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From Classic Aspects of the Stress Response to Neuroinflammation and Sickness: Implications for Individuals and Offspring

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Accumulating evidence suggests that exposure to psychological stressors leads to increased expression of pro-inflammatory cytokines and activation of inflammatory-related pathways in the central nervous system. Several logical predictions arise from these findings: (1) stressor exposure should produce changes in behavior that are reminiscent of acute illness; (2) administration of anti-inflammatory agents should ameliorate some behavioral consequences of stressor exposure; and (3) there should be convergence between anatomical and neurochemical pathways activated by stressor exposure and those involved in mitigating sickness behaviors. Importantly, these predictions have been tested in our laboratory across multiple stressor paradigms (footshock, maternal separation, and during acute alcohol withdrawal) using two species (rats and guinea pigs), suggesting that sickness may represent a more general motivational state that can be elicited by a diverse range of psychological challenges. Implications of these findings for understanding stress-related changes in behavior, mood and neuroinflammatory processes will be discussed with special reference to implications for the individual and reproductive fitness.

The concept of stress has suffered a long and contentious history with little agreement even today about what it entails (e.g., McEwen & Wingfield, 2003). The problem becomes particularly apparent when one tries to operationalize the term for scientific study, and even worse when one seeks to determine the impact of stress on individuals or populations. In its crudest form, the concept of stress can be broken down into three principle components which I will describe in some detail below, using what is known about central nervous system (CNS) regulation of the stress response as a lens through which consequences of stressor exposure might be viewed. The first component must be the evocative agent: the general construct of stress can be parsed into categorically distinct threats (often termed stressors), each of which may activate the major stress responsive systems to varying degrees. The *stress response*, therefore, becomes the second principle component and refers to the constellation of changes (behavioral, physiological, or psychological) provoked by the actual or perceived threat. Finally, the impact of stress exposure on the overall health of the organism (Component III) must in some way be a function of the stress response(s) that have been evoked by the stressor. As a result, stress-responsive systems have been studied extensively in biomedical research as core systems that mediate and/or modulate nearly all disease-related processes (whether infectious, traumatic or genetic in nature). Ecologists, on the other hand, are particularly interested in the impact of anthropogenic stressors on the welfare and reproductive fitness of diverse species. With that in mind, the goal

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of the following review is to help bridge the gap between these seemingly disparate fields.

The Classic Stress Responsive Systems

Two classic systems that are principally activated during times of stress are the sympathetic nervous system (SNS) and the hypothalamic-pituitary-adrenal (HPA) axis. Though they will be discussed categorically below, it is in fact the combined effort of the SNS and HPA axis – among other critical endocrine and neural systems – that ultimately comprise an organism's response to stress. These systems are activated rapidly in response to stressful stimuli and have a broad impact on diverse aspects of physiological functioning. Indeed, many of the delayed and/or long-term consequences of stressor exposure are set into motion as a downstream consequence of the initial SNS and HPA responses. In this regard, indirect measures of SNS activation (such as increased heart rate, blood pressure, or hyperthermia) or direct measures of SNS output (plasma concentrations of epinephrine and norepinephrine) and HPA activation (corticosteroid concentrations in plasma, tissue or excrement) are often used as an index for the severity of a stressor that has been encountered. Regardless of which measure is examined, the magnitude of the stress response is best defined as 'area under the curve' whenever possible because this measure integrates peak response with duration of stressor exposure (Barnum, Blandino Jr, & Deak, 2008; Pacak & Palkovits, 2001). Note, however, that for these measures to be useful indices of the stress response, they must be (a) assessed with respect to a known baseline or non-stressed condition in the same animal or a group of conspecifics that have been otherwise treated identically; (b) evaluated in a threatening context, since pleasurable experiences such as sexual intercourse (Bonilla-Jaime, Vazquez-Palacios, Arteaga-Silva, & Retana-Marquez, 2006), euphoria produced by drugs of abuse (Goeders & Clampitt, 2002), or anticipation of palatable food (Pecoraro, Gomez, Laugero, & Dallman, 2002) also elicit profound activation of these same physiological response systems but do not fit the intuitive mold of 'stress'; and (c) considered within the context of circadian rhythms, as corticosteroids and catecholamines both evince diurnal variation. Some caution is therefore prudent in the interpretation of physiological measures that are used to infer that a given response is a manifestation of stress.

