Brain, Behavior, and Immunity 23 (2009) 1–9

Contents lists available at ScienceDirect

Brain, Behavior, and Immunity

journal homepage: www.elsevier.com/locate/ybrbi

Presidential Address

Psychobiological responses to social threat: Evolution of a psychological model in psychoneuroimmunology

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ARTICLE INFO

Article history:
Received 2 August 2008
Received in revised form 25 August 2008
Accepted 25 August 2008
Available online 10 September 2008

Keywords:
Social status
Stress
HPA axis
Inflammation
Cytokines
Cognition
Psychology

ABSTRACT

There exists a bidirectional network of interactions between the central nervous system, the endocrine system and the immune system. The existence of these pathways allows stressful life experience to impact the immune system with important implications for health. One powerful elicitor of changes in the autonomic, endocrine and immune systems is threat to social status. This review describes the development of a human model of social status threat that specifies a set of contextual, psychological and biological pathways that may underlie the health consequences of threats to social status and regard. The role of cognitive processes in shaping the physiological response to the social world will be emphasized.

1. Introduction

The field of psychoneuroimmunology has evolved rapidly over the past 25 years. The first "official" psychoneuroimmunology meeting, organized by Mark Laudenslager, Marty Reite and Linda Crnic, took place at a dude ranch in Tanque Verde, New Mexico in 1986. The meeting included about 50 individuals, primarily immunologists and psychologists, who were engaged in psychoneuroimmunology research at that time (summarized in Cohen, 1987; see Supplementary Fig. S1). The meeting addressed fundamental questions: *Is there any evidence that there is a specific interaction between the brain and the immune system*? *If so, are the interactions trivial or important*? *How are they mediated-humorally or via innervation of lymphoid organs*? *Are they bidirectional*? Questions regarding the best methods to utilize in this new interdisciplinary field arose. At one point, a verbal fight broke out as researchers argued about the immune measures that should and should not be studied in this developing field. A major issue that persisted throughout the meeting was the survivability of psychoneuroimmunology as a scientific discipline, given the resistance at that time to the notion of brain-immune system communication. Despite this underlying apprehension, it seemed that we all experienced the excitement of being involved in a new field with such promise.

The field of psychoneuroimmunology clearly survived and is, in fact, thriving. It is abundantly clear that the knowledge base and sophistication of approaches have evolved tremendously. Some of the questions posed at that meeting have been a focus of careful, intensive investigation with impressive results (e.g., innervation of immune organs). At the same time, other topics remain vexing. For example, we argued then about the definition of stress, and, sadly, the argument continues (Kemeny, 2003a). We argued about the most fruitful psychological models on which to base PNI investigations. This issue remains a concern for many.

So where are we now, 22 years later, with regard to the P in PNI? It is clear from both animal and human studies that exposure to stressors can impact immune cell traffic and function in myriad ways. Thanks to the elegant studies conducted by Janice Kiecolt-Glaser and Ronald Glaser as well as many others, we have made great strides in our understanding of the effects of short-term and chronic naturalistic stressors on the immune system in humans (Glaser, 2005; Glaser and Kiecolt-Glaser, 2005; see Segerstrom and Miller, 2004 for a meta-analytic review of this research). Similarly, studies in rodents and other animal models have defined virologic and immunologic processes that can be disturbed by stressors as well as the mechanistic pathways that underlie these effects (Dhabhar and McEwen, 2006; Moynihan, 2003). The evidence suggests that stress-induced malfunctions in these neuroimmunological pathways can play an important role in the course of specific diseases, such as viral infections (see Kemeny and Schedlowski, 2007).

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doi:10.1016/j.bbi.2008.08.008

In addition to the stress literature, there is a strong and coherent set of findings on the bidirectional relationships between depression and the immune system. Exciting findings have emerged from the laboratories of Robert Dantzer, Keith Kelley, Andrew Miller, Raz Yirmiya and others regarding the role of inflammatory cytokines in the etiology of depressive behavior (see Raison et al., 2006; Dantzer et al., 2008; Dantzer and Kelley, 2007).

However, I would suggest that our understanding of the *mind* in PNI remains somewhat limited. Clearly, the effects of stressful experiences on the immune system are not uniform across individuals, even when the nature of the stressor and other contextual factors are identical. The magnitude, duration and even direction of effects can vary dramatically across individuals (see Kemeny and Laudenslager, 1999; Segerstrom et al., 2001). While genetic and other factors play an important role, it is clear that a variety of behavioral individual differences, both stable traits as well as cognitive and affective state responses, appear to account for important variation in immunologic processes (see Kemeny, 2006).

The stress and coping model developed by Lazarus and Folkman (1984), has served as the conceptual basis for many investigations of such individual difference factors as they relate to the immune system. This model presents the researcher with a variety of potential psychological mediators and moderators of the effects of stressful life experience on the immune system. This is an elegant theoretical framework that has been utilized in a highly successful way in health psychology to predict a variety of disease outcomes. However, the use of such psychological models in psychoneuroimmunology, with the large number of potential immunological outcomes, has resulted in an immense two-dimensional space of potential relationships, with one-dimension representing all the possible psychological variables relevant to stress (e.g., threat, anxiety, optimism, active coping) and the other representing the large range of potential immune processes that can now be studied in humans.

