Neurobiology of Stress 25 (2023) 100552

Contents lists available at ScienceDirect

Neurobiology of Stress

journal homepage: www.elsevier.com/locate/ynstr

Special issue dedicated to Dr. Bruce S. McEwen

In the dawning days of 2020, the excitement and promise of a New Year was shattered by frantic texts, emails and phone calls that were quickly spreading throughout the scientific family of Dr. Bruce S. McEwen, more affectionally known as the McEwenites. Was it true? Do you know what happened? Is Bruce okay? Rapid searches of the internet failed to provide definitive information or simply provided glimmers of hope that perhaps the news we received was incorrect. But this false hope was replaced with the tragic reality that our mentor, colleague and friend had passed away. In the months that followed, numerous tributes were published detailing Bruce's impact on the neuroscience community, many of which were written by members of Bruce's scientific family (Hill et al., 2020; Marrocco and Galea, 2023; Galea et al., 2020; Dhabhar et al., 2020; Sapolsky, 2020). These tributes highlighted Bruce's role as a pioneer in our understanding of the effects of adrenal and gonadal steroids in the central nervous system, his desire to translate such observations to the clinical setting and ultimately his goal of raising awareness of the role of stress in brain disorders to a broader public. His work had, and continues to have, an impact on disciplines far afield from his own, including public health, developmental psychology, and public policy.

Much more importantly, Bruce worked tirelessly and selflessly to promote the work of his colleagues and was especially dedicated to his mentees and junior colleagues. Bruce's reputation contains much more than just tremendous scientific breadth and depth. He was widely known for his kindness and openness to ideas and fellow scientists regardless of rank or origin, something all who knew him were touched by. That openness and engagement helped build a scientific family that now spans generations and continents. It is in this spirit that we organized this special issue dedicated to Bruce for *Neurobiology of Stress*. The articles in this Special Issue reflect the breadth of Bruce's scientific influence upon his mentees, as well as his collaborative approach to science.

This Special Issue begins with a contribution from Craig McEwen, in which he highlights their collaborative partnership that examined the socio-economic effects of chronic stress, especially as it relates to how developmental trajectories may be impacted by early life exposure to allostatic load (McEwen, 2022). Cheryl Conrad (Conrad, 2022) describes the impact that Bruce had on her career trajectory and how joining the McEwen lab helped her establish life-long collaborations and friendships with the McEwenites in her commentary on Sonia Lupien's contribution to this Special Issue. Lupien and colleagues addressed an important question that emanated from conversations with Bruce; namely, do individuals experiencing emotional stress exhibit alterations in hypothalamic-pituitary-adrenal (HPA) axis and sympathetic nervous system (SNS) activity (Lupien et al., 2022). Their results indicate that the perception of stress may not be correlated to what investigators use as physiological and endocrine biomarkers of stress. Also evolving from discussions with Bruce was Andrew Miller's interest in the mechanistic role of neuroinflammation in the pathogenesis of major depressive illness. More recent studies from the Miller lab described in this Special Issue are examining the cellular and molecular determinants of inflammation in depressive illness, which are providing greater insights into the immunological profiles of patients with stress-related neuropsychiatric disorders (Bekhbat et al., 2022).

Bruce and his long-time collaborator Eliot Stellar expanded the concept of allostasis to integrate the impact of stress upon the individual and how chronic stress could make individuals more vulnerable to subsequent pathophysiological challenges, which they referred to as allostatic load (McEwen et al., 1993). This concept is discussed in many contributions to this Special Issue, including a study by Zachary Weil and coworkers which discusses the recovery and the increased risk of developing co-morbidities in individuals exposed to traumatic brain injury (Weil et al., 2022). Gerson Hernandez and Roberta Brinton remind us of Bruce's broader interests in neurosteroid activity in the mammalian brain in their manuscript that describes how allopregnanolone, by acting as an allosteric modulator of GABA-A receptors, may serve as an allostatic load modulator to reverse neuroplasticity deficits related to the decline of estrogen activity in Alzheimer's disease (Hernandez et al., 2022).

The clinical studies described above provide prime examples of the translational nature of Bruce's science from the perspective of the individual to society across the lifespan. This approach is also reflected in the preclinical studies by Bruce's mentees and collaborators. For example, Rebecca Kann and Russel Romeo discuss how age-related differences in the HPA axis, specifically increases in pituitary levels of ACTH and adrenal levels of corticosterone, may be responsible for differences in stress reactivity during puberty in male and female rats (Kann et al., 2022). These sex-dependent and age-related differences in the endocrine profile of the HPA axis could impact responses to early life adversity. In this regard, Elizabeth Gould and coworkers describe sex-specific differences in the ability of neurogenesis to buffer against early-life adversity-induced avoidance behaviors in male and female mice (Waters et al., 2022). From a synaptic perspective, Ilia Karatsoreos and colleagues describe how HPA axis dysfunction negatively impacts glutamatergic signaling in stress responsive regions like the hippocampus, prefrontal cortex, and amygdala, thereby providing greater insight into the role of the glutamate system in stress-related neurological disorders (Kinlein et al., 2022). Teri Milner and colleagues also examined glutamatergic signaling and describe that chronic stress differentially impacts the distribution of glutamate receptor subunits in hippocampal

