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Editorial: Stress and development: Biological and psychological consequences

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This Special Issue of *Development and Psychopathology* is devoted to the psychological and biological consequences of stress across the developmental course. Contributions in this Special Issue address topics that are central to elucidating the impact that stress exerts on developmental outcomes. These issues are investigated through examining a diverse array of populations, including rodent and nonhuman primate samples, as well as cohorts of maltreated children and adolescents with and without posttraumatic stress disorder (PTSD), children who were adopted from Romanian orphanages at differing points during infancy, aging Holocaust survivors and their offspring, children with depressive disorder, adolescents with schizotypal personality disorder, and adults with bipolar and unipolar mood disorders.

Despite its ubiquitous nature, and the fact that it is experienced by virtually all organisms, formulating a consensual definition of the construct of stress has proven to be a difficult task (Chrousos & Gold, 1992; Levine & Ursin, 1991). The experience of stress engenders both biological and psychological responses. The biological response to stress includes the activation of specific brain circuits and neuroendocrine systems (Lopez, Akil, & Watson, 1999; Vazquez, 1998).

Psychological responses to stress vary among individuals, and range from adaptive coping to depression. Further, psychological factors can be the initial link in a chain of events that leads to a biological stress; anticipation of stress and perceived lack of control can trigger a stress response on their own accord (Sapolsky, 1994). Individual differences in the response to stress are a focus of many of the articles in this Special Issue. Although the experience of persistent stress is generally associated with negative outcomes such as maladaptation, dysfunction, and psychopathology, not all organisms who are exposed to stressful experiences are affected in the same fashion (Sapolsky, 1994). Similar stressful experiences may not affect biological and psychological functioning in the same way in different organisms. Likewise, there may be different pathways from stressful experiences that eventuate in the same outcome.

There is a close correspondence between the psychological and biological consequences of stress; however, we do not possess enough information to be certain about the exact nature of the relations between these two domains of inquiry (Lopez et al., 1999). Research on the links between the psychological and biological aspects of stress continues to evolve. A major approach to unraveling their interrelation emphasizes that if we can comprehend the neurobiology of stress through investigating which brain circuits are correlates of, or are altered by, the stress response, then this knowledge will provide important in-

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sights into the brain mechanisms that mediate the impact that stress exerts on mood, cognition, and behavior (Lopez et al., 1999).

The response to stress entails not only the activation of the many brain structures and regions involved in sensory, motor, cognitive, and emotional functions, but also that of other systems, such as the autonomic, endocrinological, and immunological. In addition, it appears that there is both a general and a stimulus-specific response to stress. The interconnections between brain circuits and the aforementioned peripheral systems play a prominent role in determining whether the response of an organism to stressful stimuli is adaptive or maladaptive (Lopez et al., 1999; Vazquez, 1998).

A number of investigators have conceptualized stress as a perceived threat to an organism's homeostasis and as a situation that causes increases in autonomic nervous system activity or hormone secretion (McEwen, 1994b, 1994c). An overt insult or homeostatic mechanism initiates a stress response; however, as the term "*perceived* stress" connotes, psychological factors can initiate a stress response on their own. There seems to be much greater variability between organisms in the magnitude and quality of response emitted to stressors that are more psychological in nature (Sapolsky, 1994). Moreover, the confluence of a number of factors, including physical status, genetic makeup, prior experience, and developmental history, determine the differential ways in which organisms may react to a stressful event (McEwen, 1994c; Sapolsky, 1994). In particular, the combination of previous experience and developmental history either sensitize or protect the organism from subsequent stressful challenges. Additionally, more long-term stress responsiveness is characterized by interindividual variability and is related, in part, to experiential influences on gene expression (Meaney, Diorio, Francis, Widdowson, LaPlante, Caldji, Sharma, Seckl, & Plotsky, 1996). In sum, then, there are multiple converging pathways—including not only the neural circuits that are activated by physical, psychological, and immunological stressors, but also the influences of genetics, early experience, and ongoing life events—that determine the neural response to different stressors (McEwen, 1994b, 1994c; Sapolsky, 1994).