The sheer magnitude of possible relations between psychological and immunological factors gives rise to a number of questions. Which psychological processes play a critical mediating role between stressor exposure, for example, and immune alteration? Is it essential that an individual experience a specific form of distress in order for an alteration in immune activity to occur or are all forms of distress equal? In other words, would immunologic differences be expected in those who respond with depression versus anxiety versus passive coping vs denial? Which immune processes are most vulnerable to these effects? What specific neurophysiological pathways support these relationships?

What kind of conceptual organization will promote research in this area and help to focus questions given this large array of possible mind-immune interactions? One approach that my colleagues and I have found useful in developing a psychological model for studies in psychoneuroimmunology is to base it on models of animal behavior and then to build onto that base the cognitive "architecture" that is available to humans as a result of their more complex frontal brain structures. Humans, for better or for worse, have highly nuanced perceptual abilities that allow them to perceive and construe a given context in a wide variety of ways and to be relatively unconstrained by the actual parameters of a context. For example, those individuals more sensitive to rejection can experience feelings of rejection and their neurobiological correlates in a neutral non-rejecting social context, as described in more detail below. In other words, the human brain allows for a great degree of latitude in psychological response to stressors as well as more benign contexts. It is critically important to understand how cognitive processes and resulting emotional states influence peripheral biology including the immune system, to map the neural substrates of these relations and to develop methods for intervening at the psychological level to improve physiological functioning and health (Kemeny, 2003b).

2. Social status threat as a social psychological model in psychoneuroimmunology

One animal model that captured my attention in 1983 while a graduate student was defeat. A professor recommended that I read a newly published article in *Science* on the effects of "defeat" on opioid analgesia, which contained a picture of the "defeated mouse in characteristic posture" (Miczek et al., 1982; see Fig. 1). This behavioral response was elicited in a social confrontation paradigm following repeated attacks. The authors concluded based on their findings that "the special biological significance of the defeat experience, and not simply the experience of being stressed, is critical to the occurrence of opioid analgesia" (p. 1522). I was struck by the potential for an important human analog to this psychobiological response and its application in the field of psychoneuroimmunology. And at the same time, this work called into question for me the notion that all behavioral and physiological responses to stressful situations are identical and can be considered equivalent to Cannon's fight-flight response (Cannon, 1929), since the fight-flight behavioral response is clearly distinct from the defeat-related response. It is interesting that a single article (and image) can trigger a series of questions that then form the basis for a central component of a research program.

A great deal is now known about what elicits defeat and analogous behaviors in animals as well as the neurobiological and peripheral correlates of this response. But what is the human analog? Is it clinical depression, as has been described? Or is defeat a model of something more fundamental that is an important ingredient of human clinical depression but also occurs outside this particular affective context? What might elicit this defeat response in humans? In what contexts would it be adaptive? What are the neurobiological effects of this response? And would some immunological changes induced in this context function as a critical part of that adaptive response to the social context or are such changes merely side effects of the neural and hormonal responses induced? How might we differentiate the fight-flight response from a defeat

Fig. 1. Defeated mouse in characteristic posture (Miczek et al., 1982).

response on the basis of elicitors, behavior and neurophysiology in humans?

Our current work is directed towards understanding the psychological and biological effects of threats to social status and social esteem in humans, building on animal models of social subordination and defeat (Dickerson et al., 2004a; Gruenewald et al., 2006a). We suggest that exposure to an uncontrollable social threat can elicit a set of psychological, behavioral and biological changes that support disengagement and withdrawal. We are interested in defining the physiological substrate for the disengagement component of this behavioral response to social status threat and determining the long-term physiological and health consequences of persistent social status threat.

Humans are social animals and are profoundly influenced by their social interactions. They share a fundamental motive to maintain social connection including social status, value and acceptance (Baumeister and Leary, 1995). Situations that threaten one's social status include those that devalue the individual in the eyes of others, demean one's social image or standing by, for example, devaluing one's competencies, traits or abilities or contain potential or explicit rejection (Gruenewald et al., 2004). Rejection, negative social evaluation, stigmatization and discrimination are experienced as aversive because they reflect a lack of social value or status (Baumeister and Leary, 1995). Threats to ones social connection or status can have a variety of adverse effects psychologically and physically, and have been shown to be associated with specific patterns of physiological change in animal models and in human studies (e.g., Cacioppo et al., 2006). Persistent activation of these physiological responses, occurring in the context of chronic social status threat, can have health consequences. Thus, such individuals may be more vulnerable to disease, in part, because of their chronic exposure to social threats (Dickerson et al., 2004a,b).

