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Editorial

Fifty years of stress and more to come: A tribute to Bruce S. McEwen

Fifty years ago, Bruce McEwen and colleagues published the first report of glucocorticoid receptors in brain (McEwen et al., 1968). This report, which showed concentrated uptake of tritiated corticosterone in the hippocampus of adult rats, was followed 4 years later by another paper using in vivo autoradiography to show that neurons in the dentate gyrus and CA fields of the hippocampus concentrated the steroid when it was injected into adrenalectomized rats (Gerlach and McEwen, 1972). Since these groundbreaking studies, the study of glucocorticoid and stress effects on the hippocampus and other parts of the brain has grown exponentially. A considerable amount of this work came directly from McEwen's laboratory at The Rockefeller University, as well as from the labs of innumerable trainees whose careers McEwen helped to launch. Over the years, substantial progress has been made and McEwen has played an indispensable role in our advanced understanding in the field. Of course there continues to be much to learn about the neurobiology, neuroendocrinology, and psychology of stress, and many scientific debates continue. McEwen's research has always been at the forefront of new findings, ideas, and resolutions in the field. Thus it is only fitting that this special issue of *Frontiers in Neuroendocrinology* is dedicated to the contributions McEwen has made to the field of stress research. The collection includes a paper by McEwen himself, as well as by his collaborators and trainees from virtually all epochs of his career. The volume represents research presented at a meeting entitled "Stress: Past, Present and Future Directions", which took place at Princeton University in 2017 and included a Festschrift event to honor McEwen's career thus far. As former postdoctoral fellows of McEwen, we have enjoyed overseeing the compilation of these illuminating articles to honor a scientist of such outstanding caliber, who has made such important contributions to the field, as well as to the lives and careers of so many other scientists, ourselves included.

The articles in this issue span multiple levels of analysis, which fittingly reflects the overarching approach taken by McEwen throughout his career. Indeed, reviews in this special issue tackle research on stress influencing outcomes at the population level (Epel et al., 2018) to the deep genome (Barlett and Hunter, 2018). Some of the papers summarize findings on stress effects in human populations, using behavioral, neuroimaging and biochemical analyses (Lupien et al. 2018; Epel et al., 2018; Dhabhar et al., 2018), while others consider animal models to investigate clinical conditions, such as diabetes, autism spectrum disorder and mood disorders (Magarinos et al., 2018; Spencer et al., 2018; Cameron and Schoenfeld, 2018). Many reviews center on stress effects in otherwise healthy animal models, focusing on cellular processes, including microglial reactivity, neurogenesis, dendritic spine plasticity (Macht and Reagan, 2018; Karatsoreos, 2018; Ortiz and Conrad, 2018; Cameron and Schoenfeld, 2018) and molecular

mechanisms, including stress effects on telomeres, epigenetics, receptor expression, mitochondrial enzymes, and non-coding elements of the genome called retrotransposons (Epel et al., 2018; Romeo et al., 2018; Picard et al., 2018; Bartlett and Hunter, 2018; de Kloet et al., 2018). The collected papers span stress effects on all aspects of the lifespan, including development, adolescence, early adulthood and old age and almost all consider both sexes, pointing out notable similarities and differences that emerge at different life stages, which create both vulnerabilities and strengths. Given the known sex differences in human diseases, such as autism spectrum disorder, major depressive disorder and drug addiction, understanding how stress impacts males and females seems increasingly relevant. Here again, McEwen has been a pioneer, studying sex difference in the context of stress as well as under other conditions, long before it was considered universally important to do so.

While the vast majority of research on stress effects on the body and brain has focused on the downside, the upside of stress, including stress resilience, has become increasingly recognized as worthy of study. Many experiences with hedonic value produce physiological stress responses, and by some definitions can be deemed "stressful", and most of these, somewhat surprisingly given the hormonal milieu, lead to beneficial outcomes in terms of brain plasticity, behavior, and overall health. Furthermore, experiences that are aversive in nature, more classically defined as "stressful" which not surprisingly produce physiological stress responses, often produce resilience or even resistance to subsequent stressors, as so-called "stress inoculation" effects. Understanding the mechanisms that promote prolonged health despite high levels of "stress" molecules either under rewarding or aversive conditions may provide clues about the processes that can be invoked in order to prevent or correct stress-induced illness. Many of the papers in this collection reflect this important trend, with an aim toward balancing the good with the bad and extracting information about healthy function to help elucidate and treat unhealthy states. As with much of the work on deleterious effects of stress on the brain and body, McEwen, his collaborators and trainees, have been at the forefront of these studies on the benefits of short-term stress (see Dhabhar et al., this issue). Indeed, the commentary in this issue by Karatsoreos (2018) suggests several steps to enable stress researchers to reframe questions in order to guide us to new "universal principles" of stress. It is likely that these efforts, in combination with those designed to understand stress-induced illness, will provide a comprehensive view of the myriad of experience-dependent changes that shape individuals and contribute to health outcomes.

Given the generative nature of McEwen's career to this date, both in terms of publications and the students he has trained and continues to



Fig. 1. Photo of Bruce McEwen, Ph.D. with the travel award winning trainees at the Stress meeting in Princeton, NJ in 2017, honoring McEwen's work in the stress field to date.

mentor, it is not surprising that the overall body of research he has influenced has run the gamut, leaving almost no domains of investigation regarding stress unexplored. Although each of these lines of study has been explored, much remains to be discovered and it is clear from this compendium, as well as from the large number of young scientists he continues to inspire and to work with (see Fig. 1), that McEwen's influence, both direct and indirect, on the study of stress will continue for years to come. We eagerly await the next installment of this work and fondly dedicate this volume to Bruce S. McEwen, Alfred E. Mirsky Professor and Head of the Harold and Margaret Milliken Hatch Laboratory of Neuroendocrinology at the Rockefeller University.

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