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Does the Current Concept of Stress Explain PTSD

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Abstract

Understanding the etiology of stress-related diseases such as PTSD requires a more fundamental understanding of stress. Since individuals may differ strongly in their response to a stressor, it is argued that stress includes not only the stimulus and the response but also the individual appraisal of the situation. This chapter discusses the stress concept, how it has evolved in the course of time, and some important components of the appraisal process. In addition to the factors controllability and predictability, outcome expectancy and feedback of the victim's own actions during the traumatic event are suggested to be important factors in the development of stress-related disease. Preliminary preclinical studies suggest that individual differences in the way in which these factors are used in the appraisal of everyday life situations may explain individual vulnerability.

Introduction

The term post-traumatic stress disorder indicates that traumatic stress is the core causal factor of this debilitating psychiatric disease. In understanding the etiology of the disease, it is crucial therefore to understand what stress actually is. The paradox of stress is that, on the one hand, it seems self-evident and obvious when examined introspectively; on the other hand stress has been extremely difficult to define in objective scientific terms or parameters. Attempts to achieve a consensus definition that is accepted across all scientific disciplines have repeatedly failed. The concept of stress has been subject of scientific debate ever since its first use in physiological and biomedical research by the renowned Hungarian/Canadian physician Hans Selye (1950). Stress was originally defined as the nonspecific response of the body to any noxious stimulus. Later, the concept was refined by distinguishing between “stressor” and “stress response.” A stressor is considered a stimulus or event that threatens homeostasis, and the stress response is the reaction of the organism aimed to regain homeostasis (Chrousos 2009). Using these definitions, stress is in fact identical to the absence of homeostasis. The term “homeostasis” was originally coined by the American physiologist Walter Cannon (1932). In his work, he conceived that many physiological variables such as blood pressure, blood glucose, and intracellular osmolality have a certain preferred set point. A deviation of this set point is counteracted by physiological responses which are aimed at restoring the optimal level. Several authors have emphasized the ambiguity and circularity of the definition of stress in terms of homeostasis in general (Day 2005; Levine and Ursin 1991; Levine 2005; McEwen 1998; Romero et al. 2009). Virtually all activities of an organism directly or indirectly concern the defense of homeostasis. Hence, the definition of stress as the absence of or threat to homeostasis is almost meaningless and needs critical consideration in the light of the current knowledge of the systems involved.

Levine and Ursin (1991) emphasized the view that stress should be considered as a process that includes the stimulus, the perceptual processing or appraisal of this input, and the behavioral and physiological output. Still, many studies and preclinical studies in particular seem to neglect this aspect of cognitive, higher-level cortical processing of information. Also, the activation of the so-called stress

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systems such as the HPA axis and the sympathetic nervous system is not necessarily a sign of exposure to stress. These systems have an important function in the cardiovascular and metabolic support of any behavioral reaction to salient environmental challenges or opportunities. For example, the response of these systems to rewarding stimuli can be just as high as to aversive stimuli (Buwalda et al. 2012). Similarly, stress systems are highly activated during the use of drugs with a strong euphoric action (Goeders 2002). Hence, without taking perceptual processes into account, there is a serious risk of circular reasoning, i.e., the activation of physiological “stress” systems and/or measurement of “stress hormone” levels cannot be used as an indicator or even proof of stress exposure. Conversely, preclinical studies often define their stimulus as aversive, usually from an anthropomorphic line of reasoning, and interpret the myriad of physiological, neuroendocrine, immune, and neurochemical changes that occur in response to it as a stress response. In conclusion, there is a need for indices that allow an answer to the question whether a stimulus is indeed perceived as a stressor in the sense that it is considered a serious threat to homeostasis and thus to physical health and psychological and well-being. This chapter will discuss these perceptual processes in more detail.

In addition to the definition problem, there is the question of the adaptive and/or maladaptive nature of the stress response. In the original formulation of the general adaptation syndrome (GAS), Selye (1950, 1976) has emphasized the initial adaptive and restorative nature of the stress response. Several decades later, however, stress earned its evil reputation after the observations that during prolonged exposure to stressors, adaptation or resistance might fail and the organism may reach a phase of exhaustion with adverse health consequences. This concept of “diseases of adaptation” led many researchers to investigate the mechanisms and consequences of the stress reaction from a pathognostic perspective. As a result of this focus, the concept of stress became framed within the context of stress-induced pathology. Research has always struggled with this dual nature of the stress response. To distinguish between the maladaptive and the adaptive consequences of the stress response, the terms “distress” and “eustress” were introduced by Selye in 1976 (Selye 1976). Despite the fact that several authors have emphasized both the adaptive and maladaptive aspects of the stress response (Dallman 2007; De Kloet et al. 2005; De Kloet 2008; Korte et al. 2005; McEwen and Wingfield 2003), it appears notoriously difficult to dissociate these two sides of the coin. Obviously, the (mal)adaptive value of stress-induced behavioral and physiological changes strongly depends on the environmental challenges the organism may meet. This is now known as the match/mismatch hypothesis and will be discussed below.

