Pathways to traumatic stress syndromes

Holly G. Prigerson[a,b], Meena Narayan[b], Michael Slimack[b], Laurel C. Beery[c] and Selby C. Jacobs[b]

Recent studies suggest the nature of the trauma, and the age, prior experiences and psychopathology of the victim significantly influence the psychiatric symptoms that emerge after a trauma. New findings have also confirmed and refined the role played by the hypothalamic–pituitary–adrenal axis and hippocampus in the pathogenesis of stress. Curr Opin Psychiatry 11:149–152. © 1998 Rapid Science Ltd

[a] Connecticut Mental Health Center, Yale University School of Medicine, New Haven, [b] Northeast Program Evaluation Center, Veterans Affairs Medical Center, West Haven, Connecticut, and [c] Western Psychiatric Institute and Clinic, Pittsburgh, Pennsylvania, USA

Correspondence to Dr Prigerson, Room 144, Connecticut Mental Health Center, 34 Park Street, Yale University School of Medicine, New Haven, CT 06519, USA
e-mail: holly.prigerson@yale.edu

Current Opinion in Psychiatry 1998, **11**:149–152

Abbreviations

HPA hypothalamic–pituitary–adrenal
PTSD post-traumatic stress disorder

Introduction

Advances in understanding are typically made when the phenomenon under study is either literally or figuratively examined under a microscope. Research on trauma and stress response syndromes is no exception. Progress in our understanding of pathways leading to traumatic stress syndromes has been the result of closer scrutiny of how stress response symptoms and syndromes vary with the type of traumatic exposure, and by the victim's age, prior experiences and psychopathology. New studies that dissect the neurobiologic aspects of traumatic stress disorders have refined our understanding of the role played by the hypothalamic–pituitary–adrenal (HPA) axis and the hippocampus in the biology of stress. In this review promising new findings about the phenomenology, etiology, and neurobiology of traumatic stress syndromes are discussed. Topics that have the potential to lead to important insights about pathways to post-traumatic stress are suggested.

Pathways to stress response syndromes

Etiology and phenomenology

Traumatic stress syndromes, such as post-traumatic stress disorder (PTSD), are unique in that etiological considerations are required for a diagnosis. According to the DSM-IV [1], an individual must be exposed to an event that is considered 'traumatic' (see the criterion A1 description of a 'life-threatening' exposure) to be given a diagnosis of PTSD. The assumption underlying the criteria established for PTSD is that exposure to a 'traumatic' event heightens an individual's risk for experiencing symptoms in each of the PTSD 're-experiencing', 'avoidance' and 'hyperarousal' domains. Nevertheless, an increasing number of studies demonstrate that reactions to trauma are not uniform and do not neatly fit into these categories. In fact, the source of trauma appears to be an important variable affecting the type of post-traumatic stress symptoms that will emerge.

What is the nature of the exposure that predisposes to stress response syndromes and do symptoms relate in a systematic way to the type of trauma? There appear to be a growing number of studies that aim to confirm the presence of post-traumatic symptomatology resulting from presumably traumatizing, yet previously unstudied experiences. For example, a study by Peck *et al.* [2] that tested the existence of PTSD symptomatology among

injured mountaineers found that one-third experienced significant psychologic problems after the accident, such as intrusive thoughts and avoidance of reminders of the accident. However, they also found that the post-traumatic symptoms associated with the mountain climbing accident were different from those secondary to automobile accidents. They report that whereas studies of road accident victims conclude that a fear of imminent death during an accident is related to the development of PTSD, they found no significant relationship between fear of dying and the onset of PTSD among their sample of injured mountaineers. Although these results indicate that accidents, whether in an automobile or on a mountain, can result in post-traumatic symptomatology, such inconsistencies put the etiologic role played by the life-threatening nature of the event (see criterion A1) into question.

A review of the recent literature on traumatic stress reveals a growing recognition that events that are presumed to be less horrific and terrifying than war, natural and manmade disasters and accidents may, nonetheless, elicit symptoms of traumatic distress. Evidence of this is suggested by a MEDLINE search on the topic of 'trauma', which yields a large number of studies on PTSD symptoms among the terminally ill and bereaved. Although several recent studies document PTSD symptomatology among individuals whose loved ones are critically ill or who have died, others document no such reaction. For example, a paper by Stuber *et al.* [3] examined the responses of children during the acute phase of hospitalization for bone marrow transplantation – an extremely aggressive treatment for an otherwise fatal illness. The children were able to appreciate the life-threatening nature of their illness and its treatment. As an interesting negative result, the children in this study reported few symptoms consistent with a traumatic stress response. Stuber *et al.* [3] claim that these findings are in contrast to recent data on survivors of childhood cancer, most of whom reported that they did not understand that their illness posed a threat to their lives, whereas reporting moderate levels of post-traumatic stress symptoms up to 10 years after completion of successful treatment.

