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The effects of allostatic load on neural systems subserving motivation, mood regulation, and social affiliation

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Abstract

The term allostasis, which is defined as stability through change, has been invoked repeatedly by developmental psychopathologists to describe long-lasting and in some cases permanent functional alterations in limbic–hypothalamic–pituitary–adrenal axis responding following recurrent and/or prolonged exposure to stress. Increasingly, allostatic load models have also been invoked to describe psychological sequelae of abuse, neglect, and other forms of maltreatment. In contrast, neural adaptations to stress, including those incurred by monoamine systems implicated in (a) mood and emotion regulation, (b) behavioral approach, and (c) social affiliation and attachment, are usually not included in models of allostasis. Rather, structural and functional alterations in these systems, which are exquisitely sensitive to prolonged stress exposure, are usually explained as stress mediators, neural plasticity, and/or programming effects. Considering these mechanisms as distinct from allostasis is somewhat artificial given overlapping functions and intricate coregulation of monoamines and the limbic–hypothalamic–pituitary–adrenal axis. It also fractionates literatures that should be mutually informative. In this article, we describe structural and functional alterations in serotonergic, dopaminergic, and noradrenergic neural systems following both acute and prolonged exposure to stress. Through increases in behavioral impulsivity, trait anxiety, mood and emotion dysregulation, and asociality, alterations in monoamine functioning have profound effects on personality, attachment relationships, and the emergence of psychopathology.

In 1988, Sterling and Eyer offered a new conceptual framework for organizing and understanding the effects of prolonged stress on human morbidity and mortality. They centered this framework on the concept of allostasis, a term coined to describe the body's adjustment to environmental demands through shifts in the operating ranges of vital biological systems. Allostasis refers to long-term functional changes undergone by physiological systems to maintain stability in contexts of extreme or protracted stress (Sterling & Eyer, 1988). From the beginning, allostasis was conceptualized as distinct from homeostasis. Whereas homeostatic processes promote stability by working within established functional ranges of physiological systems, allostatic processes modify these operating ranges (Lupien et al., 2006; McEwen & Stellar, 1993). Although the earliest discussions of allostasis referred to physical processes involved in blood pressure regulation and immune system responding (Sterling & Eyer, 1988), the concept has since been expanded to include adaptations to other biological systems, and changes in psychological functioning in response to a range of environmental challenges.

Allostatic adaptations to high-risk environments promote coping and in some cases survival (Mead, Beauchaine, & Shannon, 2010), yet altering the operating ranges of biological systems often comes at a cost, such as increased likelihood of disease. McEwen and Stellar (1993) termed this cost "allostatic load," and likened it to the wear and tear on the body of repeated adaptive responses to stress over time. Such wear and tear shapes future responses to stress, and may result in maladaptive stress responding. Lupien and colleagues (2006) highlight a variety of ways in which stress responses may become maladaptive, including chronic activation to multiple individual stressors, lack of adaptation to a chronic stressor, prolonged responding following a stressor, or inadequate responding to one or more stressors (see also McEwen, 1998a, 1998b).

In developmental psychopathology research, allostatic load has been discussed most often in reference to limbic–hypothalamic–pituitary–adrenal (LHPA) axis functioning (see e.g., Lupien, McEwen, Gunnar, & Heim, 2009). As described in detail elsewhere (Lupien et al., 2006; Mead et al., 2010), exposure to real or perceived stress triggers a cascade of reactive processes across multiple biological systems. Early in this cascade, corticotropin-releasing hormone is excreted from the hypothalamus. This triggers subsequent release of adrenocorticotropin from the pituitary gland. In turn, adrenocorticotropin triggers the release of adrenal stress hormones, including both glucocorticoids and catecholamines, particularly cortisol and norepinephrine (NE). Catecholamine release facilitates fight/flight/freeze responding, providing for confrontation, escape, or immobilization to cope with the stressor. This short-term activation of stress response systems

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is usually considered adaptive. Over time, however, repeated activation may confer long-lasting and in some cases permanent changes in functioning that give rise to a host of detrimental physiological and psychological outcomes (Mead et al., 2010).

Cognitive factors may also mediate allostatic effects (Lupien et al., 2006, 2009). Early and protracted exposure to chronic stress (e.g., maltreatment, family conflict) can produce cognitive responses that are either biased toward detecting (i.e., sensitized to) or accustomed to experiencing (i.e., habituated to) threat (e.g., Pollak & Sinha, 2002; Pollak & Tolley-Schell, 2003; Rieder & Cicchetti, 1989). Sensitized responses that trigger stress-related neural processes and LHPA axis reactivity unnecessarily are likely to accelerate allostatic effects, whereas habituated systems that fail to respond when it is appropriate to do so may increase risk for exposure to truly threatening stressors (Lupien et al., 2006).

In response to stress, catecholamine reactivity, sympathetic nervous system (SNS) activation, and glucocorticoid release increase energy, attention, vigilance, and memory formation (Charney, 2004; Sanchez, 2006). Cortisol production in particular facilitates conversion of protein and fats into energy, and encourages food-seeking behaviors to replenish reserves depleted during active coping (Charney, 2004; Lupien et al., 2006; Sanchez, 2006). However, when triggered repeatedly, excess cortisol release has detrimental effects, because LHPA axis activation increases insulin levels and insulin resistance, and promotes accumulation of body fat. Consequently, allostatic load increases risk for type II diabetes, hypertension, atherosclerosis, and coronary artery disease (Brindley & Rolland, 1989; Lupien et al., 2006). Similar processes have damaging effects on immune system functioning (Lupien et al., 2006).

Allostatic effects on the glucocorticoid system are well documented among rodents and nonhuman primates (see, e.g., Parker, Buckmaster, Sundlass, Schatzberg, & Lyons, 2006). For example, mice exposed to repeated stress exhibit delays in wound healing compared to nonstressed mice (Romana-Souza et al., 2010). Social isolation and maternal deprivation early in life alter LHPA axis responding in adulthood among rodents (Rentesi et al., 2010; Weintraub, Singaravelu, & Bhatnagar, 2010). Chronic social stress caused by disruptions to housing arrangements yields increases in both corticosterone (the rodent homologue of cortisol) and anxious behaviors (Schmidt et al., 2010). Prenatal stress-induced elevations of corticosterone among mothers produce altered body fat concentrations and glucose tolerance in offspring (Franko, Forhead, & Fowden, 2010). Finally, among primates, sustained glucocorticoid release exacts damage to the hippocampus—a neurodegenerative effect of stress (Uno, Tarara, Else, Suleman, & Sapolsky, 1989).

Parallel allostatic effects have been hypothesized among humans, particularly on immune, metabolic, and cardiovascular functioning (see Lupien et al., 2010; McEwen & Stellar, 1993). Rodent and nonhuman primate studies have also prompted inferences about the psychological sequelae of stress, including depression, anxiety, and cognitive impairment (e.g., Schmidt et al., 2010; Tronche et al., 2010; Weintraub et al., 2010). For example, low socioeconomic status (SES) predicts longitudinal increases in daily cortisol output during childhood (Chen, Cohen, & Miller, 2010), and parental loss experienced during childhood predicts increased cortisol responding to environmental challenges in adulthood (Tyrka et al., 2008). As early as infancy, social deprivation, maternal emotional withdrawal, and harsh parenting are associated with elevated baseline cortisol levels, disrupted cortisol reactivity, and altered patterns of diurnal cortisol secretion (Bugental, Martorell, & Barraza, 2003; Kertes, Gunnar, Madsen, & Long, 2008; Wismer Fries, Shirtcliff, & Pollak, 2008). Maltreated children, particularly those who exhibit atypical cortisol functioning, are at increased risk for developing both internalizing and externalizing disorders (Cicchetti & Rogosch, 2001; Kaufman, 1991). These children are also more likely to experience posttraumatic stress disorder (PTSD), the severity of which is correlated with urinary cortisol concentrations (De Bellis et al., 1999).

Limitations to Inferring Allostatic Processes in Humans

Despite the plausibility of allostatic effects among humans who experience repeated stress, negative outcomes cannot be attributed to allostatic load definitively for several reasons. First, unlike animal models in which stressors can be introduced and removed in a controlled manner, stress research with humans is necessarily correlational. Although some approaches have capitalized on quasiexperimental designs in innovative and important ways (Fisher & Stoolmiller, 2008; Fisher, Stoolmiller, Gunnar, & Burraston, 2007), these findings are more speculative than those derived from animal research, because random assignment of humans to stressors, which is a requirement for causal inference, is indefensible ethically. Second, the experience of stress among humans is rarely discrete. For example, individuals who incur family stressors associated with poverty are often exposed to neighborhood violence and low levels of parental education (Jones, Foster, Forehand, & O'Connell, 2005). Thus, the effects of a single stressor, even when repeated, are impossible to distinguish from correlated stressors and risk factors. Third, we cannot know for certain whether apparent allostatic effects are attributable to the stressor itself, to genetic vulnerabilities that segregate within stressful environments, or to other third variables. Gene × Environment correlations (*r*GEs) are particularly relevant. It has long been recognized that genetic vulnerabilities for some behavioral traits are correlated with environmental risk exposure (see, e.g., Beauchaine, Hinshaw, & Gatzke-Kopp, 2008; Rutter, 2007). Thus, emerging biological adaptations may be associated with stressful life events due to direct causal factors, correlated third variables, direct genetic influences, or indirect genetic influences that confer vulnerability only in high-risk environments.

These limitations to inferring allostasis are remediated—at least in part—when comparative studies with animals are

conducted to characterize analogous stress-related processes and outcomes. However, the utility of such models is limited by the degree to which animal models provide valid analogs/homologues to human stress responding and behavior (see, e.g., Parker et al., 2006). To date, such analogs have been quite useful in characterizing the functioning of the glucocorticoid system, as illustrated by our current understanding of allostatic mechanisms in animals and humans.

Although usually not framed in allostatic load terms (see Romero, Dickens, & Cyr, 2009), similar analogies should also be informative regarding the effects of stress on phylogenetically old neural systems that are structurally and functionally similar across species, including serotonergic neural networks involved in mood regulation, dopaminergic neural networks involved in motivation, and noradrenergic neural networks involved in social affiliation. Comparative studies addressing allostatic effects on these monoamine neurotransmitter systems among animals may yield valid insights into similar processes among humans. Given this, our objective in writing this paper is to extend thinking about allostatic processes to functioning within monoamine neural systems affecting broad classes of human behavior. As we review below, stress-induced alterations in the functioning of central serotonergic, dopaminergic, and noradrenergic networks may have longstanding adverse effects on behavior, conferring risk for (a) anxiety and depression, (b) impulsivity and externalizing conduct, and (c) asociality and disturbed attachment relationships, respectively. Although effects of child maltreatment and other forms of trauma on these and other neural systems have been articulated (e.g., Mead et al., 2010; Perry, 2008; Perry, Pollard, Blakely, Baker, & Vigilante, 1995; Teicher et al., 2003), the literature has not been organized within an allostatic load framework to date.