What is the psychology of social status threat in humans? An individual experiences social status threat in *contexts* that involve social devaluation, for example in response to discrimination, stigmatization and rejection (see Fig. 2). The *cognitions* associated with exposure to social status threat involve the perception of being evaluated negatively by others. Individuals who are repeatedly exposed to threats to their social status are more likely to have negative social perceptions, i.e., perceiving a given social context as threatening to one's social value or status. These entrained negative social perceptions may lead to expectations of negative evaluation even in an ambiguous or benign context. For example, chronically rejected individuals have a lowered threshold for perceiving negative social interactions and more intense emotional reactions in those contexts (Downey et al., 2004). Exposure to more negative social contexts over a lifetime should increase these psychological responses to both negative and neutral or ambiguous social contexts (see Chen et al., 2006; Gruenewald et al., 2006a,b). *Individual difference factors* that appear to sensitize the individual to such threats include "sensitivity to rejection" and "fear of negative evaluation", among others (Gruenewald et al., 2006a,b; Dickerson and Kemeny, 2004). These individual differences factors play a critical role because they shape the cognitive appraisal of the social context such that even benign, neutral or ambiguous contexts can be appraised and responded to as a social threat. Prolonged exposure to social status threats, as occurs in individuals with low socioeconomic status or a stigmatized identity (e.g., based on race), or increased sensitivity to such contexts can create a biological vulnerability with health consequences (see below). A key question we are addressing is whether the same pattern of physiological arousal will occur in a relatively benign context appraised as threatening as in the context of an actual social threat.

3. Psychological predictors of HIV progression

Some of our work on individual difference factors predicting the rate of HIV progression supports the notion that social devaluation can impact health and that certain psychological characteristics that shape appraisal of the social world can enhance these effects. In early work, we examined predictors of HIV progression in HIV positive gay and bisexual men. This group has two stigmatized characteristics, their sexual identity and their HIV status, and are at risk of social status threat and devaluation as a result. One of our first indications that such social status threat might have health implications came from a study spearheaded by Steve Cole

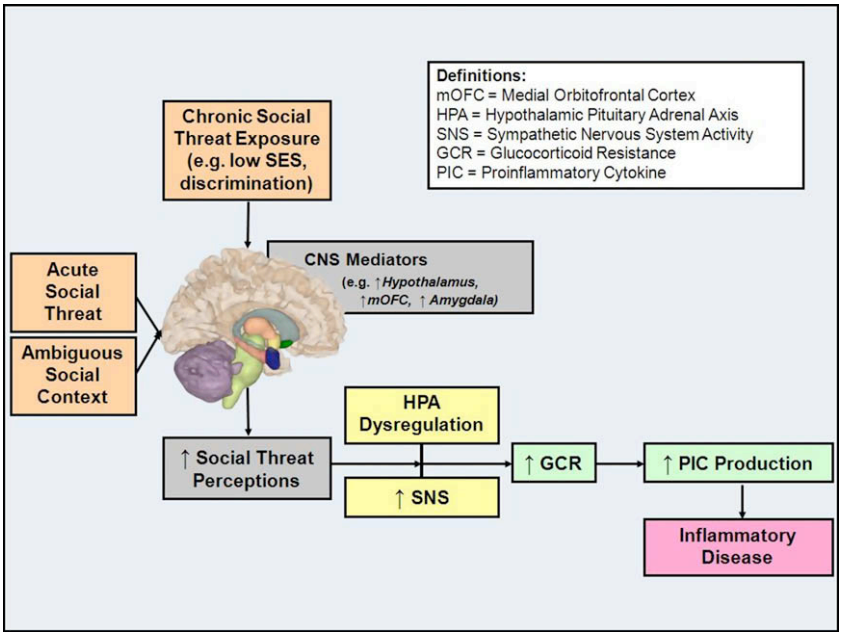

Fig. 2. Social threat conceptual model. Chronic social threat exposure, such as discrimination, devaluation or rejection, creates a neural sensitivity to acute social threat experiences as well as ambiguous social contexts, such that neurohormonal pathways (HPA, SNS) become more easily activated, resulting in GCR, increased production of PICs over time, and enhanced risk for inflammatory activity and disease. Social threat perceptions mediate these effects.

when he was a post-doctoral fellow in my research lab. He found that rates of HIV progression differed over a 9-year follow-up period in HIV positive men "in the closet" about their homosexuality (Cole et al., 1996a) as well as those more sensitive to rejection around their homosexuality (Cole et al., 1997). These are two inter-related manifestations of sensitivity to social evaluation and rejection. The rejection sensitivity findings were particularly striking, with those higher in sensitivity to rejection demonstrating significantly increased rates of CD4 T cell decline, onset of AIDS and mortality over a 9-year follow-up (see Fig. 3). Highly rejection-sensitive individuals died on average 2 years earlier than their less rejection-sensitive counterparts. All individuals were asymptomatic at the baseline assessment, and analyses in this study and our others controlled for baseline immune status, and confounding factors including demographics, medical treatment, and health behaviors that can influence disease progression as well as other psychological factors such as depression, coping, etc. Choosing to conceal homosexuality (being in the closet) also predicted greater levels of disease in an HIV negative sample, including greater rates of infectious disease (Cole et al., 1996b).

A series of additional studies of predictors of HIV progression were conducted during that time that included measures that capture self-relevant constructs such as self-devaluation in various samples of HIV positive, gay men. For example, in one study, Suzanne Segerstrom, when she was a graduate student in my research lab, coded interviews about methods of coping with HIV using a coding process that involved differentiating various forms of attributions of blame for negative events. One form of negative attribution assumes that the cause of the negative event is a negative and stable attribute of the self. This form of attributional style has been shown to predict negative psychological states including depression as well as adverse health outcomes in non-HIV infected samples. Those HIV positive men in our sample who attributed negative events in their lives to characterological aspects of themselves (traits that are difficult to change) showed a steeper decline in CD4 T cells levels over time compared to individuals with other, less deleterious forms of attributions (Segerstrom et al., 1996). In studies of two other subject samples, the negative self or self-reproach items in a depression inventory predicted CD4 decline while other components did not (e.g., Kemeny and Dean, 1995), suggesting the possibility that negative cognitions related to the self may be a potent component of depressive thinking processes as they relate to physiology.

