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The Neuroscience of Despair

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The gray fog of depression never drifted far from David Foster Wallace. His time in and out of psychiatric wards formed some of the background for his acclaimed novel *Infinite Jest* (1996), an exploration—satirical and loving in equal measure—of turn-of-the-millennium America. One of Wallace's main concerns was to bridge the existential islands we each inhabit; *Infinite Jest* envisions a society of individuals struggling to relate to each other, ensnared by their addictions to escapism and personal fulfillment. His prose meticulously constructs the inner lives of drug addicts and bureaucrats, their myriad contradictions apparent to everyone but themselves. In a 1993 interview, Wallace said that "really good fiction could have as dark a worldview as it wished, but it'd find a way both to depict this world and to illuminate the possibilities for being alive and human in it."

In 2008, a year after deciding to quit the antidepressant Nardil because of its potent side effects, Wallace committed suicide at the age of forty-six. His friend and fellow author Jonathan Franzen wrote, "David had 'good' reasons to go off Nardil—his fear that its long-term physical effects might shorten the good life he'd managed to make for himself; his suspicion that its psychological effects might be interfering with the best things in his life.…" But Franzen thought there also were bad reasons for quitting the drug: "the old addict's consciousness, the secret self, which, after decades of suppression by the Nardil, finally glimpsed its chance to break free and have its suicidal way."

Whether or not Franzen's words faithfully capture Wallace's predicament, the circumstances of Wallace's suicide reflect a striking fact: taking drugs to alleviate depression and related maladies has become entirely normal. This normalization would not have been possible without an extensive decades-long shift in our understanding of depression—a turn away from its social and psychological dimensions toward postulated chemical and biological causes. The shift reflects important changes in the theoretical and practical commitments of psychiatry more broadly and gives occasion for thinking about contemporary psychiatry's image of what mental disorders are—an image that at times distorts the complex nature of mental illness.

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The new way of looking at mental disorders has been variously called the "psychopharmacology revolution," the "neuromolecular gaze," the "medical model," and the "pharmacocentric approach." The terms capture different facets of a conception of mental disorders that seeks their origins in the neurophysiological processes of the brain. Under this conception, mental disorders are natural entities that inhere in the brain and generate the first-person experience of the illness. They are primarily caused by malfunctions of neurobiology, as opposed to harmful social settings or psychological conflicts within the self.

Wallace knew firsthand this shift toward predominantly neurobiological accounts and therapies for mental disorders. About fifty pages into *Infinite Jest* there is a deeply tragic yet almost comical scene that places a mirror before the new image of mental illness. Two characters watch a TV documentary entitled "*SCHIZOPHRENIA: MIND OR BODY?*" This is what follows:

> And so but since the old CBC documentary's thesis was turning out pretty clearly to be *SCHIZOPHRENIA: BODY*, the voiceover evinced great clipped good cheer as it explained that well, yes, poor old Fenton here was more or less hopeless as an extra-institutional functioning unit, but that, on the up-side, science could at least give his existence some sort of meaning by studying him very carefully to help learn how schizophrenia manifested itself in the human body's brain . . . they could scan and study how different parts of poor old Fenton's dysfunctional brain emitted positrons in a whole different topography than your average hale and hearty nondelusional God-fearing Albertan's brain, advancing science by injecting test-subject Fenton here with a special blood-brain-barrier-penetrating radioactive dye and then sticking him in the rotating body-sized receptacle of a P.E.T. Scanner. . . .

The unnamed "they" who hope to discover a neurobiological basis of schizophrenia seem incapable of recognizing the abyss of Fenton's suffering. They treat him as nothing more than an instance of schizophrenia. The consolation that science promises is completely lost on Fenton, whose "worst delusional fears came true" amid the whirring of the P.E.T. scanner. The scene is absurd, but, as we will see, it strikes closer to home than we may wish to admit.

Together with the popular success of psychoactive medications like Prozac and Xanax, the change in the commitments of psychiatry has created ways of talking about mental illness that would have seemed outrageous or even nonsensical less than a century ago. Many of us now

blithely accept that depression results from an imbalance of neurotransmitters. While the neurobiological understanding of mental disorders is still at a rudimentary stage, drugs that alter brain chemistry have definite palliative effects, and we increasingly look for and accept explanations of mental illness in neuroscientific terms. We might still take older explanations drawn from psychoanalysis or social psychiatry to hold some value, but we tend to assume that they can be reduced to neurobiology.