Finally, it is important to realize that individuals may strongly differ in the way they deal with environmental challenges. A traumatic-like event will trigger post-traumatic stress disorder (PTSD) only in about 10–15 % of the individuals, despite exposure to similar uncontrollable, unpredictable, and potentially life-threatening situations (Creamer et al. 2006; Kessler et al. 2005). Similar percentages were obtained in a rat model of PTSD (Cohen and Zohar 2004; Cohen et al. 2004). The notion that the majority of the population is resilient to traumatic life events has led to a paradigm shift in preclinical stress research. It appears to be essential to dissociate susceptible from resilient individuals on the basis of predefined behavioral and physiological characteristics. Relatively few studies take this approach (Russo et al. 2012; Schmidt 2010). In addition to these experimental studies, there is accumulating evidence from a wide variety of species living in the wild that individuals may differ in their coping style (Koolhaas et al. 1999). Recent ecological evidence shows that these coping styles should be considered as individual adaptations to different environmental conditions. Resilience and vulnerability then become a matter of match or mismatch between coping style and environmental demands. This individual variation in coping style within a species has fitness value and apparently protects the species against fluctuations in the natural environment (Dingemanse and Wolf 2010; Sih et al. 2004). Understanding the individual susceptibility to stress-related disease such as PTSD may benefit from understanding of the biological basis of this individual differentiation in coping style.

Stress and the Appraisal Process

Controllability, Predictability

The terms controllability and predictability are central in the definition of a stressor. These terms date back to a series of elegant experiments by Martin Seligman, Stephen Maier, and Jay Weiss (Seligman and Maier 1967; Weiss 1972) in the late 1960s and early 1970s of the last century. Using a yoked control stress paradigm, these authors concluded that it is not the physical nature of an aversive stimulus that induces somatic diseases such as stomach wall erosions or behavioral disorders such as learned helplessness, but rather the degree in which the stimulus can be controlled and/or predicted by an individual. Although the concept of controllability and predictability has strongly contributed to the present insights in stress physiology and the development of stress-related pathology, there are a few problems with this concept. For example, there is a lot of evidence from the human literature that it is not the *actual* control that counts, but the *perceived* control (Salvador 2005). For preclinical studies this means that stimuli that are considered as stressors from the anthropomorphic point of view may not necessarily be stressors from the animal point of view. This raises the question how to objectively assess whether a stimulus is perceived as a stressor in terms of predictability and controllability. In a recent paper, we argued that an uncontrollable condition can be distinguished from a controllable one by the adrenaline response and the slow recovery of the activity of the HPA axis and the sympathetic nervous system (Koolhaas et al. 2011). This is illustrated, for example, in a comparison of the physiological response of rats that win a dominance fight with the response in the animal that loses the social interaction (Fig. 1). Although the magnitude of the corticosterone response is virtually identical, the recovery of the response takes almost twice as much time in the loser compared to the victor. The speed of recovery of the HPA axis response is determined by a delayed onset of negative feedback control mechanisms. This delayed onset includes a fast non-genomic action of glucocorticoids on neuronal excitability mediated by both mineralocorticoid receptors (MR) and glucocorticoid receptors (GR) (De Kloet et al. 2008). It is suggested that the stressful nature of a stimulus acts in particular through this fast glucocorticoid action. Also the magnitude of the cardiovascular response to winning and losing a social interaction is identical, but the difference is in the recovery

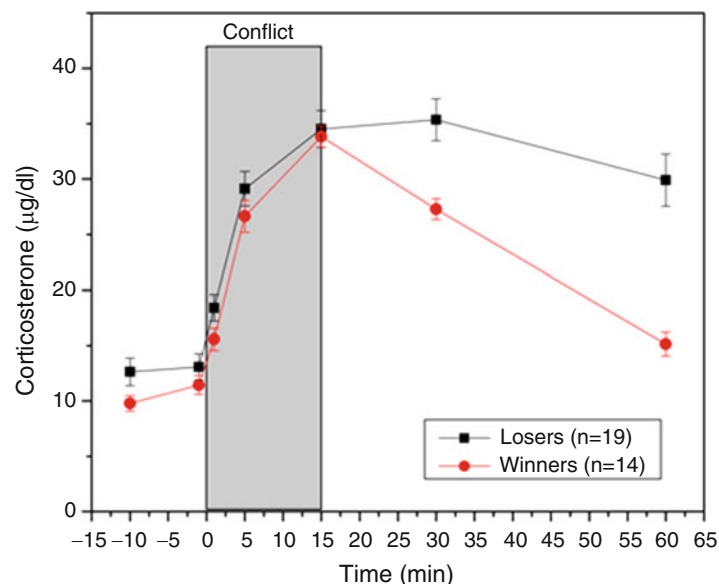


Fig. 1 Course of plasma corticosterone in male rats before, during, and after either winning or losing a social conflict. Animals were provided with permanently implanted jugular vein cannulas to allow undisturbed blood sampling during the social interaction