https://doi.org/10.1016/j.ynstr.2023.100552

Available online 6 June 2023

CA3 synapses (Dolgetta et al., 2022). They also describe potential allostatic load mechanisms for decreased oxycodone conditioned-place preference following chronic stress. A contribution from Sumantra Chattarji and coworkers further interrogates the effects of stress upon glutamatergic activity in hippocampus and amygdala (Naskar et al., 2022). They report that riluzole, which facilitates astrocytic synaptic clearance of glutamate, reverses stress-induced changes in hippocampal CA1 spine density, changes not observed in the basal amygdala. Richard Hunter and his student Andrew Bartlett show how a retrotransposon derived ncRNA, B2 SINE RNA, which is activated by glucocorticoids, binds to and modifies the transcriptional activity of the glucocorticoid receptor (Bartlett et al., 2023). Thus, demonstrating that transposon ncRNA has a direct role in glucorticoid feedback and in tuning the transcriptional response to stress.

Jordan Marrocco and coworkers provide data to suggest that a stressful stimulus produces molecular signatures that influence responses to subsequent stressors, findings that are consistent with Bruce and Eliot's allostatic load hypothesis (Caradonna et al., 2022). In another example of the consequences of stress-mediated increases in allostatic load, Hannah Burzynski, Lawrence Reagan and colleagues discuss how the combination of the cholinesterase inhibitor pyridostigmine bromide and repeated stress impairs the cholinergic anti-inflammatory pathway in an experimental model of Gulf War Illness (Burzynski et al., 2022). Their studies have identified neuroinflammation as a critical mechanistic mediator in the progressive cognitive deficits affecting Gulf War veterans. Matt Hill and coworkers examined the effects of different stressors on the endocannabinoid system in male and female rats. They report that different stressors (i.e., restraint, swim, foot shock) differentially impact anandamide (AEA) and 2-arachidonoyl glycerol (2-AG) in the hippocampus, amygdala and prefrontal cortex. Their findings provide insight into the role of AEA and 2-AG in stress-mediated plasticity (Vecchiarelli et al., 2022).

Another example of how Bruce was a pioneer in neuroendocrinology was his appreciation and understanding of the importance of taking a circuit-based approach when examining the effects of acute and chronic stress. This is reflected in the contribution by Juan Nacher and coworkers, in which they describe how stressful experiences affect inhibitory circuits and ultimately synaptic plasticity of limbic brain regions, as well as the ability of interventions to restore the plasticity of inhibitory circuits (Perez-Rando et al., 2022). Mikaela Land and Rebecca Shansky delve deeper into these circuit-based approaches to discuss the potential mechanistic mediators of stress-induced effects upon structural plasticity (Laine et al., 2022). They discuss their findings in the context of stress-related pathology, especially as it relates to the underrepresentation of female rodents in preclinical studies. Nikolaos Daskalakis, Onno Meijer and Ron de Kloet discuss this limited understanding of the sexually dimorphic activities of glucocorticoids in the context of how MR/GR occupancy impacts cellular, endocrine and behavioral endpoints (Daskalakis et al., 2022). By 'rolling back the clock', they discuss the broader role of glucocorticoids in allostasis and allostatic load. To further probe the role of glucocorticoids in allostasis and allostatic load, Conor Liston and colleagues have developed cutting-edge technologies that allow for examination of in vivo cellular recording during working memory tasks (Witztum et al., 2023). These approaches provide opportunities to investigate how chronic stress-induced changes in allostatic load at the synaptic level regulates behavior. Functional connectivity also plays an important role in stress-induced pathologies, including cognitive deficits observed in patients with depressive illness. Since cognitive symptoms are more severe in women compared to men, Liisa Galea and coworkers examined how cognitive bias may be differentially affected by sex across development (Hodges et al., 2022). These studies identified sex- and age-dependent differences in functional connectivity and cognitive bias, which provides a framework for guiding future studies in males and females across the lifespan.

We would like to thank Elsevier and Dr. Rita Valentino, Editor-in-Chief of *Neurobiology of Stress*, for providing us the opportunity to serve as Guest Editors of this Special Issue. We are hopeful that the articles in this Special Issue effectively encapsulates the influence that Bruce continues to exert on the field of neuroendocrinology. More importantly, these contributions reflect the admiration of Bruce's trainees and colleagues and how he will continue to positively impact our scientific and personal lives.

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Matthew Hill
University of Calgary, Canada

Richard Hunter
University of Massachusetts, Boston, USA

Lawrence Reagan*
University of South Carolina, USA

* Corresponding author.
E-mail address: lawrence.reagan@uscmed.sc.edu (L. Reagan).