We generally think that this counts as progress—that science has uncovered or will uncover the real causes of mental disorders like depression and schizophrenia, and will yield therapies that cure these illnesses at their neurobiological roots. But as more and more mental experiences get swept within the purview of neuroscience—from mental disorders like schizophrenia to everyday decisions like "Should I buy Coke or Pepsi?"—we ought to think about how this came about, what it means for our self-understanding, and whether the new outlook can give an adequate account of mental disorders. How did we come to think of some forms of melancholy as a disorder called depression that is ultimately caused by chemical processes and properly treated by drugs that act on these processes? A look back at the historical developments that have led to this situation may offer some insight into the broader trend of uncritically embracing neuroscientific ways of describing our selves and our society.

Shifting Definitions

In the two decades following the Second World War, depression was considered a relatively rare disorder, more likely to be experienced by hospitalized patients than otherwise healthy people. Today, however, the Centers for Disease Control and Prevention estimates that 9.1 percent of adults in the United States are currently experiencing depression. A recent editorial in *Nature* claimed that "measured by the years that people spend disabled, depression is the biggest blight on human society—bar none." What accounts for this change?

It will help to identify two broad periods in psychiatry's standard conception of depression: before 1980, when psychoanalysis still held sway, and after 1980, when depression became defined according to symptom-based classification. These two periods are marked by contrasting criteria for diagnosis in the *DSM* (*Diagnostic and Statistical Manual of Mental Disorders*), the "bible" of clinical psychiatry published by the American Psychiatric Association. While the use of the *DSM* in the everyday practice of clinical psychiatry varies greatly and some psychiatrists hardly

use it at all, it standardizes definitions of mental disorders and supplies a *lingua franca* for research, thereby providing a basis for measuring the prevalence of mental disorders and agreeing on their diagnoses.

The change that occurred in 1980 was pivotal for two reasons: first, it introduced a qualitatively different notion of depression, one that focused on overt symptoms rather than internal psychological stresses; second, in ignoring patient history and social context as criteria for diagnosis, it unintentionally led to an increase in the number of diagnoses.

First, the qualitative change. In the *DSM-I* (1952) and *DSM-II* (1968), non-delusional forms of depression had been regarded as manifestations of an underlying anxiety disorder. For example, the *DSM-I* classified the non-delusional form of depression, which it called "depressive reaction," as follows:

> The anxiety in this reaction is allayed, and hence partially relieved, by depression and self-depreciation. The reaction is precipitated by a current situation, frequently by some loss sustained by the patient, and is often associated with a feeling of guilt for past failure or deeds. The degree of reaction in such cases is dependent upon the intensity of the patient's ambivalent feeling toward his loss (love, possession) as well as upon the realistic circumstances of the loss.

Depression is understood here as a sort of defense mechanism for the underlying condition of anxiety set off by challenging life circumstances. While today we typically think of anxiety as a fleeting reaction to a challenging situation, in the 1950s and 1960s it was seen as a prolonged mental condition of distress associated with many of the symptoms that now define depression. Depression has largely taken the place of anxiety as the illness category for these symptoms. Sociologist Allan V. Horwitz, a leading researcher on the history of depression, wrote in a 2010 *Milbank Quarterly* article that "beginning in the 1970s until the present, *depression* rather than *anxiety* has become the common term used to indicate the breadbasket of common psychic and somatic complaints associated with the stress tradition," including melancholy, nervousness, malaise, and an array of physical, interpersonal, and financial problems.

Another aspect of the qualitative change was that the *DSM* definition of depression ceased relying on an interpretation of the patient's lived experience. Under the *DSM-I* and *DSM-II*, in order to be diagnosed with depression, a patient's malaise had to be an abnormal reaction to difficult life circumstances, one that exposed an underlying anxiety disorder. The patient's specific psychology and life history were all weighed in the

diagnosis, not just the observable symptoms and behavior (such as loss of appetite or inability to sleep).

But beginning with the *DSM-III* (1980), depression came to be defined almost exclusively by clusters of symptoms. The diagnostic criteria for a major depressive episode according to the *DSM-III* include at least four of eight symptoms—ranging from insomnia and fatigue to feelings of worthlessness and disinterest in daily activities—which must be present almost every day for at least two weeks. Later *DSMs* further expanded and refined these criteria. Post-1980 editions of the *DSM* do not conceptualize depression as a reflection of an underlying anxiety disorder, and they do not necessarily see it as a reaction to difficult life circumstances.