The sympathetic nervous system is a fast-acting response to stress that can be detected within seconds of stressor onset, assuming that the onset is a punctate event (i.e., one with a clearly defined beginning and end, such as detection of a predatorial attack). In other cases, SNS activation is often described as a steadily escalating 'tone', where over the course of hours, days or months (depending on the nature of the stressor), general activity of the SNS is increased, leading to increased metabolic demand and gradual wear-and-tear on physiological systems (allostatic load) that may eventually culminate into physiological failures (allostatic overload) (McEwen & Wingfield, 2003).

Mechanistically, the vital nature of SNS responses to stress is underwritten by the redundancy evident in the system. For instance, SNS activation leads to the release of the catecholamines epinephrine and norepinephrine from sympathetic

nerve terminals that innervate all organs of the body and the musculature, allowing for rapid and profound changes in whole organism physiology. Epinephrine and norepinephrine are also released from the adrenal medulla into the general circulation where it acts as an endocrine signal (i.e., affecting distal targets) that helps prolong the action of neurally-derived catecholamines. These peripheral cascades of catecholamines are regulated by autonomic structures in the CNS such as the locus ceruleus (LC), nucleus of the solitary tract (NTS), the ventrolateral medulla (VLM) and the medial amygdala. Importantly, these structures all communicate to other structures in the CNS using predominantly (though not exclusively) norepinephrine and epinephrine, and are sensitive to internal homeostatic threats (hypoxia, hypoglycemia, immune stimuli, toxin and toxicant exposure, etc). These structures (particularly the LC) receive extensive input from brain structures involved in threat perception from the forebrain, thereby regulating peripheral sympathetic outflow through descending projections that activate sympathetic chain ganglia (see Guyton & Hall, 2006) for a general overview of SNS organization and function). Together, the redundant release of catecholamines directly onto target tissues from sympathetic nerve terminals, into the general circulation and locally within the CNS produces a coordinated, whole body response to stressful stimuli.

Though activation of the hypothalamic pituitary-adrenal (HPA) axis is somewhat slower to develop (usually within 3-5 min of stressor onset), the impact of corticosteroid release from the adrenal cortex is equally profound, though on a somewhat more protracted timeline. Every nucleated cell in the body expresses corticosteroid receptors, though the relative expression of these receptors differs markedly across cell and tissue types (Spencer, Young, Choo, & McEwen, 1990) and ultimately determines organ sensitivity to corticosteroids. Corticosteroids (cortisol in humans, corticosterone in rats) are the ultimate effector of the HPA response and are the end-product of a series of hormonal secretions that are initiated by cells in the paraventricular nucleus (PVN) of the hypothalamus (Dallman et al., 1987). As a result, the hypothalamus generally, and the PVN more explicitly, receives neural input from numerous other nuclei in the CNS involved in the perception of threat (i.e., stress) and is therefore uniquely situated as a final site of integration for the stress response. From a teleological perspective, this allows diverse threats to the organism (i.e., stressors) to activate a single effector response (corticosteroid release). The stereotyped release of corticosteroids in response to diverse stressors leads to mobilization of glucose from the liver, alterations in gene expression patterns and changes in cellular metabolic activity among other far-reaching consequences, all of which ultimately promote survival in the face of diverse threats (Munck, Guyre, & Holbrook, 1984).