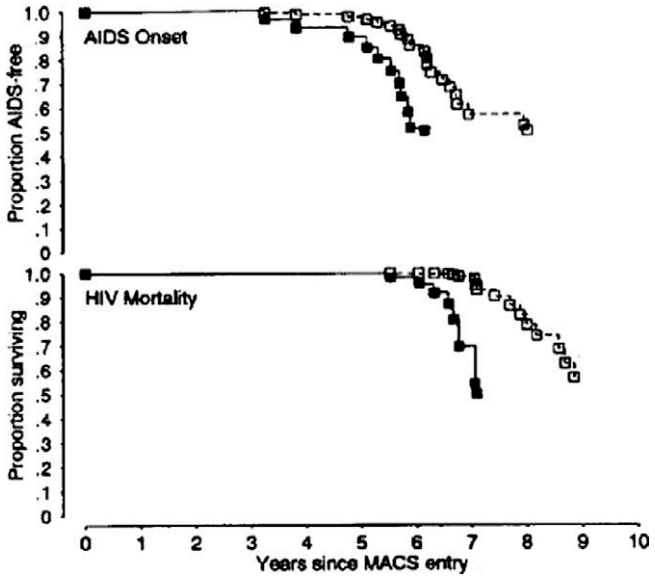

Fig. 3. Times to AIDS onset and HIV-related mortality for gay men at the 75th percentile (closed points) and the 25th percentile (open points) on homosexuality-specific rejection sensitivity. Values come from Cox proportional hazards regressions controlling for all biobehavioral covariates, and estimates are truncated at median event time to facilitate comparison and to avoid extrapolation beyond observed data. MACS, multi-center AIDS Cohort Study (Cole et al., 1997).

In another sample of HIV positive gay men, Cole and our group found that rejection sensitivity predicted elevated HIV viral load and poorer virologic and immunological outcomes in response to treatment (Cole et al., 2001, 2003). Specifically, viral load was elevated 8-fold in rejection-sensitive individuals in comparison to those without this trait. All individuals began highly active antiretroviral therapy (HAART) medication during a 1-year follow-up period. Those with higher levels of rejection sensitivity at entry into the study showed a significantly weaker response to the medication, with less reduction in viral load and CD4 T cell recovery, controlling for potentially confounding factors. In addition, rejection-sensitive individuals had higher levels of autonomic nervous system (ANS) activity (at rest and in response to a variety of laboratory provocations) and ANS activity mediated the relationship between this trait and viral outcomes. *In vitro* work by Cole confirmed that norepinephrine can enhance replication of the CCR5- and CXCR4-tropic strains of HIV-1 as well as viral gene expression (Cole et al., 2001), suggesting direct effects on viral replication (see Cole and Kemeny, 1997, 2001 for review).

What emerges from these studies is that view of the self and individual differences in perception of one's social status or regard by others can predict virologic and immunologic processes and disease outcomes over and above the effects of medical and behavioral factors. These data support the importance of cognitive processes in shaping individuals' responses to the social environment.

4. Human experimental models of social status threat

In the HIV work, we began to see a consistent set of relationships among social status or social esteem threats, individual difference factor related to sensitivity to social context, and physiological responses that facilitate HIV progression. However, it is difficult to understand the nuances of these psychobiological relationships in studies of complex diseases using longitudinal designs. In the next phase of work on this topic, we took an experimental approach to address some fundamental questions, attempting to build on animal models of submissive behavior and subordinate rank. Based on animal work, we proposed that uncontrollable social threats would influence a set of inter-related neurobiological processes resulting in: activation of the hypothalamic-pituitary axis (HPA) and release of cortisol, increased production of pro-inflammatory cytokines and increases glucocorticoid resistance. I have worked with two individuals, Sally Dickerson and Tara Gruenewald, who were graduate students in my research lab at UCLA, on conceptualizing the psychobiological effects of threats to social status and studying their physiological effects and cognitive and affective mediators. We conducted a series of experimental studies comparing the effects of an uncontrollable social threat task to an identical stress task without a social component in order to focus in on the psychological and biological consequences of uncontrollable social threat.

4.1. Social threat and HPA activation

There is emerging evidence from animal studies that subordinate rank in a social status hierarchy confers a set of physiological risks including activation of the HPA, particularly in species where high-ranking animals maintain dominance through social rather than physical intimidation, where hierarchies are more stable, and where low rank means greater exposure to social stressors (Sapolsky

et al., 2002; Sapolsky, 2005; Cavigelli, 1999; Eberhart et al., 1983), as is the case in humans. A common pattern of physiological reactivity in subordinate animals is greater HPA reactivity, which translates into greater basal cortisol levels, a slower response to challenge, and impaired sensitivity of the HPA to negative feedback regulation (Sapolsky, 2005). These effects are thought to reflect the persistent exposure to social stressors coupled with limited coping resources (Abbott et al., 2003). Indeed, primates who are poor at distinguishing between threatening and neutral stimuli have elevated basal cortisol (Ray and Sapolsky, 1992).