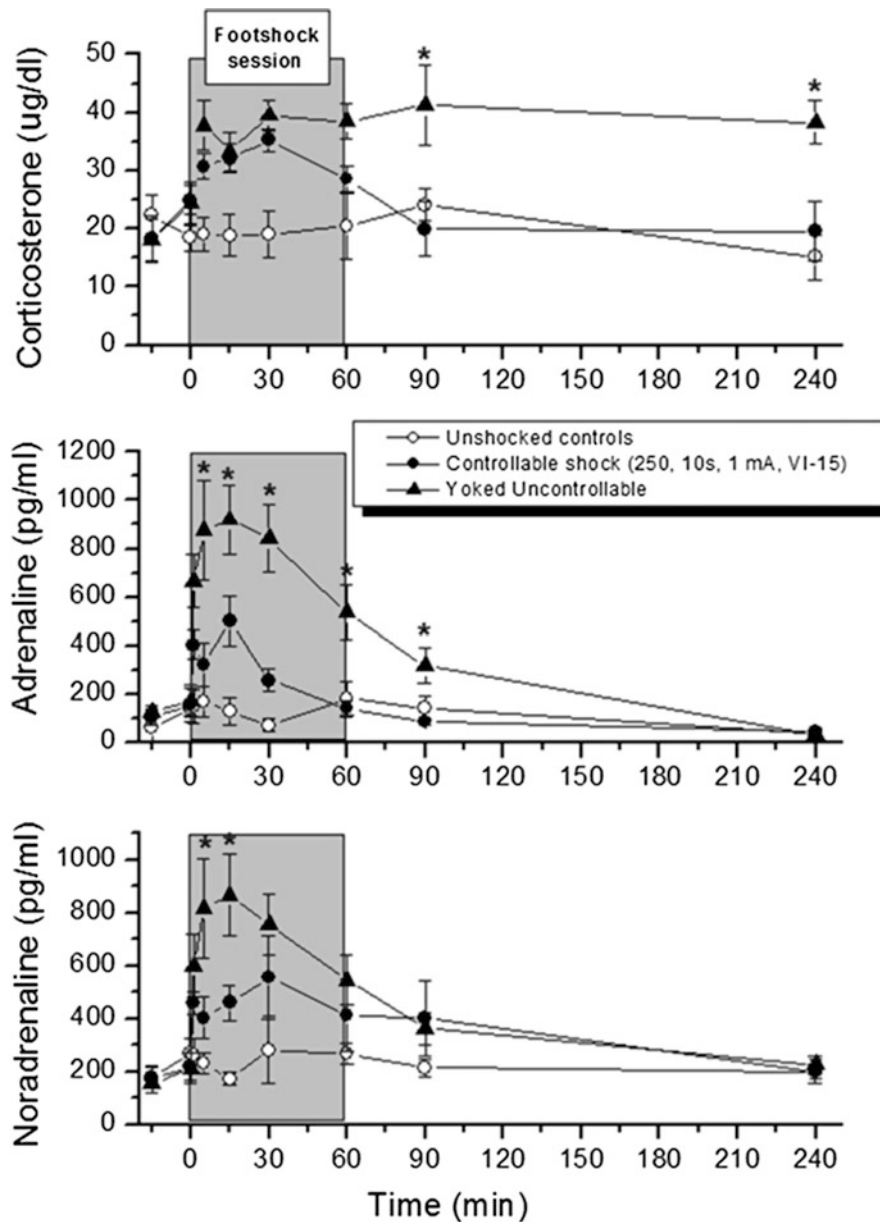


Fig. 2 Course of plasma corticosterone, adrenaline, and noradrenaline in a foot shock paradigm. Animals were either exposed to a situation in which they could switch off the shock (controllable) or a yoked control condition in which they received exactly the same amount of shocks as the controllable condition without having any control over it. The full control group did not receive any shocks (Swenson and Vogel 1983)

phase of this response. The defeated animal shows a delayed recovery. In carefully controlled experiments, it was shown that the uncontrollable condition is characterized by the release of adrenaline (de Boer et al. 1990). Using controllable and yoked uncontrollable foot shocks in rats, Swenson and Vogel concluded already in 1983 that a delayed recovery of the corticosterone response and the release of adrenaline characterize an uncontrollable aversive situation (Swenson and Vogel 1983). A graphic presentation of their original data is given in Fig. 2. We can conclude that a controllable environment can be distinguished from an uncontrollable situation by the angle of the downward slope of the physiological responses and the presence of an adrenaline response.

