaled down by body weight.

The developmental view replaces the idea of a fixed chemical defect with a trajectory. Risk can accumulate, compensate or change direction. A vulnerability can remain silent until another developmental demand exposes it. Protective experiences can strengthen alternative pathways. Illness becomes something that unfolds through time rather than a chemical abnormality appearing fully formed.

And development does not occur in isolation inside the skull. The circuits being built are continuously shaped by what the person experiences.

18.11 Development Depends on Experience

The nervous system develops by interacting with the world. Experience changes synapses, alters gene expression, modifies stress responses and trains expectations. This is not an alternative to biology. It is one of the mechanisms by which biology is constructed.

Learning provides the most obvious example. A cue that repeatedly predicts danger can acquire the power to evoke fear. A cue that predicts reward can acquire motivational value. Repeated avoidance can prevent a feared prediction from being corrected. Repeated success can change expectations about effort and control. Each of these psychological descriptions corresponds to changes in neural activity and plasticity.

Experience can also have broader physiological effects. Chronic sleep disruption changes endocrine, immune and cognitive function. Repeated social threat can alter stress reactivity. Exercise affects metabolism, neurotrophic signalling and mood-related networks. Parenting, education, trauma and social stability influence the situations to which a developing nervous system must adapt. None acts through a single pathway, but all can become biologically embedded.

This is why the old opposition between ’biological’ and ’environmental’ causes is misleading. An environmental event influences the brain only by becoming a biological event somewhere along the chain. Sensory input changes firing. Stress changes hormones. Learning changes synapses. Social rejection changes autonomic and endocrine responses. Biology is not what remains after experience is subtracted; biology is the medium through which experience has lasting effects.

The reverse is equally true. Biology influences how experience is interpreted. Temperament, sensory sensitivity, reward responsiveness and cognitive style affect what a person notices and how strongly events are learned. Two people can live through the same situation but encode it differently because their nervous systems enter the experience with different histories and predispositions.

Psychotherapy makes this interaction particularly visible. It uses conversation, attention, memory, behavioural practice and social interaction to produce changes in prediction and regulation. If psychotherapy is effective, those changes must be instantiated in the brain. Its psychological mode of entry does not make the outcome non-biological.

Once experience is understood as a biological force, the chemical-imbalance debate becomes less polarized. Molecules matter. So do circuits. So does learning. The next step is to extend the same logic outward again, because experience itself is shaped by social environments.

18.12 Social Environments Affect Biology

A brain does not merely receive an abstract quantity called environment. It lives inside a body, and that body exists in families, workplaces, schools, neighbourhoods and cultures. These social settings can alter the frequency and intensity of stress,

opportunity, safety, sleep, exercise, nutrition and interpersonal connection. Each of these can influence biology.

Consider chronic social stress. Persistent insecurity can keep threat-monitoring systems active, disrupt sleep, alter autonomic balance and change endocrine and immune signalling. Social isolation can affect mood and motivation. Stable relationships can buffer stress responses. Employment conditions can shape daily rhythms and perceived control. None of these effects requires a mysterious pathway from 'society' to 'mind.' They act through ordinary biological mechanisms.

This does not mean that poverty, trauma or loneliness inevitably produce psychiatric illness. Social exposures interact with genetics, development and existing coping resources. Two people can respond differently to the same environment, and the same person can respond differently at different stages of life. Social biology is probabilistic, not deterministic.

The point is that causal explanation cannot stop at the synapse if the factors driving the synapse lie outside it. A drug may reduce anxiety while the person remains in a chronically threatening environment. An antidepressant may improve sleep and motivation while social isolation continues to reinforce hopelessness. Biological treatment can still help, but the persistence of upstream pressures may limit what one molecular intervention can accomplish.

Conversely, changing the environment can alter biology without directly administering a chemical. Improved sleep schedules change neuromodulatory and hormonal states. Regular physical activity alters metabolic and neurotrophic signalling. Supportive social contact changes stress physiology. Learning a new behavioural strategy changes circuit activity. The boundary between 'biological treatment' and 'social intervention' becomes less sharp once causal chains are followed all the way through.

This multilevel view also avoids a common misunderstanding. Saying that social conditions influence mental illness does not imply that symptoms are imaginary or that medication is unnecessary. Saying that neurotransmitters matter does not imply that social context is irrelevant. Both claims can be true because causes operate at multiple levels simultaneously.

The question, then, is not whether mental illness is biological. Of course it involves biology: every perception, memory, emotion and action depends on a living nervous system. The more difficult question is what follows from that fact. Does biological mean chemical? Does explaining one molecular pathway make the higher levels dispensable?

18.13 Why Rejecting Reductionism Does Not Mean Rejecting Neurobiology

Criticism of the chemical-imbalance story is sometimes heard as criticism of biological psychiatry itself. If depression is not simply low serotonin, perhaps biology has failed. If schizophrenia is not simply excess dopamine, perhaps mental illness should be

explained only through meaning, relationships or society. This conclusion makes the same mistake as chemical reductionism, only in the opposite direction.

The failure of a simple biological explanation does not make the phenomenon non-biological. It tells us that the biology is richer than the explanation. A hurricane is physical even though it cannot be explained by the state of one air molecule. A heart is biological even though knowing the properties of one ion channel does not explain circulation. Complex organisation does not become less material because many levels are required to understand it.

Mental states are especially multilevel. Molecules influence synapses. Synapses participate in circuits. Circuits generate patterns of perception, memory and action. Those patterns occur in bodies with hormonal, immune and metabolic states. Bodies interact with environments, and environments include other people. Causation can travel through this hierarchy in several directions.

Bottom-up effects are obvious: a drug binds a receptor and behaviour changes. But top-down effects are equally biological. A frightening interpretation can activate autonomic and endocrine responses. A learned expectation can alter pain. A social interaction can change stress physiology. A decision to practise a skill repeatedly can remodel the circuits that perform it. Higher-level descriptions do not float above biology; they organise biological activity.

Reductionism becomes a problem when one level is treated as sufficient for every question. Molecular explanations are indispensable when we ask how an SSRI blocks a transporter or how a benzodiazepine modulates GABA-A receptors. Circuit explanations are better when we ask how threat is regulated. Cognitive explanations may be needed to understand persistent negative expectations. Social explanations become relevant when chronic insecurity or isolation continually drives the system. The correct level depends on the question.

This perspective also changes what a psychiatric drug is. It is not necessarily a substance that corrects one hidden chemical defect. It is an intervention that changes a multilevel adaptive system at a molecular entry point. The downstream consequences may include altered plasticity, different emotional processing, new learning and changed behaviour. In some cases the drug may make other forms of change easier rather than completing the treatment by itself.

The chemical-imbalance metaphor was therefore wrong in its simplest form, but the lesson should not be that chemistry is unimportant. Chemistry is extraordinarily important. A few milligrams of a molecule can alter sleep, fear, attention, motivation, perception or the sense of self. The mistake is to confuse the power of chemistry with the completeness of chemical explanation.

A mature neurobiology of mental illness must therefore be both biological and non-reductionist. It must allow genes, transmitters, circuits, development, learning, bodies and social environments to interact without pretending that one level cancels the others. This is harder than saying that a chemical is too high or too low, but it is much closer to the kind of system the brain actually is.

Once we abandon the idea that every patient with a diagnosis shares one chemical defect, individual variation moves to the centre of the problem. The next chapter asks why the same pill can produce very different outcomes in different people.

Fig. 18.3 | Many paths to the same symptom