Sickness and Neuroinflammation as a Consequence of Stress

While SNS and HPA responses to stress occur rather quickly, these responses inandof themselves do not readily explain the diverse range of long-term consequences of stress. For instance, exposure to relatively intense stress in rodents leads to reduced food and water consumption (Deak et al., 1999a; Dess, Raizer, Chapman, & Garcia, 1988; Marti, Marti, & Armario, 1994), decreased so-

cial and sexual behavior (Retana-Marquez, Salazar, & Velazquez-Moctezuma, 1996; Short & Maier, 1993; Uphouse, Selvamani, Lincoln, Morales, & Comeaux, 2005), and reduced activity/exploration in a novel environment (Woodmansee, Silbert, & Maier, 1993). Because these changes often persist for several days following stressor termination, they cannot be explained readily at a mechanistic level by activation of the principle stress responsive systems, the SNS and HPA axis, because these responses have largely resolved by the time the behavioral adaptations emerge. It is therefore advantageous to examine physiological and behavioral processes that occur in a protracted fashion following termination of the prototypical stress responses, and these effects will be the subject of the following discussion.

When this constellation of behavioral changes is viewed from the perspective of motivation rather than as individual behavioral changes, the overall pattern of changes seems to suggest decreased propensity to engage in goal-directed behavior. For many years, the biomedical research community has likened these changes to depressive-like tendencies (Gronli et al., 2005). While this interpretation provides clarity on clinical implications of intense stressor exposure, it does little to advance our understanding of brain mechanisms underlying such widespread consequences of stress. Moreover, this interpretation would seem to violate the implicit evolutionary presumption that the stress response – and behavioral consequences that ensue – somehow act in an *adaptive* manner to promote survival.

In light of this, we prefer to view the constellation of behavioral changes observed after stressor exposure as *recuperative responses* rather than pathological ones. In doing so, it becomes immediately apparent that the collective changes in behavior observed after intense stressor exposure are strikingly similar to those observed during acute illness produced by infection, termed sickness behaviors (Hart, 1988; Kent, Bluthe, Kelley, & Dantzer, 1992a). In fact the similarities between consequences of stressor exposure and acute illness extend well beyond behavioral changes and include alterations in neurotransmitter release (A.J. Dunn & Welch, 1991), changes in cognitive function (Gibertini, Newton, Friedman, & Klein, 1995; Pugh et al., 1999), as well as changes in peripheral immune function (see Maier & Watkins, 1998 for a review). These similarities led us to propose that many behavioral consequences of stressor exposure – particularly ones indicative of a general malaise – may be aptly described as 'stress-induced sickness behaviors' (Hennessy, Deak, & Schiml-Webb, 2001). This hypothesis arose from numerous empirical findings. First of all, stress can increase the expression of pro-inflammatory cytokines in the CNS (Deak et al., 2005b; Nguyen et al., 1998), and these factors are also known to be critical for the generation of sickness behaviors precipitated by acute illness (Bluthe et al., 1999; Kent, Bluthe, Kelley, & Dantzer, 1992a; Kent et al., 1992b). Injection of lipopolysaccharide (a component of cell walls of gram negative bacteria that is often used to mimic infection) or direct administration of pro-inflammatory cytokines provokes a similar complement of behavioral changes as intense stressor exposure (Hennessy et al., 2004; Plata-Salaman & French-Mullen, 1992). Acute stress also increases expression of acute phase proteins and evokes a sustained increase in core body temperature, effects

that can persist for days following stressor termination (Deak et al., 1997). Indeed, exposure to psychological stressors produces a fever response that is commonly used as a rapid and sensitive index of SNS activation (Barnum, Blandino Jr, & Deak, 2007; Oka, Oka, & Hori, 2001). Finally, and perhaps most compelling, central administration of anti-inflammatory agents can reverse many sickness-like changes provoked by stress (Hennessy et al., 2007; Milligan et al., 1998; Schiml-Webb, Deak, Greenlee, Maken, & Hennessy, 2005). Together, these data support the view that acute illness and stressor exposure produce many similar sequelae that are coordinated through common biological pathways.