Controversies in Conceptualizing and Delimiting Allostatic Load

Despite emerging popularity, particularly in developmental psychopathology research, allostatic load models of stress reactivity have not been adopted without criticism. For example, prolonged evironmental challenge sometimes confers lifelong alterations in stress responding through means other than glucocorticoid release, energy mobilization, and/or energy expenditure, which are primary mechanisms of allostatic load as the construct is typically defined (see McEwen & Seeman, 1999; see also Romero et al., 2009). Other biological responses and adaptations to stress, such as those exerted through altered neurotransmitter reuptake and transport, dendritic plasticity, epigenisis, and other programming effects, are rarely considered as mechanisms of allostasis. Yet certain neural processes, particularly those initiated noradrenergically, are important components of the LHPA axis stress response system (see, e.g., Day, 2005; Kiss & Aguilkara, 1992; Reeder & Kramer, 2005). Indeed, nopepinephrine is unique in serving both neurotransmitter and neurohormone functions (e.g., Silverberg, Shah, Haymond, & Cryer, 1978). Futhermore, the effects of prolonged stress on physiological systems include long-term structural and functional neural adaptations in brain regions that mediate hormonal responding (see McEwen, 2006). In addition, during certain sensitive periods, cortisol receptors modulate neurodevelopment in brain structures that are usually not considered part of the stress response system (Zoli et al., 1990). Thus, although dinstinguishing between different forms of biological adaptation (e.g., neural, epigenetic, hormonal) may have heuristic utility, these distinctions are not clear-cut given considerable structural and functional interdependence among systems and mechanisms of functional change.

In their early articulation of allostasis, Sterling and Eyer (1988) recognized the importance of neural processes in regulating stress reponding, although they did not define such neural processes directly (see also Sterling & Eyer, 1981). This may be in part because hormone systems, particularly the glucocorticoid system, were much better understood at the time than neural mechanisms of stress reactivity. In fact, much if not most of the literature addressing (a) structural and functional changes in neurotransmitter systems, (b) neural plasticity, and (c) epigenetic changes in DNA expression following stress and adversity emerged after the allostatic load hypothesis was set forth. Thus, restricting the mechanisms of allostatic load to LHPA axis activity and reactivity may be at least in part an artifact of the temporal sequencing of scientific discovery. Nothing in the term allostasis, which is defined as "stability through change" (Sterling & Eyer, 1988, p. 636), precludes a broadened scope of biological mechanisms. As we outline below, extending the allostatic framework to monoamine systems may confer conceptual advantages for understanding the effects of protracted stress on the development of personality and the emergence of psychopathology. Fortunately, allostasis has not been a particularly contentious contruct at the conceptual level (Romero et al., 2009).[1]

Applying the Allostatic Framework to Monoamine Neural Systems

In general, central serotonergic, dopaminergic, and noradrenergic responses to stress unfold much more quickly than glucocorticoid responses (Britton, Segal, Kuczenski, & Hauger, 1992; Schommer, Hellhammer, & Kirschbaum, 2003), yet to one extent or another, reactivity of each of these neurotransmitter systems modulates downstream LHPA responding (Douglas, 2005; Gunnar & Vasquez, 2006; Morilak et al.,

1. Additional criticisms of the allostatic load framework have been articulated, leading to explication of alternative theories such as the reactive scope model (Romero et al., 2009). In general, these alternatives do not dispute the core tenet of allostasis: that exposure to prolonged stress can alter the functioning ranges of biological systems. Further description of debates over the term allostasis and the concept of allostatic load are beyond the scope of this article. Interested readers are referred to other sources for such accounts (e.g., Dallman, 2003; Korte, Koolhaas, Wingfield, & McEwen, 2005; McEwen & Wingfield, 2003a, 2003b; Romero et al., 2009; Walsberg, 2003).

2005). Nevertheless, allostatic effects on central neurotransmitters have thus far been overshadowed by extensive efforts to characterize such effects on the glucocorticoid system (e.g., Cicchetti, Rogosch, Gunnar, & Toth, 2010; Gunnar & Vasquez, 2006; Lupien et al., 2006; McEwen & Stellar, 1993). Because allostatic effects on glucocorticoids have been described so extensively, we do not discuss the LHPA axis further, except insofar as it interacts with central monoamine systems. Similarly, because the effects of allostatic load on many physiological systems (e.g., cardiovascular, immune) have been described in detail elsewhere (e.g., McEwen, 1998a, 1998b; McEwen & Stellar, 1993; Sterling & Eyer, 1981, 1988), they are not considered here. In focusing on allostatic processes that induce structural and/or functional changes in monoamine systems, we (a) draw on findings from rodent and nonhuman primate research, (b) distinguish between the effects of acute versus chronic stressors when possible, and (c) differentiate between short-term from long-term outcomes across development.

It is important to note that we use a very broad definition of stress, which is usually characterized in terms of exposure to and/or psychological sequelae of social deprivation, material deprivation, or abuse. However, additional risk factors such as repeated exposure to nicotine and other drugs of abuse also induce long-term functional changes in the operating ranges of vital biological systems, with apparent life-long consequences for behavioral and social functioning (see, e.g., Gatzke-Kopp, 2011). For example, long-term downregulation is often observed in central dopamine networks following repeated overactivation, whether such activation is initiated through external environmental mechanisms (e.g., abuse, neglect, gambling) or more direct physiological manipulation (e.g., ingestion of stimulants including nicotine; see Beauchaine & Neuhaus, 2008).[2] Of importance, the body is indifferent to the source of excess activation, whether endogenous or exogenous. Furthermore, alterations in brain systems that process reward and stress following prolonged use have already been conceptualized in an alostatic framework by others (e.g., Koob, 2009). Thus, rather than focus solely on psychological stress as a mechanism of allostasis, we also discuss the effects of selected endogenous "stressors" on monoamine functioning. However, we do not include discussion of substances or insults that damage neural tissue directly. Readers are referred elsewhere for such accounts (e.g., Fryer, Crocker, & Mattson, 2008; Gatzke-Kopp, 2011). Rather, we focus on stressors that alter the operating ranges of monoamine functioning, consistent with the definition of allostasis (Lupien et al., 2006; McEwen & Stellar, 1993). We begin with a brief overview of central monoamine neurotransmitters. More detailed associations between each neurotransmitter and specific behavioral traits are presented in later sections.

Brief Overview of Monoamine Neurotransmitters

Serotonin (5-HT), dopamine (DA), and NE are all monoamine neurotransmitters. They are classified as such based on a common amine (nitrogen) group. Monoamines can be subdivided further into tryptamines such as 5-HT, which are synthesized from the amino acid tryptophan, and catecholamines such as DA and NE, which are synthesized from the amino acid tyrosine (other monoamine categories are not discussed here). Among the monoamines, a long history of research links 5-HT functioning to mood regulation, trait and state anxiety, and impulsive aggression among rodents, nonhuman primates, and humans (see, e.g., Beauchaine, Klein, Crowell, Derbidge, & Gatzke-Kopp, 2009; Crowell, Beauchaine, & Linehan, 2009; Mead et al., 2010; van Goozen, Fairchild, Snoek, & Harold, 2007). As described below, repeated and chronic stress exposure may alter 5-HT functioning, with long-term adverse effects on mood and emotion regulation (Mead et al., 2010).

In contrast to 5-HT, both DA and NE, which are produced by the adrenal glands, promote energy mobilization. Release of these catecholamines facilitates exploration of the environment, fight/flight/freeze responding, and recruitment of the LHPA axis, among other functions. In subserving these roles, catecholamines including DA and NE enhance vigilance and focused attention, and increase SNS activity, raising blood pressure and cardiac output (see e.g., Beauchaine et al., 2009; Morilak, 2007).

Given these activating functions, it is not surprising that central catecholamine expression is associated with individual differences in approach-related traits, including social affiliation, reward dependence, impulsivity, novelty-seeking, extraversion, and aggression (see Beauchaine, 2001; Beauchaine, Hinshaw, & Pang, 2010; Beauchaine & Neuhaus, 2008; Buckholtz et al., 2010; Caspi et al., 2002; Castellanos & Tannock, 2002; Cloninger, 1986, 1987; Depue & Collins, 2001; Sagvolden, Johansen, Aase, & Russell, 2005). As detailed below, allostatic effects on catecholamine function may induce life-long changes in these behavioral traits, conferring risk for psychopathology among vulnerable individuals (Mead et al., 2010; Perry, 2008).

Much of the literature linking monoamine expression to behavior makes primary functional distinctions among neurotransmitters. Typically, these distinctions are similar to those made here, with 5-HT, DA, and NE being linked to mood regulation, approach motivation, and social affiliation, respectively. However, it is important to recognize that these functional distinctions, though useful heuristically, are oversimplifications. For example, it is now recognized widely that both DA and NE play important roles in at least some aspects of mood and emotion regulation (e.g., Ashby, Isen, & Turecki, 1999; Dremencov, el Mansari, & Blier, 2009; Forbes & Dahl, 2005; Forbes et al., 2009; Laakso et al., 2003), and

2. As described in later sections, downregulation of biological systems following repeated activation is a general mechanism through which allostatic processes operate (see Friedhoff & Miller, 1983; Sterling & Eyer, 1988).

that 5-HT networks gate central DA activity (e.g., Gershon, Vishne, & Grunhaus, 2007). Thus, monoamine systems are neither functionally discrete nor structurally independent. Nevertheless, it is useful to discuss each within the context of the primary behavioral trait it subserves. With this caveat in mind, we now turn to discussing allostatic effects on serotonergic, dopaminergic, and noradrenergic neurotransmission. We note at the outset that the sections below are necessarily selective given voluminous literatures, including recent comprehensive reviews of the effects of stress on each neural system (e.g., Chaouloff, 2000; Firk & Markus, 2007; Gatzke-Kopp, 2011; Morilak, 2007; Morilak et al., 2005; van Goozen et al., 2007).

Allostatic Effects on Serotonergic Functioning: Implications for Anxiety, Depression, and Emotion Dysregulation

Exposure to stressful environments—particularly repeated and prolonged exposure—often affects mood and emotion regulation capabilities, amplifying risk for future psychopathology (Perry, 2008; Shields, Cicchetti, & Ryan, 1994). As we have already noted, and as following sections of this article reveal, no single neural system subserves behavioral, mood, and/or emotion regulation functions. Nevertheless, alterations in central 5-HT expression likely play a critical role in linking early adverse experiences to later problems in these areas. Studies conducted with animals reveal that chronic stress induces functional changes in central monoamine neurotransmitter systems, including 5-HT, and studies conducted with humans indicate that chronic stress often precedes mood disorders (see Firk & Markus, 2007; Lapiz-Bluhm, Soto-Piña, Hensler, & Morilak, 2009; Mead et al., 2010). Moreover, rich literatures link central and peripheral 5-HT expression to mood symptoms and emotion regulation capabilities in adolescents and adults (see, e.g., Crowell et al., 2008, 2009; Davidson, Putnam, & Larson, 2000; Mann & Currier, 2007). However, given that monoamine functioning is shaped by genes, environment, and *r*GE interactions (e.g., Caspi et al., 2003; Caspi, Hariri, Holmes, Uher, & Moffitt, 2010), there are large individual differences in response to stress exposure. Genetically influenced temperamental predispositions may moderate the effects of stress on neurotransmitter systems, which may determine whether allostatic processes are invoked. Among resilient individuals, homeostatic processes may be adequate to meet the demands of chronic stress, with no long-term alterations in 5-HT functioning. Vulnerable individuals may not be so fortunate.