Regarding predictability, it is important to notice that natural selection has sculpted physiology and behavior to meet the most likely environmental demands plus a modest safety margin. Thus, a physiological response is not only an attempt to defend a set point but rather a response to some prediction. McEwen has addressed this issue in his seminal work on allostasis (McEwen and Stellar 1993; McEwen 1998; McEwen and Wingfield 2003). Allostasis is defined as the process of achieving stability through change in anticipation of physiological requirements (Sterling and Eyer 1988). Indeed, in anticipation of a challenging situation, strong anticipatory behavioral and physiological responses can be observed (Koolhaas et al. 2011). Hence, predictability can be assessed by the presence or absence of such anticipatory behavioral and physiological responses.

We may conclude that the use of the terms “stress” and “stressor” should be restricted to conditions and stimuli where predictability and controllability are at stake. Unpredictability is characterized by the absence of an anticipatory response. Loss of control may be reflected by a delayed recovery of the response and the presence of an adrenaline response. Both animal (Kvetnansky et al. 2013) and human researches (Esler 2009) have demonstrated that the presence of adrenaline co-transmission and the induction of the adrenaline-synthesizing enzyme PNMT in sympathetic nerves may be an explicit biomarker of a recurrent and/or chronic stress state.

A second problem with the concept of controllability and predictability is that they are generally operationally defined as binary factors, i.e., full control or complete absence of control often using strongly aversive stimuli. However, in everyday life situations controllability is graded from absolute control via threat to control to loss of control. For example, a dominant male may have full control in a stable social environment, but only partial control or may experience threat to lose control in socially unstable conditions. This condition in which a dominant male has difficulties to control the social environment (the executive monkey) leads to a cardiovascular type of stress pathology such as hypertension and cardiac arrhythmias (Ely and Henry 1978; Fokkema et al. 1995; Manuck et al. 1983; Sapolsky 1995). Thus, while controllability/predictability reduces the impact of environmental challenges to the body, very effortful and demanding coping might actually increase the effects of these challenging events. Hence it may be argued that effortful and demanding coping efforts exceed the normal ability to cope and actually represent non-coping in spite of the fact that the challenging event can be controlled. This graded degree of controllability and predictability in the development of stress-related pathology requires further attention.

Indeed, the term post-traumatic stress disorder already suggests dissociation between “normal” life stress and traumatic stress. This raises the question when a stressor becomes a traumatic stressor. Traumatic stressors are almost by definition unpredictable and uncontrollable severe life-threatening events (e.g., combat, assault, accidents, natural disasters, etc.). Apparently, we have to consider not only qualitative aspects in terms of uncontrollable/unpredictable stimuli but quantitative aspects as well. An individual’s appraisal of a situation and its reaction may vary from full control to only partial or complete loss of control. Moreover, a stressor may be mild in terms of its potential consequences or it may be life-threatening. A traumatic event that is life-threatening is likely to be uncontrollable and unpredictable. Obviously, such events robustly activate the main neuroendocrine stress-responsive systems (notably the HPA axis) that, although initially adaptive, can become deregulated (i.e., either prolonged hyper(re) activity or sustained hypo(re)activity) and may increase vulnerability for stress-related psychopathologies (e.g., depression, anxiety disorders, fibromyalgia, fatigue, burnout, PTSD). If one considers controllability and predictability as one factor, this leads in theory to a two-dimensional constellation with stressor intensity as the second dimension. The third factor or dimension will be the duration of the stressor.

Chronic Stress

The chronic character of stress is generally considered to be an important factor in the development of various forms of stress-related pathology. However, time may interfere in a rather complex way in the development of stress pathology. First, chronic stress in fact often consists of a series of intermittent exposures to stressors resulting in recurring stress responses. After a first exposure to a stressor, adaptive processes such as consolidation of memory processes (see below) are activated at the same time. This implies that the response to subsequent exposures to the same stressor might be the net result of both adaptive and maladaptive processes. Second, several studies show that merely the factor time after the first exposure to a stressor is sufficient to cause changes in behavior and physiology. In preclinical social stress models, it was shown that a single or double social defeat on two consecutive days is sufficient to induce changes in behavior and neurobiology that gradually develop within 3 weeks and that may last for many months (Kole et al. 2004; Koolhaas et al. 1997; Von Frijtag et al. 2000). Figure 3 gives an example of this phenomenon. Two defeats cause a reduction in the arborization of the apical dendrite of hippocampal pyramidal neurons 3 weeks later. Functionally, the reactivity of the neuron changes from long-term potentiation to long-term depression (Kole et al. 2004). Similarly, van Dijken observed progressive changes in behavior and HPA axis in the weeks following a single series of foot shocks (Van Dijken et al. 1992; van Dijken et al. 1993). This situation seems to be comparable to the PTSD patient, who often also experienced a single traumatic life event and seems to develop disease symptoms months and years later. The temporal dynamics in behavior and physiology after a traumatic life event is schematically

