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# Key Questions and a Research Agenda for the Future

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To our knowledge, this book represents the first comprehensive effort to conceptualize post-traumatic stress disorder (PTSD) in terms of the basic neurobiological mechanisms that promote normal adaptation to stress. We believe that PTSD may be distinct among psychiatric disorders because of the wealth of laboratory research and animal models that can help us understand the pathophysiology of this disorder. In our own effort to synthesize some of the major themes presented throughout this book, we offer the following questions.

1. What defines "normal" as opposed to "traumatic" stress? What differentiates normal from traumatic stress?
2. What are the major similarities and differences between the neurobiology of the stress response generally observed experimentally, and that observed among PTSD patients?
3. What neurobiological aspects of the stress response have yet to be explored in PTSD?
4. To what degree do peripheral events influence central neuronal function in PTSD?
5. Do the somatic consequences of stress help us understand the adverse health findings associated with exposure to traumatic events and PTSD?
6. Which neural mechanisms seem most applicable to PTSD?
7. Which neural mechanisms of memory seem most applicable to PTSD?
8. Is allostasis a useful concept for PTSD?
9. What animal models that are applicable to PTSD?
10. Are there any useful clinical applications of laboratory paradigms currently used in PTSD research with humans?
11. Where should we direct future research on the clinical pharmacology of PTSD?
12. How can we understand, from a neurobiological perspective, the fact that PTSD is usually associated with at least one other comorbid psychiatric disorder?
13. What should be the future agenda for research on PTSD?

## 1. WHAT DEFINES "NORMAL" AS OPPOSED TO "TRAUMATIC" STRESS? WHAT DIFFERENTIATES NORMAL FROM TRAUMATIC STRESS?

The definition of stress has always been somewhat circular. The event that precipitates stress is a stressor, but the response to a given stressor, designated stress, varies greatly across individu-

als. Stressors that are part of the normal vicissitudes of modern life, and that give rise to no demonstrable psycho- or physio-pathology in most people, may be severe stressors for other (predisposed) individuals and thus lead to overt symptomatology. Thus, the response (stress) differs widely despite the same evoking stimulus (stressor). In addition to the difference in response to a given stressor that depends upon individual vulnerability, there are also differences in responsiveness to the same stressor that depend upon context (controllable versus uncontrollable stress). Finally, the type of stressor (e.g., footshock versus restraint) may also produce large response differences from one individual to another.

Part of the difficulty in working on the neurobiology of stress and PTSD is the fact that stress needs to be defined operationally for each investigation. This holds for both preclinical and clinical studies. It will be increasingly important to provide full documentation of the defining characteristics of stressors employed in preclinical studies if we hope to compare and contrast findings in a rational manner. Similar issues plague clinical studies. For example, epidemiological studies of the effects of past stress exposure have been hampered by difficulties in defining stress and its various presentations; not only must major life stressors be categorized, but so must those events comprising the "social stress" that varies as a function of family, community, and social support.

In summary, investigations of stress have been hampered by a lack of clear definition. While many might substitute "stress" for "pornography" in the now famous statement of Justice Potter Stewart—"I shall not attempt today to further define the kinds of [pornographic] material . . . but I know pornography when I see it"—it is apparent that this attitude will not be useful in research endeavors on the effects of stress.

## 2. WHAT ARE THE MAJOR SIMILARITIES AND DIFFERENCES BETWEEN THE NEUROBIOLOGY OF THE STRESS RESPONSE GENERALLY OBSERVED EXPERIMENTALLY, AND THAT OBSERVED AMONG PTSD PATIENTS?

Among the most consistent observations in PTSD patients and in laboratory animals exposed to stress are changes in catecholaminergic systems. For example, both exposure of PTSD patients to traumatic reminders and exposure of rats to a neutral stimulus previously paired with stress increase sympathetic nervous system activity. Many PTSD patients have increased urinary catecholamine levels and decreased platelet $\alpha_2$ and lymphocyte $\beta$ adrenergic receptors; PTSD patients also exhibit potentiated behavioral, biochemical, and cardiovascular responses to yohimbine. These findings suggest that the pathophysiology of PTSD involves altered peripheral catecholaminergic function.