Even for findings within one type of terminal illness (e.g. leukemia or cancer) the experience of being traumatized appears to vary with the relationship to and the age of the victim. Kazak *et al.* [4•] found that parents of childhood survivors of leukemia had significantly higher rates of post-traumatic stress symptoms than either the childhood survivors themselves or comparison participants and their parents. Baider and De-Nour [5] reported that among 283 female patients diagnosed with early-stage breast cancer, none met diagnostic criteria for PTSD, primarily because the individuals did not exhibit symptoms of increased arousal. This is similar to our work with bereaved individuals who have been traumatized by the death, or impending death, of a close friend or relative. Although we found that many recently bereaved have high levels of intrusive thoughts and moderate to high levels of avoidance of reminders of the deceased, hyperarousal is not a prominent feature of a syndrome we refer to as 'traumatic grief' [6–10]. Interestingly, the non-PTSD symptoms of yearning, searching, and longing for the deceased appear to form a single cluster of symptoms that are unified with the traumatic distress symptoms [6–10]. Thus, in the case of a traumatic, or devastating loss, the syndrome appears to include a synthesis both of traumatic distress and of separation distress symptoms.

Picking up on the theme that different sources of trauma may lead to unique clusters of psychiatric symptoms associated with PTSD, Deering *et al.* [11•] reviewed the literature comparing patterns of comorbidity in PTSD from different sources of trauma. They found that substance abuse tends to be a consequence of exposure to combat, whereas panic and phobic symptoms are more common in traumas with unusual levels of arousal and unpredictability. By contrast, they conclude that somatization is more prevalent among victims who have endured physical suffering [11•]. That review, as well as the studies described above, may be seen as part of a larger movement towards greater specificity in linking particular traumatic experiences to the symptoms that follow.

Taken together, the reports described above illustrate the recent trend in the trauma literature to confirm the existence of PTSD symptomatology in a wider variety of stressful experiences. They also suggest an emerging dissatisfaction with the previously held assumption that the response to trauma results in a single symptomatic picture. The move appears to be toward a more complete and accurate portrayal of the psychiatric symptoms that follow from particular traumatic experiences and that take respondent characteristics such as age and relationship of the victim into account.

Whereas the response to trauma appears to vary with the type of traumatic exposure, evidence is mounting that prior trauma, regardless of type, is an important factor in the etiology of PTSD. A few notable studies that support the vulnerability to PTSD created by prior trauma include the work of Fontana *et al.* [12], who found that both war trauma and sexual trauma were powerful contributors to the development of PTSD among female Vietnam veterans. Similarly, Rodriguez *et al.* [13] found that 86.7% of women who were in outpatient treatment for childhood sexual abuse met criteria for current PTSD, compared with 19.4% of the women who were in treatment for problems in their committed relationships. They also found that both childhood sexual and physical abuse accounted for a significant proportion of the variance in

PTSD symptoms. These are just a few of the studies that support the conclusion that prior traumatic experiences create a diathesis to PTSD symptomatology that may exist irrespective of the type of early trauma. The mechanisms through which prior trauma creates a vulnerability to PTSD is a topic that deserves to be investigated further.

Several studies have also begun to focus on the role of prior psychopathology in the onset of PTSD. According to Deering *et al.* [11•], PTSD rarely appears as a singular disorder at any point in its course. Those authors claim that 62–100% of PTSD patients experience at least one other psychiatric disorder, and they suggest that comorbid disorders may not be separate from PTSD, but rather precede or create a vulnerability to PTSD. Interestingly, a study by Chubb and Bisson [14] dissected the effects of prior and enduring mental health difficulties on the impact of a major trauma by isolating the influence of particular disorders. They find that chronic schizophrenia is in some way protective against the development of psychologic sequelae after major traumatic events, whereas major depressive and anxiety disorders represent a major predisposing factor to the development of post-traumatic stress symptomatology. Further research is needed to determine the ways in which the mental encoding of the traumatic event differs based on the psychiatric history of the victim.