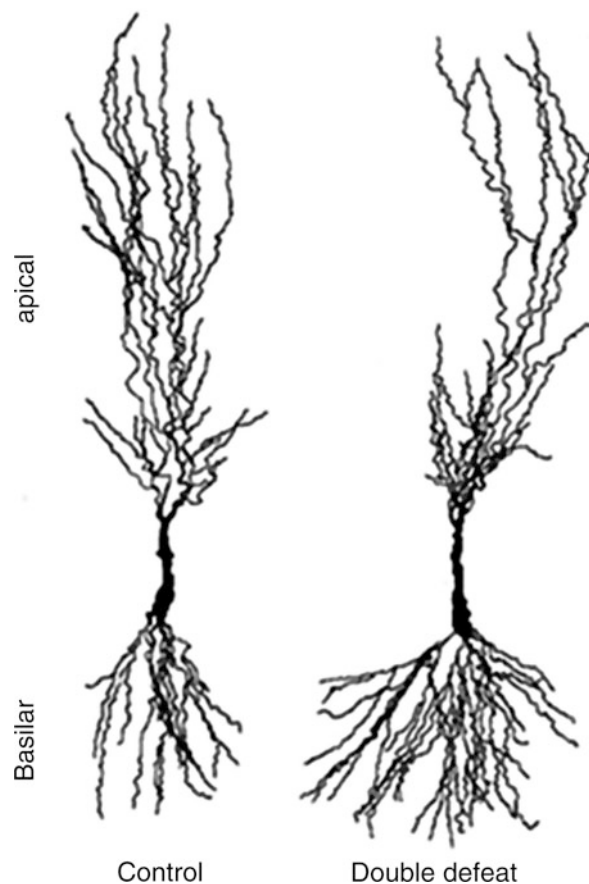


Fig. 3 Morphology of hippocampal pyramidal neurons of a male rat exposed to defeat on two subsequent days 3 weeks earlier and a non-defeated control. Animals were left undisturbed in the 3-week period between the social defeat and the analysis of the morphology (Kole et al. 2004)

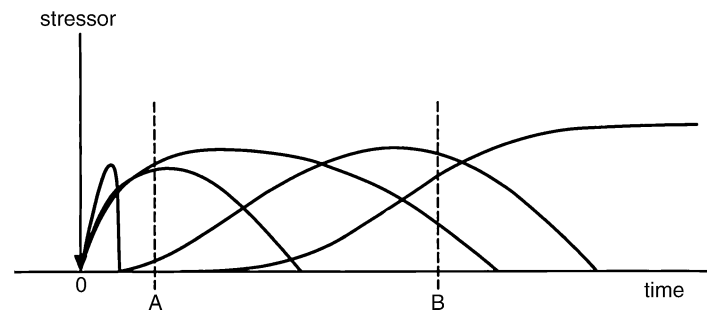


Fig. 4 Schematic presentation of the temporal dynamics of behavioral and physiological changes induced by a stressor

presented in Fig. 4. A more dynamic view of the response to a stressor implies that the set of symptoms measured at time point A will be different from the symptoms at time B. PTSD patients seem to get gradually trapped in a downward spiral. To understand these temporal dynamics, we may learn from the current views on the role of stress hormones in the neurobiology of learning and memory and the role of sleep. The two main stress systems, the hypothalamic-pituitary-adrenal (HPA) axis and the sympathetic-adrenal-medullary (SAM) system, play a major role in the consolidation of emotional memory. The action of these two systems on learning and memory strongly depends on the timing of the physiological response in relation to the stressor. Glucocorticoids from the adrenal cortex secreted during and immediately after the stressor enhance memory consolidation. They act directly on the amygdala which is the main brain area involved in emotional learning. This glucocorticoid action on memory consolidation is facilitated by circulating catecholamines from the SAM system. These catecholamines affect the processing of emotional events in the amygdala indirectly via afferent vagal nerves. In contrast to the enhancing effects on memory consolidation, memory retrieval is generally impaired by the activation of the HPA axis and adrenal medulla. For a recent review on stress and memory, we refer to Schwabe and Wolf (2014). In understanding PTSD, the stress effects on memory consolidation seem to be more important.