Serotonin is a modulatory neurotransmitter that innervates much of the brain. Release of 5-HT is determined by synthesizing and catabolizing enzymes, pre- and postsynaptic receptors, and molecules controlling intracellular traffic and extracellular transport (see Holmes, 2008). Serotonergic neurons from the dorsal raphe nucleus project to central nervous system structures implicated in anxiety, emotion, and self-control, including the septohippocampal system, the amygdala, and the frontal cortex. The septohippocampal system inhibits ongoing behaviors when environmental cues encourage conflicting responses (Gray & McNaughton, 2000). Hippocampal 5-HT_{1B} receptors play an important role in inducing behavioral control when there is competition between acting and restraining response tendencies, such as inhibiting an aggressive impulse when angry or frustrated (e.g., Evenden, 1999; Soubrié, 1986). Such halting of ongoing behavior is induced by state anxiety, the affective consequence of septohippocampal activation. As articulated by Gray and others (e.g., Beauchaine, 2001; Corr, 2004; Fowles, 1980; Gray & McNaughton, 2000), those high in septohippocampal activity tend toward trait and state anxiety, deliberate choice, and passive avoidance of real and imagined threats. In contrast, those with deficient septohippocampal system functioning are more likely to engage in impulsive behaviors, even when environmental cues suggest impending punishment.

The amygdala, which receives septohippocampal input and projects to the prefrontal cortex (PFC), also plays a prominent role in stress-evoked fear and anxiety, particularly conditioned fear (LeDoux, 1998). Serotonergic projections from the dorsal raphe nucleus to the amygdala facilitate anxiety and fear conditioning (see Graeff, Viana, & Mora, 1997). Lesion studies with rodents indicate that the amygdala also activates monoaminergic systems in the medial PFC in response to stress (Goldstein, Rasmusson, Bunney, & Roth, 1996). Among humans, threatening stimuli such as angry faces reliably induce amygdala activity, which is likely related to increased 5-HT release in the basolateral amygdaloid nucleus (e.g., Stein, Simmons, Feinstein, & Paulus, 2007). The amygdala and hippocampus are also targets of stress hormones including cortisol (van Stegeren et al., 2007).

Finally, the dorsolateral and ventromedial prefrontal cortices convey stress-related information to cortical and subcortical brain regions, and are integral to the regulation of thoughts, actions, and emotions (LeDoux, 1998). Both acute and chronic stress can alter serotonergic inputs from the raphe nuclei to these structures, potentially compromising 5-HT functioning and receptor structure (see Chaouloff, 2000). Moreover, the PFC is exquisitely sensitive to the detrimental effects of stress. In some cases, even mild uncontrollable stressors may lead to compromised cognitive abilities, including deficits in working memory, cognitive flexibility, and emotional control (see Arnsten, 2009).

Biological adaptations to environmental stress occur through several mechanisms (see Perry, 2008). Among these, genetic vulnerabilities often moderate relations between stressful experiences and later behavior problems (see Mead et al., 2010). In addition, epigenetic effects on neural structure and function can lead to experience-dependent variation in gene expression. Epigenetic mechanisms of adaptation include activation, silencing, and alterations of gene expression through DNA methylation or RNA transcription (e.g., Perrone-Bizzozero & Bolognani, 2002). Stress exposure can also affect important neurodevelopmental processes including neurogenesis, migration, differentiation, apoptosis, arborization, synaptogenesis, synaptic sculpting, and myelination

(Perry, 2008). These processes are easiest to study in animals, among which random assignment to stressful and nonstressful environments can be used. Fortunately, many findings from such studies appear to translate well to humans, including those linking 5-HT functioning to fear conditioning, anxiety, and to a lesser extent aggression. However, the limitations of applying animal models to humans should be kept in mind, particularly regarding complex behaviors that are affected by psychological and other cognitive mechanisms. These may include certain forms of emotional lability, posttraumatic stress reactions, clinical depression, self-injurious behaviors, and suicide. Nevertheless, in efforts to better understand these behaviors, it is necessary to juxtapose well-controlled experimental findings from animals with correlational studies addressing the biological and behavioral sequelae of stress exposure among humans.

Effects of acute stress on 5-HT functioning

Animal studies. Acute stressors, which are those circumscribed by events lasting seconds to days, are common in daily life and activate a cascade of biological responses. These include sympathetic and parasympathetic nervous system reactions that follow a very rapid time course, and LHPA axis responses that unfold over longer time periods. Almost immediately following exposure to a stressor, catecholamines including DA, NE, and epinephrine are released from the adrenal glands, with corresponding activation of the SNS. This facilitates large increases in cardiac and metabolic output to cope with the stressor. The LHPA axis responds more slowly, releasing glucocorticoids, which facilitate more protracted metabolic responses, as outlined above (see Conrad, 2008).

Temporary disruptions of homeostasis are necessary for the organism to energize quickly and mount an effective response to serious threats (see Cazakoff, Johnson, & Howland, 2010). Many areas of the brain are activated by such stressors, including several brain stem nuclei, the periaqueductal gray, the dorsal raphe nucleus, the locus coeruleus, the medial and cortical amygdaloid nuclei, multiple hypothalamic nuclei, the lateral septum, the nucleus accumbens, the hippocampus, and various cortical regions (see López, Akil, & Watson, 1999). Although SNS responses to acute physical and/or psychological challenges are largely similar across classes of stressors, different brain regions, neurotransmitter systems, and neuroendocrine responses may be involved in adapting to distinct subtypes of stress (see e.g., Pacak & Palkovits, 2001).

Of relevance to this discussion, the LHPA axis and 5-HT neural systems are structurally and functionally interconnected, and both contribute to the effects of acute stress on psychological adjustment (see Cassano & D'mello, 2001; Sullivan Hanley & Van de Kar, 2003; Tsigos & Chrousos, 2002). Serotonergic efferents activate hypothalamic corticotropin-releasing factor neurons, contributing to cortisol production (Liposits, Phelix, & Paull, 1987). Furthermore, acute corticosteroid administration attenuates growth of 5-HT_{1A} receptors throughout the rat hippocampus (Chalmers, Lopez, Vasquez, Akil, & Watson, 1994). Rats exposed to acute stress, including restraint, forced swim, and ether exposure, show decreased 5-HT_{1A} messenger RNA levels (i.e., gene expression; mRNA) in hippocampal regions (López, Liberzon, Vázquez, Young, & Watson, 1999). Of importance, activation of 5-HT_{1A} receptors is essential for synaptic plasticity and neurogenesis in the adult hippocampus (e.g., Djavadian, 2004). mRNA is of interest because of its role in transcribing segments of DNA into functional amino acid sequences. Reduced mRNA signifies reduced transcription, indicative of gene silencing.

In a functional sense, acute stress elicits phasic 5-HT neural firing and increases both 5-HT release and turnover in the raphe nuclei, amygdala, and PFC (Heym, Trulson, & Jacobs, 1982; Inoue, Koyama, &Yamashita, 1993; Kawahara, Yoshida, Yokoo, Nishi, & Tanaka, 1993; Pei, Zetterström, & Fillenz, 1990). Rats exposed to uncontrollable tail shocks also display anxious social behavior, which is mediated by increased 5-HT action on 5-HT_{2C} receptors in the basolateral amygdala (Christianson et al., 2010). Acute stress is also associated with reduced serotonin transporter (5-HTT) mRNA levels in the raphe pontis, one of the raphe nuclei (Vollmayr, Keck, Henn, & Schloss, 2000). This is noteworthy because reuptake of 5-HT from the synaptic cleft to presynaptic terminals is mediated entirely by 5-HTT (see Martinowich & Lu, 2007). In response to stressful events, 5-HT levels increase temporarily in targeted brain regions. However, those with less efficient 5-HTT activity, which is conferred by the short (s) allele on the promoter region of the *5-HTT* gene, may not maintain extracellular 5-HT at normal levels (see Xie et al., 2009). Thus, 5-HTT receptor availability determines the size and duration of serotonergic responses, which may have implications for depression, anxiety, aggression, and suicide (Hariri et al., 2002; Lesch et al., 1996; Sander et al., 1998; Silva et al., 2010).

Human studies. Among humans, many serotonergic circuits are phylogenetically old, modulating emotion, motor behavior, cognition, and pain sensitivity. Serotonin also modulates neuroendocrine functions involved in appetite, reproductive activity, sleep, and circadian rhythms. Thus, acute stress affects much more than physiological arousal. Psychological and physical hardships also affect core behavioral systems involved in emotional responding and emotion regulation. Emotional reactions facilitate behavior via automated, rapid, and dynamic responses to stress, which allow a person to react quickly to salient information (Cole, Martin, & Dennis, 2004; Ekman, 1992; Gross, 1998). Ideally, homeostatic processes support adaptive activation and deactivation of neural systems subserving emotion regulatory functions. As outlined above, however, allostasis is invoked when the operating ranges of these biological systems are altered by repeated activation through chronic stress exposure (McEwen, 1998a). Animal studies reveal that such changes occur via serotonergic hyperactivity in affective brain structures, decreased activation of receptors involved in 5-HT reuptake and regulation, and/or epigenesis (see Adamec, Holmes, & Blundell, 2008).

On occasion, the experience of stress is circumscribed and extreme, leading to PTSD and/or other psychaitric conditions (Mead et al., 2010; Perry, 2008). Such outcomes are more likely among those with life histories of early adversity or other traumae (see Xie et al., 2009). As a result, there are few studies on the effects of traumatic experiences without previous trauma exposure (Nemeroff et al., 2006). In one such study, however, risk for PTSD and depression among adults following hurricane Katrina was affected not only by proximity to the disaster, but by lack of social support and the low-expression variant of the 5-HTT linked polymorphic repeat (*5-HTTLPR*) polymorphism (*s/s*; Kilpatrick et al., 2007). Those with the highest exposure, lowest support, and the *s/s* genotype were at 4.5 times greater risk of developing major depression or PTSD than those in the lowest risk group. Similar vulnerability factors appear to moderate the relation between chronic stress exposure and the development of certain psychiatric disorders (e.g., Koenen et al., 2009; Uher & McGuffin, 2010). To date, no studies addressing the effects of a single acute stressor on 5-HT functioning among children have appeared in the literature.

Effects of chronic stress on 5-HT functioning

Animal studies. Many diverse forms of psychopathology can be understood as adaptations to environments characterized by chronic stress (see Mead et al., 2010; van Goozen et al., 2007). At one extreme, experiences of neglect, abuse, homelessness, exposure to interadult violence, or warfare can lead to lasting neurobiological and behavioral changes (Perry, 2008; Perry et al., 1995). However, vulnerable individuals may also be affected by stressful experiences that vary in duration or are of milder intensity, including parental rejection and invalidation, family conflict, poverty, and/or illness. Once again, animal studies provide important insights into the neurobiological and behavioral sequelae of repeated exposure to stressors differing in type and severity. For example, rats exposed to restraint for 1 hr per day over 24 days exhibit increased 5-HT levels across diverse brain regions (Adell, Garcia-Marquez, Armario, & Gelpi, 1988). Of importance, when exposed to future acute stressors these rats respond with decreased 5-HT levels in many of the same brain regions, including the brain stem and hypothalamus. This likely reflects neural adaptations brought about through altered 5-HT release and metabolism (Adell, Trullas, & Gelpi, 1988). Analogous processes have been reported in other monoamine systems following prolonged exposure to stress (see below).