In this regard, it is interesting to note that sickness responses to infection are thought to reflect a goal-directed process (i.e., a motivational state) designed to promote recuperation, not a debilitated state for the animal (Aubert, 1999; Dantzer, 2004; Hart, 1988). Evidence to support this hypothesis comes from the simple observation that sickness behaviors are more readily observed in the home cage environment of laboratory animals (i.e., a safe haven) than in a novel environment where threats are unknown. In a very clever study, it was shown that sick dams fail to rebuild their nest and retrieve pups at normal ambient temperatures, but readily do so in a cold environment that threatens her offspring (Aubert, Goodall, Dantzer, & Gheusi, 1997). Data from our own laboratory suggest that rats exhibit normal swim behavior while sick after doses of LPS that evoke a pronounced fever and increased cytokines that persist for 2-3 days (Deak, Bellamy, & Bordner, 2005a; Deak et al., 2005c). Such plasticity of behavior during times of immunological threat supports the view that sickness itself is a goal-directed, recuperative response. Our central argument, therefore, is that intense stressor exposure is followed by a similar recuperative period, mediated by common neural mechanisms.

Mechanistically, increased expression of pro-inflammatory cytokines in the CNS is likely to be the common biological mechanism that unites the consequences of stressor exposure and acute illness (Maier & Watkins, 1998). Of the many inflammatory factors that have been identified, Interleukin-1 (IL-1) appears to be particularly inducible by stress and the hypothalamus is a key structure where such changes are prevalent (Deak et al., 2005b). It is important to note, however, that not all stressors increase expression of IL-1 in the CNS. For instance, exposure of rats to simple restraint in a Plexiglas tube, brief social defeat or insulin-induced hypoglycemia had no effect on hypothalamic IL-1, while exposure to footshock, tailshock or immobilization all elicit profound increases in hypothalamic IL-1 (Deak, Bellamy, & D'Agostino, 2003; Nguyen et al., 1998; Plata-Salaman et al., 2000; Shintani, Nakaki, Kanba, Kato, & Asai, 1995). Interestingly, if simple restraint was administered in combination with a hypoglycemic challenge or on an orbital shaker, two procedures that change both the nature and intensity of the restraint experience, then increased hypothalamic IL-1 was in fact observed (Deak et al., 2005b). To the extent that increased IL-1 can be used to more broadly infer neuroinflammation, there are several potential explanations for these findings. First of all, there may be an *identifiable threshold* of stress that is necessary to provoke a neuroinflammatory response. Though stressor intensity is a notoriously difficult construct to define operationally, stressor intensity is often inferred based on the magnitude of the corticosteroid response observed (eg. Pace et al., 2005). In this

regard, it is noteworthy to mention that increased hypothalamic IL-1 and plasma corticosterone concentrations bare little association if any (Barnum et al., 2008; Deak et al., 2005b).