Studies over the past year have refined our understanding of the ways in which traumatic events alter brain structure and function. Below we review some promising inroads that have been made in neurobiologic research on stress.

Biology of stress

The HPA axis and the hippocampus have been the focus of research on the biology of stress. The glucocorticoid cascade hypothesis of aging (for review [15•]) has helped to elucidate the effects of stress, and more specifically of cortisol, on the brain. This hypothesis states that peripheral cortisol increases with age, resulting in damage to the hippocampus. Loss of the hippocampal feedback inhibition of the HPA axis leads to progressive increases in peripheral cortisol with further hippocampal damage and associated memory deficits.

One possible hypothesis for the finding of hippocampal atrophy is that elevated cortisol levels during and after the traumatic event result in irreversible neurotoxic damage to the hippocampus. A recent study by Bremner *et al.* [16] demonstrated significantly elevated levels of corticotrophin releasing factor in the cerebrospinal fluid of patients with PTSD levels compared with in healthy control individuals. This finding is consistent with the chronic increase in neuronal corticotrophin releasing factor release after exposure to stress. Paradoxically, Yehuda *et al.* [17] have proposed an enhanced negative feedback at one or more sites of the HPA axis, resulting in lower cortisol levels observed in chronic PTSD. Prospective studies of individuals at heightened risk for exposure to trauma could help to determine whether abnormalities in the HPA axis and hippocampal atrophy are a consequence of PTSD secondary to significant trauma, or whether they are risk factors that increase susceptibility to developing PTSD.

There has been an increasing interest in evaluating anatomic areas other than the hippocampus in PTSD. Using positron emission tomography techniques, a recent study by Shin *et al.* [18•] revealed increased regional cerebral blood flow in ventral anterior cingulate gyrus and right amygdala and a decreased regional cerebral blood flow in Broca's area. Further evidence for limbic and paralimbic systems mediating emotions associated with PTSD symptoms has come from a study by Rauch *et al.* [19] that audiotaped traumatic and neutral scripts in conjunction with positron emission tomography. Studies have also begun to narrow in on the neurobiologic subsystems involved in PTSD symptomatology. Southwick *et al.* [20], evaluating the frequency of panic attacks in patients with PTSD in response to a serotonergic or noradrenergic pharmacologic challenge, found the evidence consistent with the existence of two neurobiologic subgroups: one with a sensitized noradrenergic system and the other with a sensitized serotonergic system. Despite these advances, no single anatomic, chemical or physiologic abnormality has been identified, and future biologic studies will need to pay closer attention to how multiple structures and functions of the brain interact in the development of PTSD.

Conclusion

Recent studies highlight the need for careful correspondence between the nature of the trauma and the symptoms that follow. Given that age, relationship to the victim and prior experiences significantly influence the onset of PTSD, such variables should be taken into account in future studies of reactions to trauma and stress. The mechanisms through which prior trauma creates a vulnerability to PTSD is another topic deserving of greater attention. Further research is needed to determine the ways in which the mental encoding of the traumatic event differs according to the prior psychopathology of the victim. With respect to research on the biology of stress, prospective studies of individuals at increased risk for exposure to trauma could help determine whether abnormalities in the HPA axis and hippocampal atrophy are a consequence of PTSD or risk factors for it. Given the absence of a single anatomic, chemical or physiologic abnormality linked to PTSD, future neurobiologic studies will have to evaluate the interactions between the multiple structures and functions of the brain. Taken

together, the greater attention recently paid to the ways in which trauma is cognitively, affectively and physiologically experienced will refine our understanding of the type of individual who is at risk after a traumatic exposure and the biologic substrates that lead to that reaction.

References and recommended reading

Papers of particular interest, published within the annual period of review, have been highlighted as:

- • of special interest
- •• of outstanding interest

1 American Psychiatric Association. *Diagnostic and Statistical Manual of Mental Disorders*, fourth edn. Washington; 1994.

2 Peck DF, Robertson A, Zeffert S. Psychological sequelae of mountain accidents: a preliminary study. *J Psychosom Res* 1996; **41**:55–63.

3 Stuber ML, Nader KO, Houskamp BM, Pynoos RS. Appraisal of life threat and acute trauma responses in pediatric bone marrow transplant patients. *J Trauma Stress* 1996; **9**:673–686.

4 • Kazak AE, Barakat LP, Meeske K, Christakis D, Meadows AT, Casey R, *et al.* Post-traumatic stress, family functioning, and social support in survivors of childhood leukemia and their mothers and fathers. *J Consult Clinical Psychol* 1997; **65**:120–129.