Among rodents, repeated stress exposure also leads to decreased 5-HT concentrations and increased in 5-HT_2 receptor binding in the PFC (Kellar & Bergstrom, 1983; Kitayama et al., 1989; Metz & Heal, 1986). Furthermore, macaques exposed to repeated disruptions of social networks, which is a form of chronic social stress, exhibit reduced 5-HT levels in the PFC, which last up to 14 months after the last stress induction (Fontenot, Kaplan, Manuck, Arango, & Mann, 1995). As noted by Fontenot et al. (1995), such findings may have implications for suicide risk among humans, because suicide victims exhibit both decreased 5-HT levels (Arango, Underwood, & Mann, 2002) and increased 5-HT_2 receptor binding in the PFC (Arango et al., 1990).

Of importance, not all brain regions exhibit reduced 5-HT neurotransmission following prolonged stress. For example, rats exposed to chronic social defeat show corresponding increases in hippocampal 5-HT release (Keeney et al., 2006). This increase in 5-HT is brought about at least in part through the inhibiting effects of glucocorticoids on 5-HT_{1A} gene expression (Kuroda Watanabe, Albeck, Hastings, & McEwen, 1994). Alterations in hippocampal 5-HT function following prolonged stress may be implicated in memory impairment, major depression, and suicide (Kudryavtseva, Bakshtanovskaya, & Koryakina, 1991; López, Chalmers, Little, Watson, 1998; Pandy et al., 2002).

Rodent studies also provide insight into links between early rearing conditions and later behavioral and neurobiological responses to stress. For example, Weaver and colleagues (2004) reported that mother rats that engage in higher rates of licking, grooming, and arched-back nursing produce pups that are less fearful and show more modest HPA responses to stress compared with offspring of mothers that engage in lower rates of these behaviors. Increased 5-HT activity at 5-HT_7 receptor density in the hippocampus appear to underlie the link between these maternal behaviors and elevated glucocorticoid receptor (GR) expression. These GR promoters (e.g., NR3C1) activate transcription factors that "turn on" the gene responsible for dampening stress responses (NGF1-A; see Weaver et al., 2004). In contrast, among pups reared by low licking, grooming, and arched-backed nursing mothers, NR3C1 is methylated. Because methylation reduces transcriptional activity, this inhibits (i.e., "turns off") binding on NGF1-A, resulting in higher stress reactivity. Research extending these findings to humans is limited. However, it appears that similar mechanisms may also explain how early stressors affect human physiology and behavior (Hyman, 2009).

Human studies. Recently, McGowan and colleagues (2009) examined the NR3C1 GR promoter among suicide victims with a history of childhood abuse. These participants were matched with nonabused suicide victims and controls who died suddenly. Compared with both control groups, suicide victims with a history of abuse showed increased cytosine methylation of an NR3C1 promoter. Furthermore, as expected from the animal studies, abused suicide victims also showed decreased NGF1-A transcription factor binding. This study lends support to a central premise of this review: research on biological mechanisms of allostasis discovered in rodents may be translated to humans. However, suicide is a complex phenotype and adversity rarely predicts suicidal thoughts and behaviors in isolation. Indeed, studies of *r*GE interactions suggest that early trauma may increase suicide risk primarily among vulnerable individuals exposed during certain developmental stages (see Teicher, 2010). Identifying

such children has clear implications for prevention and early intervention (Beauchaine, Neuhaus, et al., 2008).

The notion that certain individuals may be more vulnerable to allostatic processes based on 5-HT genotypes has received recent empirical support. For example, among patients with chronic fatigue, Smith, Maloney, Falkenberg, Dimulescu, and Rajeevan (2009) reported that both 5-HTR_{3A} and 5-HTR_4 receptor polymorphisms were associated with greater effects of allostatic load across the life span, as indexed by multiple measures of metabolic, cardiovascular, inflammatory, LHPA, and SNS functioning. Although the authors did not specify which variants of these 5-HT receptor polymorphisms predicted allostatic load effects, it is likely that alleles conferring more efficient uptake were implicated. These variants have been linked with symptoms of depression and anxiety, and related behavioral traits such as harm avoidance (Barnes & Sharp, 1999; Melke et al., 2003; Yamada et al., 2006). Of note, 5-HTR_4 receptors are expressed in the hippocampus (Waeber, Sebben, Nieoullon, Bockaert, & Dumuis, 1994), and 5-HTR_{3A} receptors are expressed in both the hippocampus and the amygdala (Niesler et al., 2001), components of the septohippocampal system. Furthermore, 5-HTR_4 knockout mice exhibit reduced sensitivity to the effects of stress (Compan et al., 2004).

Extensive research has also demonstrated that those who inherit certain variants of 5-HT regulating genes are more sensitive psychologically to the effects of stress, including early adversity, abuse, and other forms of maltreatment. For example, Brezo and colleagues (2010) followed over 1200 individuals for 22 years and found that three variants of the 5-HTR_{2A} gene interacted with histories of sexual and/or physical abuse to predict later suicidal behavior. Furthermore, abuse predicted later depression among those with certain variants of the *5-HTR$_{1A}$* and *5-HTT* genes. If replicated, prediction of suicidal behavior and depression by different genes following adversity may suggest partially independent etiological pathways.

In another impressive prospective study, suicidal ideation and variation in the *5-HTTLPR* gene were assessed among maltreated and control children from low SES backgrounds (Cicchetti, Rogosch, Sturge-Apple, & Toth, 2010). Maltreated children were at highest risk for suicidal ideation, regardless of the number of *s* alleles. However, among those who experienced fewer types of abuse (1–2 versus 3-4), *s*-allele carriers (*s*/*s*, *s*/*l*) demonstrated higher levels of suicidal ideation than *l*/*l*-allele carriers. Thus, the *s*-allele conferred greater sensitivity to the effects of early adversity. A number of similar findings have been reported in the literature (see Uher & McGuffin, 2008, 2010).

Implications for personality and psychopathology

Well-controlled studies conducted with animals have long demonstrated that exposure to stress early in life can induce long-lasting, often dose-dependent effects on biological development and behavioral adjustment (see e.g., Mead et al., 2010; Meaney, 2001). Until recently, most of these studies examined effects of stress on LHPA axis functioning. However, similar paradigms are now being used to examine the effects of stress on central 5-HT structure and function. Among other findings, this research demonstrates that exposure to stress (a) decreases 5-HT_{1A} messenger RNA levels and 5-HT_{1A} binding in the hippocampus, (b) temporarily increases 5-HT levels in the basolateral amygdala, and (c) decreases NGF1-A transcription factor binding, resulting in increased sensitivity to the effects of stress. Of importance, the behavioral effects of early life stress on rodents are amplified by exposure to social defeat during adulthood, leading to higher rates of passive–submissive behavior and fewer active coping efforts (Gardner, Thrivikraman, Lightman; Plotsky & Lowry, 2005).

In research conducted with humans, 5-HT may be the most widely studied monoamine neurotransmitter in its relations to psychopathology (see, e.g., Anguelova, Benkelfat, & Turecki, 2003; Retz, Retz-Junginger, Supprian, Thome, & Rosler, 2004; Uher & McGuffin, 2008). To date, however, much of this research has been descriptive, demonstrating 5-HT dysfunction across a wide range of psychiatric conditions spanning both the internalizing and externalizing spectra (e.g., Brezo et al., 2010; Uher & McGuffin, 2008). More recently, research has emerged addressing both changes in 5-HT function following exposure to stress, and differential vulnerabilities to stress conferred by genes ivolved in serotonergic neurotransmission, particularly in septohippocampal structures. Among other findings, this research demonstrates (a) functional alterations in 5-HT networks that are similar to those observed among animals exposed to stress, (b) greater psychological vulnerability to the effects of early adversity among those with the short allelic variant of the *5-HTTLPR* gene, and (c) greater effects of allostasis across the life span among genetically vulnerable individuals who exhibit lower levels of septohippocampal 5-HT function due to reduced 5-HTR_{3A} and 5-HTR_4 receptor expression. One or more of these effects have been linked with increased risk for depression, suicide, and aggression (e.g., Aniseman et al., 2008; Caspi et al., 2003; van Goozen et al., 2007).

Allostatic Effects on Dopaminergic Functioning: Implications for Approach Motivation and Behavioral Impulsivity

Depending on how central DA networks are parsed, either three or four systems are typically identified based on the primary function served by each. However, similar to our statement above regarding monoamine neurotransmitters in general, central DA networks are neither structurally discrete nor functionally independent. Structural interconnections are observed across systems, and some DA circuits modulate others through feedback and feedforward mechanisms (see Gatzke-Kopp & Beauchaine, 2007a; Sagvolden et al., 2005). Nevertheless, it is useful to discuss each DA system in the context of its primary function.

Dopamine neurons originating in the substantia nigra and projecting to the dorsal striatum, including the caudate and putamen, comprise the nigrostriatal pathway (Swartz, 1999). This DA network subserves motor, sensorimotor integration, and fight/flight/freeze functions. Although functional compromises in the nigrostriatal system are observed in certain psychiatric and medical disorders including attention-deficit/hyperactivity disorder (ADHD; Gatzke-Kopp et al., 2009; Shannon, Sauder, Beauchaine, & Gatzke-Kopp, 2009) and Parkinson disease (see DeLong, 2000), our focus here is on other DA networks for which allostatic effects have been documented.

Another DA system, the tuberoinfundibular, originates in the arcuate nucleus of the hypothalamus and projects to the pituitary gland. This DA system is integral to hormone regulation, and may play a minor role in modulating cortisol secretion (e.g., Gudelsky, Berry, & Meltzer, 1989; Kitchen, Kelly, & Turner, 1988). However, because allostatic effects on the LHPA axis have been reviewed in detail elsewhere (e.g., Lupien et al., 2006, 2009; Mead et al., 2010), we do not focus on the tuberoinfundibular pathway.

The mesolimbic, another DA system, includes structures originating in the ventral tegmental area, projecting forward to the ventral striatum, the nucleus accumbens, and the amygdala, among other structures (see Gatzke-Kopp & Beauchaine, 2007a). This DA system comprises what is often referred to as the primary reward center of the brain. Phasic neural firing within mesolimbic brain regions is observed in response to novelty, unconditioned reinforcers, and environmental cues for conditioned reinforcers (e.g., Ljungberg, Apicella, & Schultz, 1992).

