Neurobiology of PTSD

by John J. Medina, PhD

Having grown up as a "military brat," I have been familiar for decades with how my family's friends coped with war experiences. I did not know the term "PTSD" in those days, but I could see the enduring, horrific marks that posttraumatic stress disorder had left on them. I learned early on that wars could keep killing soldiers long after the peace treaties had been signed and weapons had been rendered silent.

In this article and the next two, I am going to explore the neurobiology of this wretchedly recursive disorder. There is good reason to do so—the literature on PTSD is expanding and changing rapidly. While some of these changes are due to advances in technology, new insights also have occurred because of the oddly changing nature of modern combat.

In our current engagements, there is often no hostile front line protecting a comparatively peaceful rear cohort (a traditional "tooth vs tail" model). Military professionals up and down the command chain are now regularly exposed to hostile situations in a manner quite different from previous war experiences. There is also a greater variety of soldiers being thrust into harm's way. Once the near-exclusive domain of 20-something males, battalions participating in contemporary firefights often have much broader age distributions. Adding to this diversity, more women are being exposed to hostile combat operations than ever before. From a research perspective, this diverse cohort can provide a better nuanced, more statistically discriminating view of how humans process traumatic experiences.

Part 1

In this article, I discuss some general facts about PTSD, a concept known as "allostatic load," and the ambiguous role of stress hormones. In the next article, I will focus on several subsystems in the brain involved in the formation of human memory and their reactions to severe trauma. In the last installment, I will discuss genetic risk factors and the future of neurobiologically oriented PTSD research.

An enduring mystery

Most definitions of PTSD include the detection of 3 distinct clusters of symptoms. The first of these is hyperarousal, which often manifests as an impaired ability to concentrate. Patients become hypervigilant, insomniac, irritable, and in the grips of increasingly fine-tuned startle responses. Behaviors within this symptom cluster provide hints to researchers interested in how trauma affects executive functions classically associated with the prefrontal cortex.

The second symptom cluster involves memory intrusions of specific traumatic events. These intrusions are often spontaneous, irrepressible, and accompanied with intense physio-logical reactions. This persistent disability has caught the attention of researchers interested in memory for-mation and retrieval abilities.

The third group of symptoms is usually classified as avoidance responses and includes distancing behaviors, attempts to edit specific thoughts, social distancing, and withdrawal. Symptoms are often associated with poor social coping strategies, substance abuse, stress-related medical disorders, and co-occurring anxiety and depressive episodes. To be classified as PTSD, symptoms must cause significant functional impairment and be present for at least 1 month.

This variety of symptoms means that PTSD can be studied by a broad range of researcher professionals interested in the effects of trauma on neurocognitive processes. But this also can be frustrating for them. Not all patients experience every symptom cluster on a regular basis. Even for those who do, the severity of the daily experience is often quite uneven. There are temporal concerns as well. About 5% of PTSD patients do not have symptoms immediately after being traumatized; symptoms can take varying lengths of time to develop (a condition termed "delayed PTSD"). Are all these diseases simple variants of a common pattern? Or do they represent different disorders and, thus, differing neurological substrates? Such questions are extremely important when formulating research directions. What's frustrating is that currently nobody knows the answers.

But there is an even greater mystery surrounding PTSD that oddly suggests a research framework. One of PTSD's most enduring mysteries does not concern its relative presence in people who have traumatic experiences but rather its relative absence. Simply put: the majority of people who experience traumatic situations do not get the disorder. Although PTSD levels are dramatically elevated in combat-experienced military populations (I have seen papers that quote prevalence statistics anywhere from 20% to 40%), not everyone who is exposed to combat acquires PTSD.

This absence is seen even in civilian cohorts. It has been estimated that 75% of the US population will experience at least 1 severely traumatic event in their lifetime. Yet PTSD develops in only about 7% of US citizens at some time in their lives. The most common outcome for persons experiencing trauma is remission. Stress-related symptoms in most persons show a dramatic decline about 90 days after the trauma has been experienced.

As mentioned, this absence provides a powerful research framework. It suggests that PTSD may be most properly explained as a disorder in which the brain's normal recovery process is somehow disrupted. This allows researchers to compare how people normally respond to severe stress, then to compare how the varieties of PTSD differ from typical responses and start designing their investigations. One of the world's foremost authorities on how stress is processed in the brain, including severe stress, is Bruce McEwen. He has created just such a framework after decades of study, and it is to his ideas that we turn next.