One of the prominent themes of this Special Issue is that stress can exert a negative impact on biological and psychological functioning throughout the developmental life span. The limbic–hypothalamic–pituitary–adrenal (LHPA) axis is the biological system most closely linked to the stress response in mammals (Vazquez, 1998). Activation of the LHPA axis by an organism's perception of physical or psychological stress leads to a series of events that result in the secretion of glucocorticoids (cortisol in human and nonhuman primates, corticosterone in rodents) from the adrenal cortex. The activation of the LHPA axis in response to physical and psychological perturbations is adaptive and critical for the survival of challenges to the organism's homeostasis. In this sense, the stress response can be said to serve a protective function (McEwen, 1998). However, the chronic mobilization of the stress response also can exert damaging, even pathogenic effects on neurons (Bremner, 1999; McEwen & Sapolsky, 1995; Sapolsky, 2000a, 2000b). Moreover, the elimination of glucocorticoids (i.e., hypocortisolism) also can damage neurons (Gunnar & Vazquez; 2001; Heim, Ehlert, & Hellhammer, 2000). Accordingly, it is in an organism's best interests to avoid both chronic glucocorticoid hyposecretion as well as hypersecretion (Sapolsky, 1996). Possible deleterious biological consequences of stress and glucocorticoid hyper- and hyposecretion include neuronal atrophy (i.e., a reduction in neuronal processes that is reversible with intervention), neurotoxicity (i.e., the actual destruction or killing of neurons as seen in PTSD and clinical depression), and "neuroendangerment" (i.e., a consequence that may occur even in circumstances where stress or glucocorticoid exposure is insufficient to cause neuronal atrophy or neurotoxicity, because the steroids can endanger neurons by making them more vulnerable, thereby impairing their capacity to survive coincident neurologic insults and increasing the likelihood that neuronal damage will emerge; Sapolsky, 1996).

Additionally, investigations that have been

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carried out with several animal species have shown that direct exposure to glucocorticoids results in decreased dendritic branching, disruption of cellular metabolism, a loss of neurons, alterations in synaptic terminal structure, and an inhibition of neuronal regeneration within the CA3 region of the hippocampus (Bremner, 1999; Sapolsky, 2000a, 2000b). Reduction of glucocorticoid exposure protects the hippocampus against the cell loss associated with chronic stress (Gould, Tanapat, McEwen, Flugge, & Fuchs, 1998). The dentate gyrus of the hippocampus may be unique within the brain in its capacity to regenerate neurons, thereby suggesting that plasticity may be possible even in the context of neuronal toxicity in humans (Cameron & McKay, 1999; Gould, 1999; Gould, Reeves, Graziano, & Gross, 1999).

In addition to the brain, the activation of the LHPA axis impacts upon other physiological systems, including those involved in metabolic processes and the immune system. The dysregulation of the LHPA axis observed in hypocortisolism appears to promote an increased vulnerability for the development of stress-related immunological disorders. The apparent lack of the protective properties of the hormone seems to be the mechanism responsible for the emergence of stress-related bodily disorders (Heim et al., 2000). Furthermore, as elucidated by several of the contributors to this Special Issue, stress also can impair cognitive functioning and memory and cause disruptions in many basic developmental processes such as neuroendocrine regulation. Moreover, stress has been implicated in the onset and maintenance of a number of mental disorders.

Another theme of this Special Issue is that changes in the LHPA axis mediate the longer term structural and functional changes in the brain that may arise due to stressful experiences (cf. Meaney et al., 1996). The effects of hormones on behavior are partially a consequence of their effects on gene expression (McEwen, 1994a; Watson & Gametchu, 1999). For example, it is well established that gonadal hormones trigger the expression of genes that control the sexually dimorphic development of the brain in utero, as well as later in life. More recently, investigators have documented the role of stress hormones, such as cortisol, in the expression of genes that govern brain function. There are glucocorticoid receptors on the surface of neurons as well as in the nucleus. In general, the surface receptors mediate short-term or *nongenomic* effects on behavior. The glucocorticoid receptors that reside in the cell's nucleus are responsible for their *genomic* effects—that is, the influence of stress hormones on the expression of genes. When stress hormones bind to nuclear receptors, they can trigger the expression of messenger RNA that codes for specific proteins. These proteins, in turn, influence neuronal structure and function, including neuronal growth, neurotransmitter synthesis, receptor density and sensitivity, and neurotransmitter reuptake. Because stress hormones can have such direct effects on the genes that control brain structure and function, research on stress in developing organisms is especially important. The identification of stress-sensitive neural processes may ultimately provide a basis for the formulation of pharmacological and behavioral interventions to ameliorate the deleterious effects of early stressful experiences (Kaufman, Plotsky, Nemeroff, & Charney, 2000).

Attention to the process of development provides valuable information about some of the factors that contribute to moderating and mediating the links between stress and its biological and psychological consequences. As reported in this issue, both Walker, Walder, and Reynolds (2001) and Lupien, King, Meaney, and McEwen (2001) find evidence of an increase in cortisol release during adolescence. With respect to structural brain changes, DeBellis, Keshavan, Clark, Casey, Giedd, Boring, Frustaci, and Ryan (1999) do not find a reduction in hippocampal volume in maltreated children and adolescents with PTSD, whereas Bremner, Randall, Scott, Bronen, Seibyl, Southwick, Delaney, McCarthy, Charney, and Innis (1995), Gurvits, Shenton, Hokama, Ohta, Lasko, Gilbertson, Orr, Kikinis, Jolesz, McCarley, and Pitman (1996), and Stein, Koverola, Hanna, Torchia, and Mc-

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Clarty (1997) have found reduced hippocampal volume in combat veterans with PTSD as well as adults who report past physical or sexual abuse. It may be that the DeBellis et al. (1999) findings represent a true developmental difference in the biological sequelae of stress exposure. The hippocampus continues to undergo maturation beyond adolescence, so it is plausible that there are maturational changes in the vulnerability of the LHPA system. This is one of several important developmental issues that merit further investigation.

