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G2B Reviews: Stress at the intersection of anxiety, addiction and eating disorders

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Genes, Brain and Behavior

We all encounter stress at various times in life, but when stress is severe or chronic it can lead to a variety of debilitating psychiatric conditions. Certain mental illnesses can have direct ties to stress, such as depression, anxiety disorders and the newly classified ‘Trauma and stressor-related disorders’ (DSM-5 2013). Not only are these some of the most commonly diagnosed of all psychiatric disorders, but they also frequently occur as secondary, comorbid conditions to other disorders. Indeed, rare is the psychiatric condition that is not in some way influenced by stress. Across a range of conditions, stress can precipitate the onset of symptoms, exacerbate symptom severity once a disorder has taken hold, and trigger relapse after a period of remission.

Given the ubiquitous role of stress in mental illness, a better understanding of its genetic, neurobiological and behavioral roots could significantly impact how we assess and treat a host of neuropsychiatric disorders. This issue of *G2B Reviews* brings together a series of articles showcasing recent advances in stress-related research. In the spirit of the journal, these reviews span the levels of genes, brain and behavior, and bridge the realms of basic research and clinical work. The full text of all eight articles is freely available on the Journal’s website – I hope you find them to be stimulating and informative.

Neural circuitry of fear and stress-susceptible behaviors

In recent years, there has been growing interest in elucidating the neural systems and circuits mediating behaviors that are particularly vulnerable to the detrimental effects of stress. The focus of Hamilton and Brigman's review is the prefrontal cortex (PFC) – a brain region known to be integral to higher-order cognitive-executive processes (Robbins & Arnsten 2009). These authors comprehensively summarize and discuss evidence linking specific subregions of the rodent PFC to performance on measures of a range of stress-sensitive

behaviors, including reversal learning, extinction and cognitive set-shifting. The result is an excellent reference and resource for readers interested in learning more about the PFC and stress (Hamilton & Brigman 2014).

The PFC is also the focus of Rozeske et al.'s review of the neural circuitry conditioned contextual fear. Anxiety disorders, such as posttraumatic stress disorder, are thought to stem in part from abnormal learning about the contexts in which traumatic events are experienced. The processing of contextual fear information has long been considered the province of the hippocampus, albeit functioning in concert with other brain regions (Maren *et al.* 2013). In their review, Rozeske and colleagues make an authoritative case for giving greater weight to the contribution of the PFC as a key node in the circuitry subserving contextual fear. Their views are likely to have a major influence on future work in this area (Rozeske *et al.* 2014).

The molecular and genetic machinery of stress

The function of neural circuits involved in stress is mediated by an incredibly rich array of neurotransmitter systems and molecular signaling pathways. Distilling the key neurochemical and molecular components of these circuits will point to novel therapeutic candidates for stress-related disorders. In this context, as the major source of inhibitory signaling in the brain, the GABA system is a canonical stress-related neurotransmitter and the target of some potent anti-anxiety medications such as Valium (Griebel & Holmes 2013). There is, nonetheless, still much to be learned about how, precisely, the myriad functional components of the GABA system mediate stress. This includes the GABA-synthesizing enzyme, glutamic acid decarboxylase (GAD65), which serves as a powerful modulator of GABAergic neurotransmission. Muller and colleagues have been at the forefront of research utilizing mouse models of absent or deficient GAD65 to study the molecule's role in stress-related behaviors. Here, they discuss how these models can inform current and future understanding of how GABA disturbances impact corticolimbic regulation of stress-related behaviors (Mueller *et al.* 2015).

Through encoding for stress-related molecules, genes have a fundamental role in shaping the response to stress. In fact, genetic factors are estimated to account for a significant proportion of the variance in risk for conditions such as anxiety and depression (Kendler 2001). Though the search for the specific genes involved is ongoing, one genetic candidate to emerge is neuronal nitric oxide synthase (NOS-1, *NOS1*), the principal source of the gaseous signaling molecule, nitric oxide, in the brain. Freudenberg, Reif and their colleagues have steered efforts in recent years to determine the relationship between *NOS1* gene variation and risk for psychiatric diseases ranging from schizophrenia to depression. Interestingly, they and others have uncovered significant connections between *NOS1* gene variants and endophenotypes, such as PFC-mediated cognitive-executive processes (e.g. working memory, impulsive control) that are perturbed by stress (Freudenberg *et al.* 2014).

Epigenetics and stress

One way in which our thinking about the biological underpinnings of stress has been radically reshaped in recent years, has stemmed from the growing appreciation of epigenetic

regulation of brain and behavior (Malan-Muller *et al.* 2014). In a timely and thought-provoking essay, Isles revisits definitions of epigenetics, past and present: from Waddington's writings 70 years ago that emphasized heritability, to current measurements of environmentally induced changes in DNA-methylation and chromatin modification in the adult brain. He cogently asserts how this exciting field can be best served when researchers take care to distinguish true epigenetic changes from mere short-term alterations in gene transcription (Isles 2014).

In what ways could an informed understanding of epigenetics impact the study of stress? As discussed by Pizzimenti and Lattal, epigenetics potentially represent a key point of mechanistic convergence of stress disorders and drug addictions. They contend that the common epigenetic changes caused by exposure to stress and drugs of abuse may go some way to account for the high rates of comorbidity evident in individuals with these disorders. Furthermore, they provide a convincing case advocating for the clinical value of identifying and targeting epigenetic mechanisms associated with the learned inhibition (extinction) of trauma and drug memories. This exciting and fast-moving area will be one to watch in the coming years (Pizzimenti & Lattal 2014).

Stress, eating and addiction

With rates of eating disorders on the rise, there has been a renewed focus on conditions ranging from anorexia nervosa to binge eating (Volkow *et al.* 2013). While there are many anecdotal reports linking stress and abnormal patterns of eating, compelling empirical evidence still remains surprisingly scant. As a path forward, Hardaway *et al.* (2014) suggest a scheme whereby anxiety and stress lead to functional disturbances in brain circuits mediating feeding behaviors that, in turn, may go on to cause abnormal patterns of eating. The authors eloquently lay out a conceptual framework that provides a tractable approach to identifying the key peptidergic and hormonal regulators of these circuits – and hence, possible therapeutic targets for eating disorders (Hardaway *et al.* 2014).

In contrast to eating disorders, there is long history of research linking stress and drug addictions, perhaps most notably alcohol-use disorders (Zorrilla *et al.* 2014). Corticotropin-releasing factor (CRF) has been a major focus of this work, given its function as a master switch for the peripheral and central nervous systems' acute and long-term response to stress. Phillips and colleagues discuss emerging support for the association of genetic variation in the CRF system with differences in alcohol consumption, not only in rodents, but also in non-human primates and humans too. The authors go on to document how pharmacological and genetic manipulations of CRF or the peptide's receptors alter alcohol intake and profoundly influence neural, endocrine and behavioral adaptations to chronic alcohol intake. The reader is left with a thorough appreciation of the role of CRF as both mediator and treatment-target for alcohol abuse (Phillips *et al.* 2014).

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