Depression and the final frontier

Unholy ghost.
Mutilator of souls.
With these words, poet Jane Kenyon begins to capture the all-consuming horror of depression. The statistics, while not as evocative, are grim: worldwide, depression afflicts 350 million people, is the leading cause of disability, and is linked with the majority of suicides. In the US, 12% of men and more than 20% of women are affected by depression in their lifetimes. Beyond its sheer prevalence, depression causes a ripple effect: it worsens outcomes for other chronic conditions (1); is strongly associated with substance abuse (2); imposes an economic burden on the US of more than $210 billion (3); and, with maternal depression, endangers the health of children and infants (4).

Despite this, federal funding for depression research has historically been scarce and hindered our understanding of depression. Consider that in 2014, the NIH allotted more than seven times the amount of money it did for HIV/AIDS than for depression ($2.97 billion versus $415 million), despite the fact that depression affects more than ten times the number of people living with HIV/AIDS (16 million versus 1.2 million).

In its current state, depression is essentially a description of a constellation of symptoms: at least two weeks of a depressed mood and/or inability to experience pleasure, along with psychophysiological changes (e.g. in sleep, appetite, sexual desire, concentration, slowing in speech and action) that impair one's ability to function (5).

What causes depression, however, remains unclear — the classic hypothesis posits that the depressed brain has a deficiency of serotonin, norepinephrine and dopamine neurotransmitters. Yet although all our known antidepressants work by increasing the amount of neurotransmitters in the body, up to one-third of people don't respond significantly to these antidepressants (6) and for others, response can take up to six weeks. This suggests that there are much more complicated pathways implicated in depression. More basic science research is needed to refine our understanding, and two emerging fields of study — genome-wide association studies and

connectomics — offer promising glimpses into the future.

Conducting large-scale genome-wide association studies (GWAS), a newer tool in the field of research, has given insight into other psychiatric conditions such as schizophrenia and bipolar disorder; however, parallel advances in depression have been harder to achieve. This is likely due to a number of factors: the heritability of depression is relatively lower (e.g. 40% compared to bipolar disorder's 70%); moreover, the high prevalence of depression and the accompanying heterogeneity of genetic and non-genetic factors necessitate larger sample sizes to achieve significant findings. Finally, there remains limited understanding of how one's genotype is related to the variable phenotypes of depression.

Connectomics is another promising tool in depression research. The NIH's Connectome Project gives glimpses of future answers about the pathophysiology of depression by helping us understand how the structure of neural circuits corresponds with functional connectivity. Recent connectomic studies about depression have shown functional changes in the default mode network (which is linked to how someone processes the self) as well as the frontal-subcortical network (which helps regulate cognition and emotions) (7). Identifying these specific areas of the brain implicated in depression have the potential to elicit targets for future therapies.

The gains we make in understanding depression's pathways will revolutionize both public health and clinical care through prevention, diagnosis, novel treatments, and reducing stigma. First, understanding genetic and environmental risk factors will help target early, life-saving interventions towards susceptible populations that help save lives. Second, a bio-marker based on a better understanding of depression's pathophysiology will allow more accurate and cost-effective ways of screening and diagnosing depression. Third, a more nuanced understanding of what causes depression will promote the development of pharmaceuticals that are mechanistically different and helpful for those who have not found relief with the currently available therapeutics. Fourth, as depression becomes increasingly seen as a disease to be treated rather than a moral failure to be hidden, those who were previously silenced by stigma may finally receive treatment.

Improving the clinical care of depression will also affect society by lessening poverty and substance abuse, as well as strengthening families and the health of the economy. The poor are disproportionately more likely to be depressed, and that same depression often perpetuates the circumstances of poverty through impaired functioning and isolation. Also, in an attempt to stymie the pain of depression and because depression disheartens people to the point that consequences are irrelevant, people are prone to engage in self-destructive behaviors such as drug abuse and unsafe sex, often with devastating individual and public health results. Moreover, maternal depression impacts the next generation: children of depressed parents have poorer nutrition, lower IQ scores, and are more likely to run afoul of the law as well as have other mental illnesses. Finally, the economic burden of depression is monumental: lost lifetime earnings because of suicides linked with depression; and workplace impairment through both absenteeism (as depressed people are debilitated from chronic fatigue or physical pain) and presenteesim (being less productive even when one shows up for work). (8)

The mind is the final frontier for basic science research. Until it has been more fully explored and claimed by science, depression will continue to wreak havoc on individuals, families, and societies. Exciting tools like genome-wide association studies and connectomics offer hope that victory is on the horizon in the battle against this Mutilator of Souls.

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