As Heffelfinger and Newcomer (2001) point out, research on adults has shown that both acute and chronic elevations in cortisol can have detrimental effects on cognitive performance, and this is presumably mediated by the hippocampus. But we know little about how elevated stress hormones impact the development of cognitive abilities. Is the normal developmental increase in cognitive capacities, such as attention and memory, impaired by exposure to stress? The answer to this question has broad social implications.

Although the papers in this Special Issue illustrate the major advances that have occurred in understanding the mechanisms by which stress affects brain structure and function, and thus contributes to the emergence and maintenance of psychological maladaptation, there are a number of challenges and obstacles that should be addressed in future research. As we have noted, scientific progress in the field will require more systematic study of the developmental course. From a developmental psychopathology perspective, knowledge of normal processes is considered to be essential for comprehending deviant or psychopathological outcomes. In this regard, we believe that it is important for scientists investigating the consequences of stress in humans to undertake more research on normative neuroendocrinological processes. For example, there are few longitudinal studies in which LHPA responses are measured repeatedly. In order for research on stress, development, and psychopathology in humans to advance, a broader basis of normative research results from longitudinal investigations must be acquired.

In addition, we believe that the field would benefit from more uniformity of method in studies of the stress response. As research in the field has progressed, the use of saliva sampling has supplanted the use of blood draw to measure hormone secretion. This is a significant methodological improvement, given that blood sampling is known to be aversive and stress-inducing to many people, especially children and adolescents. But more refinements are needed. One significant advance would be a uniform salivary assay procedure for cortisol. Further, as the field moves forward, it will be necessary to broaden the focus to encompass all of the neurohormonal messengers involved in the LHPA axis. This would include adrenocorticotropic hormone and corticotropin releasing factor. Also, our understanding of the temporal course of the neurohormonal response is limited. We need to know more about the rise time and temporal latency of the peak response to acute stressors. A single measure is not sufficient to document the dynamic course of LHPA responsivity, from baseline through the stress response. Again, consistency in method and measurement are crucial if progress is to be made.

Greater attention to individual differences is also needed. It is now well documented that both genetic and prenatal factors affect the neural systems that govern the stress response. These individual differences appear to be linked with differences in behavior. For example, higher levels of LHPA activity are linked with shy, withdrawn tendencies (Schmidt, Fox, Rubin, & Sternberg, 1997), whereas low levels are associated with aggressiveness (McBurnett, Lahey, Rathouz, & Loeber, 2000). It thus appears that congenital differences in LHPA activity can influence behaviors that are related to risk taking or impulsivity. These propensities, in turn, would be expected to affect the likelihood that the individual will encounter stressful events. In sum, there is a relationship between congenital LHPA responsivity and stressful postnatal experiences, and this makes it more difficult to differentiate the effects of stress from its determinants. Sophisticated longitudinal research designs will be needed to disentangle these complex interactional processes.

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Related to this, we need more investigations aimed at determining the effect of experimental and clinical settings on neuroendocrinological responses. Levels of stress hormones measured when the individual is in such settings, even in the absence of stressful procedures, are unlikely to reflect the baseline that would be measured in more familiar surroundings. Further, a substantial research literature suggests that not all persons who have been exposed to the same adverse experiences are uniformly affected (Luthar, Cicchetti, & Becker, 2000). Some children, for example, function extremely well even in the presence of adversity. To date, all of the research on resilient adaptation in the face of adversity has focused on psychological factors as mediators, moderators, or as developmental outcomes. Future research should examine the biological stress responses of such resilient individuals to ascertain whether their patterns of neuroendocrine regulation differ from nonresilient stress-affected children. Moreover, investigators who have identified groups of resilient individuals should utilize structural and functional neuroimaging techniques to determine whether their brains are different from those of more vulnerable individuals.

Finally, the issues of prevention and brain plasticity will become increasingly salient in the field of stress research. Would the provision of developmentally sensitive interventions prevent or ameliorate the adverse neurobiological consequences of stress exposure? It remains to be determined whether or not intervention can normalize brain organization only at particular developmental periods, or whether neural plasticity is operative across the life course (Cicchetti, in press). Extant empirical work on the psychological and biological sequelae of trauma suggests that intervention provided as soon as possible after a trauma has occurred could more effectively impact on neural organization and thereby prevent brain changes that might become less amenable to intervention over time (Toth & Cicchetti, 1998).

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