While a variety of stressful events can activate the HPA in humans, we showed that acute *social* threats are reliable and powerful elicitors of HPA activation. In a meta-analytic review of 208 acute laboratory stress studies, Sally Dickerson and I found that contexts in which individuals were subjected to negative social evaluation during a relatively uncontrollable motivated performance task, were associated with substantially greater cortisol responses compared to similar stressful tasks without this social evaluative component (Dickerson and Kemeny, 2004). Exposure to uncontrollable social evaluative threat was also associated with slower recovery of cortisol to baseline levels (see Fig. 4). We also confirmed earlier studies in animals that uncontrollable tasks overall elicit greater activation of the HPA than controllable tasks. These findings were interesting to us, in part because they tended to challenge the prevailing notion, introduced by Selye (1956), that the HPA responds non-specifically to all types of stressors. We found that many highly distressing types of experiences, such as watching gruesome films, had no impact on levels of cortisol. Neither did engaging in difficult tasks. We found instead that the system is more selectively activated, with social evaluative threat one consistent and strong elicitor.

This link between uncontrollable social threat and HPA activation was confirmed in a laboratory study, conducted by Tara Gruenewald and our group, comparing performance on stressful tasks with or without social evaluative threat (SET). SET involved the presence of others during the performance tasks. The SET condition elicited more negative self-appraisals and self-conscious emotions and greater HPA activation than the condition that included the same difficult tasks without SET (Gruenewald et al., 2004; see Fig. 5). Cortisol increases were greater in participants who experienced greater increases in negative self-related appraisals and emotions in response to the task, but were unrelated to levels of distress, depression, anxiety, etc. In addition, "subjective" social status defined in relation to a proximal group moderated the impact of social evaluative threat on cortisol levels (Gruenewald et al., 2006a,b).

4.2. Social threat and inflammation

Homeostatic maintenance of immune activation is critical to maintaining an individual's health. There is a bidirectional communication between the host immune system and the HPA axis mediated by soluble steroid hormones and cytokines (e.g., Mulla and Buckingham, 1999). Glucocorticoids represent important regulators of the development, homeostasis, effector functions and cellular trafficking of the innate and adaptive immune system (e.g., Sternberg, 2001). Cortisol exerts its effects by signaling through the glucocorticoid receptor. While glucocorticoids are not always anti-inflammatory, disruption of the neuro-immuno-endocrine loop by hyper- or hypo-activation of the HPA axis can cause systemic changes in inflammation (Webster et al., 2002) It is important to understand factors that contribute to inflammatory up-regulation because inflammatory processes play a significant role in a variety of diseases, including cardiovascular and autoimmune, as well as in aging (Gémes et al., 2008).

Animal studies have demonstrated that social status disruption is associated with increased production of pro-inflammatory cytokines (PIC) and decreased sensitivity of immunologic cells to down-regulation by glucocorticoids, such as cortisol (i.e., glucocorticoid resistance; GCR). Links have been demonstrated between social status threat exposure, GCR and PIC production in a mouse model of social disruption (SDR), for example. Socially defeated mice showed activation of the HPA and SNS (Engler et al., 2005) as well as an increase in glucocorticoid resistance in splenocytes (Avitsur et al., 2001; Bailey et al., 2004; Stark et al., 2001). SDR mice also showed increased levels of IL-1 and IL-6. The glucocorticoid resistant animals had higher PIC responses in the spleen, liver and other organs (Quan et al., 2001). This research suggests the importance of GCR as a mediator of the effects social status on inflammatory end-points. Other animal models have also demonstrated increased production of PIC with social threat.

We have been interested in determining whether acute and chronic social threat and their cognitive and affective consequences can impact inflammatory processes in humans. Sally Dickerson and our group conducted an experimental study in which negative self-conscious thoughts and feelings were induced to determine if this induction was sufficient to elicit an increase in inflammatory cytokine levels (Dickerson et al., 2004a,b). Subjects engaged in writing activities designed to promote either negative self-cognitions/emotions or neutral cognitions/emotions on three separate days in the lab. TNFα receptor levels were measured from oral mucosal transudate that derives from serum; TNFα receptor levels correlate highly with TNFα levels in serum. The negative self-blame condition induced significantly increased levels of TNFα receptor on each experimental day compared to the neutral condition. Higher levels of negative self-related psychological responses were associated with larger increases in TNFα receptor levels; there were no associations with other psychological responses such as anxiety.