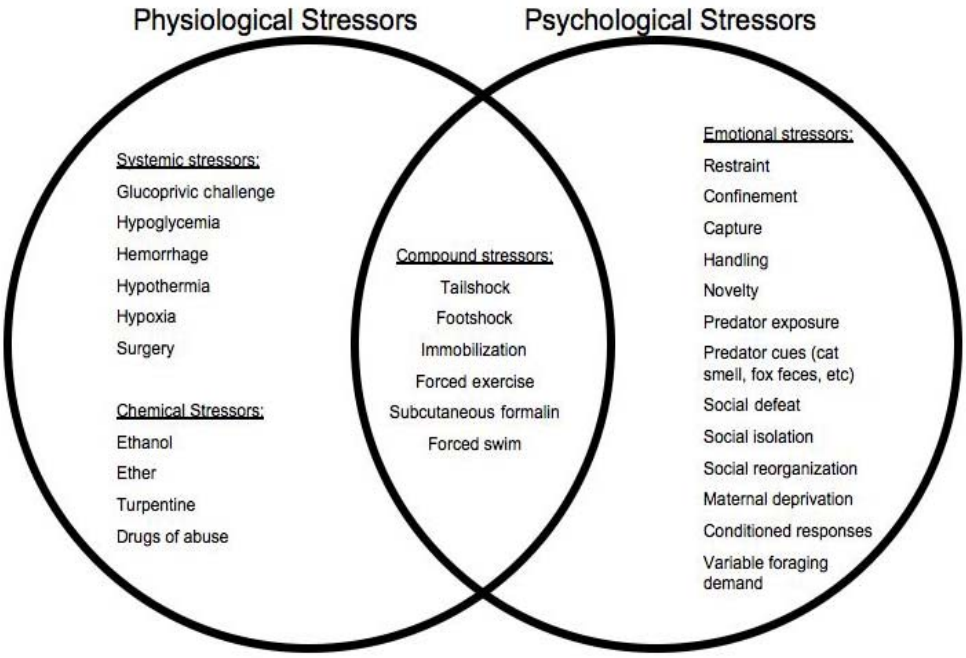

Figure 1. Venn diagrams categorizing the most commonly used stressor paradigms. Available data supports the view that most threats to mammalian species can be separated into at least two separate categories, described here as "physiological" and "psychological" stressors. Note, however, that some stressors are not readily classified into either category because the response they produce is significantly more profound than for other, more categorically distinct, stressors. To account for this, we use the term "compound stressors" to refer to stressors which fall in the overlapping portions of the Venn Diagram.

An alternative explanation for the apparent stressor-specific increases in hypothalamic IL-1 is that features of the stressors themselves are recognized in a categorically distinct fashion by the CNS and that only specific categories of stressors can activate a neuroinflammatory response. Indeed, there is general agreement among stress researchers that threats can be divided into at least two distinct categories based on the brain systems they activate (Dayas, Buller, Crane, Xu, & Day, 2001; Herman, Prewitt, & Cullinan, 1996; Sawchenko et al., 1996; Sawchenko, Li, & Ericsson, 2000). 'Psychological' stressors (also referred to as emotional, processive and neurogenic) are detected by the cognitive or perceptual apparatus of the organism and include paradigms such as restraint, novelty and predator exposure among others (see Figure 1). These stressors seem to preferentially activate forebrain and limbic structures such as the amygdala, prefrontal cortex, and hippocampus that send descending and/or lateral inputs to the PVN, thereby leading to activation of the HPA axis. 'Physiological' stressors (also referred to as physical, homeostatic or systemic), on the other hand, represent dire threats to organismic

functioning. As such, physiological stress encompasses internal threats to homeostasis such as hypoglycemia, hypoxia, hemorrhage, and immune challenge. These threats are detected largely by vital regulatory centers in brainstem autonomic nuclei including the VLM and NTS. These structures provide direct noradrenergic drive to the PVN through ascending fiber tracts, thereby leading to activation of the HPA axis (Herman & Cullinan, 1997).

Interestingly, some stressors yield brain activation patterns that do not fit neatly into the psychological or physiological categories, but instead seem to uniquely activate both sets of brain structures (Dayas et al., 2001). In this regard, if emotional and physiological stressors are opposite ends of the spectrum, then some stressors may lie more centrally because they uniquely comprise characteristics of both poles. This premise is depicted in Figure 1 where Venn diagrams are used to provide an overview of the numerous stressors employed in the laboratory setting. Note that direct empirical data is not available for all of these stressors, so stressors were arranged based on intuitive similarity to other stressors and/or the common outcomes produced by them.

To the extent that stressor intensity may be reflected by activation of quantitatively greater numbers of stress-responsive brain structures, stressors that fall in the central domain (termed 'compound stressors') would be expected to produce the most severe outcomes. From a functional neuroanatomical perspective, this would be reflected by a 'compound' drive to hypothalamic structures (particularly the PVN) because drive to the PVN would arrive from brainstem structures as well as forebrain/limbic structures. It is under these circumstances that activation of a neuroinflammatory response – indicated by increased expression of IL-1 and possibly other cytokines – is most likely to occur. Initial support for this hypothesis comes from our recent work showing that exposure to restraint in combination with a hypoglycemic challenge increased IL-1 in the hypothalamus, while neither stressor alone had any effect (Deak et al., 2005b). Whether this is due to activation of both psychological (restraint) and physiological (insulin-induced hypoglycemia) stress circuits or is a synergistic response produced by direct metabolic challenge to hypothalamic neurons (produced by insulin) during an otherwise mild stressor (restraint) remains to be determined. Regardless, the dual nature of the threat led to tell-tale signs of neuroinflammation, underscoring the potential impact for individuals when faced with multiple threats (i.e., stressors) that, if encountered individually, would otherwise have little consequence. In fact, it is likely to be the synergistic interaction among diverse threats – rather than the additive or cumulative ones – that are conceptually difficult to predict, yet represent the most profound threats to the health and vitality of all species.