The *DSM-III* was lauded as the triumph of science over the ideological approaches that supposedly tainted earlier *DSMs*. In a 1982 debate on the *DSM-III*, Gerald Klerman, former head of the Alcohol, Drug Abuse and Mental Health Administration, hailed the manual as a victory for psychiatry, which often spends "more time fighting ideological battles than generating data." He pointed out the advantage of diagnostic criteria "based on manifest descriptive psychopathology rather than on presumed etiology—psychodynamic, social, or biological." Melvin Sabshin, medical director of the American Psychiatric Association for over two decades, wrote in a 1990 journal article that the move to the *DSM-III* was a decisive shift from a "predominance of ideology over science" to a "predominance of science over ideology."

Among other things, Klerman and Sabshin praised the fact that the *DSM-III* grounded diagnosis purely on symptoms. Symptom-based classification had played a minor role in the earlier manuals because psychiatrists generally thought that a focus on symptoms could distract from the underlying personality conflicts at the core of mental illness. In the aim of integrating psychiatrists with competing theoretical views, the *DSM-III* remained agnostic about the causes of disorders like depression.

While the new approach to mental disorders proved a boon to the standardization of psychiatry, it also unintentionally expanded the diagnostic category of depression. As compellingly argued by Horwitz and NYU professor Jerome C. Wakefield in *The Loss of Sadness* (2007), in attempting to draw more objective boundaries between normality and disorder, the *DSM-III* largely ignored patient history and social context as criteria for diagnosis, allowing many normal reactions to life circumstances to become classified as depression. For example, what we sometimes regard as normal sadness or grief over loss could be diagnosed as depression if it satisfied the necessary symptom criteria for major depressive disorder.

And, as Horwitz and Wakefield describe, "the *DSM-III* abandoned the *DSM-II* distinction between 'excessive' versus proportionate reactions to an 'identifiable event such as the loss of a love object or cherished possession,'" even though many other disorder categories in the *DSM-III* rely on similar distinctions to prevent normal responses to life circumstances from being diagnosed as disorders. By removing the distinction between excessive versus proportionate reactions, the *DSM-III* invited a wider variety of conditions to be classified and treated as depression. The result has been, in the view of Wakefield and Horwitz, "a massive pathologization of normal sadness that, ironically, can be argued to have made depressive diagnosis less rather than more scientifically valid."

A similar pattern played out in the decision to remove the "bereavement exclusion" from the criteria for diagnosing major depressive disorder in the manual's most recent edition, the *DSM-5*. (Published in 2013, the title of this new edition swapped the Roman numeral for an Arabic numeral.) The bereavement exclusion had been put in place to avoid diagnosing people grieving the death of a loved one as clinically depressed. Part of the justification for removing the bereavement exclusion is that grief and depression can coexist in a single patient; removing the exclusion enables such patients to receive appropriate treatment. As a concession to objections that the new edition pathologizes normal grief, the *DSM-5* includes a "Note" explaining that symptoms of grief may closely resemble symptoms of a depressive episode. The note concludes that the decision of whether a patient is merely grieving or is also experiencing a depressive episode "inevitably requires the exercise of clinical judgment based on the individual's history and the cultural norms for the expression of distress in the context of loss."

This may not be sufficient for distinguishing between grief and depression, especially when the psychiatrist who led the *DSM-5*'s Mood Disorders Workgroup reported that the group "decided to remove the bereavement exclusion from the major depressive episode diagnosis based on data indicating that when a patient meets the criteria for a major depressive episode, the response to treatment is identical to that for any major stressor preceding a major depression." The assumption here—that an equivalent response to treatment for grieving and depressed patients justifies classifying the former as depressed—is clearly wrong (as has been more fully discussed by Jerome Wakefield in a recent paper in *Clinical Psychology Review*). Even so, the *DSM-5*'s note attempts, however feebly, to bring the patient's life history and social context back into the sphere of diagnosis. We might wonder, though, why the same logic would

not also apply to *other* personal losses that can trigger the symptoms of depression, such as divorce or financial ruin. The *DSM*'s symptom-based framework does not take into account life history or social context in these cases, arguably resulting in a faulty conception of depression and a widespread pattern of overdiagnosis.

All the aforementioned changes—the shift around 1980 from a focus on anxiety to depression, the move to symptom-based diagnosis and the consequent widening of the category of depression—only tell half of the story. We next need to see how they coincided with an increasingly firm commitment to neurobiological accounts of and drug treatments for depression.