As outlined above, an extensive literature links individual differences in mesolimbic DA activity and reactivity to approach-related behavioral traits, including novelty-seeking (e.g., Cloninger, 1986, 1987), positive affectivity (e.g., Ashby et al., 1999; Forbes et al., 2009), and impulsivity (e.g., Buckholtz et al., 2010). In normative samples, high levels of central DA expression predict trait positive affectivity (Ashby et al., 1999; Berridge, 2003), whereas low levels predict trait irritability (Laakso et al., 2003). Atypically low levels of neural responding within mesolimbic structures confer vulnerability to externalizing behavior disorders. For example, among those with ADHD, both with and without comorbid conduct disorder (CD), blunted neural activation in mesolimbic structures is observed during reward tasks (e.g., Durston, 2003; Durston et al., 2003; Vaidya et al., 1998; Volkow et al., 2009). According to current theory, low central DA activity, particularly in the striatum, is experienced as aversive, motivating affected individuals to seek external reward to upregulate their chronically negative mood state (Beauchaine et al., 2010; Gatzke-Kopp & Beauchaine, 2007a; Sagvolden et al., 2005). Consistent with this reward-seeking interpretation, DA agonists reduce hyperactivity, impulsivity, and aggression (e.g., MTA Cooperative Group, 1999) by normalizing DA neurotransmission within mesolimbic structures (Volkow, Fowler, Wang, Ding, & Gatley, 2002). Abnormally low mesolimbic DA activity also confers risk for antisocial personality development and both alcohol and drug abuse and dependence (see Beauchaine et al., 2010; Beauchaine & Neuhaus, 2008; Robinson & Berridge, 2003; Sagvolden et al., 2005).

A final DA system, the mesocortical, projects forward from portions of the mesolimbic system to cortical areas including the dorsolateral PFC, the medial PFC, the anterior cingulate cortex, and the temporal cortex (see Gatzke-Kopp & Beauchaine, 2007a; Swartz, 1999). These neural structures play integral roles in executive functioning, attention, monitoring one's behavior, and coordinating behaviors in the service of distal goals (Fan, Hof, Guise, Fossella, & Posner, 2008; Rothbart, Sheese, & Posner, 2007). Given the importance of these functions to so many aspects of behavior regulation and self-control, disruptions in dopaminergic PFC circuitry confer risk for a wide range of psychiatric conditions spanning both the internalizing and externalizing spectra (see e.g., Forbes et al., 2010; Hsu, Langenecker, Kennedy, Zubieta, & Heitzeg, 2010; Luciana, 2006). The literatures linking PFC function and dysfunction to self-regulation and psychopathology are therefore vast and cannot be reviewed here. Interested readers are referred elsewhere for such accounts (e.g., Fuster, 2008; Luciana, 2006). Instead, we focus below on selected findings that suggest allostatic effects on developing mesocortical structures.

Of importance, both feedback and feedforward connections link the mesolimbic and mesocortical DA systems. As a result, increasing prefrontal DA levels pharmacologically leads to decreased DA levels in the nucleus accumbens, a mesolimbic structure (Louilot, LeMoal, & Simon, 1989). Conversely, decreasing prefrontal DA increases DA levels in the nucleus accumbens. Thus, the mesocortical DA system inhibits subcortical DA expression. Disruption of this feedback system may be one neural substrate of impulsivity (Tisch, Silberstein, Limousin-Dowsey & Jahanshahi, 2004). Shannon et al. (2009) reported reduced functional connectivity in both feedback and feedforward directions between mesolimbic and mesocortical structures among adolescents with ADHD and/or CD. Top-down modulation of mesolimbic activity by mesocortical structures may be especially important to self-regulation (e.g., Phillips, Walton, & Jhou, 2007). As outlined below, such modulation may be vulnerable to allostatic effects given experience-dependent development of both midbrain and cortical DA systems (see Arnsten, 2009; Halperin & Schulz, 2006; Spear, 2007; Sullivan & Brake, 2003).

Important considerations in discussing allostatic effects on central DA networks concern (a) the sensitivity of mesolimbic structures during certain developmental periods to long-term functional changes brought about by excessive activation (Gatzke-Kopp, 2011; Lapiz et al., 2003), and (b) developmental consequences of such functional changes for later maturing mesocortical structures that receive direct mesolimbic input (see, e.g., Beauchaine, Neuhaus, et al., 2008; Lukkes, Watt, Lowry, & Forster, 2009; Perry, 2008; Schore,

1996). In general, brain development advances both sequentially and hierarchically, with the more complex cortical regions maturing last (see, e.g., Benes, 2006). Thus, the mesolimbic DA system, which is phylogenetically old, matures very early in life, whereas mesocortical structures continue to develop into early adulthood (e.g., Gogtay et al., 2004). As articulated by others, optimal development of later maturing brain regions is likely to be disrupted if input from early maturing brain regions is compromised (see Benes, 2006; Perry, 2008).

Effects of acute stress on mesolimbic and mesocortical dopamine function

Animal studies. Among rats, one means of inducing acute stress is through single episode restraint paradigms. In general, these episodes increase extracellular DA concentrations in mesolimbic and mesocortical structures, including the ventral tegmental area, the nucleus accumbens, and the medial PFC (Imperato, Puglisi-Allegra, Casolini, & Angelucci, 1991; Morrow et al., 1997). Furthermore, increased phasic DA firing in the ventral tegmental area may continue for up to 24 hr after a single restraint experience (Anstrom & Woodward, 2005).

A second means of inducing acute stress among both rats and nonhuman primates is through brief social defeat. This typically involves exposing target animals to dominant males, rendering the target subordinate (see Martinez, Calvo-Torrent, & Pico-Alfonso, 1998). Following such threats, subordinate rats display increased accumbal and cortical DA expression (Tidey & Miczek, 1996). Similarly, postmortem studies indicate increased DA turnover in limbic forebrain structures among rodents forced to defend against attack (Puglisi-Allegra & Cabib, 1990). In addition, increased transient DA release and increased neural burst frequency are observed in the ventral tegmental area among rats forced to interact with aggressive conspecifics (Anstrom, Miczek, & Budygin, 2009).

Of importance, acute stress associated with social defeat also sensitizes animals to the behavioral effects of strong DA agonists (Miczek, Covington, Nikulina, & Hammer, 2004). For example, subordinate male rats that are exposed to aggressive conspecifics self-administer more cocaine than those in control social conditions. Furthermore, they demonstrate increased motoric behavior after amphetamine challenge compared to both controls and dominant conspecifics (Covington & Miczek, 2005). Although the precise mechanisms of such sensitization processes are not understood fully, these findings may have implications for drug use among humans who are reared in abusive and otherwise violent environments (Mead et al., 2010).

Human studies. Despite the relative high frequency of acute daily stressors, few studies have examined the effects of acute stress on DA functioning among humans. However, in one such study (Pruessner, Champagne, Meaney, & Dagher, 2004), college students were asked to report on maternal caregiving quality and neglect. A lab-induced psychosocial stressor elicited greater DA release in the ventral striatum, as measured by positron emission tomography (PET), among students who reported low levels of maternal care in childhood. Extending this work, Engert, Joober, Meaney, Hellhammer, and Prussner (2009) examined the relationship between parental quality of care and behavioral responding to reward among college students, as measured by performance on a monetary incentive card-sorting task following administration of methylphenidate. For students who reported high levels of parental care, DA agonist administration was associated with decreased performance accuracy during the task. In contrast, reward-induced performance accuracy of low parental care participants was enhanced by methylphenidate. Although intriguing, these studies are difficult to interpret because they are wrought with possible third variable explanations including retrospective recall biases of parental care quality and *r*GEs, among others.

Effects of chronic stress on mesolimbic and mesocortical dopamine function

Animal studies. A number of chronic stress paradigms appear in the animal literature. These include repeated restraint episodes, protracted exposure to social hierarchies (in contrast to brief social dominance paradigms), prolonged social isolation, and separation of pups from their mothers. As outlined above, acute stressors often increase DA release in both mesolimbic and mesocortical structures (Imperato et al., 1991; Morrow et al., 1997). However, when certain stressors are repeated, prolonged phasic neural firing may induce long-term downregulation of mesolimbic DA activity, an experience-dependent neural adaptation that is likely effected through several mechanisms, including altered D_2 and D_3 receptor availability, changes in DA transporter efficiency, and weakened neural connections between mesolimbic and mesocortical structures (Arnsten, 2009; Braun, Lange, Metzger, & Poeggel, 2000; Henry et al., 1995; Meaney, Brake, & Gratton, 2002; Thomas, Beurrier, Bonci, & Malenka, 2001). Of importance, such downregulation can occur over seemingly short periods of time (see Cabib & Puglisi-Allegra, 1996). In fact, following only 5 days of daily restraint, rats exhibit decreased mesolimbic DA release (Imperato, Cabib, & Puglisi-Allegra, 1993; Sheikh et al., 2007). Similar effects are found following exposure to chronic unpredictable stress. For example, Rasheed, Ahmad, Pandey, Chaturevi, and Lohani (2010) exposed rats to immobilization, forced swimming, overnight soiled caging, foot shocks, cold exposure, day night reversal, and fasting for 7 days. Exposure to these chronic unpredictable stressors decreased DA levels in the frontal cortex, hippocampus, and striatum. Downregulation of striatal DA function is also observed among rodents following repeated exposure to dominant males (e.g., Isovich, Mijnster, Flugge, & Fuchs, 2000; Lucas et al., 2004). Among other behavioral effects outlined below, chronic stress exposure reduces DA

neurotransmission in the prefrontal cortex, resulting in impaired spatial working memory (Mizoguchi et al., 2000).

The effects of chronic stress on central DA systems have also been explored in nonhuman primates, often by evaluating correlates of low status within social hierarchies (Grant et al., 1998). For example, in cynomolgus monkeys, D_2 receptor availability did not differ among those housed individually. When subsequently placed together, however, PET indicated lower availability of D_2 receptors among monkeys that assumed socially subordinate roles, highlighting the importance of social environment in modulating DA functioning. In addition, similar to findings from studies with rodents (Miczek et al., 2004), cocaine was experienced as more reinforcing among the subordinate monkeys than the dominant monkeys (Morgan et al., 2002).

It is critical to note, however, that not all forms of protracted stress affect central DA functioning equally. In contrast to the downregulation of DA neurotransmission often observed following prolonged restraint and social stress, isolation rearing and maternal separation often yield enhanced DA expression in some brain structures, yet reduced DA turnover and innervation in others (see Crespi, Wright, & Möbius, 1992; Jones, Hernandez, Kendall, Marsden, & Robbins, 1992; Lukkes et al., 2009). For example, isolation-reared rats exposed to mild foot shocks exhibit greater and longer lasting DA release in the nucleus accumbens than controls (Fulford & Marsden, 1998), yet both DA turnover and DA innervation in the PFC are reduced (Braun et al., 2000; Eells, Misler, & Nikodem, 2006).

Maternal separation also induces long-lasting functional changes in central DA systems. For example, compared with controls, rat pups exposed daily to prolonged maternal separation exhibit increased nucleus accumbens DA neurotransmission and motoric activity when placed in novel settings (Brake, Zhang, Dioro, Meaney, & Gratton, 2004; Fulford & Marsden, 1998). These rats also respond to acute mild stressors, including tail pinches, with greater increases in nucleus accumbens DA release than controls. Separation exposed rats also exhibit lower densities of nucleus accumbens core and striatal DA transporter sites. Of importance, these neural adaptations result in sensitization to the behavioral effects of cocaine and amphetamines in adulthood (Meaney et al., 2002).

As noted above, medial PFC dopamine turnover and DA fiber innervation decrease during postweaning social isolation, which may reflect an experience-dependent neural adaptation to regulate altered extracellular DA levels in the midbrain (Braun et al., 2002). Of importance, excess DA release in the nucleus accumbens during stress exposure, which is often observed among isolation-reared rats, is *enhanced* by decreased DA activation in the medial PFC (Doherty & Gratton, 1996; Pascucci, Ventura, Latagliata, Cabib, & Puglisi-Allegra, 2007; Del Arco & Mora, 2008). As outlined above, the mesocortical DA system shares strong interconnections with mesolimbic structures, and inhibits mesolimbic activation as a mechanism of behavioral and emotional control. Isolation rearing in particular appears to alter both the strength of mesolimbic–mesocortical connections, and the inhibiting influence of mesocortical networks over phylogenetically older brain systems subserving behavioral approach.

