Stress and the brain: individual variability and the inverted-U

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It is a truism that the brain influences the body and that peripheral physiology influences the brain. Never is this clearer than during stress, where the subtlest emotions or the most abstract thoughts can initiate stress responses, with consequences throughout the body, and the endocrine transducers of stress alter cognition, affect and behavior. For a fervent materialist, few things in life bring more pleasure than contemplating the neurobiology of stress.

The early years of the field of stress biology were dominated by the first half of the neuroendocrine loop, namely the ability of the brain to initiate the body's stress response. Stress physiology was born early in the last century, in the Paleolithic era of Walter Cannon implicating the sympathetic nervous system in the 'fight or flight' response, and in Hans Selye identifying glucocorticoids as the other main mediator of the stress response. These foundational findings took the field in many directions. One was the revolutionary work of Geoffrey Harris, Roger Guillemin and Andrew Schally showing that the brain is an endocrine gland, secreting releasing and inhibiting hormones into the hypothalamic-pituitary portal system; in many ways, the decades-long arc of that revolution was bracketed by stress research, in that corticotropin-releasing hormone was the first of the principal hypothalamic hormones whose existence was inferred physiologically and the last to be isolated and biochemically characterized.

The half of the loop concerning the brain regulating the body also encompasses the historic welcoming of psychologists into the field; this came with the demonstration that the stress response, conceptualized in the context of acute physical crisis, can be robustly activated by purely psychological states, such as loss of control, predictability and social support. And that half of the loop also incorporates the fact, first deeply appreciated by Selye, that makes stress biology a branch of medicine: prolonged stress increases the odds of being sick. This has facilitated the birth of other subfields (for example, psychoneuroimmunology), and is now an area of tremendous amounts of reductive research. As a result, we have a fairly good idea as to how, say, a fleeting, stressful thought changes transcriptional events relevant to oxidative metabolism in your big toe.

In many ways, the pendulum has swung and, in recent decades, the field has come to be dominated by the second half of the loop, namely the effects of the peripheral stress response on the brain. This is certainly reflected in the collection of papers in the present issue. Collectively, they highlight a number of important themes.

Reductive mechanisms underlying stress effects in the brain

A major one, naturally, has been the ever-increasing insights into the mechanisms by which stress affects the brain. For example, decades of work have fruitfully explored the disruptive effects of stress on hippocampal-dependent declarative memory processes and on frontocortical-dependent executive function and behavioral regulation. It is only in more recent years that we have gained insight into the signal transduction pathways and transcriptional events that mediate these stress effects[1,2]. Moreover, some of these mechanistic insights contain surprises that have upended dogma. One, for example, concerns neuroinflammation and the textbook knowledge that glucocorticoids are uniformly anti-inflammatory. However, it is now recognized that this is not always the case, and that glucocorticoids and stress can even worsen facets of neuroinflammation in a brain region–specific manner[3]; the novel depressogenic effects of neuroinflammation[4] provides a mechanistic route by which stress predisposes to depression.

Early life stress and adult opportunities that should not be lost

Another theme concerns the complex and supremely important intersection of brain development and adult neuroplasticity. A canonical body of knowledge shows how stress in early life, particularly in the perinatal period, can have predominately adverse neurobiological consequences stretching long into adulthood[5]. These effects can have an extraordinarily long reach, changing the trajectory of brain aging, and even having multi-generational effects, through the non-genetic transmission of behavioral and physiological traits. The mediating mechanism for these long-term effects has increasingly been shown to be epigenetic, a current focus of intense amounts of work.

Running in parallel with this is the evidence of plasticity in the adult nervous system. The excitability of synapses change, dendritic spines come and go within minutes, dendritic processes expand or retract, and circuitry remaps. And then there is, of course, the revolution of adult neurogenesis. Little in the brain, it turns out, is set in stone.

When combined, these two sets of findings produce conclusions that are both salutary and alarming and should galvanize action. First, early life adversity can leave broad and permeating scars of neurobiological dysfunction long into the future, even unto the proverbial generations. Second, there is far more potential for lessening, halting or even reversing these consequences of early life stress in the adult than anyone could have imagined. Third, the longer the intervention is delayed,

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the more of an uphill battle there will be to be make things better.