We Have Just the Drug You Need

The therapeutic potential of the first antidepressants was realized serendipitously before there was any such thing as a basic neurobiological theory of depression. In 1952, researchers observed that an anti-tuberculosis drug undergoing clinical trials exerted a powerful mood-altering effect on patients, affecting some patients' moods for better and others for worse, while some alternated between elation and depression. This discovery led, after a decade of further research, to the first clinical use in treating depression of a kind of drug called an MAOI (pronounced by saying each letter, it stands for monoamine oxidase inhibitors). Also in 1952, researchers noticed that a different drug being used to help induce anesthesia had a calming effect; this led to the discovery of a family of drugs called TCAs (for tricyclic antidepressants).

Early MAOIs and TCAs represented an advance for psychiatric treatment, but they came with a host of deleterious side effects. Today these drugs are prescribed less frequently than a newer class of antidepressants, the SSRIs (selective serotonin reuptake inhibitors) that have been developed since the 1970s. The improved safety and effectiveness of SSRIs (which include the famous brand names Prozac, Paxil, and Zoloft) over the older MAOIs and TCAs enabled primary care physicians to prescribe antidepressants, which previously only psychiatrists were allowed to do, making antidepressants more readily available. Even the SSRIs, however, are generally ineffective. Many patients find that antidepressants do not alleviate their depression, and some find that the drugs have no impact on their moods at all. A 2002 meta-analysis published in the journal *Prevention and Treatment* found that for six of the most prescribed antidepressants, placebo control groups matched 82 percent of the medication

response. This situation led a 2014 article in *Nature* to claim that "five decades of work on antidepressant drugs have not made them more likely to lift people out of depression." It has also led pharmaceutical companies to develop secondary drugs intended to enhance the effectiveness of antidepressants, with multi-drug treatment becoming more common.

Despite the limited effectiveness of antidepressants and the theoretical gaps in understanding how they work, they have immensely shaped the theory and practice of psychiatry. The drugs provided clues to chemical processes involved in depression, which fueled attempts to formulate hypotheses for neurobiological causes of depression. These hypotheses were first formulated by looking at the biochemical effects of antidepressant drugs and attempting to infer the neurobiological abnormalities they were thought to fix.

But antidepressants were much more than an example of new technology changing the course of scientific research; they also helped widen the range of symptoms thought to be caused by depression. The Food and Drug Administration loosened restrictions on direct-to-consumer advertisements in the late 1990s, allowing pharmaceutical companies to run ads for antidepressants in national magazines, television shows, and elsewhere. Many of these advertisements limned the most general and benign symptoms included in the *DSM*'s criteria for depression (like irritability and fatigue) and their role in interpersonal problems and workplace difficulties, implicitly pushing the idea that drugs could relieve everyday human troubles.

Before these changes in FDA regulations, pharmaceutical companies advertised mostly to physicians and psychiatrists in specialized medical journals rather than mainstream outlets. The change in regulations allowed for "educational" advertising that focused on the disorder instead of the drug itself. As Horwitz writes, Prozac advertisements showed women happily performing work and family roles, using slogans like "better than well." Pharmaceutical companies sold the idea of depression as much as the drugs themselves, promoting the belief that depression stems from a chemical imbalance in the brain, with a marketing apparatus rival in scope to national political campaigns. (By 2000, pharmaceutical companies were spending over $2 billion in direct-to-consumer advertising. By comparison, spending by candidates in the 2000 presidential election totaled a mere $343 million.) This marketing effort played no small part in shaping the public's understanding of depression.

The sales of antidepressant drugs increased in kind. According to a 2002 article in the *Journal of the American Medical Association*, "patients

treated for depression were 4.8 times more likely to receive an antidepressant in 1997 than in 1987." And a 2005 article in *Health Affairs* reported that in a period of merely five years, between 1996 and 2001, overall spending on SSRIs and other new antidepressants rose from $3.4 billion to $7.9 billion. Edward Shorter writes in *A History of Psychiatry* (1997) that antidepressants became so popular that "patients began to view physicians as mere conduits to fabled new products rather than as counselors capable of using the doctor-patient relationship itself therapeutically." While this description may overstate things, it seems likely that the growing popularity of antidepressants and other psychoactive drugs began to reshape our conventional notions of mental disorders.