The next logical question becomes, How do you get from the immediate perception of threat and activation of classic stress responsive systems (SNS and HPA axis) to neuroinflammation and a sickness-like syndrome? This question becomes particularly puzzling when one considers the prominent role of corticosteroids as counter-regulators of immune processes. That is, corticosteroids are widely known for their ability to inhibit inflammatory processes and are used clinically as a therapeutic tool to rapidly supplant inflammatory processes (Munck et al., 1984). However, the doses necessary to produce anti-inflammatory effects are typically

supraphysiological and there are numerous reports indicating that corticosteroids are necessary for normal progression of the immune response (Fleshner, Deak, Nguyen, Watkins, & Maier, 2002) and that lower doses of corticosteroids activate signal transduction pathways that promote inflammatory-gene expression. Indeed, there is compelling evidence that actions of corticosteroids (i.e, whether the effects are pro- or anti-inflammatory in nature) depend heavily on the tissue/cell types to which they bind (Sorrells & Sapolsky, 2007). With that said, removal of endogenous corticosteroids via adrenalectomy dramatically increases expression of IL-1 in the CNS provoked by stress (Nguyen et al., 1998; Nguyen et al., 2000), suggesting that corticosteroids constrain the development of neuroinflammation in response to stress. In contrast, the release of norepinephrine in both central nervous system structures and peripheral immune organs has been shown to increase the expression of proinflammatory cytokines (Blandino Jr, Barnum, & Deak, 2006; Johnson et al., 2005). Together, these findings suggest that neuroinflammatory consequences of stress may be mechanistically intertwined between the stimulatory actions of the SNS and the inhibitory influence of the HPA axis, though much work clearly remains to be done.

The Broader Impact of Stress-Related Neuroinflammation for Evolution and Ecology

Though the framework provided here focuses rather selectively on the ability of stress to increase pro-inflammatory cytokines in the CNS and its relationship to stress-induced sickness behaviors, the impact of cytokines and neuroinflammation extends well beyond an acute behavioral syndrome (summarized in Figure 2). Indeed, there are numerous laboratories examining the impact of neuroinflammation on cognitive function, mood, and affective disorders as well (Deak, 2007; Dunn, Swiergiel, & de Beaurepaire, 2005). From an evolutionary standpoint, these effects can be viewed as proximate consequences of stress insofar as they produce a readily observable and immediate impact on functioning of the individual. However, there is a broader cost to the individual that may not be immediately apparent and it is these costs that are most difficult to quantify. Because these costs are still for the affected individual (not offspring), I would suggest use of the term ‘distal consequences’ to describe them. For instance, normal aging of the CNS across the lifespan is associated with a transition to a greater pro-inflammatory cytokine balance, an effect that may be accelerated by repeated stressor exposure (Frank et al., 2006). Similarly, neuroinflammation is causally related to the development of neurodegenerative disorders such as Alzheimers Disease and Parkinson’s disease and may account for the earlier age of onset and worsening of symptoms produced by stress (eg. Whitton, 2007). Finally, our discussion has centered largely around neuroinflammation, but it is important to recognize that many of the same inflammatory-related changes are observed in other systems as well. As such, activation of inflammatory-related pathways during times of stress has been associated with the development and/or exacerbation of cardiovascular disease (Black, 2002), rheumatoid arthritis and Crohn’s Disease, as well as autoimmune disorders such as multiple sclerosis, lupus and Type I Di-

