

# nature neuroscience

## Focus on stress

We present a special issue focusing on recent advances in the understanding of the effects of stress on the nervous system and behavior, as well as the role of the nervous system in regulating responses to stress.

In the 100 years since Walter Cannon first described the role of the sympathetic nervous system in the “fight or flight” response<sup>1</sup>, we have learned a great deal about how animals respond to stress. Stress can be defined as any deviation from homeostasis (a term also coined by Cannon), and although often thought of as solely harmful, stress, and the body’s appropriate responses to it, serve important roles in maintaining health. The stress response involves intricate interactions between the CNS, the peripheral nervous system and the rest of the body. Although much is known about the peripheral response, research investigating the role of the brain, as well as its interactions with peripheral systems, has made great strides in recent years, especially with the advent of new technologies allowing greater manipulation of the genes and circuits involved. In this issue, we present a collection of Commentaries, Perspectives and Reviews highlighting recent developments in the field.

One of the themes that emerges when studying stress is the idea of an inverted U-shaped curve of responses to increasing amounts of stress: the effects of stress on any number of biological endpoints depends on its duration and intensity. On page 1344, Robert Sapolsky discusses this and other themes that have emerged from the study of stress over the past 100 years. Another such theme is the importance of individual differences in stress response. Individual differences can of course be a result of both genetic (or epigenetic) and environmental factors. In their Review on page 1421, Heike Tost, Frances Champagne and Andreas Meyer-Lindenberg discuss the role of environmental influences in shaping the brain and, ultimately, mental health and wellbeing. In particular, the authors focus on the social environment, discussing research showing that elements of our environment, such as urbanicity, can indeed act as stressors and increase vulnerability to psychiatric disease.

Chronic or uncontrollable stress is indeed a key factor contributing to vulnerability to many different psychiatric diseases. On page 1386, Scott Russo and colleagues discuss interactions between the immune system and the stress response as contributing to the vulnerability to mood disorders. Their Review discusses findings from studies in both rodents and humans; indeed, much work on stress responses in rodents is motivated by the goal of eventually translating such insights into therapeutic advances. In a Perspective on page 1347, Ahmad Hariri and Andrew Holmes discuss such efforts in translating findings from rodents to humans in the context of post-traumatic stress disorder (PTSD). Much is already known about the circuitry underlying anxiety and related disorders such as PTSD, as discussed by Gwendolyn Calhoun and Kay Tye on page 1394, and the hope is that such understanding of circuit dysfunction in these diseases may lead to therapeutic advances.

Once circuits involved in responding to stress were identified, researchers turned to investigating the cellular and molecular

mechanisms underlying their responses. In their Review on page 1353, Bruce McEwen and colleagues discuss the molecular mechanisms underlying the brain’s response to stress, including genetic and epigenetic factors. These molecular cascades can lead to structural and synaptic plasticity in neurons, as discussed by Sumantra Chattarji and colleagues in a Review on page 1364. These authors discuss how stress has different effects in different brain regions, highlighting the hippocampus, amygdala and prefrontal cortex in particular.

The prefrontal cortex is a region particularly affected by stress. In a Review on page 1376, Amy Arnsten discusses the molecular mechanisms underlying the effects of stress on prefrontal circuits. She also highlights how the effects of stress in this most newly evolved part of the brain can lead to disruptions in cognition and may be a factor in schizophrenia. One important function of the prefrontal cortex is in regulating decision-making and motivated behaviors. On page 1405, Nick Hollon, Lauren Burgeno and Paul Phillips discuss how stress alters these behaviors. The authors examine the circuits underlying these effects, focusing on the mesolimbic dopamine pathway and its interactions with the prefrontal cortex. As is seen in other arenas, they highlight the varied influences stress can have depending on the duration, intensity and controllability of stress.

One major factor influencing the stress response that is often overlooked is sex. Females and males have different responses to stress, and the degree and sign of these differences also depend on age. On page 1413, Tracy Bale and Neill Epperson review the vast literature describing sex differences in responses to stress across the lifespan. This work informs not only our understanding of physiology in healthy individuals, but also the differing prevalence of psychiatric diseases in males and females. Although much work is still needed to understand the mechanisms underlying such sex differences, the importance of studying both males and females is increasingly recognized, not least by funding agencies such as the US National Institutes of Health<sup>2</sup>.

Research focusing on the brain’s role in the stress response has made substantial progress in recent years, but there is much work still to be done. The intricate relationship between stress and psychiatric disease adds urgency to this work, as new and more efficacious treatments for these diseases are sorely needed. Our hope is that these Reviews and Perspectives will stimulate further research into the mechanisms and circuits underlying the central response to and regulation of stress, and that they provide a window into the exciting developments in this field. ■

1. Cannon, W.B. *Bodily Changes in Pain, Hunger, Fear and Rage* (D. Appleton & Company, New York, 1915).
2. Clayton, J.A. & Collins, F.S. *Nature* **509**, 282–283 (2014).