A second factor in the consolidation of memory is sleep. It is generally thought that re-experiencing events of the past day during the sleep phase is essential for the storage of information into long-term memory (Stickgold 2013). Sleep is essential for the strengthening and qualitative reorganization of new memories (Landmann et al. 2014). This re-experiencing of traumatic life events may be considered as repeated exposure to stressors and may in that way be perceived as chronic stress, despite the fact that the actual traumatic event has long passed by. Indeed, van Liempt et al. (van Liempt et al. 2013) found enhanced HPA and the SAM activity related to an increased sleep fragmentation in PTSD patients. It is tempting to consider the possibility that this re-experiencing of traumatic events and the associated activation of physiological stress systems will contribute to a further consolidation of the memory process and experience of chronic stress. Notice that the interaction between peripherally circulating hormones, sleep, and learning and memory processes in the brain may be highly adaptive; it prepares the individual for an adequate response to similar situations in the future. Again, the question is when this adaptive process may become maladaptive.

Match/Mismatch Hypothesis

The match/mismatch hypothesis was originally developed in relation to the adult consequences of early life stress. This hypothesis suggests that early life stress prepares the individual for the environmental conditions that he or she is likely to meet in adulthood. When these adult conditions indeed match to the

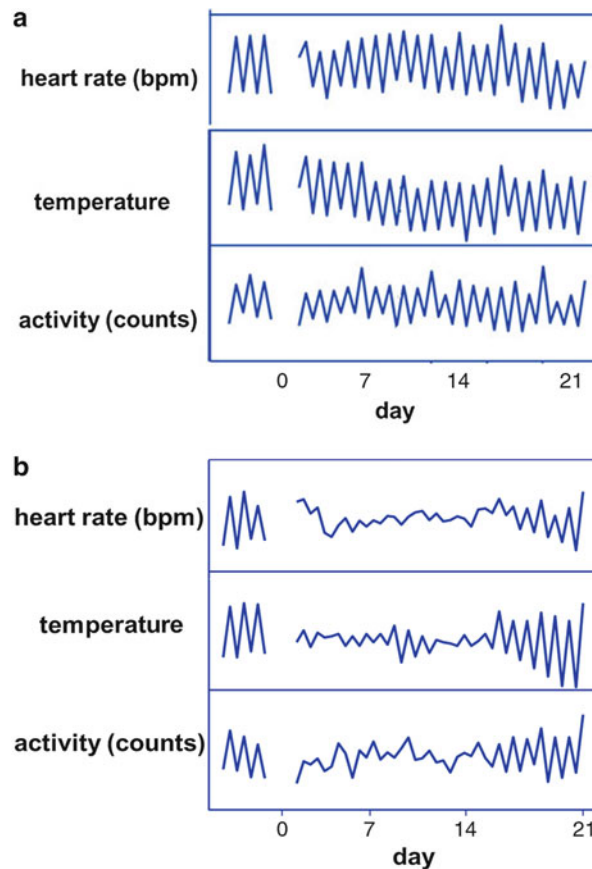


Fig. 5 Circadian amplitude of heart rate, body temperature, and activity of male rats before and after a social defeat measured by permanently implanted radio telemetry equipment. The animals were experienced winners before the exposure to social defeat. **(a)** Animals that initially resisted the dominant male; **(b)** animals that submitted without resistance (Meerlo et al. 1999)

early life environment, the individual is resilient. However, in a situation where the adult environment differs from the conditions in which the individual grew up (mismatch), it may develop stress pathology (Gluckman et al. 2007; Schmidt 2010). This hypothesis may also hold for the behavioral and physiological changes induced by traumatic life events in adulthood. In this view, the behavioral and physiological changes induced by a traumatic life event may be adaptive and support survival in situations in which there is a high likelihood of similar traumatic events. However, these changes are useless when similar traumatic events never occur again. In that situation, PTSD can be considered as a disease of adaptation.