Multi-level meanings of stress effects

Another theme is the disconnect between the 'meaning' of a stress effect on the neuron, the brain structure and the organism. A prime example of this concerns the hippocampus, frontal cortex and amygdala[6]. Extensive work has shown that, in the first two structures, stress and glucocorticoid excess will decrease synaptic plasticity, cause atrophy of dendritic processes and even cause a loss of total volume or gray matter volume. These findings have been appropriately interpreted as bad things for the organism, and underlie some of the adverse neurocognitive consequences of depression, posttraumatic stress disorder and childhood poverty. A different picture occurs in the amygdala, particularly the basolateral amygdala, where stress and glucocorticoids increase synaptic plasticity and foster expansion of dendritic processes (which raises challenging questions regarding the mechanisms by which glucocorticoid signaling has diametrically opposite effects in these regions). At first glance, this can readily be interpreted as a good thing—after all, who wouldn't want their neurons to be more strongly and broadly integrated into circuits? However, this amygdaloid hypertrophy can be anything but beneficial, as it contributes to the adverse effects of stress on fear acquisition and extinction: when we are stressed, we learn more readily to be afraid when there is no need to and less readily detect when we are safe. The road to a crippling anxiety disorder is paved with perky amygdaloid synapses.

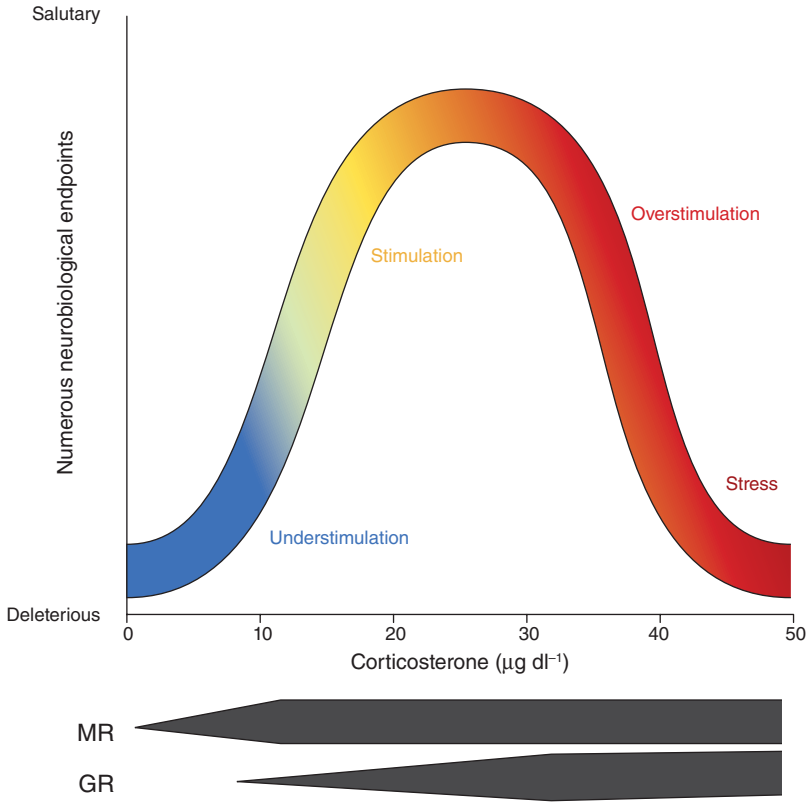

Figure 1 Conceptualization of the inverted-U in the context of the benefits and costs of stress. A broad array of neurobiological endpoints show the same property, which is that stress in the mild-to-moderate range (roughly corresponding to 10–20 μg dl^{-1} of corticosterone, the species-specific glucocorticoid of rats and mice) has beneficial, salutary effects; subjectively, when exposure is transient, we typically experience this range as being stimulatory. In contrast, both the complete absence of stress, or stress that is more severe and/or prolonged than that in the stimulatory range, have deleterious effects on those same neurobiological endpoints. The absence of stress is subjectively experienced as understimulatory by most, whereas the excess is typically experienced as overstimulatory, which segues into 'stressful'. Many of the inverted-U effects of stress in the brain are explained by the dual receptor system for glucocorticoids, where salutary effects are heavily mediated by increasing occupancy of the high-affinity, low-capacity MRs and deleterious effects are mediated by the low-affinity, high-capacity GRs.

The ubiquitous, but nonspecific, role of stress in psychiatric disorders

These amygdaloid effects serve as a segue to the ever stronger evidence for stress as a risk factor for an array of neuropsychiatric disorders, including depression, anxiety, schizophrenia and various addictive behaviors[7,8]. These linkages both take the form of early life stress predisposing toward adult illness and periods of acute stress during adulthood triggering episodes of disease. The breadth of these stress effects implies, at the same time, their nonspecificity. A good example of this is seen with the immunophilin FKBP5, which, as a glucocorticoid receptor co-factor, is highly pertinent to stress neuroendocrinology; variants of the *FKBP5* gene are associated with altered risks of depression, anxiety and PTSD[9]. As another example, consider the *DISC-1* gene (Disrupted in Schizophrenia-1), whose cytoskeletal protein product interacts extensively with the signal transduction pathways of stress signals; despite the specificity implied by DISC-1's name, abnormalities in the structure or regulation of the protein have been implicated not just in schizophrenia, but in depression and bipolar disorder as well[2].