The allostatic load

Most of us are used to hearing the word "homeostasis." It was first coined in the 1800s by French scientist Claude Bernard to explain a biological creature's need to maintain some type of steady internal state. Working something like a biological thermostat, homeostasis has been invoked to explain phenomena ranging from psychology to biochemistry.

Bruce McEwen coined the word "allostasis" to explain an overarching framework for human response to stress, and it was meant to ally itself directly with the notion of homeostasis. "Allo" from the Greek word "allos," or "other," means "different"; "stasis" means "a condition of balance between different forces." Allostasis, according to McEwen, is achieved by a normally well-regulated interlocking system of communications among the brain, the endocrine system, and the immune system. These systems help keep the body stable ("safe") during times of trauma by being able to adjust themselves on command.

In times of fight or flight, a creature needs to greatly increase the flow of oxygen to its muscles (for us that means our legs). When the threat is over, the body returns to homeostasis. It can do so because of its extraordinary ability to adapt to rapidly changing circumstances. The ability to do that in a healthy, regulated way is known as allostasis.

This simple notion predicts several things. First, stress, left alone, is neither harmful nor toxic. Whether the stress becomes damaging is the result of a complex interaction between the outside world and our physiological capacity to manage it. The body's reaction to stress is partly a matter of what stress it encounters, partly the duration of the stress, and partly the somatic substrates (many of which are genetic) that the person brings to the experience. McEwen has even given a name to the point at which stress becomes toxic—the "allostatic load." You could call the allostatic load a "system breach." PTSD also can be thought of as a system breach. Because people will have different allostatic load thresholds, their response to the stressors they encounter will also be different.

This idea gives researchers a useful framework with which to begin understanding not only the commonalities of human response to severe stress but also its maddening variability. Great strides have been made for many years on the subject, including physiological ones. There also have been a few dead ends as will be described next.

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PTSD Neurobiology

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A nice story gone wrong

A number of years ago, a really terrific story regarding the effects of catecholamine on brain function appeared to be developing. It all had to do with the evolutionary view of human response to stress.

Evidence had been accumulating for decades that the human stress response was built to respond maximally to acute stress exposure only. The evolutionary argument was couched like this: either the saber-toothed tiger ate you or you ran away from him, but the issue was settled in less than 5 minutes. The various allostatic mechanisms of the body were not built to deal with severe stressors lasting a long time. If the body was consistently exposed to elevated levels of catecholamine, deregulation of the system might occur. It might be possible to render the normally flexible allostatic switches stuck into the "on" position, abolishing not only their primary function but also their normal regulation.

