NEUROSCIENCE

Shining Light on Depression

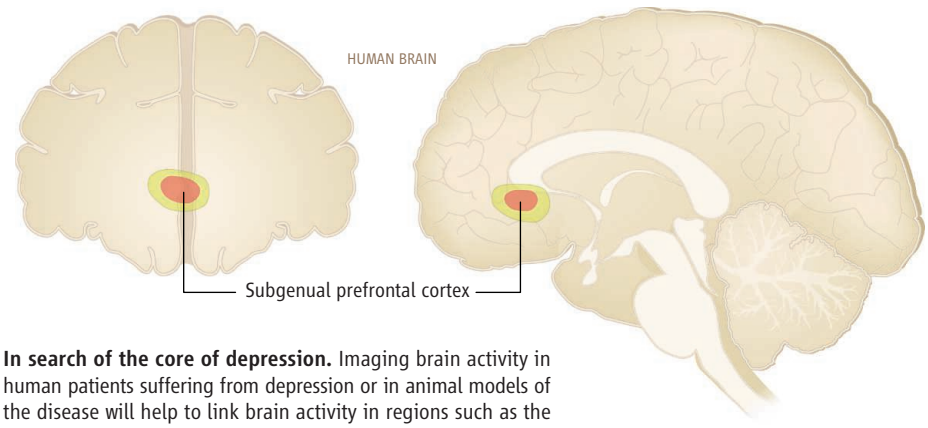
Real-time, high-speed optical imaging is a promising approach for elucidating networks of brain activity associated with depression.

Thomas R. Insel

Just as research during the Decade of the Brain (1990–2000) forged the bridge between the mind and the brain, research in the current decade is helping us to understand mental illnesses as brain disorders. As a result, the distinction between disorders of neurology (e.g., Parkinson's and Alzheimer's diseases) and disorders of psychiatry (e.g., schizophrenia and depression) may turn out to be increasingly subtle. That is, the former may result from focal lesions in the brain, whereas the latter arise from abnormal activity in specific brain circuits in the absence of a detectable lesion. As we become more adept at detecting lesions that lead to abnormal function, it is even possible that the distinction between neurological and psychiatric disorders will vanish, leading to a combined discipline of clinical neuroscience (*1*).

But before we can understand depression as a brain disorder, we need information on the specific neuronal circuits that contribute to the hopeless despair that forms the core of this illness. Neuroimaging studies of people with depression might be helpful for identifying brain regions of interest, but the temporal and spatial resolution of current functional magnetic resonance imaging and positron emission tomography may not capture the real-time dynamics of brain function that are most relevant to mood and cognition. In a new approach, Airan *et al.* report on page 819 of this issue the use of optical imaging to capture cellular activity at millisecond resolution in brain slices (*2*). Their study, which uses rodents with some of the behavioral features of depression, does not define the neurobiology of depression in humans, but it demonstrates how optical imaging—in this case, using voltage-sensitive dyes—can identify changes in brain activity, enabling correlations between real-time cellular activity and changing affective state.

The findings of Airan *et al.* are consistent with other results that implicate the hippocampus in rodent studies of depression. Chronic or intense stressors, such as social defeat, result in behaviors that resemble human depression, and these stressors have been reported to reduce hippocampal neurogenesis (*3*). They also down-regulate the hippocampal expression of brain-derived neurotrophic factor (*4*), a molecule that promotes neuron survival, proliferation, and differentiation. Clinically effective antidepressants increase hippocampal neurogenesis (*5*), and blocking neurogenesis during treatment prevents the antidepressant effect in rodents (*6*).



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In search of the core of depression. Imaging brain activity in human patients suffering from depression or in animal models of the disease will help to link brain activity in regions such as the hippocampus and prefrontal cortex to behavioral disorders (*10*, *11*).

What about the hippocampus and human depression? Major depressive disorder is associated with cognitive deficits and dysregulation of the hypothalamic-pituitary-adrenal (HPA) axis, part of the neuroendocrine system that controls the stress response. Because the hippocampus is involved in both forming new memories and regulating the HPA axis, one might expect a link between depression and the hippocampus. Indeed, some human neuroimaging studies have reported a subtle reduction in the size of the hippocampus in patients with depression (*7*), and postmortem studies have reported alterations in hippocampal gene expression (*8*). But the evidence thus far is unconvincing. Humans with hippocampal lesions have memory deficits but not mood disorders (*9*). And none of the imaging or postmortem findings have been shown to be specific to the hippocampus or to major depressive disorder. Although the absence of evidence is hardly evidence of absence, most recent clinical studies of the neurobiology of depression have been following a different lead.

Neuroimaging studies of humans with major depressive disorder have largely pointed to prefrontal sites, especially implicating an area in the midline subgenual anterior cingulate cortex, often denoted as area 25 (see the figure) (*10*, *11*). Not only does this region appear abnormal on structural and functional scans (*10*, *11*), but also it is enriched with the serotonin transporter, a target for many antidepressant drugs. Individuals inheriting a risk allele within the promoter of the serotonin transporter gene have reduced volume of area 25 and reduced functional coupling of this region to the amygdala, a subcortical region implicated in the regulation of emotion (*12*). An initial study of treatment-resistant depressed patients reports that deep brain stimulation adjacent to area 25 relieves the symptoms of major depressive disorder (*13*).