When memory consolidation is indeed the core process in both the adaptive and the maladaptive responses to trauma, it becomes important to ask the question what exactly is stored and remembered. Some recent preclinical studies using social defeat in rats may shed light on this. The long-term behavioral and physiological consequences of social defeat seem to depend on the behavior of the losing animal during the actual social interaction itself. Animals that do resist the dominant for a while before true subjugation or losing the fight hardly show any long-term consequences. However, defeated animals that did not resist the dominant initially or showed clear signs of submission without any behavioral counteractions appeared to develop long-term changes in behavior and physiology (Kinn Rod et al. 2014; Meerlo et al. 1999; Walker et al. 2009; Wood et al. 2010). Figure 5 illustrates this phenomenon using the circadian rhythm of heart rate, body temperature, and activity as readout. This leads to the hypothesis that the direct feedback or evaluation of the victim's actions during the actual traumatic event is crucial for its long-term consequences. Appraisal is then not only the appreciation of the challenging

environment but just as well the direct cognitive processing of coping with that challenge. Despite the overall negative outcome, which is defeat, this evaluation of its own actions might still be positive, i.e., “given my limited resources, I have done my best.” If the end result of this evaluation process is however negative (“I could have done better and took the wrong decisions”), this might be the start of a downward spiral in the subsequent memory consolidation process. Although we realize that there is a serious risk of anthropomorphic reasoning based on preclinical studies in rats, we feel that understanding the cognitive processing of the behavioral response during a traumatic life event itself is the key to understanding whether or not pathological consequences may occur, i.e., maladaptation.

Individual Differentiation

The international literature on PTSD is rather consistent in its observation that the development of PTSD is relatively rare. Usually between 5 % and 10 % of the individuals exposed to traumatic events ultimately develop PTSD (e.g., Creamer et al. 2006; Davidson et al. 1991; Kessler et al. 2005; Lloyd and Turner 2003). Several authors have argued that personality factors such as trait hostility/anger, neuroticism, and trait anxiety may explain a considerable part of the individual vulnerability (Jaksic et al. 2012). Obviously, the relationship between human personality and vulnerability to PTSD is correlational. Causal questions require experimental data. Preclinical studies on animal personality may shed some light on the biological background of individual variation in vulnerability and resistance. Naturalistic studies in a wide variety of animal species show that individuals can be categorized in distinct behavioral phenotypes. Several terms are used for this phenomenon. Sih et al. (2004) used the term behavioral syndrome, whereas Groothuis and Carere (2005) preferred the term behavioral profile. More specifically, research has focused on two distinct patterns of reaction to stressful conditions or coping style. The term coping style refers to alternative response patterns in reaction to challenges that are stable over time and across various situations (Koolhaas et al. 1999). For example, animals characterized by a proactive coping style are offensive toward male conspecific rivals, are impulsive in decision-making, score high in frustration tests, take risks in the face of potential dangers, and are novelty seekers (David et al. 2004; Groothuis and Carere 2005; Steimer and Driscoll 2005). The reactive coping style is characterized by low levels of offensive aggression and a more readily acceptance of environmental changes. Extensive studies, using a variety of learning tasks, show that behavioral flexibility is one of the main differences between proactive and reactive coping (Coppens et al. 2010). The proactive individual acts on the basis of predictions, whereas the reactive individual relies more on direct environmental input. This difference can be demonstrated, for example, in a reversal learning task. The proactive individual has great difficulties in changing from a once learned task into a new one. It is rigid and makes much more mistakes than a reactive coping individual. When the behavior of a proactive coping individual is indeed mainly based on previous experience, we have to reconsider the concepts of predictability and controllability. The general stress literature emphasizes the importance of unpredictability of stressors. However, notice that unpredictable is not the same as a wrong prediction. Intuitively, one may expect a large impact when an originally fully predictable and controllable situation suddenly deteriorates and becomes unpredictable and uncontrollable. It is surprising that the factor outcome expectancy has not been studied more frequently. Amat et al. showed that previous experience with a controllable foot shock made male rats more resilient to a subsequent uncontrollable foot shock (Amat et al. 2006). However, when the previously positive experiences suddenly change into a negative one, rats seem to be more vulnerable. This is demonstrated, for example, in an experiment in which animals were socially defeated after they had already ten winning experiences (Meerlo et al. 1999). A single social defeat in these experienced winners completely abolished their circadian amplitude of heart rate, body temperature, and physical activity for a long

period of time (Fig. 5b). Similarly, losing territory ownership and lowering in social rank has been demonstrated to exert greater immune-suppressing effects than social subordination per se in a mouse model of chronic subordination stress (Bartolomucci 2007). This suggests that a violation of positive outcome expectancy might be a serious or even traumatic experience in proactive individuals that strongly rely on predictions and expectancies. It is important to notice that the long-term changes in behavior and physiology were only observed in animals that do not resist during the social defeat. This emphasizes again that feedback of the behavioral response during the traumatic event might be important as discussed above.