Stress exposure can also occur prenatally. In fact, a large literature exists in which the effects of stress exposure among pregnant rats on their pups have been described. Most of this literature addresses alterations in LHPA axis functioning, which is beyond the scope of this paper (see above). However, a sizable number of studies have also examined the effects of prenatal stress exposure on central DA functioning. Below we provide examples of some such effects, including exposure to stimulants. As noted above, we exclude discussion of neurotoxins that damage central nervous system tissues directly, focusing instead on insults that alter ranges of functioning in central DA systems, consistent with the allostatic load model (McEwen & Stellar, 1993; Lupien et al., 2006).

Several authors have described alterations in mesolimbic and mesocortical DA function among rats and monkeys exposed to prenatal stress. For example, Henry et al. (1995) found (a) increased D_2 receptor binding in the nucleus accumbens, (b) decreased D_3 receptor binding in both the nucleus accumbens core and shell, and (c) sensitization to self-administration of amphetamine among adult offspring of rats exposed to repeated restraint in the last week of gestation (about one-third of total gestation). Similar findings of increased D_2 receptor densities in the dorsal frontal and medial prefrontal cortices have also been reported (Berger, Barros, Sarchi, Tarazi, & Antonelli, 2002). Thus, prenatal stress appears to have differential effects on DA receptor subtypes. Of importance, trait impulsivity and sensitivity to cocaine reinforcement have been linked with reduced availability of *both* D_2 and D_3 receptors in the nucleus accumbens (Dalley et al., 2007). This renders the above findings somewhat difficult to interpret. To confuse matters further, like social isolation, prenatal stress exposure may be associated with reduced DA levels in some brain regions, yet increased DA levels in others (e.g., Alonso, Navarro, & Rodriguez, 1994; Kippin, Szumlinski, Kapasova, Rezner, & See, 2008; Roberts et al., 2004; Takahashi, Turner, & Kalin, 1992). Consistent among studies, however, are strong associations between (a) prenatal stress exposure, (b) altered DA functioning, including compromised neurodevelopment of mesocortical and mesolimbic pathways (see Arnsten, 2009; Berger et al., 2002; Carboni et al. 2010), and (c) sensitization to amphetamine and cocaine in adulthood (Berger et al., 2002; Jones, Marsden, & Robbins, 1990; Kippen et al., 2007).

A large literature also exists addressing the effects of prenatal stimulant exposure on central DA systems. This literature demonstrates that strong stimulants—including nicotine—induce long-lasting and in many cases permanent changes in the structure and function of developing DA networks, both mesolimbic and mesocortical. For example, exposure of pregnant rats to nicotine on gestational days 4–21 reduces nucleus accumbens DA responding among their adult offspring

and decreases DA concentrations in the cerebral cortex (see Glatt, Bolaños, Trksak, & Jackson, 2000; Kane, Fu, Matta, & Sharp, 2004; Navarro, Seidler, Whitmore, & Slotkin, 1988). Prenatal exposure to cocaine produces similar downregulation of mesolimbic DA function (e.g., Minabe, Ashby, Heyser, Spear, & Wang, 1992), and even at low doses induces permanent structural irregularities in the developing anterior cingulate cortex (Stanwood, Washington, Shumsky, & Levitt, 2001), a DA-rich network critical to self-monitoring and behavior regulation (see Gatzke-Kopp et al., 2009). Behaviorally, rats exposed prenatally to strong stimulants exhibit hypoactivity in their rearing environments (e.g., Johns, Means, Means, & McMillen, 1992).

Thus, chronic elevation of DA neural firing in the nucleus accumbens induced by strong stimulants among rodents and nonhuman primates downregulates tonic DA activity (Scafidi et al., 1996), sensitizes phasic DA responding to such stimulants (Berger et al., 2002; Jones, Marsden, & Robbins, 1990; Kippen et al., 2007), and suppresses the strength of developing connections between mesolimbic structures and the PFC (Thomas et al., 2001). As we have already noted, such connections are integral to effective behavior regulation.

Finally, chronic stress exposure also affects central DA functioning through indirect pathways, including LHPA axis responding. GRs found in the nucleus accumbens enhance sensitivity of DA receptors. As a result, exposure to glucocorticoids during gestational days or early postnatal days increases mesolimbic DA activity in adulthood (MacArthur, McHale, Dalley, Buckingham, & Gillies, 2005; MacArthur, McHale, & Gillies, 2007).

Human studies. In contrast to the dearth of acute stress studies conducted with humans (see above), somewhat more literature addressing the effects of chronic stress on central DA expression exists. However, these studies are not experimental, which precludes causal inference about the effects of stress exposure on DA functioning. Nevertheless, many if not most findings are consistent with those observed in experiments conducted with animals (see above), providing a considerable degree of confidence that the effects of chronic stress on central DA systems are analogous across species.

Several studies have evaluated central DA functioning among children and adults who reported early adversity including abuse during childhood. Initially, such studies focused on urinary dopamine-β-hydroxylase, a DA metabolite that is consistently reduced in children with abuse histories (for a review, see Glaser, 2000). However, correspondences between levels of central DA and its peripheral metabolites are far from one to one. Accordingly, newer studies have used PET technology, providing for direct assessment of central DA function. In one such study, Dillion et al. (2009) found that retrospectively reported childhood adversity (emotional, physical, and/or sexual abuse) predicted decreased neural activity in the left pallidus during anticipation of reward. Maltreated individuals also reported higher levels of anhedonia, which has been linked with deficiencies in mesolimbic DA responding to incentives (e.g., Cabib & Puglisi-Allegra, 1996; Dunlop & Nemeroff, 2007). Reduced DA binding in the ventral striatum has also been reported following psychosocial stress among college students who experienced poor parental care as children (Pruessner et al., 2004).

In addition, consistent with the animal literature, studies conducted with humans point toward the importance of prenatal stressors in affecting later DA functioning. For example, maternal exposure to stress has been linked with poor attention regulation, ADHD, and other externalizing behaviors in childhood, over and above the effects of confounds such as maternal nicotine use and sociodemographic risk (Gutteling et al., 2005; Huizink, Robles de Medina, Mulder, Visser, & Buitelaar, 2002; O'Connor, Heron, Golding, Beveridge, & Glover, 2002; Rodriguez & Bohlin, 2004). As noted above, the pathophysiology of ADHD is linked primarily to central DA dysfunction (see Gatzke-Kopp et al., 2009; Sagvolden et al., 2005).

Stimulant exposure in particular appears to alter mesolimbic DA functioning for impressively long time intervals. For example, fetal nicotine exposure, which is most harmful during the second and third trimesters (Slotkin, Lappi, & Seidler, 1993), decreases both tonic and phasic responding of DA cells in the nucleus accumbens. As a result, higher levels of stimulation are required to promote DA release (Kane et al., 2004). As noted above, behavioral traits such as impulsivity and novelty seeking have been linked to such DA insensitivity. Not surprisingly, nicotine exposure during pregnancy is associated with higher rates of externalizing behaviors in offspring (e.g., Linnet et al., 2003; Ernst, Moolchan, & Robinson, 2001). Moreover, links between prenatal nicotine exposure and later conduct disorder are observed over and above the effects of parental income, antisocial tendencies, prematurity, birth weight, and poor parenting practices (Fergusson, Horwood, & Lynskey, 1993; Gatzke-Kopp & Beauchaine, 2007b).

Although the magnitude of effects among humans may not be as large as once thought (Frank, Augustyn, Knight, Pell, & Zuckerman, 2001), prenatal cocaine exposure appears to have similar effects to those reported in rodent studies, including downregulation of basal DA activity (Scafidi et al., 1996) and delayed maturation of mesocortical DA networks (Warner et al., 2006). Together, these effects result in poor behavior regulation (Ackerman, Riggins, & Black, 2010) and difficulties with sustained attention and other executive functions (Arnsten, 2009; Richardson, Conroy, & Day, 1996).

Implications for personality and psychopathology

The literature reviewed above demonstrates profound effects of stress, particularly protracted stress, on both the structure and function of developing dopaminergic neural networks. Elegant experiments with rodents in particular demonstrate that acute stressors of various kinds increase dopaminergic neurotransmission in both mesolimbic and mesocortical structures, and prolonged stressors sometimes downregulate

and sometimes upregulate dopaminergic neurotransmission, depending on the nature of the stressor and the brain region under study. In general, stressors that downregulate DA neurotransmission involve direct exposure to threat (e.g., physical restraint, aggressive conspecifics), whereas stressors that upregulate DA neurotransmission involve neglect (e.g., isolation rearing, maternal separation).

Studies conducted with animals indicate that prolonged stress exposure also alters structural and functional connectivity between mesolimbic brain regions subserving behavioral approach and mesocortical brain regions subserving behavior and emotion regultion. Studies conducted with humans, although not experimental, suggest similar effects, which may result in increased behavioral impulsivity, problems with sustained attention, risk for externalizing behavior disorders, memory impairment, anhedonia, and sensitization to strong stimulants later in life.

In our view, long-term functional changes in DA networks brought about through excessive activation and associated neural adaptations fit well into an allostatic load framework. Even though time frames of stress induction are often shorter than those studied in LHPA axis models, dopaminergic neural networks exhibit altered ranges of functioning, which is the very definition of allostasis (Sterling & Eyer, 1988), following stressors of various kinds. In many cases, these functional changes facilitate more effective coping in an organism's rearing environment (see Gatzke-Kopp, 2011). For example, downregulation of mesolimbic DA systems following repeated exposure to local threat may increase behavioral impulsivity, including increased exploratory behaviors that enable the organism to seek new less threatening environments. However, neural and behavioral adaptations that facilitate exploration may comprise vulnerabilities in other contexts (Mead et al., 2010). As already noted, altered DA responding among humans, especially when coupled with exposure to potentiating environmental risk factors, may confer risk for negative affectivity, school failure, drug use, criminality, and eventual antisocial personality development, among other outcomes (see Beauchaine et al., 2009, 2010). These trajectories argue strongly for both early detection of vulnerability and early intervention, when developing monoamine systems remain plastic (Beauchaine, Neuhaus, et al., 2008).

Allostatic Effects on Noradrenergic Functioning: Implications for Social Affiliative Behavior and Attachment

Among rodents, nonhuman primates, and humans, primary noradrenergic projections emerge from in the locus coeruleus (LC), which combined with its efferent projections, is often referred to as the LC–NE system. This network innervates portions of the hippocampus, hypothalamus, spinal cord, cerebellum, frontal cortex, and somatosensory cortices, among other structures (see Simpson & Lin, 2007). The LC–NE system shares extensive reciprocal projections with central 5-HT and DA networks (Stockmeier & Ordway, 2007), and contains neurons expressing mRNA for 5-HT_{1A}, 5-HT_{1C}, 5-HT_{2C}, and D_3 receptors (Pompeiano, Palacios, & Mengod, 1994; Suzuki, Hurd, Sokoloff, Schwartz, & Sedvall, 1998). Not surprising, given extensive interconnections with DA networks in particular, stimulation of neurons in the ventral tegmental area activates the LC–NE system (Deutch, Goldstein, & Roth, 1986), consistent with the shared functional role of DA and NE in mounting sympathetic stress responses (see above).