This report demonstrates that parents of a child with a life-threatening illness are often more traumatized than are the children themselves.

5 Baider L, De-Nour AK. Psychological distress and intrusive thoughts in cancer patients. *J Nerv Ment Dis* 1997; **185**:346–348.

6 Prigerson HG, Frank E, Kasl SV, Reynolds CF III, Anderson B, Zubenko GS, *et al.* Complicated grief and bereavement-related depression as distinct disorders: preliminary empirical validation in elderly bereaved spouses. *Am J Psychiatry* 1995; **152**:22–30.

7 Prigerson HG, Maciejewski PK, Newsom J, Reynolds CF III, Frank E, Bierhals EJ, *et al.* The inventory of complicated grief: a scale to measure maladaptive symptoms of loss. *Psychiatry Res* 1995; **59**:65–79.

8 Prigerson HG, Bierhals AJ, Kasl SV, Reynolds CF III, Shear MK, Newsom JT, *et al.* Complicated grief as a distinct disorder from bereavement-related depression and anxiety: a replication study. *Am J Psychiatry* 1996; **153**:1484–1486.

9 Prigerson HG, Bierhals AJ, Kasl SV, Reynolds CF III, Shear MK, Day N, *et al.* Traumatic grief as a risk factor for mental and physical morbidity. *Am J Psychiatry* 1997; **154**:616–623.

10 Prigerson HG, Shear MK, Frank E, Silberman R, Reynolds CF III. Clinical case conference: traumatic grief: a case of loss-induced distress. *Am J Psychiatry* 1997; **154**:1003–1012.

11 • Deering CG, Glover SG, Ready D, Eddleman HC, Alarcon RD. Unique patterns of comorbidity in post-traumatic stress disorder from different sources of trauma. *Comp Psychiatry* 1996; **37**:336–346.

This study raises the important question of whether comorbid disorders may actually precede PTSD. It also describes specific ways in which psychiatric symptoms differ according to the type of trauma experienced by the victim.

12 Fontana A, Schwartz LS, Rosenheck R. Post-traumatic stress disorder among female Vietnam veterans: a causal model of etiology. *Am J Public Health* 1997; **87**:169–175.

13 Rodriguez N, Ryan SW, Van de Kemp H, Foy DW. Post-traumatic stress disorder in adult female survivors of childhood sexual abuse: a comparison study. *J Consult Clin Psychol* 1997; **65**:53–59.

14 Chubb HL, Bisson JI. Early psychological reactions in a group of individuals with pre-existing and enduring mental health difficulties following a major coach accident. *Br J Psychiatry* 1996; **169**:430–433.

15 • Sapolsky RM. Why stress is bad for your brain. *Science* 1996; **273**:749–750.

This review is a masterful synthesis of research on the effects of stress, and more specifically of cortisol, on the brain, and reviews Sapolsky's well-known glucocorticoid cascade hypothesis.

16 Bremner JD, Licinio J, Darnell A, Krystal JH, Owens MJ, Southwick SM, *et al.* Elevated CSF corticotropin-releasing factor concentrations in post-traumatic stress disorder. *Am J Psychiatry* 1997; **154**:624–629.

17 Yehuda R, Teicher MH, Trestman RL, Levengood RA, Siever LJ. Cortisol regulation in post-traumatic stress disorder and major depression: a chronobiological analysis. *Biol Psychiatry* 1996; **40**:79–88.

18 • Shin LM, Kosslyn SM, McNally RJ, Alpert NM, Thompson WL, Rauch SL, *et al.* Visual imagery and perception in post-traumatic stress disorder. A positron emission tomographic investigation. *Arch Gen Psychiatry* 1997; **54**:233–241.

This article proposes that the ventral anterior cingulate gyrus and right amygdala play a role in re-experiencing phenomena of PTSD based on increased regional cerebral blood flow changes in these regions during viewed and generated visual mental images of combat in patients with PTSD compared with in control individuals.

19 Rauch SL, van der Kolk BA, Fisler RE, Alpert NM, Orr SP, Savage CR, *et al.* Using positron emission tomography and script-driven imagery. *Arch Gen Psychiatry* 1996; **53**:380–387.

20 Southwick SM, Krystal JH, Bremner JD, Morgan CA, Nicolaou AL, Nagy LM, *et al.* Noradrenergic and serotonergic function in post-traumatic stress disorder. *Arch Gen Psychiatry* 1997; **54**:749–758.