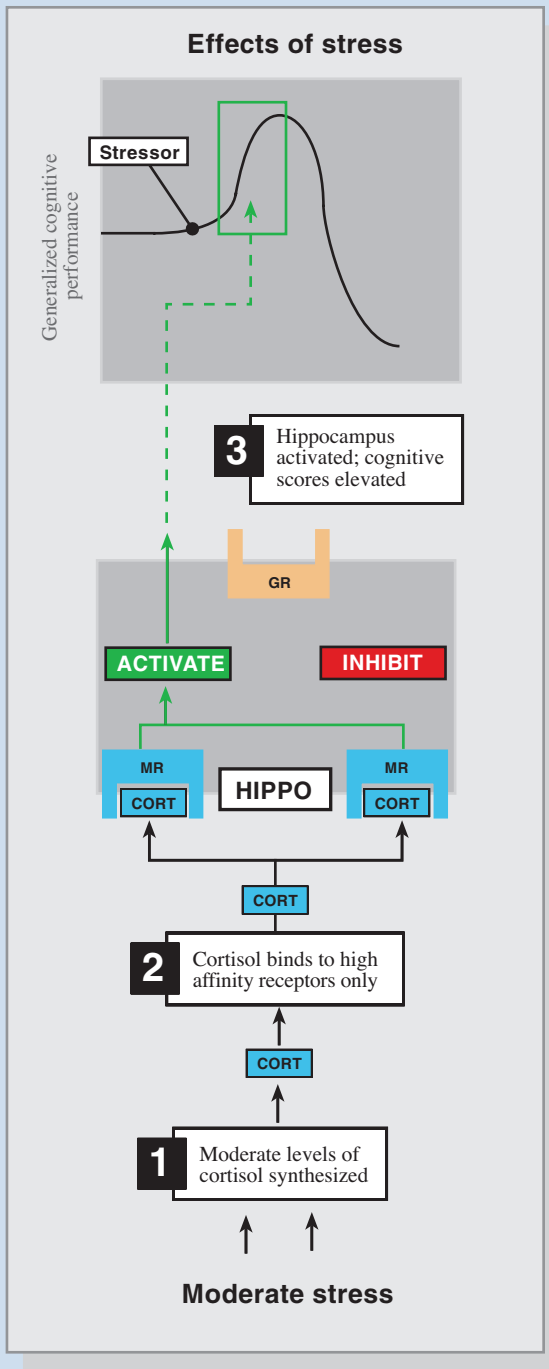
Unfortunately, complex human culture can produce stressors that last a long time: bad marriages, bad bosses, combat, and so on. The accompanying overload of catecholamines was found to damage a wide variety of systems, including regions in the brain. Populations of cells within the hippocampus were shown to alter their electrical relationships, change the density of their dendritic connections, or simply die. This meant that prolonged elevation of certain stress hormones could literally cause brain damage. It was found that moderate levels of cortisol bound to high-affinity mineralocorticoid receptors in the hippocampus, which could transiently increase hippocampal function. (This was used to explain the finding that moderate amounts of stress could improve cognition—especially memory.) But large, prolonged exposure of cortisol

Figure

PTSD and stress hormones

Effects of stress on cognitive functioning

Evidence suggests a molecular explanation for the observation that while moderate stress improves hippocampal-mediated cognitive processing, severe acute or chronic stress can inhibit the same processing.



PTSD, posttraumatic stress disorder; GR, glucocorticoid receptors; MR, mineralocorticoid receptors; CORT, cortisol; HIPPO, hippocampus.

not only bound mineralocorticoid receptors but also glucocorticoid receptors. When that occurred, cell damage soon followed. Hippocampal function was greatly reduced (**Figure**).

Is that what occurs in PTSD? Do chronic levels of stress hormones damage areas of the brain in such fashion that behavior is altered? Some researchers certainly thought so. It seemed like an elegant, if tragic explanation of an otherwise complex behavior.

There was only one problem to this very nice story. It was wrong, or at least it was not the whole picture. When scientists began measuring levels of stress hormone immediately following traumatic events (a motor vehicle accident, to cite one case), they found a really odd thing: cortisol levels actually went down in many patients. Even in these noncombat populations, this plummeting effect was actually a risk factor for PTSD. PTSD was much more likely to develop later in patients in these cohorts who had lowered amounts within 3 hours of the event than in those who had not.

A similar phenomenon was observed in military populations with PTSD. Their catecholamine levels were also reduced when compared with nonaffected controls (even when taking into account release patterns over the diurnal cycle). This was odd, despite evidence that the release of hypothalamic corticotropin-releasing factor (CRF) levels were actually elevated in these same populations. CRF stimulates the secretion of adrenocorticotropin from the pituitary gland. This important signal mediates the overall release of catecholamine from the adrenals. The story got more confusing as the research matured. Other studies showed that combat veterans with chronic PTSD had elevated peripheral catecholamine levels.

If all this sounds a bit contradictory, then I am communicating successfully. Clearly, it was not what the researchers were expecting.

Conclusions

What does all this mean? I use this catecholamine story to underscore the difficulty in attempting to describe complex behaviors such as those in PTSD at the cellular and molecular levels. There are actually some reasons this catecholamine story may make sense, a topic I will take up in a future issue, in Part 2. But for now, it serves as a powerful reminder: when you dramatically perturb a normally smooth running but indescribably complex interlocking system of allostatic switches, the observations may not be quickly explained, or even intuitively understood. In discussing the biology of something as complex as PTSD, which is what this series is about, that may be the most important introductory lesson of all.

Dr Medina is a developmental molecular biologist and private consultant, with research interests in the genetics of psychiatric disorders. □