It remains unclear to what degree these changes actually reflect central events, or are derived from changes in peripheral catecholamines. A considerable body of data from nonhuman animal studies suggests that changes in peripheral levels of norepinephrine and epinephrine may contribute to changes in acquisition and consolidation of memory, as well as contribute to anxiety states. Future studies should be directed to unraveling the relative contributions of peripheral and central catecholaminergic alterations in the pathophysiology of PTSD.

A key component of the acute response to stress is activation of the hypothalamic-pituitary-adrenal (HPA) axis. Several recent animal studies have demonstrated that exposure to stressful events early in life can have profound and longlasting consequences; these sequelae may be qualitatively different and differ quantitatively from the changes elicited by acute stress exposure. For example, acute stress exposure increases HPA function. In contrast, PTSD patients paradoxically exhibit decreased HPA function, including decreased 24-hour urinary cortisol lev-

els, increased glucocorticoid receptor density, supersuppression in response to dexamethasone, and blunting of the corticotropin-releasing-hormone (CRH)–adrenocorticotropic-hormone (ACTH) response. However, these same parameters of altered HPA function can also be observed in adult rats subjected to mild stressors during critical developmental periods (such as transient maternal separation); in contrast, more "severe" stressors typically induce increased HPA tone. There are several other areas of similarity between PTSD and effects of stress in rodents and other animals. The neural mechanisms of fear conditioning, extinction, and sensitization have been extensively investigated in laboratory animals, and appear to hold clues as to the mechanisms underlying the morbidity and chronicity of PTSD. In addition, there are some similarities in certain aspects of the adrenergic and opioid response to both normal and traumatic stress.

The similarities and differences between animal studies and changes observed in PTSD indicate that there is a compelling need for more work in laboratory animals to determine the role of different stress intensities, duration, and contingencies (i.e., escapable versus inescapable) in various central and peripheral systems; only recently have contemporary approaches been brought to bear on these issues. In addition, studies of the effect of different stressors during critical developmental periods are clearly indicated.

## 3. WHAT NEUROBIOLOGICAL ASPECTS OF THE STRESS RESPONSE HAVE YET TO BE EXPLORED IN PTSD?

Studies in laboratory animals have shown myriad responses to stressors. Stress has been shown to alter the function of virtually every neurotransmitter system; similarly, a wide array of nuclei in the CNS are involved. Clinical studies of PTSD have only started to assess the function of a few of the relevant brain regions and transmitter systems that basic science studies implicate.

The amygdala appears to mediate or modulate many of the emotional aspects of stress, such as fear conditioning, extinction, sensitization, and recall of traumatic memories. There have been, to our knowledge, no studies of amygdala function in PTSD. Similarly, the amygdala can be considered as part of an extended neural network of structures that subserve emotion, including prefrontal cortices, hippocampus, and reticular formation. Studies examining the relationship of amygdala function to other areas connected with the amygdala are lacking, particularly in primates. In part, the paucity of data on these regions is due to a lack of appropriate methodologies for studying these regions in man. Certain in vivo imaging techniques, particularly studies of blood flow by echo planer and other fast-scan MRI, may be well suited to this task.

Other imaging techniques that can detect significant changes in regional volumes may also be useful in defining the sites of pathology in PTSD. For example, several recent MRI studies have indicated a reduction in hippocampal volume in PTSD patients; this fits well with the effects of chronic stress on hippocampal neurons. However, the animal data indicate that there is significant potential for recovery after chronic stress- or glucocorticoid-induced morphological changes in hippocampal neurons. This discrepancy emphasizes the need for long-term studies of the effects of chronic stress in laboratory animals.