We then determined whether experimental induction of social threat could increase production of pro-inflammatory cytokines

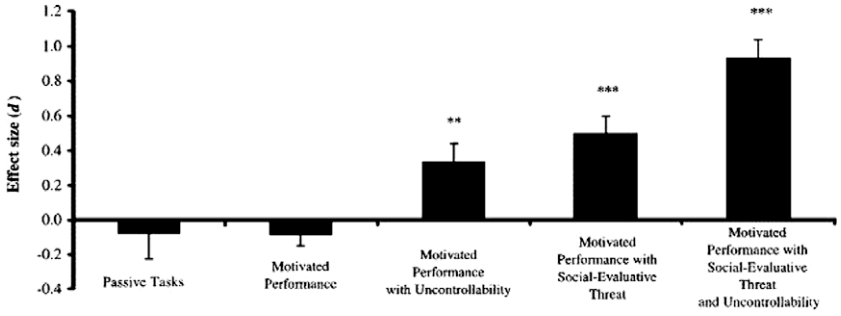

Fig. 4. Mean (±SEM) cortisol effect size (*d*) for studies using passive tasks ($k = 21$), motivated performance tasks ($k = 24$), uncontrollable motivated performance tasks ($k = 69$), motivated performance tasks with social-evaluative threat ($k = 43$) and uncontrollable motivated performance tasks with social-evaluative threat ($k = 51$). $^{**}p < 0.01$. $^{***}p < 0.001$ (Dickerson and Kemeny, 2004).

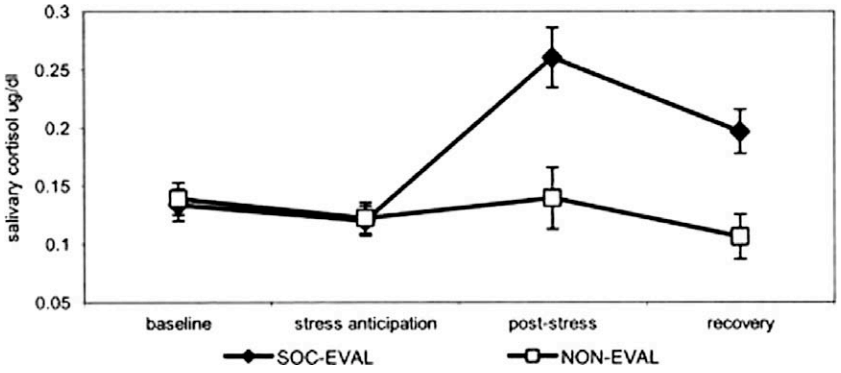

Fig. 5. Mean (±SE) salivary cortisol values in SOC-EVAL and NON-EVAL stressor conditions across the session. In the *SOC-EVAL condition* of the study, participants were informed that they would perform the activities in front of a panel of evaluators who would judge their performance, while participants in the *non-evaluative (NON-EVAL) condition* were informed that they would perform these activities while alone in the room. The set of challenging and demanding laboratory tasks that the participants were instructed to perform included having to give a 5-min speech and then perform a 5-min mental arithmetic task on a computer. The tasks represent a modified version of the Trier Social Stress Task (TSST; Gruenewald et al., 2004).

from mononuclear cells, and whether this context could also induce glucocorticoid resistance, thus providing a mechanism for persistent inflammatory activity. In a study conducted by Sally Dickerson and our group, subjects were exposed to an experimental SET task—a context that involved either performing stressful tasks with an evaluative audience or performing these stressful tasks without the evaluative audience (Dickerson et al., submitted for publication). All participants showed increases in measures of ANS activity—blood pressure, and heart rate—with no differences across conditions, suggesting equivalent engagement with the tasks. We found that pro-inflammatory cytokine production (TNFα) by peripheral blood mononuclear cells increased from pre- to post-stressor in the social threat condition, with effects maintained at the 40 min recovery point, but no changes in the condition without social threat. The changes in TNFα production correlated with cognitive appraisals of social evaluation but not with other psychological responses to the tasks (e.g., task difficulty), suggesting that perceptions of social threat may be a key mediator of these effects. In addition, those in the SET condition showed increased glucocorticoid resistance, demonstrating decreased sensitivity to the suppressive effects of glucocorticoids on TNFα production compared to those in the non-SET conditions. These results indicate that TNFα production increases with exposure to a social threat, and that this inflammatory response may be tied to social threat perception. They also demonstrate that social threat can induce glucocorticoid resistance acutely, which may serve to promote persistent inflammatory activity (see also Buske-Kirschbaum et al., 2007; Steptoe et al., 2007 for lab studies and Cole et al., 2007; Cole, 2008; Miller et al., 2002 for studies of GCR and chronic threat).

In these and other studies, we have found that social threat exposure and perceptions of social threat can activate the HPA, induce elevations in pro-inflammatory cytokines and contribute to resistance of inflammatory cytokine producing cells to the anti-inflammatory effects of glucocorticoids. It is possible that chronic HPA activation, for example in the context of persistent social threat, causes an "adaptive" down-regulation of the glucocorticoid receptor, rendering glucocorticoids unable to exert their anti-inflammatory effects. These effects could then leave individuals more vulnerable to inflammatory disease (Kemeny et al., 2004). We have also shown that individual difference factors that capture sensitivity to social threat or neutral social contexts, such as fear of negative evaluation and rejection sensitivity, predict up-regulation of these and other related immunological systems (see also Cole et al., 1999).