Appreciating the importance of stress is critical for understanding the neurogenetics of psychiatric illness, as stress is the poster child for the environment part of gene × environment interactions. Beginning with the landmark demonstration of the role of serotonin transporter gene polymorphisms in depression risk[10], the genetics of mental illness has been repeatedly shown to be about stress/diasthesis and about vulnerability to stress.

Thus, a variety of themes appear in these papers. Two even larger ones at least tacitly run through all of them and, I hope, will shape research in stress neurobiology for years to come.

The humdrum and the fascinating versions of the obligatory question of what is stress

Seemingly within moments of Selye popularizing the word stress in the world of biomedicine, the definitional debate began. Is stress more about the unpleasantry in the outside world (that is, the stressor) or the resulting changes in the body (that is, the stress response)? Or is it mostly about the neurobiological and psychological space floating between the two? This eventually wearisome debate inevitably constituted the first session of virtually every stress conference for decades; it has finally lost steam, with a sense that the word encompasses all of the above—let a thousand flowers bloom, but just remember to define your particular flower in the Methods section.

The far more interesting version of this question addresses the fact that in any species you'd care to study, different individuals respond to stress differently; there are typically dramatic individual differences as to whether a particular event or internal state is even perceived to be stressful. In other words, what is stress…for this individual? Of course, individual variability is not always the case; a severe injury, a major

burn or a sprint from a predator will reliably activate the stress response and evoke an aversive subjective sense in virtually any organism. But these are not the circumstances of stress that are most pertinent to understanding health and disease in contemporary life. Instead, individual differences are most notable as we navigate life's social exigencies.

Individual differences in stress biology were once mostly an experimental irritant: oh no, because of variability we need a bigger sample size. However, individual variability as to whether something is perceived as stressful, and in resilience and vulnerability to stress-related disease, should be viewed as the most important topic in the field. After all, one person's stress envelope is pushed by getting up at the crack of dawn to bird-watch, and another's by a stint as a mercenary in Somalia. To best appreciate the importance of individual differences in stress responsiveness, it is worth focusing on the single most important concept in the field.

The inverted-U

When viewed from a distance, the effects of stress on the brain and behavior are often worse than murky, where a stressor might increase some endpoint in one setting, have no effect in another and decrease it in a third. To anyone working in the field, what was apparent from the start was that the response to stress depends on the nature, intensity and duration of a stressor (which at least partially translates into a dependence on the pattern of activation of the sympathetic nervous system, the adrenocortical axis and the other mediators of the stress response).

This represents progress and allows one to begin to corral that array of heterogeneous and often diametrically opposite findings into some groupings: for example, the contrasting responses to physical versus psychological stressors, to biotic versus abiotic stressors, to continuous versus intermittent stressors, and so on. Enormous unifying clarity came with the recognition that, to a large extent, the effects of stress in the brain form a nonlinear 'inverted-U' dose-response curve as a function of stressor severity: the transition from the complete absence of stress to mild stress causes an increase in endpoint X, the transition from mild-to-moderate stress causes endpoint X to plateau and the transition from moderate to more severe stress decreases endpoint X.

A classic example of the inverted-U is seen with the endpoint of synaptic plasticity in the hippocampus, where mild-to-moderate stressors, or exposure to glucocorticoid concentrations in the range evoked by such stressors, enhances primed burst potentiation, whereas more severe stressors or equivalent elevations of glucocorticoid concentrations do the opposite[11]. This example also demonstrates an elegant mechanism for generating such an inverted-U[12]. Specifically, the hippocampus contains ample quantities of receptors for glucocorticoids. These come in two classes. First, there are the high-affinity low-capacity mineralocorticoid receptors (MRs), which are mostly occupied under basal, non-stress conditions and in which occupancy increases to saturating levels with mild-to-moderate stressors. In contrast, there are the low-affinity, high-capacity glucocorticoid receptors (GRs), which are not substantially occupied until there is major stress-induced glucocorticoid secretion. Critically, it is increased MR occupancy that enhances synaptic plasticity, whereas increased occupancy of GRs impairs it; the inverted-U pattern emerges from these opposing effects.

There are abundant additional examples of inverted-U effects of stress in the hippocampus; this is also the case elsewhere in the brain (mediated by mechanisms other than the MR/GR duo, which is mostly specific to the hippocampus)[13–18].

Thus, a morass of conflicting data is eliminated by recognizing the prevalence of inverted-U's. But even greater insight is provided when considering the collective nature of the various inverted-U's; in general, the effects of mild-to-moderate stress (that is, the left side of the U) are salutary, whereas those of severe stress are the opposite. In other words, it is not the case that stress is bad for you. It is major stress that is bad for you, whereas mild stress is anything but; when it is the optimal amount of stress, we love it.