abetes. Perhaps even worse, increased IL-1 in the CNS sensitizes later stress reactivity that can be observed days to weeks later (Deak, Bellamy, & Bordner, 2005a; Johnson et al., 2002; Schmidt, Aguilera, Binnekade, & Tilders, 2003), suggesting that the impact of chronic stress across the lifespan may feed-forward into progressively more deleterious stress consequences. To this end, activation of inflammatory pathways in the CNS may more generally portend the erosion of individual health. From an ecological perspective, this would be more likely manifest as reduced longevity (due to greater susceptibility to predation) rather than full-blown disease states.

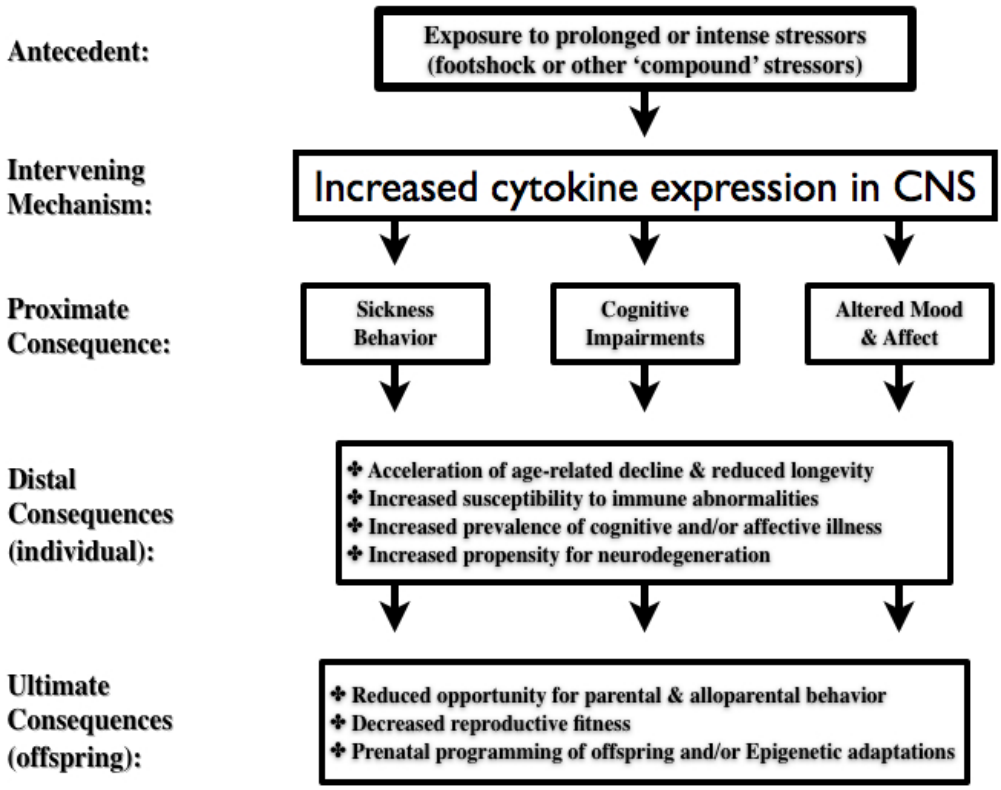

Figure 2. Schematic summary of central cytokine involvement in proximate, distal and ultimate consequences of stressor exposure.

The intrinsic or extrinsic factors that lead an individual to develop a given pathology in response to stress is not currently known in most cases. However, much the same as the ecologist is accustomed to thinking about speciation being driven by the various pressures of natural selection, the same principles may be turned inwardly towards the physiology of the individual. That is, we each possess a diverse range of organs and tissues that operate at some level of efficacy. The weakest of these organs or tissues – perhaps as a result of prior insult, developmental programming, or genetic liability – would be expected to show greater deterioration, wear-and-tear, or overt disease as a result of stress, thereby manifesting as

individual differences in stress reactivity. In the end, the disease states provoked or exacerbated by stressor exposure will undoubtedly enhance susceptibility to predation in the wild.