Tonic NE levels are associated with vigilance, attention, and nonspecific arousal, whereas phasic activation of the LC–NE system, whether through administration of NE agonists or exposure to a wide range of attention-evoking stimuli and stressors, facilitates classical conditioning, enhances acoustic startle responses, and promotes active avoidance (escape) behaviors (e.g., Aston-Jones, Iba, Clayton, Rajkowski, & Cohen, 2007; Davies, Astrachan, Kehne, Commissaris, & Gallager, 1984; Detke, Rickels, & Lucki, 1995). Thus, among other functions, LC–NE activation subserves coping efforts in the face of stress (Cecchi, Khoshbouei, Javors, & Morilak, 2002). This occurs primarily through modulating effects of NE on other neural systems. In fact, phasic increases in NE enhance neurotransmission—both excitatory and inhibitory—across widely distributed neural networks, thereby increasing the efficiency of those networks (Stockmeier & Ordway, 2007). Some evidence also suggests that phasic LC–NE responding modulates LHPA axis responding, although such findings are inconsistent (see Morilak, 2007).

Norepinephrine has received less attention than 5-HT and DA in models of personality. Nevertheless, Cloninger and colleagues (e.g., Cloninger, 1987; Cloninger, Svrakic, & Przybeck, 1993; Cloninger, Svrakic, & Svrakic, 1997) have articulated a theory linking individual differences in NE functioning to a trait they refer to as reward dependence. According to Cloninger's biosocial learning model, those high in reward dependence tend toward social affiliation, and are described as ". . . eager to help and please others, persistent, industrious, warmly sympathetic, sentimental, and sensitive to social cues and personal succor . . ." (Cloninger, 1987, p. 576). Of importance, low rather than high levels of NE are associated with such behaviors.

Although tendencies toward reward dependence are somewhat heritable, more variance in the trait is accounted for by environmental effects than by genetic effects (Gillespie, Johnstone, Boyce, Heath, & Martin, 2001). Indeed, as seen above for both 5-HT and DA, central NE networks are highly sensitive to functional changes brought about by excessive exposure to stress. Furthermore, allostatic effects on the NE system confer vulnerability to anxiety, depression, and PTSD, at least in part through regulation of neuronal gene expression (Duman & Newton, 2007). Although not the focus of this review, allostatic effects on LC–NE function also have significant health consequences given noradrenergic mechanisms of vascular control, cardiac output, and blood pressure regulation (e.g., Nakaki, Nakayama, Yamamoto, &

Kato, 1990; Philbin, Bateman, & Mendelowitz, 2010). As a result, stress-induced elevations in LC–NE activity confer risk for hypertension and cardiovascular disease (see, e.g., Goldstein, 1981).

Finally, consistent with its role in social affiliation more broadly, NE figures prominently in several modern theories of attachment (e.g., Kraemer, 1992), both in the acquisition of infant–mother bonds (Moriceau, Roth, & Sullivan, 2010), and in the consolidation of attachment representations (Schore, 2003). According to these theories, NE plays a pivotal role in "tuning" infants' responses to attachment-relevant cues by increasing neural signal to noise ratios via its neuromodulatory effects (see Atkinson et al., 2009). For example, during the sensitive period in which rat pups acquire preferences for their mothers' odor, LC–NE activation suppresses stress-induced cortisone release and amygdala reactivity, thereby attenuating fear conditioning. Following this acquisition, NE levels return to normal and odor-induced fear conditioning is restored (see Moriceau et al., 2010; Raineki et al., 2010).

Taken together, this literature suggests that LC–NE system is integral to the expression of emotional arousal, social affiliation, mood regulation, and attachment. All of these behaviors are affected strongly by environmental experiences, suggesting that LC–NE functioning may be particularly sensitive to the effects of allostasis.

Effects of acute stress on NE functioning

Animal studies. The effects of acute stress on central NE networks have been well characterized in work with animals. As noted above, noradrenergic neurons in the LC–NE system respond with phasic activation to most if not all salient stimuli, habituating as saliency declines (e.g., Aston-Jones, Rajkowski, & Cohen, 1999). Accordingly, acute stressors, most of which are highly salient, induce large phasic increases in LC–NE neural firing, thereby facilitating arousal, vigilance, attention allocation, and fear conditioning (see Morilak, 2007). Studies conducted with rodents, cats, and reptiles demonstrate phasic increases in LC–NE activity in response to loud noises (Abercrombie & Jacobs, 1987), restraint (Cecchi, Khoshbouei, & Morilak, 2002), cold exposure (Pardon, Ma, & Morilak, 2003), electric shock (Maynert & Levi, 1964), and exposure to aggressive conspecifics (Audet & Anisman, 2010). During restraint stress, NE levels become elevated in a wide range of brain regions, including both cortical and subcortical structures innervated by the locus coeruleus and other source nuclei (Morilak et al., 2005). Typically, extracellular NE concentrations return to normal within 30 min (see Morilak et al., 2005). However, rats exposed to intermittent foot shocks for as little as 1 hr exhibit increased NE concentrations in the hippocampus and cerebral cortex for up to 7 days (Shinba, Ozawa, Yoshii, & Yamamoto, 2010).

Similar to findings outlined above for 5-HT and DA, central NE expression is also affected by the stress induced by maternal separation. In fact, even brief periods of maternal separation produce elevations in central NE among offspring (Bergamasco et al., 2005). For example, rhesus monkeys housed adjacent to but separated from their mothers for only 4 days exhibit increased NE metabolites in their cerebrospinal fluid (Bayart, Hayashi, Faull, Barchas, & Levine, 1990). Of importance, whether induced by exposure to acute stress or administration of noradrenergic agonists, phasic increases in NE induce anxious behaviors and reduce social behaviors (Cecchi, Khoshbouei, Javors, et al., 2002; Cecchi, Khoshbouei, & Morilak, 2002; Khoshbouei, Cecchi, Dove, Jovor, & Morliak, 2002; see also Welberg & Plotsky, 2007).

Human studies. Very few studies have addressed the effects of acute stress on central NE functioning among humans. However, noradrenergic dysregulation has been recognized for some time as an important etiological factor in the development of anxiety disorders (e.g., Sullivan, Coplan, Kent, & Gorman, 1999), certain subtypes of depression (e.g., Gold & Chrousos, 2003), and PTSD following stressors of various kinds, both acute and protracted (e.g., Southwick et al., 1993). In fact, concentrations of NE in cerebrospinal fluid correlate positively with the severity of PTSD symptoms (Geracioti et al., 2001). In contrast, those with less reactive LC–NE systems may be in part protected from adverse effects of acute stress (Wirtz, Siegrist, Rimmele, & Ehlert, 2008).

Among the few studies that have evaluated effects of acute stress on noradrenergic functioning in humans, most have examined NE levels in blood plasma. Several short-term stressors, including sleep deprivation (Costa et al., 2010), and mental challenges such as color-word Stroop tasks and mental arithmetic (Huang, Franco, Evans, & Acevedo, 2010), increase plasma NE. Such effects are larger among those who are depressed (Weinstein et al., 2010). These findings are consistent with those described immediately above regarding the effects of acute stress on NE functioning in animals.

Evidence also suggests that genetic influences on central NE expression may confer vulnerability to PTSD among some individuals (Morilak, 2007), providing a mechanism through which differential susceptibility to acute stress is conferred. Despite the defining role of environment in precipitating post traumatic stress, behavioral genetics studies indicate that PTSD is considerably heritable (True et al., 1993). As noted above, high tonic NE facilities both vigilance and classical conditioning. Accordingly, those with more active noradrenergic systems, which are conferred in part through the dopamine β-hydroxylase (DβH) 1021C/T gene allele (Mustapić et al., 2007), may be more likely to acquire conditioned fears, predisposing them to PTSD and other anxiety disorders (Amstadter, Nugent, & Koenen, 2009). In turn, noradrenergic hyperactivity of the LC–NE system likely contributes to undifferentiated emotional arousal and consolidation of fear memories, thereby maintaining symptoms (Cahill, Prins, Weber, McGaugh; 1994; Pitman, 1989). As outlined by Amstadter et al. (2009), several genes involved in NE neurotransmission—both central and peripheral—may confer vulnerability

to PTSD, including variations in the NE transporter ($SLC6_{A2}$), the α_{2C} NE receptor (ADR_{A2C}), and both β_1 (ADR_{B1}) and β_2 (ADR_{B2}) adrenergic receptor genes, among others.

Effects of chronic stress on NE functioning

Animal studies. The effects of chronic stress central NE function have also been studied in work with rodents. In general, this work demonstrates consistent, long-lasting, and widespread increases in central NE neurotransmission, higher plasma NE levels, and sensitization to the effects of NE following a host of protracted stressors, including isolation rearing (Gavrilovic, Spasojevic, & Dronjak, 2010), chronic intermittent cold stress (Buffalari & Grace, 2009), repeated foot shocks (Swiergiel, Leskov, & Dunn, 2008), and prolonged maternal separation (e.g., Swinny et al., 2010). For example, Swinny et al. (2010) demonstrated that as adolescents, rat pups that were separated from their mothers for 2 hr each on postnatal days 2–14, exhibited tonic LC neuronal firing rates that were twofold higher than pups that underwent separation for only 15 min per day. Maternal separation also resulted in less branching and decreased length of LC dendrites. Long-term alterations in the structure and function of central NE systems following prolonged stress appear to be effected in part through glucocorticoid-mediated changes in preproglucagon mRNA in the nucleus of the solitary tract, a structure responsible for coordinating peripheral and neuroendocrine stress responses (Zhang et al., 2010).

As outlined above for central DA networks, stress incurred by female rats, both during and in some cases *before* pregnancy, can alter noradrenergic functioning among their offspring, often well into adolescence and adulthood. For example, male offspring of mothers exposed to 21 days of chronic stress before pregnancy exhibit increased hippocampal NE expression at 2 months of age (Li et al., 2010). Furthermore, adult offspring of rats exposed to prolonged restraint stress (often in the last week of pregnancy) demonstrate anxiety, depression-like symptoms, increased noradrenergic sensitivity to amphetamines, and increased drug use in adolescence and adulthood (e.g., Carboni et al., 2010; Koehl et al., 2001). Thus, as in the case of DA reviewed above, early exposure to stress, even prenatal exposure, may have serious and sometimes life-long consequences for affected organisms.

Human studies. Literature addressing the effects of chronic stress on noradrenergic function among humans is limited. As noted above, however, it has been recognized for some time that noradrenergic deficiencies characterize anxiety disorders, depression, and PTSD (e.g., Gold & Chrousos, 2003; Southwick et al., 1993; Sullivan et al., 1999). Furthermore, similar to most findings presented in this article, the research conducted with humans that does exist, although not experimental, is generally consistent with findings from the animal literature.