A Deficient Theory

It is really not known how drugs alleviate the symptoms of mental disorders," wrote neuroscientist Elliot S. Valenstein in his book *Blaming the Brain* (1998), "and it should not be assumed that they do so by correcting an endogenous chemical deficiency or excess." Valenstein was referring to chemical deficiency (or chemical imbalance) theories of depression, which postulate that depression results from low concentrations of certain neurotransmitters in the brain. Valenstein's words remain true today: every time a new neurobiological theory seems like it might explain depression, evidence comes along to demonstrate the theory's inadequacies. The last half century of attempts to formulate such a theory can be summed up by Kafka's remark: "Like a path in autumn: no sooner is it cleared than it is once again littered with fallen leaves."

The original chemical deficiency theory of depression dates back to 1965, when Harvard psychiatrist Joseph J. Schildkraut hypothesized that low levels of catecholamines—a kind of neurotransmitter, or brain chemical—were associated with depressive disorders, with high levels corresponding to feelings of elation. The paper remains one of the most frequently cited in the history of psychiatry. While the hypothesis may appear rudimentary today, it laid the groundwork for current chemical imbalance theories of depression.

Schildkraut inspired the development of the monoamine hypothesis, which postulates that deficiencies in certain neurotransmitters such as serotonin and dopamine cause depression. (Monoamines are a class of neurotransmitters that includes serotonin, dopamine, and catecholamines, such as norepinephrine.) In contrast to early antidepressant drugs, which were discovered serendipitously, the later SSRIs were designed on the

basis of the monoamine hypothesis. They were expressly engineered to increase the amount of serotonin available in synapses, the junctions between neurons. While SSRIs have proven to be more effective than most other antidepressant drugs, we know little about how they work beyond their immediate biochemical effects. One particular problem scientists have tried to understand is that while the physical effects of SSRIs and other antidepressant drugs transpire within minutes after consumption, the psychological effects typically take nearly two weeks to manifest. This difficulty has prompted further hypotheses and speculative modifications to the monoamine theory, but no empirically bulletproof explanation has thus far been found.

Evidence suggests that nothing close to the simple chemical deficiency hypothesis can be right. Despite intense efforts to correlate serotonin deficiencies with depression, most studies have been unable to do so. The same goes for other monoamines, too. Only about 25 percent of depressed patients actually have low levels of serotonin or norepinephrine, according to Valenstein, suggesting that other processes are involved.

These shortcomings have not stopped the chemical imbalance theory from shaping popular discourse about depression and mental illness in general. Advertisements for antidepressants and anti-anxiety medications have frequently appealed to the chemical imbalance hypothesis, sometimes cartoonishly depicting the deficiency in neurotransmitters that was supposed to cause depression. A Prozac advertisement that ran in *Newsweek*, *Time*, and other popular magazines around 1997 and 1998 explained:

> When you're clinically depressed, one thing that can happen is the level of serotonin (a chemical in your body) may drop. So you may have trouble sleeping. Feel unusually sad or irritable. Find it hard to concentrate. Lose your appetite. Lack energy. Or have trouble feeling pleasure.... To help bring serotonin levels closer to normal, the medicine doctors now prescribe most often is Prozac.®

The advertisement respects FDA regulations against false drug advertising statements by including the qualification "one thing that can happen," though it presents a seductive explanation of a whole range of woes we experience on a daily basis. The mismatch between the empirical status of the chemical deficiency hypothesis and its portrayal in pharmaceutical advertisements led a 2005 paper published in *PLOS Medicine* to conclude: "The incongruence between the scientific literature and the claims made in FDA-regulated SSRI advertisements is remarkable, and possibly unparalleled." This kind of aggressive advertising on the part

of the pharmaceutical companies (among other practices like political lobbying, incentivizing doctors to prescribe their products, and promoting screening for depression) has led many authors to lambast the pharmaceutical industry for selling the idea of depression just as much as its treatment.

The chemical deficiency hypothesis may itself be deficient, but it helped make possible a new subdiscipline, biological psychiatry, in which mental disorders are understood as arising from facts about the biology of the person. Most psychiatrists today point to more complex explanations than those offered by Schildkraut in the 1960s. For instance, in a 2011 letter to the *New York Review of Books*, two psychiatrists wrote of "recent advances in neuroscience research that demonstrate that depression is not a disease of a single neurotransmitter system or brain region but probably a disorder that involves multiple neural circuits and neurotransmitters." Schildkraut himself stressed that his chemical imbalance hypothesis was "undoubtedly, at best, a reductionistic oversimplification of a very complex biological state," and that it was properly regarded as a heuristic rather than a sufficient explanation of the neurobiology of depression. Yet the form of explanation, in which a mental disorder is related to a neuronal abnormality, has not changed since Schildkraut's hypothesis first took hold, and today we seem ever more committed to neurobiological explanations of mental illness. How far can they go?