In vivo imaging methods, however, are probably of limited utility for examining such changes as the dystrophic alterations in hippocampal pyramidal cells observed after chronic stress. These changes (as opposed to overt cell loss or atrophy) are decreased dendritic spine density and changes in branching patterns of processes. Detection of such changes currently requires sophisticated computer-based assessments of histological material; it does not seem likely that current in vivo imaging methods will be able to determine such changes in man at any time in the near future. Since neuronal plasticity is much more common than once thought, it seems appropriate to actively investigate morphological changes in PTSD patients. We believe that it is time to

consider the development and implementation of a brain bank focusing on PTSD.

In addition to needing a greater focus on structural abnormalities associated with PTSD, we also believe it necessary to apply sophisticated clinical neuropharmacological techniques to the study of neurotransmitters that have received insufficient attention in PTSD. This is particularly true for CRH, neuropeptide Y, oxytocin, excitatory amino acids, and the gamma-aminobutyric acid (GABA)-benzodiazepine system.

## 4. TO WHAT DEGREE DO PERIPHERAL EVENTS INFLUENCE CENTRAL NEURONAL FUNCTION IN PTSD?

The relative involvement of peripheral versus central mechanisms in emotion and stress has been an ongoing area of study and controversy for over a century. As noted in the section addressing question 2, there are several changes in catecholaminergic parameters in PTSD; many of these changes are probably attributable to changes in peripheral catecholamine systems. The difficulty in monitoring central neurochemical events has plagued biological psychiatry. Since there are robust changes in peripheral markers of catecholamine function, and since peripheral events can theoretically influence central processes both directly and indirectly, it is appropriate to examine the degree to which central systems are impacted by peripheral events. Such studies may conceivably lead to pharmacological interventions that may be of some utility in PTSD.

## 5. DO THE SOMATIC CONSEQUENCES OF STRESS HELP US UNDERSTAND THE ADVERSE HEALTH FINDINGS ASSOCIATED WITH EXPOSURE TO TRAUMATIC EVENTS AND PTSD?

Most studies of the somatic consequences of stress are correlational in nature. There has been very little hypothesis-driven research concerning the somatic consequences of chronic stress in PTSD. Moreover, the factors that may increase the risk of adverse health outcomes for PTSD patients are not specific to this disorder. However, given the high incidence of comorbidity in PTSD, it seems appropriate to investigate the somatic consequences of stress in any attempt to reveal potential interventions that are specifically useful in PTSD.

Among individuals exposed to "nontraumatic" stress, there are a number of characteristics that predispose individuals to adverse health outcomes. These include altered sympathetic tone and concomitant cardiovascular hyperreactivity, smoking, drug abuse (including alcohol abuse), and a host of other factors. Many of these attributes appear to apply to PTSD patients. For example, many PTSD patients exhibit increased sympathetic tone, while alcohol and substance abuse are very frequently present. In general, available epidemiological studies indicate that exposure to trauma in general and the development of PTSD in particular are important risk factors for adverse health outcomes. In view of the paucity of rigorous, hypothesis-driven research published to date, further research is clearly needed to address the relationship between trauma, PTSD, and medical illness.

## 6. WHICH NEURAL MECHANISMS SEEM MOST APPLICABLE TO PTSD?

Fear conditioning, extinction, and sensitization are the three neural mechanisms that seem most applicable to PTSD. All these mechanisms provide major links through which a large body of laboratory findings can be reconceptualized and applied to PTSD.

Fear conditioning may account for the common observation in PTSD that sensory and cognitive stimuli associated with or resembling the original frightening experience elicit panic attacks, flashbacks, and a variety of autonomic symptoms. Pervasive anxiety may be due to contextual fear conditioning.

A failure in the neural mechanisms underlying extinction may relate to treatment-resistant avoidance behavior and the persistence of traumatic memories.