How do we resolve the differences between rodent studies that implicate the hippocampus and human studies that implicate the midline prefrontal cortex? Of course, the discrepancies might be attributed to neuroanatomical differences between rodent and human brains. Rodents have at most a primitive subgenual anterior cingulate cortex, whereas this region in the primate brain shows extensive connections with subcortical and cortical targets (*14*). But other fundamental issues should be kept in mind when jumping from studies of rodent behavior to human psychopathology. Human psychiatric disorders are complicated amalgams of affective, cognitive, and behavioral abnormalities. We might model aspects of one of these dimensions, such as helplessness or memory loss, in rodents; but we are then studying an aspect of the disorder, not the disorder itself.

Major depressive disorder, the result of an unfortunate convergence of genetic and environmental factors, is certainly more than the

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sum of its observable parts. Identifying brain regions correlated with "the parts" will be an important next step for human imaging studies, but the field will need to avoid high-tech phrenology. Understanding the neurobiology of abnormal mood regulation will not be accomplished through the identification of a focal lesion or a single explanatory hot spot. The task will be to define altered activity within a functional neuronal network that might well include both the ventral hippocampus and midline prefrontal cortex (*15*). The importance of the new report by Airan *et al*. is the demonstration of abnormal network dynamics in a defined circuit through the use of a technique with combined spatial and temporal resolution that we have not even begun to consider for human studies. We are not able to apply voltage-sensitive dye imaging to people with major depressive disorder, but studies in model animals that help us to link behavior to real-time circuit information will be the foundation for understanding depression as a brain disorder.

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EVOLUTION

An Embarrassment of Switches

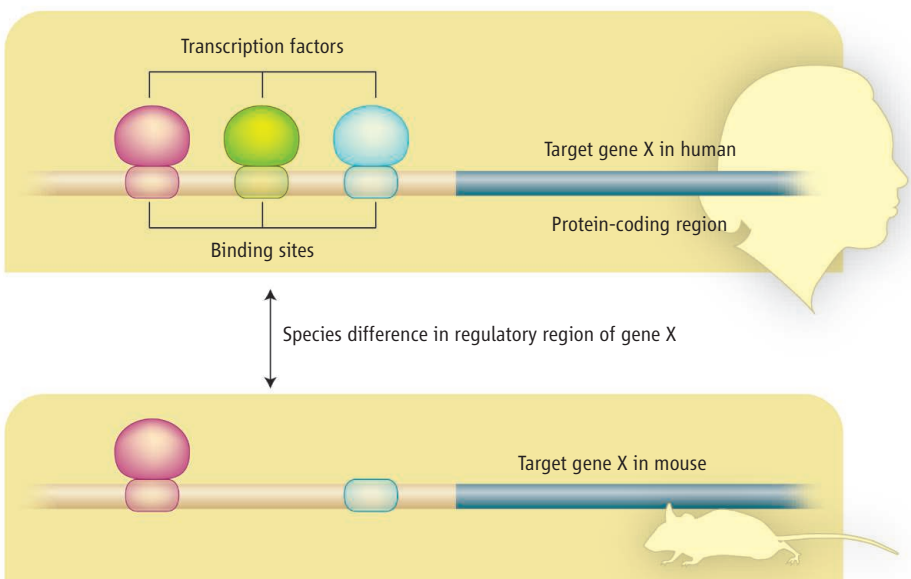
A surprising abundance of evolutionary changes in transcription factor binding sites may obscure the causes of phenotypic divergence.

Leonid Kruglyak and David L. Stern

What makes a human different from a chimpanzee or a mouse? Of course, we know the answer in broad outline. Mutations in the genome, sifted by natural selection, cause changes in appearance, physiology, and behavior—what geneticists call the phenotype. But we have only a vague picture of a more detailed answer. Precisely which mutations generate phenotypic evolution? It's not that we can't find the mutations. Today's DNA sequencing technology readily identifies all differences between two genomes. There are simply too many differences—tens of millions between human and chimp, for example (*1*). An unknown fraction of these mutations alter the phenotype. Nonetheless, the molecular effects of mutations provide a rough guide to their phenotypic effects. Some mutations change the amino acid sequence of proteins, thereby altering their functions, and some change so-called cis-regulatory regions, altering when and where proteins are produced. We know a lot about the first class, but much less about the second. Several recent papers, including one by Borneman *et al*. on page 815 of this issue (*2*), demonstrate a surprising abundance of cis-regulatory changes between closely related species.

It is easy to identify mutations that alter proteins, because of the simplicity of the genetic code. Linear strings of DNA nucleotide triplets encode proteins, and each triplet always specifies a particular amino acid. Thus, mutations that alter a protein can be immediately read off from the DNA sequence. By contrast, we are only beginning to understand how the cis-regulatory code works (*3*). Cis-regulatory regions contain short strings of nucleotides, from 6 to 20 nucleotides in length, scattered irregularly in the vicinity of the protein-coding DNA. Proteins called transcription factors bind to these short DNA strings—transcription factor binding sites—to regulate the production of messenger RNA and thus the synthesis of proteins. In 1975, King and Wilson found that only about 1% of amino acids differed between a set of human and chimpanzee proteins (*4*). They thus proposed that changes in cis-regulatory regions—evolutionary switching of transcription factor binding sites—might cause the majority of phenotypic differences between species. This hypothesis has gained support from studies over the past decade (*5*).

Recent computational studies across species illustrate that many transcription factor binding sites have evolved quickly. That is, binding sites present in one species are often absent in another (*6*–*8*). New findings provide experimental evidence for this conclusion.



Man or mouse? Both the presence and absence of transcription factor binding sites in a genome, as well as the binding of transcription factors to sites that are present, can differ between species and may account for differences in gene expression and phenotype.

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