The Limitations of the Medical Model

Contemporary psychiatry largely adheres to what is called the "medical model," treating mental disorders including depression as diseases or harmful deviations from normal bodily functioning no different in kind from physical maladies like heart disease or arthritis. Since the medical model aims to cure the patient by correcting the underlying pathology, treatment is ideally directed at whatever neurological dysfunction is thought to produce depression.

In its strong form, the medical model rules out the possibility that intentionality—the power of minds to represent or be *about* something—plays a genuine causal role in producing mental illness. Mental health specialists Derek Bolton and Jonathan Hill claim in *Mind, Meaning, and Mental Disorder* (1996) that modern psychiatric diagnosis "has borrowed the assumption that intentionality has run out, that there has been a disruption of functioning, and that a non-intentional causal process is responsible." In this picture, causal processes run through the brain, and

they are independent of the meaningful thoughts of the bearer—our first-person experience is just along for the neurobiological ride, so to speak. And to understand depression, all we would have to do is figure out the neural mechanisms that cause it. But if this assumption is wrong—if intentionality *is* present within mental phenomena and cannot be reduced to mere mechanisms and processes—then biological psychiatry would have a gaping blind spot, and would never be able fully to resolve depression or other mental disorders.

Another problem for neurobiological explanations of depression is that a mere correlation between a particular brain state and symptoms of depression in some people does not prove that other people with that brain state have a disorder. As Horwitz and Wakefield say in *The Loss of Sadness*, "the findings of current studies of neurochemicals and depression are often uninterpretable because they do not adequately make this distinction" between disorder and normal responses to difficult circumstances.

Further, showing a correlation between a brain state and symptoms of depression does nothing to determine a direction of causality between these two. In a 2002 review of neurobiological approaches to mood disorders in *Biological Psychiatry*, the authors explained that "we do not know if any of the abnormalities…, both of a structural and functional variety, precede the onset of the disorder, co-occur with the onset of the disorder, or follow by some time the expression of the disorder." Unless we know that particular brain states actually precede symptoms of depression, it remains plausible that the arrows of causation point in the other direction—that one's personal history or mood gives rise to the neurophysiological patterns. In that case, a neurobiological account would be less an explanation of the disorder than a description of the concomitant brain processes.

The best evidence for the causal direction implied by neurobiological explanations of depression is arguably the fact that psychoactive drugs do affect moods. If we could know the full range of biochemical effects of an antidepressant drug in the brain, we might be able to infer the original neurophysiological dysfunction, provided that the drug effectively alleviates depression and does not simply cover it over by acting on certain symptoms. The difficulties to such an approach have been well documented: not only are antidepressants at best marginally more effective than placebos in treating depression, but they often work almost as well on a range of other maladies, including anxiety, attention deficit disorder, and substance abuse. The latter observation suggests that these drugs do not target specific neurophysiological abnormalities responsible for depression, but instead alter very general brain functions.

A more general worry with an exclusively biological or medical approach is the assumption that conditions like depression are what philosophers call "natural kinds"—categories that exist in nature and are independent of human thought—that inhere in brain processes. While it is generally safe to consider electrons and cancer cells as natural kinds, the naturalness of mental conditions like depression, which we come to know in a very different way than these other entities, is fiercely contested. Though the full philosophical dimensions of the problem cannot be explored here, it might be enough to remind ourselves that our conception of depression—even within professional psychiatry—is sensitive to sociocultural pressures in a way that our conceptions of helium and electrons and cancer cells are not. The role that social and cultural forces have played in shaping our notions of depression has been well documented in Allan Horwitz's *Creating Mental Illness* (2002) and Dan Blazer's *The Age of Melancholy* (2005). Someone committed to an entirely biological account of mental illness would need to rebuild categories like depression from the neurobiological ground up, showing which brain states correspond to which symptoms—a task that depending on one's philosophical persuasion will be exceedingly difficult or altogether impossible.

What Role for Society?

When researchers study mental disorders nowadays, biological causes are usually given priority over potential psychological and social causes. The 1999 Surgeon General's report on mental health reflects this priority:

> Mental disorders are characterized by abnormalities in cognition, emotion or mood, or the highest integrative aspects of behavior, such as social interactions or planning of future activities. These mental functions are all mediated by the brain. It is, in fact, a core tenet of modern science that behavior and our subjective mental lives reflect the overall workings of the brain. Thus, symptoms related to behavior or our mental lives clearly reflect variations or abnormalities in brain function.

