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To Bend and Not Break: The Neurobiology of Stress, Resilience, and Recovery

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As a young boy walks out of a theater with his two wealthy parents, his life is changed in an instant: a mugging goes awry, shots are fired in the night, and his parents are murdered in front of his eyes. He becomes an orphan, haunted by the memory of the event. He retreats inward, struggling for years to come to term with the events, before ultimately learning to channel his anguish constructively.

Meanwhile, a different man decides to forgo a stable job to pursue his dream to become a comedian. He knows his family is depending on him, but his jokes fall flat. His wife and child die in a freak accident. A series of bad decisions lead to utter ruin and physical deformity. Having lost everything, the man is driven to despair. Unable to recover from his loss, he descends into madness.

Though the orphan and the comedian both face extraordinary trauma, their subsequent paths diverge markedly: the boy goes on to become the Dark Knight, dedicating his life to fighting injustice; the comedian becomes the Joker, singularly bent on wreaking as much havoc on the world (and himself) as possible. How can we explain such different trajectories?

When, in a letter to a friend, Benjamin Franklin famously penned that “in this world nothing can be said to be certain, except death and taxes,” he perhaps should have added one more inevitability: stress (1). Stress may be broadly defined as a systemic physiologic response to a perceived threat. In the face of danger, increases in blood pressure, heart rate, and glucose availability enable a potentially life-saving “fight-or-flight” response. Stress also impacts the brain, modulating functions such as cognition, memory formation, and pain perception.

Yet this remarkable ability to enter a state of physical and mental readiness almost instantaneously is not without consequence: for superheroes and mortals alike, stress changes people. On one hand, in keeping with the idea that “what doesn’t kill me makes me stronger,” manageable stress can have an inoculating effect, increasing one’s future capacity for tolerating similar adversity in the future. However, excessive stress can overwhelm compensatory systems and precipitate debilitating psychopathology including, most notably, post-traumatic stress disorder (PTSD). In this respect, the stressed brain is not unlike an

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exercised muscle: manageable doses can fortify the system, whereas an overload can cause permanent damage.

Understanding the varied responses to stress starts with understanding the neurobiology of stress itself. The two most well-described elements of the stress response are the sympathetic nervous system and the hypothalamic-pituitary-adrenal axis. Sensing danger, these two systems are activated in parallel. The locus coeruleus and adrenal glands release norepinephrine as part of a systemic activation of the sympathetic nervous system. Simultaneously, the lateral nucleus of the hypothalamus generates corticotropin-releasing hormone. Corticotropin-releasing hormone then multiplies its effect by inducing the pituitary to produce adrenocorticotropic hormone. Finally, at the end of this cascade, adrenocorticotropic hormone drives production of cortisol from the adrenal glands. Together, cortisol and norepinephrine regulate wide-ranging systems from blood pressure to the consolidation of fearful memories in the amygdala (2,3). From this understanding, scientists wondered if moderating the adrenergic response could prevent stress-related mental illness.

Unfortunately, such hopes have not been realized. Many early treatment approaches were premised on blocking a hyperadrenergic state (e.g., with beta-blockers and clonidine), but the results of these studies have been mixed (4). Fascinatingly—and confounding for translational research efforts—subsequent work then showed that PTSD may be associated with both hypo- and hyperactivity of the hypothalamic-pituitary-adrenal axis (5). This led to a shift toward the idea that more important than the magnitude of the stress response is the ability to tightly regulate and recover from stress. “Resilience,” a term originally defined in terms of material elasticity, has also been adopted to describe the mental elasticity of rebounding from adversity.