What constitutes optimal good stress? It occurs in a setting that feels safe; we voluntarily ride a roller coaster knowing that we are risking feeling a bit queasy, but not risking being decapitated. Moreover, good stress is transient; it is not by chance that a roller coaster ride is not 3 days long. And what is mild, transient stress in a benevolent setting? For this we have a variety of terms: arousal, alertness, engagement, play and stimulation (**Fig. 1**).

Entire careers are spent exploring different parts of the inverted-U. At the far left is the realm of an under-stimulatory environment, with profoundly adverse effects seen in impoverished environments ranging from childhood (with, for example, the nightmarish Romanian orphanages as an extreme) to old age, from humans to zoo animals in sterile cages. The upswing of the inverted-U is the domain of any good educator who intuits the ideal space between a student being bored and being overwhelmed, where challenge is energized by a well-calibrated motivating sense of 'maybe'; after all, it is in the realm of plausible, but not guaranteed, reward that anticipatory bursts of mesolimbic dopamine release are the greatest[19]. And the downswing of the inverted-U is, of course, the universe of "stress is bad for you". Thus, the ultimate goal of those studying stress is not to 'cure' us of it, but to optimize it.

Individual differences meet the inverted-U

It is useful to superimpose the world of individual differences in stress responsiveness and vulnerability onto the inverted-U concept, as it allows one to frame the differences in terms of the width, height or symmetry of the U-shaped curve. Most of all, it allows one to hone in on a critical question. For any particular stressor, setting and context, where along the axis of stressor severity is the peak of an individual's inverted-U? In other words, what is the point of transition at which someone's experience turns from stimulation to stress, from striving to learned helplessness, from growing from challenge to crumbling? And from this come additional questions. What are the mechanisms by which adversity shifts inverted-U's to the left (that is, an increased vulnerability to subsequent stress)? What conditions foster inverted-U's that are shifted to the right (that is, resilience)[20]?

These questions should be a primary focus of the field for years to come. It is indisputable that extremes of stress are bad for the brain, a fact pertinent to developmental neuroscience, neurogerontology, and everything in between. It is also equally indisputable that optimal amounts of stress enrich and sustain us. Hopefully, as knowledge continues to accumulate at the rate showcased in this issue, we will gain the means to spend more of our lives experiencing the left sides of our inverted-Us.

COMPETING FINANCIAL INTERESTS
The author declares no competing financial interests.

1. McEwen, B. *et al. Nat. Neurosci.* **18**, 1353–1363 (2015).
2. Arnsten, A.F. *Nat. Neurosci.* **18**, 1376–1385 (2015).
3. Sorrells, S.F. *et al. Neuron* **64**, 33–39 (2009).
4. Hodes, G. *et al. Nat. Neurosci.* **18**, 1386–1393 (2015).
5. Tost, H. *et al. Nat. Neurosci.* **18**, 1421–1431 (2015).
6. Chatterji, S. *et al. Nat. Neurosci.* **18**, 1364–1375 (2015).
7. Holon, N. *et al. Nat. Neurosci.* **18**, 1405–1412 (2015).
8. Calhoon, G. & Tye, K. *Nat. Neurosci.* **18**, 1394–1404 (2015).
9. Hariri, A.R. & Holmes, A. *Nat. Neurosci.* **18**, 1347–1352 (2015).
10. Caspi, A. *et al. Science* **301**, 386–389 (2003).
11. Diamond, D.M. *et al. Hippocampus* **2**, 421–430 (1992).
12. McEwen, B.S. & Sapolsky, R. *Curr. Opin. Neurobiol.* **5**, 205–216 (1995).
13. Chrousos, G. *Nat. Rev. Endocrinol.* **5**, 374–381 (2009).
14. Baldi, E. & Bucherelli, C. *Nonlinearity Biol. Toxicol. Med.* **3**, 9–21 (2005).
15. Luksys, G. & Sandi, C. *Curr. Opin. Neurobiol.* **21**, 502–508 (2011).
16. Prager, E. & Johnson, L. *Sci. Signal.* **2**, re5 (2009).
17. Roozendaal, B. *Psychoneuroendocrinology* **25**, 213–238 (2000).
18. Sapolsky, R.M., Romero, L. & Munck, A. *Endocr. Rev.* **21**, 55–89 (2000).
19. Fiorillo, C.D., Tobler, P. & Schultz, W. *Science* **299**, 1898–1902 (2003).
20. Russo, S.J. *et al. Nat. Neurosci.* **15**, 1475–1484 (2012).