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EJN Stress, Brain, and Behavior Special Issue

Editorial

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Stress is a cross-species phenomenon throughout phylogeny that can have important consequences both for individuals as well as for societies. Highly specific stress responses have evolved to enable individuals to optimally adapt to challenging situations and these processes can have a major impact on whole body physiology, brain function, behavior, and affect higher cognitive processes, such as decision-making and mood. If these adaptive responses are dysregulated or occur out of context, they can result in maladaptation and disease. Excessive stress, especially during developmentally sensitive periods, is a risk factor for a wide range of mental health conditions. This special issue gathered an impressive amount of contributions illustrating recent advances in stress research from a broad perspective, including contributions from the fields of neuroendocrinology, genetics, systems biology, behavioral and cognitive neuroscience, computational neuroscience, psychiatry, translational and applied neuroscience.

This issue contains a number of highly relevant focused review articles and research reports that each highlight a specific aspect of how stress can affect the brain and consequently behavior. There are certain overarching themes that emerge from the included papers. One is certainly the timing of the stressful challenge and the context. Especially early in life exposure to adversity has lasting impacts on brain and behavior (Čater and Majdič, 2021; Clinton et al., 2021; Roque et al., 2021; Wang et al., 2021), specifically also with regard to addiction and reward circuitry (Albrecht et al., 2020; Rudolph et al., 2020; Levis et al., 2021; Mooney-Leber et al., 2021), pain responding (Melchior et al., 2021), epigenetic programming (Alyamani et al., 2021; Womersley et al., 2021), neuroinflammation (Friend et al., 2020; Marsland et al., 2021) and in interaction with the metabolic regulation (Berry et al., 2021). Beyond this, it is even unclear how 'normative' developmental experiences contribute to stress-related behaviors (Farber et al., 2020), but it may be that broader environmental factors,

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such as access to green space may contribute to resilience and reduced stress responding (Rojas-Carvajal et al., 2021).

At the *cerebral* level, the effects of stress exposure are also highly circuit- ,region- and cell-type specific (Lv et al., 2021). This is illustrated by the example of the bed nucleus of the stria terminalis (BNST), which is a highly stress-responsive region in the brain involved in social behavior (Flanigan and Kash, 2020) or the hippocampus and amygdala, where stress has highly impactful and lasting effects (de Sousa Maciel et al., 2020; Ineshen et al., 2020; Saha et al., 2020). Applying linear mixed modeling from electroencephalogram (EEG) signals indicated that frontal EEG power can discriminate stress from resting state, but this approach is not effective to identify more fine-grained differences (e.g., time pressure or socio-evaluative threat) of the stress response (Ehrhardt et al., 2021). Finally, it is emerging that stress and stress-related disorders have differential impacts on various neuronal sub-populations, especially the so-far largely overlooked important role of glial cell populations as microglia or astrocytes in relation to stress (Balog et al., 2021; Sanguino-Gómez et al., 2021).

There is also a growing body of research exploring the impact of stress at the *behavioral* level. Specifically acute stress may alter inhibitory behaviors (Lago et al., 2019; Roxburgh et al., 2020), impair flexible updating of avoidance responses (Lemmens et al., 2021) and cognitive control (Husa et al., 2021), or promote passive avoidance (Binti et al., 2021) as well as approach behaviors towards addiction-relevant cues in smokers (Zlomuzica et al., 2021). In addition to acute stress, these effects may also result from long term work-related stress (e.g. Burnout) which leads to persistent changes to attention/inhibitory control processes (Pakarinen et al., 2021). Acute stress alters memory processes both at the initial formation (McManus et al., 2021) and subsequent consolidation during sleep (Denis et al., 2021), although effects may be more subtle than initially assumed (McManus et al., 2021). Acute stress can also facilitate the consolidation of other experiences with low emotional component taking place in association with the stressful situation (Lopes da Cunha, 2021), a process in which the activation of glucocorticoid receptors seems to be involved (Lopes da Cunha, 2021) comprising actions not only in neurons, but also in non-neuronal cells (Buurstede et al. 2021**)**. Finally, these behavioral effects of stress may be (at least partially) driven by cortisol which can modulate emotional responses to pictures (Langer et al., 2021; Zerbes et al., 2020).

Several articles report important individual differences in the behavioral effects of stress (Sepp et al., 2020) that may be partially explained by early life adversity (Young et al., 2022). Sex-dependent differences of stress effects are also a matter of increasing attention in the literature and, in this issue, they were related to differential effects of acute stress on prefrontal cortical function and their mediation by glucocorticoid receptors (Velli et al., 2021) or with the interaction with genetic factors in providing stress vulnerability (Consentino et al., 2021). Importantly, Furman et al. (2021) present a novel female mouse model of chronic social stress and a modified model of chronic social defeat stress in male C57BL/6 mice, and illustrate the importance of including both sexes in stress studies, given their differential psychobiological outcomes (i.e., while stress reduced sociability in both males and females, long-term neuroendocrine and emotional memory disturbances were also observed in males). Significant sex differences were also reported in both cortisol stress response and telomere dynamics (Thomas et al., 2020). There is a growing literature that associates resilience with stress adaptation. In this special issue, Barczak-Scarboro et al. (2021) demonstrated that more resilient Special Operation Forces combat service members recover faster from physiological stress than less resilient counterparts.

The translational value of pre-clinical data to the human diseased condition is highly dependent on the validity of the animal model used to address specific hypotheses. In their meta-analysis of the recent Forced Swim Test (FST) literature, Molendijk et al. (2021) critically examines and provides new perspectives on the validity of this model to address specific stress-related neurobiological questions (Molendijk et al., 2021; Gorman and Hollis, 2021).

Another important aspect that is now getting the long-deserved attention is the focus the interaction between stress responses and mechanisms and processes outside the brain. One very important example of this is the interaction between sex differences and the effects of stress exposure. There is mounting evidence that males or men are reacting fundamentally different to stress compared to females or women on molecular, physiological, circuit and behavioral levels. The one-sided focus on male individuals especially in preclinical research in the past decades has hampered our understanding of the stress biology, which is highlighted in an number of papers in this special issue (Balog et al., 2021; Flanigan and Kash, 2020; Levis et al., 2021). Another example is the interaction between stress responding in the brain and autonomic responses in the heart and how these interactions may contribute to hypertensive disease (Legaz et al., 2020); and a final example is the interaction between the brain and gut health during stress (Doney et al., 2021). Furthermore, new possible players - such as histamine- are proposed to explain the link between stress and depression (Hersey et al., 2021).

Finally, this special issue underlines the importance of fine-tuning our stress definitions, stress manipulations (Kilinc et al., 2021; Walker et al., 2020; Zhou et al., 2021) and stress-related read-outs (Hales et al., 2021), which need to bridge highly focused single molecule, circuit or behavioral analyses with large-scale big data generated from multi-omics approaches or machine learning behavioral algorithms (Lyons et al., 2021).

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