Plasma NE levels are consistently elevated among maltreated children (De Bellis et al., 1999), children and adolescents who have been abused sexually (De Bellis, Lefter, Trickett, & Putnam, 1994), adults who were abused sexually as children (Lemieux & Coe, 1995), and those with PTSD (e.g., Geracioti et al., 2001). Furthermore, elevations in plasma NE immediately following motor vehicle accidents portend subsequent PTSD reactions among children and adolescents (Pervanidou et al., 2007). This sensitivity to trauma appears to occur in part due to preexisting genetic vulnerability conferred by the *DβH 1021C/T* allele (Mustapić et al., 2007; Tang et al., 2010). DβH converts DA to NE, with differing levels of efficiency depending on *1021C/T* allelic status. More efficient NE neurotransmission may confer vulnerability to allostatic load, as indicated by research demonstrating that (a) increasing NE levels pharmacologically potentiates basolateral amygdala reactivity to fear-inducing stimuli (Onur et al., 2009); (b) cumulative stress confers elevations in composite biomarkers of allostatic load, including NE (Glover, Stuber, & Poland, 2006); and (c) exposure to trauma increases risk for PTSD following subsequent traumas in a dose–response fashion (Neuner et al., 2004).

Finally, exposing those with PTSD to trauma-related stimuli increases NE levels in cerebrospinal fluid (Geracioti et al., 2008). Similarly, larger increases in plasma NE are observed following exposure to trauma cues among those with versus without PTSD, even when both groups incurred the initial trauma (Liberzon, Abelson, Flagel, Raz, & Young, 1999). Furthermore, increased urinary NE concentrations are observed among women who were abused sexually both in childhood and adulthood compared with women who were abused in childhood only (Friedman, Jalowiec, McHugo, Wang, & McDonagh, 2007). Although such findings are difficult to interpret, one possibility is that early exposure to sexual abuse sensitized the NE system to similar experiences later in life. This interpretation is consistent with animal literature in which similar sensitization processes have been found (e.g., Koehl et al., 2001).

Implications for personality and psychopathology

As is the case for both 5-HT and DA, stress incurred during development confers both immediate and in some cases long-lasting alterations in central NE function. In fact, among rodents, noradrenergic dysregulation is sometimes observed in the offspring of mothers that were exposed to stress before pregnancy. In almost all research evaluating the effects of stress on central and peripheral NE function, increased neurotransmission is observed in the LC–NE system and its projections. As reviewed above, this system is a primary component of stress responding. Accordingly, LC–NE activation promotes vigilance, tunes attention, increases arousal, facilitates escape behaviors, and initiates SNS responses.

From an evolutionary standpoint, chronic LC–NE activation following stress, including that observed following traumas of various kinds including childhood maltreatment, physical abuse, and sexual abuse, functions to increase one's immediate likelihood of survival. In the long run, how-

ever, when LC–NE stress reactivity fails to habituate, adverse effects on both mental and physical health often ensue. As outlined above, chronically elevated NE and excessive NE reactivity have been linked with anxiety, depression, PTSD, and asociality. All of these behavioral traits promote withdrawal. Thus, vulnerable individuals who by no fault of their own incur trauma are likely to minimize social contact and avoid new experiences, both of which are essential for recovery. Although considerable research remains to be conducted, newer work linking NE function to attachment suggests that those who incur trauma early may develop insecure attachment styles, which is likely to affect the quality of close relationships for life. Finally, chronically elevated NE compromises hippocampal function, impairing memory, with likely consequences for learning and both academic and occupational functioning.

Implications for Prevention, Intervention, and Social Policy

In this review, we describe how long-term functional changes in central monoamine systems may be brought about by exposure to a variety of stressors, including various forms of maltreatment and trauma, and exposure to strong stimulants such as nicotine, methamphetamine, and cocaine. Alterations in monoamine functioning following such stressors confer increases in state and trait anxiety, behavioral impulsivity, emotional lability, and/or asociality, depending on which system or systems are affected. Of importance, many of the same stressors can induce concurrent long-term functional alterations in 5-HT, DA, and NE neurotransmission. This is sobering given the broad range of behavioral response tendencies that are affected adversely, placing individuals at risk for school failure, delinquency, substance abuse and dependence, underemployment, PDSD, anxiety, depression, and difficulties maintaining close relationships.

Although not exhaustive, this list of adverse outcomes indicates how important successful prevention and intervention programs are if we wish to reduce the burden placed on affected individuals and families. As we and others have noted, biological processes involved in behavior regulation have direct implications for prevention and intervention that cannot be ignored if we wish to translate recent gains in our understanding of the neural underpinnings of behavior into more effective treatments (see e.g., Adam, Sutton, Doane, & Mineka, 2008; Beauchaine et al., 2008; Blair & Diamond, 2008; Dawson, 2008). Accordingly, below we briefly consider selected implications of altered monoamine function for prevention and intervention. Interested readers are referred elsewhere for more thorough accounts (e.g., Cicchetti & Gunnar, 2008).

Consider a male child born to a young disadvantaged mother who lives in a very high risk neighborhood. Assume that this young mother (a) has incurred significant abuse herself, (b) experiences her life as very stressful, (c) is trait impulsive, and (d) uses alcohol, tobacco, and other drugs including strong stimulants regularly. Because impulsivity is highly heritable, this mother's child, through no fault of his own, is likely to experience ADHD very early in life, expressed centrally as mesolimbic DA dysfunction (see Beauchaine et al., 2010). Unfortunately, the stress incurred by his mother both before and during pregnancy is likely to downregulate DA function further, exacerbating genetically inherited impulsivity. The same experiences may also upregulate NE function, inducing social wariness and contributing to attachment difficulties. Given the mother's own impulsivity and abuse history, she is likely to parent poorly, which may include neglect, coercive discipline, abuse, or other forms of maltreatment. These experiences may alter her child's monoamine function further, worsening his impulsivity and asociality, traits that hinder school readiness and his ability to bond with teachers and other adults. As a result of accumulating risk, he drops out of high school and spends much of his time loitering in a neighborhood high in criminality, drug use, and violence. In such contexts, impulsive boys are at much greater risk for delinquency that they are in protective neighborhoods (e.g., Lynam et al., 2000). Thus, he is arrested for petty theft before being caught selling drugs, for which he is imprisoned at age 17. By age 30, he has been in and out of prison several times, and appears to be on a life-long trajectory of antisocial behavior (see Beauchaine et al., 2009).

There is an almost limitless number of such high-risk scenarios that disadvantaged individuals face. Indeed, much of what we have learned about the developmental psychopathology of stress exposure has come from studies of children who incurred one or more of a wide range of stressors associated with some form of maltreatment (see Cicchetti & Rogosch, 2001; in press; Shackman, Wismer Fries, & Pollak, 2008) or adverse rearing experiences (e.g., Dozier, Peloso, Lewis, Laurenceau, & Levine, 2008; Fisher & Stoolmiller, 2008; Fisher et al., 2007; Marshal, Reeb, Fox, Nelson, & Zeanah, 2008; Pollack et al., 2010; Wiik et al., 2011). Nevertheless, the specific situation depicted above is not uncommon in the United States, and combined with knowledge of allostatic effects on monomanine functioning, provides some insights into prevention and intervention strategies.

Few would argue with the suggestion that the best form of treatment for any disorder is primary prevention. In the case at hand, this means avoidance of stress exposure, especially for biologically vulnerable individuals. As we have seen, severe enough stress, even when incurred before pregnancy, can induce long-lasting functional alterations in both DA and NE neurotransmission, with significant consequences for adjustment. Primary prevention requires a prenatal environment in which stress to the mother is minimized. Although the scope of stressors that induce functional changes in monoamine neurotransmission among offspring remains to be elucidated fully, mothers should almost certainly not be exposed to extreme stressors such as homelessness, abuse, or other forms of trauma, conditions that aggregate disproportionally in poor neighborhoods.

Given the scope of poverty in the United States, reducing risk among poor mothers is a daunting undertaking, especially during restrictive budgetary climates such as the present

one. However, when weighed against the costs of school dropout, substance abuse, crime, and incarceration, primary prevention may be a very good investment. At present, although there are no cost–benefit analyses available for primary prevention programs of the sort advocated here, well designed delinquency prevention programs introduced in early childhood are less expensive than costs associated with untreated delinquency (e.g., Farrington & Welsh, 1999). Nevertheless, such programs are only effective when they are multifaceted, including parent training, preschool education, home visits, and both social and emotional learning programs for children. Primary prevention programs would likely require similar levels of investment. To date, successful models of primary prevention such as those used successfully to reduce alcohol and tobacco use among expectant mothers have relied on public awareness campaigns. In the present case, this will not be sufficient. Rather, the public and legislators must be convinced that significant investment in prevention will not only improve mental health outcomes but also save money in the long term. To date, such arguments have been less successful than most mental health advocates would like.

Among those for whom primary prevention has failed or is unavailable, early intervention is essential. Brain plasticity is highest in young childhood (see, e.g., Dawson, 2008), especially for early-maturing structures such as many discussed here. Furthermore, development of early-maturing brain regions affects the organization and functioning of later maturing brain regions that are essential for effective planning, executive functioning, and self-control (Beauchaine et al., 2010; Beauchaine, Neuhaus, et al., 2008), skills that are important throughout life. For example, functional deficiencies in early developing DA networks involved in motivation can induce functional compromises in prefrontal DA systems, and in patterns of functional connectivity between the mesolimbic and mesocortical DA systems (see above). Although relatively little has been written about the effects of early intervention on these specific brain regions, several studies have demonstrated positive effects of early intervention on other biological systems (e.g., Bakermans-Kranenburg, Van IJzendoorn, Mesman, Alink, & Juffer, 2008; Marshall et al., 2008). Early intervention therefore holds much promise in reversing neural deficiencies that are incurred through exposure to stress.

Conclusions and Future Directions

In this article, we provided an updated review of the effects of acute and chronic stress on the structure and function of central (and in some cases peripheral) monoamine systems. In doing so, we suggested that long-term alterations in serotonergic, dopaminergic, and noradrenergic function, which are brought about by a host of acute and protracted stressors, can be conceptualized in an allostatic load framework. Stress-induced alterations in these systems reflect the very definition of allostasis: stability through change. Although most of the literature on allostatic load has focused on the LHPA axis, monoamine systems both regulate and are regulated by glucocorticoids. Moreover, LC–NE activation in particular is integral to stress responding.

To date, most studies addressing the effects of stress on monoamine function have examined main effects. However, as the literature outlined above suggests, these neural systems and the behavioral traits they subserve do not operate independently. As we have reviewed elsewhere, for example, propensities toward impulsivity and associated externalizing behavior that result from chronically low mesolimbic DA activity may be offset by trait anxiety, which emerges from 5-HT and NE networks (e.g., Beauchaine, 2001). In the multimodal treatment of ADHD (MTA) study, comorbid anxiety predicted superior treatment response among children with ADHD and CD (Jensen et al., 2001). In contrast, concurrent 5-HT and NE dysregulation may be especially debilitating, because both contribute to anxiety and mood dysregulation.

In the future more research is needed addressing the effects of psychotherapy, pharmacotherapy, and ordinary corrective experiences on central monoamine function. Although describing mechanisms of allostasis may be an important step in specifying the etiologies of anxiety disorders, mood disorders, impulse control disorders, and suicide, this knowledge should ultimately be put to use in formulating new and more effective interventions (see, e.g., Beauchaine, Neuhaus, et al., 2008).

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