The study of resilience, or the ability to “bend and not break,” has been motivated by several observations. First, the immediate response to adversity is both universal and contextually adaptive. From an evolutionary perspective, the capacity to recall sensory cues connected to danger and associate them with the corresponding threat has clear survival advantages. Thus, it is critical to remember that many symptoms of PTSD (e.g., hypervigilance) can be advantageous while still in a stressful situation (such as a combat zone) and may become pathologic only when they persist beyond the immediate trigger. A second key observation is that while virtually everyone will experience an extreme stress at some point in their lives (such as violence, loss, persecution, or poverty), most will not develop PTSD. The changes that most people experience in response to stressors are transient. In this sense, PTSD can be thought of not as an abnormal development of various symptoms, but rather as a disease of failed recovery. In recent years, this conceptual framework has been backed by remarkable basic and translational studies that shed light on the molecular basis of recovery from trauma.

One key discovery in the study of resilience has been the role of neuropeptide Y (NPY), a small and abundant protein that counteracts anxiogenic effects of the sympathetic nervous system and hypothalamic-pituitary-adrenal axis. Some of the most exciting findings in this area have come from translational human studies (6). One experiment examined U.S. Army Special Forces soldiers during physically and mentally demanding military training. Relative

to non-Special Forces soldiers, this elite unit mounted a more intense stress response (as measured by cortisol levels) but had fewer psychological sequelae (7). This remarkable ability of the Special Forces soldiers may be explained by their generating higher serum levels of NPY than the other soldiers, even though the baseline levels were equal between the groups. Furthermore, during the training, NPY levels correlated positively with behavioral performance and negatively with PTSD-like symptoms. Combined with retrospective studies demonstrating that veterans with PTSD have significantly lower levels of NPY compared to veterans without PTSD, these results suggest that NPY may provide some of the "mental elasticity" to effectively down-regulate the stress response once it is no longer necessary (8).

Although these studies illustrate one key element of the innate stress response system, a trait as complex as resilience requires an animal model to fully describe the relevant biological pathways. In this issue of *Biological Psychiatry*, Sillivan *et al.* (9) describe a mouse model that they have developed to isolate the biologic determinants of resilience. Doing so required overcoming two principal shortcomings of previous animal models. First, as the postulated role of epigenetics in PTSD has grown, the authors used inbred mice to control for genomic differences. Second, previous experimental designs have relied on behavioral tests to measure the resilience of mice. This testing itself alters neurochemistry, thereby confounding post hoc analysis. The authors circumvent this "observer effect" in a clever way: instead of subjecting mice to trauma and then measuring resilience using behavioral tests, the authors establish that resilience can be predicted by behavior during the initial trauma. In other words, the authors find that the resilience of a mouse can be measured not only after the mouse has been stressed, but during the stress itself.

The results that follow are intriguing. Male mice, all genetically identical and exposed to the exact same environment, nonetheless segregate into two distinct groups: those that can learn to decouple an innocuous cue from the associated shock, and those that cannot. The two groups show differences not only in the primary behavioral test, but also in other PTSD-related behaviors (e.g., hyperarousal), stress hormone levels, markers of synaptic activation, and RNA expression in brain regions associated with learning and memory. Promisingly, differences in RNA expression between the two groups largely corresponded to genes previously described in human genetic studies of PTSD (9). Fascinatingly, female mice do not segregate into "stress-resistant" and "stress-sensitive" groups and instead respond homogenously as stress-sensitive—thereby suggesting that sex may be another complicating factor.

Sillivan *et al.*'s (9) animal model allows us to dissect a topic like resilience more deeply—and the more we do so, the more nuanced our understanding becomes. We now see that even when genetic and environmental factors are tightly controlled, subtle biological differences may still predispose individuals to having different responses to stress. An improved understanding of this process would have far-reaching implications not only for the prevention and treatment of psychiatric disease but also societal stigma towards mental illness. Perhaps, in overcoming his own traumatic past, Bruce Wayne understood this exact point. In *The Killing Joke*, as the Dark Knight towers over his nemesis, he does not finish him off but instead empathizes with his enemy. "It doesn't have to end like that," starts

Batman, “I don’t know what it was that bent your life out of shape, but who knows? Maybe I’ve been there too” (10).

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