To reach its conclusion, the passage rehearses a philosophical picture deeply rooted in biological psychiatry: on one side are brain functions, on the other side are mental functions, and the interaction between them is one-way from the former to the latter. Our "subjective mental lives" are a consequence of neurophysiological processes; the question of why some person is experiencing anxiety, depression, or despair is then to be sought

in a particular biological fact. Of course, we do not yet know what those facts are, but we generally expect future scientific research eventually to reveal them.

To illustrate how potentially problematic this reasoning is, consider a different case to which it applies. Suppose you are an abnormally kind person, going to exceptional lengths to fulfill others. Why, we might wonder, are you so kind? It would generally be odd to look for an answer to this question by searching for an abnormality or variation in brain function, even though your kindness certainly might be associated with one. Yet this is what the picture commits us to, as it gives explanatory priority to biology instead of a person's social environment or personal history.

This is a far cry from the 1950s and 1960s, when mental illnesses were largely understood as psychosocial problems. Social psychiatry, studying the impact of the social environment on the mental health of the individual, gained momentum in the United States following World War II. Inspired by Freud's psychoanalysis and Durkheim's pioneering work in sociology, the trend was based on the assumption that mental illnesses were the product of social dynamics. Driven by both theory and social activism, social psychiatry focused on primary prevention—thwarting the onset of diseases instead of only treating them after they arose. After modest success and influence in the 1950s and 1960s, such as the passage of the Community Mental Health Act of 1963 (which established local mental health centers across the country), social psychiatry lost its stature to biological psychiatry. Today, interest in the social context of mental illness is marginal. The agenda of the National Institute of Mental Health, which once focused on community-based research on mental illness, is now dominated by biological and epidemiological studies of specific disorders, along with estimates of their economic costs.

It is a banal but important point that how we conceive of a problem largely determines how we respond to it. There is nothing inherently wrong with arguing that the causes of an illness lie at a particular biological level. And as has been demonstrated by the success of antidepressants and other psychoactive drugs, treating depression at the biological level *works*, at least to a limited but sometimes life-saving degree. But we should be more cognizant of the fact that when depression is understood as an essentially neurobiological problem, we will limit ourselves to neurobiological solutions—to drugs or other treatments like electroconvulsive therapy that act more or less directly on the brain—while forgoing other potentially helpful therapies and prevention strategies.

Some scholars argue that while social conditions and intentional thought processes do profoundly affect the expression of mental illness, these effects are to be understood solely through the lens of biology. Eric Kandel, a neuroscientist and Nobel laureate, writing in *Psychiatry, Psychoanalysis, and the New Biology of Mind* (2005), proposed along these lines that the guiding question for psychiatry ought to be: "How do the biological processes of the brain give rise to mental events, and how in turn do social factors modulate the biological structure of the brain?" Notice that Kandel aims to understand the social contributions to mental illness in a thoroughly non-intentional manner. Instead of explaining depression as a result of a person's distinctive experience of grieving for a loved one, for example, Kandel wants psychiatry to explain that person's depression only in terms of changes to the brain that occur after the death of a loved one. For Kandel and biological psychiatry, "these social influences will be biologically incorporated in the altered expressions of specific genes in specific nerve cells of specific regions of the brain." The broader project is to understand social influences only with regard to their impact on gene expression (which in turn gives rise to particular brain states), rather than on the patient's psychology.

Even if one were to agree with Kandel's assumption that the impact of social phenomena on the brain should be understood as a non-intentional causal process, there are serious practical concerns that remain. While it might be theoretically possible to incorporate social patterns of interaction into psychiatry by analyzing their effects on the brain, it is very likely that such an approach would still focus only on the more immediate causes rather than on potential long-term social and environmental causes. This is evidently already the case. For instance, most of the research related to schizophrenia today concerns itself with genetic mechanisms, even though a harmful social environment is a much greater risk factor. As the authors of a 2012 article in *Nature Neuroscience* put it, "there is strong epidemiological evidence supporting a causal role for social environmental risk factors in neuropsychiatric disease, but very little empirical or theoretical accounts of how these factors may impact the brain." Once it is assumed that only non-intentional processes that run through the brain are responsible for mental illness, social elements tend to acquire a secondary status. They may be seen as indirect causes of mental illness, and thus less amenable to scientific analysis.