Procedures and Practices

The line of reasoning presented above has its consequences for both clinical and preclinical stress researches. Stress research is notoriously known for its large individual variation in both the acute stress response and the development of stress-related disease. A fundamental question that might explain this variation but has hardly been addressed in most studies is whether the condition to which the individual is exposed is indeed perceived as a stressor. To answer this question, research should pay attention to the speed of recovery of the physiological response and the presence or absence of an anticipatory response. In addition, the presence of a plasma adrenaline response can be considered as an indicator that a challenge is indeed perceived as uncontrollable and hence as a stressor. In line with this, the presence of adrenaline co-transmission and the induction of the adrenaline-synthesizing enzyme PNMT in sympathetic nerves may be an explicit biomarker of a recurrent and/or chronic stress state. By taking these aspects of the physiological response into account, one might be able to distinguish individuals that have perceived the challenge as a stressor from individuals that somehow managed to cope with the challenge. This focus on the individual is also important in preclinical studies using animal models. Studies of coping style and animal personality in a wide variety of species show that individuals are differentially optimized for different environmental conditions. This implies that a certain challenge might be perceived as a stressor only by one type of individual and not by the other.

Although the concept of uncontrollability and unpredictability as main characteristics of a stressor is well accepted, it is important to notice that individuals are usually not naïve in everyday life. They have predictions and individuals may even differ in the degree in which they rely on predictions. Therefore, research should pay more attention to the concept of outcome expectancies and wrong predictions by explicitly including previous experience in the experimental approach.

In view of the fact that adaptation and maladaptation are strongly based on the processes of memory consolidation, it seems important to consider in more detail what exactly is remembered from the stressful event. Recent studies of social defeat in rats suggest that feedback from the victim's own actions during the stressful event might be a crucial determinant of the course of subsequent adaptive or maladaptive processes. This requires a detailed assessment of the behavior of the victim during the stressful event and the victim's own appraisal of it.

Concluding Remarks

One may conclude that the rather global use of the stress concept is inadequate to explain the development of PTSD. When one considers stress in terms of a challenging environmental condition (i.e., a stressor), it does not explain why only a limited number of individuals develop disease symptoms. Neither does stress, considered as the response of the body to a stressor (i.e., stress response), explain the development

of PTSD. Hence, it was emphasized that the way in which individuals perceive a challenging environment will be the key in understanding the development of stress pathology. Controllability and predictability are the key factors in the appraisal process. This raises the problem to assess when a stimulus is perceived as uncontrollable or unpredictable. Preclinical studies suggest that the speed of recovery of the acute stress response and the release of adrenaline might be the key factors that dissociate an uncontrollable from a controllable condition. It is surprising that plasma or tissue adrenaline does not receive more attention in the stress literature. Despite all the evidence for the involvement of the HPA axis and the plasma catecholamines in the consolidation of the traumatic experience, these studies still have no answer to the question when this memory consolidation leads to adaptation and when to pathology. Based on some preclinical studies of social defeat, we argue that three factors might be crucial in the appraisal process leading to adaptation or disease. First, previous experience and outcome expectancy seem to be important determining factors for the magnitude of the stress response and its long-term consequences. Second, it is suggested that the direct feedback from the victim's own actions during the traumatic event is crucial for the progressive adaptive or maladaptive changes in the course of the days and weeks after the traumatic event. Finally, studies of individual differentiation in coping style show that proactive individuals strongly rely on predictions. They are resilient under stable environmental conditions but vulnerable when outcome expectancies are violated. PTSD research in general and preclinical studies in particular may benefit from a shift in focus toward appraisal and the individual differentiation in the appraisal process.

Key Facts

- The stress was originally defined by Hans Selye in 1950 as the adaptive response of the body to any noxious stimulus.
- The significance of appraisal was demonstrated experimentally in a preclinical study by Seligman and Weiss in 1972.
- The magnitude of the neuroendocrine and sympathetic responses to aversive conditions can be as high as the response to rewarding situations.
- The difference between aversive and rewarding conditions is the speed of recovery of the physiological response.
- The focus on individual differences in stress vulnerability and animal personality can be considered as a paradigm shift in preclinical stress research.
- Individuals differ in the degree in which they rely on active control and predictions in their response to a challenge.
- Recent evidence suggests that feedback from the victim's own actions during the traumatic event might be an important determinant of its long-term consequences.

Summary Points

- The current use of the stress concept is inadequate to explain PTSD.
- The appraisal process is the key to understanding stress pathology.
- Stress terminology should be restricted to uncontrollable and unpredictable conditions and wrong predictions.
- Plasma adrenaline and the speed of recovery of the stress response dissociate controllable from uncontrollable challenges.
- The anticipatory response dissociates a predictable from an unpredictable challenge.

- The direct feedback or cognitive processing of the behavioral response during the traumatic event might be central in the development of PTSD.
- Predictability should include expectations.
- The key to individual vulnerability to stress-related disorders might be coping styles in terms of the degree in which individuals rely on active control and predictions.

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