The impact of stress is not restricted to the individual and often extends to one's offspring as well. Such 'ultimate consequences' come in the straight-forward sense that reproductive behavior is often diminished during peak periods of stress, an effect that is also observed during acute illness, particularly for females (Avitsur & Yirmiya, 1999). Poor health associated with accelerated aging may reduce the opportunity for parental and alloparental behavior, thereby reducing social transmission of critical knowledge and skills later in life. Some of the most profound effects of stress on offspring occur by altering maternal behavior. Rat dams that spend more time licking and grooming their offspring yield litters that are more resilient to stress later in life, while maternal deprivation/neglect produces the opposite effects (Kaffman & Meaney, 2007). Similar effects have been observed in non-human primates where the amount of time the mother spends foraging predicts stress reactivity and mental health of her offspring, presumably because conditions where food is scarce or difficult to acquire lead to greater neglect of offspring (Gorman, Mathew, & Coplan, 2002; Rosenblum & Paully, 1984). As such, the impact of escalating foraging demand would be expected to have a particularly adverse impact on mammalian species where parental investment is high.

With that said, we must resist the call to view stress, stress responses or the consequences of stress in a purely deleterious manner. Recall instead that the principle stress responses (SNS and HPA axis) in addition to the inflammatory response have been highly conserved across the course of evolutionary history and therefore must provide significant adaptive benefit towards survival. For instance, exposure to acute stress has been shown to improve several aspects of wound healing and immune function, while chronic exposure to stressors can produce immunosuppressive effects (Deak et al., 1999b; Dhabhar & McEwen, 1997). These findings challenge the prevalent dogma that stress has only deleterious effects on immune function and remind us that the stress response has many adaptive qualities.

Insight into the adaptive nature of the stress response can also be gleaned by examining the evolution of the endocrine and inflammatory systems more generally. Modern evolutionary views argue that endocrine systems such as the HPA axis evolved initially from unicellular organisms where they were expressed as intracellular signaling cascades, which evolved into cell-to-cell signaling pathways in multicellular organisms, and so forth (Roth et al., 1985). Evidence for high affinity corticosteroid receptors in yeast cells (*Candida albacans*) suggests that rudimentary "HPA axes" may have followed a similar evolutionary path (Malloy, Zhao, Madani, & Feldman, 1993). Though it has not been stated explicitly, the elements of neuroinflammation discussed here are all considered to be part of the 'innate' immune response, which is phylogenetically the most ancient component of the vertebrate immune system. This evolutionary framework suggests that activation of inflammatory pathways by stress is likely to generalize across taxonomic orders, though clearly more work is necessary to test this hypothesis. Based on available data, however, it is reasonable to conclude that stress-related neuroinflammation and the sickness-like cascade that ensues must also have some adap-

tive value. To my mind, it makes good evolutionary sense that the magnitude of the recuperative response provoked by stress should somehow vary as a function of stressor intensity. Whether 'stressor intensity' in this case more aptly refers to crossing some identifiable threshold or is defined by unique features of the stress experience itself remains to be determined. Regardless, it is clear that hallmark signs of neuroinflammation can be provoked by the assembly of two threats that individually are without influence on neuroinflammation, as when hypoglycemia was combined with restraint as a unitary challenge (Deak et al., 2005b). In this regard, one might speculate that exposure to threats such as low-level toxin or toxicants from the environment might interact synergistically with, or lower the threshold for, otherwise innocuous threats (brief capture, increased foraging demand, anthropogenic noise, etc) to produce more severe consequences for the individual than would otherwise be expected from isolated threats alone. But in the end, the principles of evolution remind us once again that conservation of biological function is as prevalent as niche adaptation. It is perhaps not so surprising, therefore, that surviving a threat of significant proportion requires a period of recuperation, and that natural selection has favored a unified biological approach (i.e., sickness) as the prevailing mechanism to promote recovery.

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