A relatively new field called social neuroscience aims to redress this state of affairs by explaining how social processes act on the brain and how the brain controls social behavior. Examples of recent work include

a 2011 study published in *Nature* that finds an association between amygdala activity and being raised in an urban environment, and a 2011 article in *Nature Reviews Neuroscience* on the role of oxytocin and vasopressin in mental disorders characterized by social dysfunction. While the field attempts to unveil causal relationships between social patterns and brain processes and thus develop new therapeutic strategies, its focus is and always will remain the brain, not human sociality. The new treatment strategies that may emerge from social neuroscience will almost certainly be brain-based interventions that are the mark of biological psychiatry. A 2014 paper coauthored by one of the pioneers of the field, John T. Cacioppo, is telling. It concludes that social neuroscience provides a perspective "in which pharmacological intervention could be viewed as a strategy for improving social function." While social neuroscience might identify certain social conditions as having important causal roles in mental illness, the only solutions that social neuroscience will be able to offer are strategies for altering the brain. This is not to fault social neuroscience itself, but to point out that it cannot address the harmful social processes that help give rise to mental disorders.

The larger concern is that in our eagerness to resort to brain-based explanations, we sacrifice an interpersonal form of understanding. While social neuroscience appears capable of illuminating myriad connections between social and biological phenomena, and therefore of uncovering the ways in which social conditions mediate mental illnesses like depression, our enthusiasm for it may turn us away from the kinds of contemplation and action through which we relate to other human beings. As Benjamin Y. Fong, a scholar of philosophy and religion, put it in a blog post on the *New York Times* website, "neuroscientists unconsciously repress all that we know about the alienating, unequal, and dissatisfying world in which we live and the harmful effects it has on the psyche, thus unwittingly foreclosing the kind of communicative work that could alleviate mental disorder."

Perhaps this verdict is a bit too harsh, but it hints at a deep ambivalence facing biological psychiatry. While the drugs for treating depression have life-saving potential, we are left with the sense that they do not treat the real causes of mental illness. When certain mental disorders are conceived as entirely natural phenomena whose origins lie in realms accessible to chemical cocktails but not human action as such, we risk assuming that it is easier or more realistic to confront the brain than to address certain unfair or deeply unsettling aspects of our existence on their own terms.

The Neuroscientific Image

Writing in the 1960s, the American philosopher Wilfrid Sellars described a shift away from what he called the "manifest image" towards the "scientific image" of human beings. By the manifest image, Sellars had in mind our everyday perceptions along with the non-scientific concepts through which we act and find our way about in the world. The scientific image, by contrast, is a theoretically unified system of description and explanation that integrates the discoveries of various sciences. For Sellars, the key difference between them is that the scientific image postulates objects and events unavailable to ordinary perception, such as electrons and brain states, to explain correlations among perceptible things, while the manifest image limits itself to introspection and unaided observation. Sellars thought that the primary question facing philosophy was how to reconcile these two ways of experiencing and knowing the world, each of which purports to be "the *true* and, in principle, *complete* picture of man-in-the-world."

The evolution in recent decades of how we think about, study, diagnose, and treat depression is a powerful case of Sellars's scientific image. This "neuroscientific image" would seem to leave no room for human agency. If all our actions are consequences of non-intentional causal processes that run through the brain, then our actions can be reduced to mere happenings like lightning strikes or lunar eclipses. This is roughly the picture that biological psychiatry works with in searching for the origins of mental disorders and devising treatments. Sellars, for his part, spent his career trying to formulate a "synoptic" view that would reconcile the manifest and scientific images. Among other things, such a view would give a satisfying account of the relation between intentional and non-intentional phenomena, bridging a rift at the root of arguments over the nature of mental illnesses. It would do justice to a biological understanding of mental disorders without denying first-person experience as a legitimate way of accounting for them.

Whether such a reconciliation is possible for our understanding of depression has yet to be seen. We currently do not have any criteria that would enable us to examine someone's brain and discern whether that person is depressed, and there are reasons for thinking that we never will. Unlike many bodily diseases, which we can diagnose by identifying harmful deviations from normal bodily functioning, we can only identify depression by interpreting a wide spectrum of experience, from bodily symptoms to the most inchoate thoughts about our role in the world.

We can be grateful to the neuroscientific image of depression for its very real success in producing drugs that have helped many patients. But this image does not give us a complete explanation of depression, let alone a real grasp of the terrible suffering it produces. In addressing one kind of pain—the kind that science can help us to diagnose and allay—we risk ignoring other, potentially deeper and more existential pains, a proper understanding of which demands entangling ourselves in the web of human thought and action.