Clinical Commentary

Biological Psychiatry

Predicting Posttraumatic Stress Disorder: From Circuits to Communities

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I am sure that you have had to deal with an occasional roughneck on the subway or in the park, but when I was about your age, each day, fully one-third of my brain was concerned with who I was walking to school with, our precise number, the manner of our walk, the number of times I smiled, who or what I smiled at, who offered a pound and who did not—all of which is to say that I practiced the culture of the streets, a culture concerned chiefly with securing the body.

—Ta-Nehisi Coates, *Between the World and Me*

To most American citizens, the idea of trauma—and its consequences—connotes images of war: soldiers are deployed to Iraq, Afghanistan, or elsewhere, and many come back with posttraumatic stress disorder (PTSD). In *Between the World and Me,* Ta-Nehisi Coates recounts for his son the everyday trauma he experienced while growing up in Baltimore: another child threatening him with a gun; his father using violence against him in a desperate attempt to keep him safe (1). He describes the world as an "array of lethal puzzles and strange perils that seem to rise up from the asphalt itself" and being forced to adapt to "a lifestyle of near-death experience." The idea of using one-third of his brain to stay safe is a powerful physical metaphor for the cost of surviving trauma. Not only does Coates survive but he succeeds beyond all reasonable expectations—including as a National Book Award winner and a MacArthur Genius. While his story is ultimately uplifting, it might induce false optimism for others exposed to similar circumstances, many of whom may never escape the lifelong consequences of these traumas. How can we understand these differences? How is it that one individual may demonstrate such striking resilience while others go on to struggle?

As a first step in answering this question, one needs to consider how the brain responds to acute stress. A seminal finding in this regard came more than a hundred years ago from Robert Yerkes and John Dodson: with mild stress, mice performed better at a difficult memory task, whereas with higher levels of stress, their performance decayed (2). A little stress may be good; a lot of stress is detrimental. Since then, numerous studies have demonstrated the same phenomenon: stress leads to an inverted U-shaped curve in which small amounts may be beneficial and large amounts are toxic. This idea has been replicated at every level from molecules to behavior and is now accepted as a general neurobiological principle.

Of note, when Yerkes and Dodson performed their first study, neither the term "stress" nor the key stress hormones (norepinephrine, glucocorticoids) were known. We now have a much more sophisticated understanding of the biological processes that underlie this phenomenon. Consider as an example the changes seen in the prefrontal cortex (PFC), a critical region of the human brain that is centrally involved in memory, learning, and abstract thought. With low levels of stress, PFC neurons are activated by small amounts of norepinephrine, which amplifies their activity; with high levels of norepinephrine, there is a receptor (α_1) that serves to shut down this critical region (3). A similar effect is seen in the hippocampus: low levels of glucocorticoid hormones facilitate learning whereas high levels inhibit it (4). Of course, at the far extreme, we know that a profound stress can lead to fear conditioning and a host of circuit-level pathological changes that characterize PTSD (for a review, see 5).

While mild acute stress may be beneficial, the impact of chronic stress may be considerably more toxic. At the cellular level, dendrites shrink in the PFC and hippocampus (6), and there is less cellular proliferation (7). At a regional level, the PFC becomes less active and less able to contribute to cognitive flexibility (3). Additional changes are seen in the hippocampus: in a healthy brain, there is ordinarily a constant stream of new neurons being born that are integral to the process of forming emotional memories; with chronic stress, these new neurons are never born and emotional memory processing becomes impaired (8). One consequence of these changes may be that individuals lack the ability to accurately contextualize fearful situations: rather than learning to associate a dangerous event with its specific circumstances, an individual may develop a more generalized sense of dread. [Of note, the mechanism by which antidepressants may work is by restoring neurogenesis in the hippocampus and thereby enabling healthier processing of emotional memories (8).] In contrast to the cellular decline in the PFC and hippocampus, chronic stress may cause an increase in functionality of neurons in the amygdala. These neurons may expand, become more active, and become more sensitive to threats (6). In total, these changes in the PFC, hippocampus, and amygdala may contribute to a system much like the "one-third of [a] brain" that Coates reserves solely to maintain his safety: major regions of the brain are diverted from their original function to the exclusive protection of the body.

Thus, there are two ways that stress can be toxic: by magnitude or by chronicity. The latter has been historically understudied, in part because the DSM has defined PTSD as resulting from a specific event. In addition, experimental considerations have led researchers to largely focus on the impact of severe acute stressors (e.g., by studying soldiers deployed to a combat zone or civilians exposed to a natural disaster). In contrast, the Grady Trauma Project, led by Kerry Ressler and Tanja Jovanovic, is a research program that embraces the complexity of "real world" trauma. Based in Atlanta, the Grady Trauma Project studies predominantly African American patients from low socioeconomic

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backgrounds who have experienced multiple traumatic events (9). The patients in this study have had both severe and chronic stress. In short, their population offers a window into the world of poverty and trauma that is often overlooked by our broader society but that Coates so shockingly exposes.

Within this complex population, Ressler's team asks the critical question we began with: to what extent is it possible to predict which individuals will go on to develop PTSD? Using a functional imaging approach, the authors demonstrate that neurophysiological signals measured within a few short weeks after an acute trauma can predict the degree of long-term impairment (10). More specifically, they show that hyperactivity of the amygdala in response to fearful faces predicts the extent of PTSD symptomatology one year following the trauma. (They also show that greater habituation of the ventral anterior cingulate cortex was associated with worse recovery.) These data are consistent with the previous literature indicating that hypersensitivity of the amygdala, as seen in chronic stress, may be a biomarker for future risk—a signal that the brain is in a constant state of alertness and may thereby struggle to cope effectively with new stressors in a complex environment. More generally, these findings speak to the potential for personalized psychiatry: that clinicians might be able to predict which individuals are at highest risk and to implement customized treatments for the small proportion (approximately 20%) who would go on to develop PTSD (9). While this rate of PTSD is approximately the same as in returning combat veterans, it also bears emphasis that this means that the majority, like Coates, are relatively resilient and do not go on to develop PTSD.

Together, Coates and the Grady Trauma Project call our attention to both the heavy burden of stress in inner-city African American communities and to the biological processes through which such stress can have long-term adverse consequences. The combination of social and scientific understanding recalls the conditions for the breakthroughs in the field of infectious diseases during the 19th century. As scientists refined the germ theory of disease, physicians mapped cholera outbreaks in poor communities. Together, they demonstrated the role of a contaminated water supply in spreading the bacteria. The medical community responded with advocacy for improved social conditions in the neighborhoods and distributed antibiotics to the people. Our field now faces a similar problem as we come to understand the predictable, adverse neurobiological sequelae of chronic stress and the unequal burden of this stress across different communities. Will we have the moral courage to address both sides of this issue with equal vigor today?

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