We argue that induction of pro-inflammatory cytokines in the context of social threat in humans may contribute to adaptive forms of disengagement behavior as are observed in subordinate animals and humans confronting an uncontrollable social threat (Dickerson et al., 2004a,b; Kemeny et al., 2004). It has become clear that these cytokines act on the brain causing what is known as "sickness behavior", i.e., inducing increases in sleep and decreases in social, sexual, aggressive, exploratory and other behaviors. Careful animal work has shown that these behavioral changes are not a function of weakness or incapacitation, but represent a motivational shift away from fight and flight for example, towards behavior that would support recuperation (Dantzer et al., 2008). This behavioral disengagement appears to be an adaptive response that allows the organism to conserve energy and, thus, maximize recuperative physiological processes (Maier and Watkins, 1998; Dantzer et al., 2008). There is also increasing evidence that these cytokines play a role in inducing depressive behavior in animal models and in human clinical depression (Raison et al., 2006; Pollak and Yirmiya, 2002).

These cytokines may also be induced in contexts of social status threat to promote disengagement behavior. For example, cytokine-induced behavioral withdrawal would be an adaptive response for a subordinate animal confronting a dominant aggressor. The link between cytokine production, GCR and submissive and defeat behavior has already been demonstrated in animals (e.g., Avitsur et al., 2001). Also, animals injected with PIC have been shown to display no offensive behavior in an aggressive encounter but only elements of defensive behavior (e.g., upright defensive posture, submissive posture; Cirulli et al., 1998). Our findings demonstrating a correlation between SET-induced self-reports of the self-conscious emotion shame and PIC levels support this hypothesis, since shame and submissiveness share commonalities in terms of behavior (e.g., shrinking, head down, gaze avoidance, slumped posture), elicitors (social self-threat) and motivation (the motivation to disengage or withdraw; Gilbert, 1997; Gruenewald et al., 2006a,b; Keltner and Buswell, 1996). Thus, the pro-inflammatory cytokines and GCR induced in response to uncontrollable social threats may be one part of the physiological response subserving an adaptive behavioral disengagement. Another inter-related part may be persistent activation of the HPA, as has been described Henry and Grim (1990), who showed that "passive coping" in rodents was associated with activation of this system. Our overall notion here is that stressors do not have uniform effects on physiology, and, instead, that "organisms meet challenges and dangers by integrated behavioral, phys-

iological patterns of response that are appropriate to the task" (Weiner, 1992).

5. The consequences of manipulating cognition to promote health

One critical area in psychoneuroimmunology is the study of interventions designed to enhance immune system functioning and health via neurobiological mechanisms. It is important to translate our understanding of linkages between psychological factors and physiological responses in order to promote physical health (Bower et al., 2002; Kemeny and Miller, 1999; Carrico and Antoni, 2008). A major thrust of our work is aimed at determining whether modification of important cognitive processes can alter physiological responses and health. We have been working in this area using a variety of experimental paradigms, intervention trials, experimental manipulations of specific intervention ingredients and cross-sectional and longitudinal investigations of potentially beneficial mental processes. As above, we are interested in the role that alterations in cognitive processes may play in impacting the immune system and health.

In a study conducted in conjunction with Fawzy and Fahey, we tested the impact of a cognitive-behavioral intervention on immune processes and health in patients with malignant melanoma. The intervention had a number of components but emphasized reductions in maladaptive cognitive processes. The 6 week group intervention, compared to a control group, increased numbers of CD16 and CD56 natural killer (NK) cells and enhanced the function of NK cells, by increasing their responsiveness to cytokine signals (see Fig. 6; Fawzy et al., 1990). In addition, the intervention resulted in reduced mortality over a 6-year follow-up period (Fawzy et al., 1993), suggesting that cognitive modification can have immunologic and health effects.

In a recent study, my colleagues and I examined the biological effects of a placebo medication in the context of asthma. There is a resurgence of interest in placebos—which are inert substances provided with the expectation of efficacy—and their physiological and health effects (e.g., Pacheco-Lopez et al., 2006). This is a tremendously useful method for understanding whether cognitions can affect biology, as long as other methodological issues are addressed. These placebo studies are fascinating because they uncouple the biological effects of a drug from the effect of the cognitive expectation associated with the giving of a medication in a medical encounter. A large literature suggests that placebos can have significant effects on subjectively experienced outcomes, such as pain and depression. However, there has been skepticism about whether or not placebos are capable of altering objectively defined peripheral, health relevant bodily systems (Hróbjartsson and Gøtzsche, 2001). My colleagues and I utilized a randomized, double blind cross-over design with mild asthmatics that involved 6 visits to the test this question. Mild asthmatics were randomized to placebo or active drug and all patients received a series of methacholine challenges to measure airway hyper-responsiveness to a lung irritant-methacholine. Placebo bronchodilator administration by a physician significantly reduced non-specific airway hyper-responsiveness following methacholine challenge compared with reactivity at baseline. Effects of placebo were almost twice that observed in the screening sessions. Thus, positive cognitive expectancies delivered in a social context, can have clinically relevant effects in an objectively defined health relevant peripheral system (Kemeny et al., 2007).

