From Chaos to Consilience: Part IIWhat the New Mind-Body Science Tells Us About the Pathophysiology of Major Depression

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We would suggest that psychiatry has spent so many years taking its diagnostic categories as God-given that it has become inured to the fact that these categories tell us very little about the etiology and fundamental nature of the conditions they purport to encompass.[1]
Nowhere is this truer than in the case of depression. While the DSM—like all mythopoetic creations—has been forced to grapple with the complexities of reality by creating an ever larger cast of characters related to one another in ever more complicated ways, the types of deep, consilient understandings of depression that would unify rather than splinter, and that would empower rather than enfeeble, our therapeutic efforts have been consigned to the province of future science.

In this—the second installment in our series on mind-body approaches to mood disorders—we suggest that the future is now. Although we are far indeed from a full understanding of all the intricacies of depression, scientific advances during the past decade in fields ranging from immunology to evolutionary biology already provide the outlines for a theory of depression that is

consistent, inclusive, and (most important) provides intellectually satisfying and testable answers to many basic questions in front of which the DSM must raise a finger to its lips in silence.

Because of space constraints, we can provide only the barest overview of this theory here. We invite you to log on to www.psychiatrictimes.com for a longer and more rigorous discussion of these ideas.

What is depression?

All over the world, depression is the most common emotional/behavioral breakdown pathway for human beings in response to environmental adversity. It is highly stereotyped but also irreducibly probabilistic.[2] It is how humans tend to feel and behave when the internal or external environment seems unmanageably threatening. Tethered to systems necessary for survival, depression is a tendency and a vulnerability, an Achilles heel of hominid evolution.

Recent data increasingly suggest that depression is an emotional/behavioral manifestation of hyperactivity in brain-body systems that evolved to cope with danger and to adapt to changing environmental demands.[3-10] Hyperactivity in these systems is linked to—and perhaps causes—reductions in the activity of CNS pleasure/novelty and executive decision-making circuitry.[11,12] Across human evolution, these "danger pathways" have been most often activated by psychosocial struggles and by pathogen invasion, which goes far toward explaining why psychosocial stress and sickness are the 2 primary environmental risk factors for depression.

Why does depression have the symptoms it does?

The short answer is that depression looks so much like a combination of terrible stress and physical illnesses because, in our view, it is essentially a disorder of pathways in the brain and body that evolved to cope with stress and infection and that produce depressive symptoms when chronically hyperactive.[3,5,6,13] Strong support for this idea comes from studies showing that when bidirectional stress—inflammatory danger pathways are chronically activated—such as occurs during treatment with the cytokine interferon-alpha—most people become depressed or, if not depressed, then exhausted, achy, and upset.[14,15] Conversely, interrupt hyperactivity in key stress-related brain regions, such as the subgenual anterior cingulate, and many profoundly depressed patients have an immediate surcease of their internal torture.[16] Recent data also demonstrate that stimulating activity in cortical areas that suppress stress pathway activity, such as the dorsolateral prefrontal cortex, also leads to profound and rapid improvements in depression.[17]

Consider a young mammal separated from its mother. First comes the terror—the wailing and the calling out. And then with time a strange thing happens. The little animal grows silent, dull, and perfectly still. This all makes eminent sense: scream out when there is hope of rescue but conserve energy and hide from predators when the time for hope has passed.

Depression is an analogue of this phenomenon, which should come as no surprise given its evolutionary origins. Thus, in addition to the anxiety, fear, and internal pain produced by danger pathway activation/dysregulation, depression is also characterized by a loss of pleasure that can be profound. This reflects the fact that in addition to danger pathway activation, depression is typically associated with hypoactivity in "pleasure pathways" running from midbrain into anterior areas of the basal ganglia (ie, nucleus accumbens). Not surprisingly, many recent studies show that chronic activation of danger pathways—such as the innate immune inflammatory system—compromises dopaminergic signaling in pleasure pathways.[18]

Why are the genes for depression so common?

Short answer: Because genes identified thus far that increase the risk of depression are not depression genes per se but rather play more general roles in regulating systems that are responsible for multiple physiological functions essential for survival and reproduction. In general, they are genes for operating and regulating danger/ adaptation/pleasure pathways in the brain and body. Most often, risk alleles for depression increase/dysregulate activity in danger pathways and/or reduce activity in pleasure and executive pathways in the face of environmental adversity.[19,20] In good times or when exposed to supportive early environments, these alleles contribute to individuals who are perhaps more successful and happier than most.[21-23] Even in bad times, these genes probably promote reproductive success by engendering creativity and intelligence[24]—how else could they survive the threshing of natural selection if they did not confer occasional high pay-off selective advantages to counter their more frequent detrimental effects?

Nonetheless, these ideas are not settled science, and alternative views exist about potential adaptive advantages of depression or even whether genes that promote depression must confer some type of adaptive advantage to be retained in the human genome. Although genes that are specific for depression or that always cause depression regardless of environmental conditions have yet to be identified, this does not prove that such genes may not yet await discovery. If such genes

were ever found, it would be expected that they would be very powerful but also very rare and therefore would account for only a tiny fraction of individuals with depression.
Would it surprise you to learn that genes reported to increase the risk of developing depression in the face of psychosocial stress also seem to increase the risk of depression in the context of sickness?[25,26] Would you predict that these risk alleles might enhance survival in the face of infection early in life and that this might also account for their high prevalence in the human gene pool?[27]

Why is depression a risk factor for other diseases and why is it progressive?
While these seem like separate questions, the new mind-body science suggests that they are actually variations on a theme. Depression, in our view, is linked to most other modern illnesses because it shares an underlying pathophysiology with them.[18,28] Millions of years of evolution favored the development and retention of extremely robust stress and inflammatory danger pathways. When death and destruction lurked around every corner, the safest policy was to fire off one's danger pathways first and ask questions later. What did it matter if body and brain tissues were damaged a little each time these pathways activated if this kept one alive for today (an idea that has been popularized as allostatic load).[29] No need to worry about heart disease, cancer, or dementia if you were likely to die of infection by age 30.
Consider our plight today, however. The boss no longer rips your arm off when he shouts at you, and many of the jobs once done by inflammation have been farmed out to sanitation and modern medicine. But the old danger pathways just go on firing off every time someone looks at us sideways. The more they fire off, the more damage accumulates. When this occurs in the arteries, it is vascular disease[30]; when it promotes insulin resistance, it is diabetes[30]; and when it disrupts glial cell integrity and disorganizes neuronal signaling, it manifests as depression.[31,32] Given enough time, the damage usually accumulates everywhere—hence the high comorbidity between depression and most other major modern maladies.
Why is remission so important?
The new mind-body science suggests that depressive symptoms are a "shout out" that the brain and body are in a state that is inimical to optimal functioning and health in the modern world. Conversely, an implication of the ideas presented here is that depressive symptoms are not likely to improve unless a person's underlying danger pathway functioning normalizes, at least to some degree.[28,33] So remission is the best indicator we currently have that a person's underlying physiology has returned to a safer state. Of course, symptoms are not perfect. If they were, remission would heal all ills.[34] In fact, we know that even when remission is achieved, patients remain at greatly increased risk for sinking again into depression when compared with those who have never suffered depression.[35]
Join us next month as we apply the implications of recent scientific advances to the practicalities of diagnosing and treating depression.

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