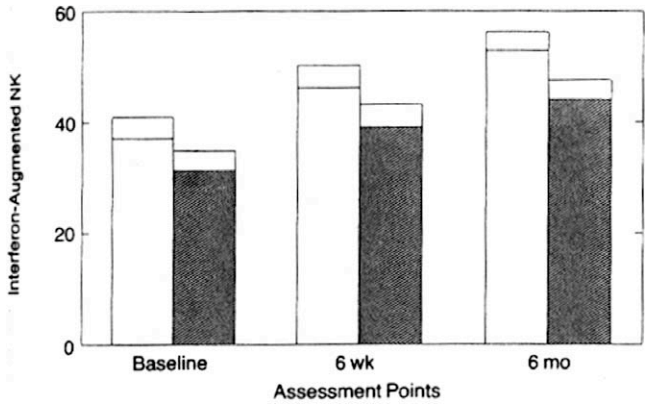

Fig. 6. Interferon alfa-augmented natural killer cell (NK) activity (percent lysis of target cells at 25:1 effector target cell ratio) at baseline, 6 weeks, and 6 months in the intervention-group (light bars) ($n = 17$) and control (dark bars) ($n = 16$) patients, with the unshaded portion of bars indicating SE (Fawzy et al., 1990).

In related work on disease-relevant expectancies, we have shown that negative expectancies about future disease course predicted the course of HIV-related symptoms (Reed et al., 1994) and mortality (Reed et al., 1999) in samples of HIV positive individuals, controlling for potential confounding factors as well as more general mood and cognitive states. We have also conducted a number of studies demonstrating immunological correlates of dispositional forms of positive expectancies. For example, we have shown that more dispositional forms of positive expectancies predict changes in natural killer cell cytotoxicity in the context of acute and persistent stressors (Cohen et al., 1999) as well as the stress of the first year in law school (Segerstrom et al., 1998).

We have also attempted to identify the psychological processes that influence and potentially reduce negative cognitions and their biological correlates, thereby serving as potentially effective ingredients in interventions. One specific psychological process that has been under investigation is "cognitive processing", which involves actively thinking about a stressor, the thoughts and feelings it evokes, and its implications for one's life and future. Cognitive processing is a central component of many forms of psychotherapy. Julie Bower, while a graduate student in my research lab, found that those HIV seropositive individuals who engaged in cognitive processing and related processes with regard to their HIV infection showed a reduced rate of CD4 T cell decline and lower rates of AIDS-related mortality, independent of health status at baseline, health behaviors and other potential confounds (Bower et al., 1998). She found a similar relationship between a related construct and natural killer cell activity in a healthy sample of women following a major traumatic event (Bower et al., 2003). These findings are supported by a study conducted by Naomi Eisenberger, while a student in my lab, in which she showed that inhibition of cognitive and affective processing of emotional experience was associated with lower CD4 T cells in a multi-ethnic sample of HIV positive women (Eisenberger et al., 2003). These findings suggest that greater awareness of one's cognitive reactions and their impact may support reductions in deleterious thought processes with beneficial consequences.

6. Future directions

My research group continues to be interested in three areas. First, we are interested in continuing to define the psychological and physiological responses to social status threats with an emphasis on inflammatory processes and disease. We are currently engaged in neuroimaging studies to determine the neural processes underlying the link between social perceptions and these peripheral systems.

Second, we are interested in comparing the social status threat model with other important psychobiological responses that have been defined in the animal literature. Research has defined at least three separable behavioral responses to social stressors: submissive/social defeat, defensive behavior and aggressive behavior. Some argue that defensiveness can be further differentiated into defensive approach, which can be considered to be overlapping with anxiety, and defensive avoidance, which may be indicative of fear (Cooper and Huhman, 2007; McNaughton and Corr, 2004). While there are studies of human variants of each of these animal behavior patterns, there has been little effort to compare them to each other to determine if in fact there are distinctive central and peripheral activation patterns that subserve the distinctive needs and adaptive responses underlying each response. It also seems important to incorporate assessment of *positive approach* responses which are associated with promoting motivation and physiological homeostasis as well as resource building, mobilization and conservation (see Kemeny and Shestyuk, 2008). Our group is interested in beginning to compare the social status threat model with other behavioral responses in order to tease out distinctive patterns of elicitors, cognitive and affective responses, as well as the neural and peripheral changes associated with each of them.

Third, we continue to be interested in pursuing the limits of the ability of cognition to influence and control peripheral systems, both in terms of activating peripheral systems that control inflammation as well as modulating these systems in order to constrain their negative impact. We have a number of intervention studies underway in different samples, with the aim of further understanding the potential value of modifying cognitions and their affective sequelae to alter neurobiological pathways central to health.

Acknowledgments

I have been very fortunate in my career to have worked closely with some incredibly creative and inspiring people. First, I thank the students who I have had the honor and pleasure of working with including: Julie Bower, Steve Cole, Sally Dickerson, Naomi Eisenberger, Tara Gruenewald, Gregory Miller, Suzanne Segerstrom and others. One of the most gratifying aspects of my career has been the opportunity to be able to play a role in the development of young scientists. I thank my mentors: Frances Cohen and Paul Ekman while a graduate student in health psychology at UCSF, and John Fahey and Herbert Weiner while a post-doctoral fellow at UCLA in immunology and psychoneuroimmunology, as well as my collaborator Shelley Taylor in much of the HIV work. I express my gratitude to Robert Ader and George Solomon for their advice, guidance and inspiration throughout my career. It has been an incredible experience to know these two remarkable pioneers who forged the path that we now follow.

Appendix A. Supplementary data

Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.bbi.2008.08.008.

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