Sensitization may explain the adverse effects of early life trauma on subsequent responses to stressful life events. Sensitization may also play a role in the chronic course of PTSD and, in some cases, the worsening of the illness over time.

## 7. WHICH NEURAL MECHANISMS OF MEMORY SEEM MOST APPLICABLE TO PTSD?

In many respects, PTSD is a disorder of memory. Research into the neural mechanisms subserving the acquisition and retrieval of traumatic events will enhance our understanding of many of the clinical features of PTSD, and may facilitate the development of novel treatment approaches. It will be important to determine if there are differences in the brain mechanisms involved in the incorporation of traumatic as compared with nontraumatic events into long-term memory, and if the retrieval mechanisms differ. In particular, pharmacological studies are indicated. This need is amplified by the recent presentation of data demonstrating that pretreatment with the β adrenoceptor antagonist propranolol decreased components of the memory of an emotionally-charged traumatic story. This study suggests that similar pharmacological interventions may be useful adjuncts for persons in whom exposure to traumatic events, such as military personnel or emergency medical professionals, is expected.

Recent studies of long-term potentiation (LTP) and long-term depression (LTD) have emphasized the relation of these effects to memory, and established the role of certain neuronal messengers—including glutamate and other excitatory amino acids, and nitric oxide—in memory. The phenomenon of LTP is much more widespread than originally suspected, and now has been demonstrated in a wide variety of brain areas. Future studies may shed light on trauma-induced changes in memory, and the elucidation of the transmitter systems involved may uncover useful therapeutic approaches for prevention or treatment of PTSD.

## 8. IS ALLOSTASIS A USEFUL MODEL FOR UNDERSTANDING PTSD?

We believe that allostasis is an excellent model for understanding PTSD. The chronicity, stability, and refractory nature of this disorder suggest that a pathologic, allostatic balance has been achieved. The best evidence to suggest this conclusion comes from research on both the adrenergic and HPA systems. Excessive adrenergic function is balanced by downregulation of alpha-2 and beta adrenergic receptors whereas allostatic HPA equilibrium is marked by lower cortisol levels, upregulation of glucocorticoid receptors, and blunting of the CRH-ACTH response. The high price of allostasis, however, is dysregulation of these key systems. As a result, PTSD patients exhibit major biobehavioral deficits in their ability to function and cope with the normal vicissitudes of life.

It is not clear when a pathological equilibrium is achieved in response to chronic stress (i.e., when allostasis appears as opposed to transient deviations from homeostasis). Similarly, is there a decay of allostasis with reversion to a true homeostatic equilibrium, or is allostasis permanent? Studies of the adaptive changes to chronic stress in laboratory animals are clearly needed, with an emphasis on longterm (months to years) studies of chronic stress.

## 9. WHAT ANIMAL MODELS ARE APPLICABLE TO PTSD?

An effort needs to be made to develop animal models that are more analogous to the human situation than most current laboratory paradigms. Criteria that need to be satisfied in any animal model of PTSD must include factors that are essential to the initiation of PTSD-like symptoms, as well as factors that influence their expression.

Important preclinical studies of nonhuman primates and other animals in this regard include investigations on the consequences of maternal neglect, protracted social and hierarchical stress,

and the impact of uncontrollable and unpredictable stress. Determination of the effects of these stressors on physiological, somatic, and behavioral functions is critical. Further attempts to discover "treatments" that reverse stress effects may provide new clinical insights.

## 10. ARE THERE ANY USEFUL CLINICAL APPLICATIONS OF LABORATORY PARADIGMS RECENTLY USED IN PTSD RESEARCH WITH HUMANS?

Of the many psychobiological strategies employed to investigate the pathophysiology of PTSD, we believe that several approaches have potential applicability as clinical tools for distinguishing PTSD from other disorders. Several techniques appear quite promising at this time, especially measurement of psychophysiological reactivity, the dexamethasone suppression test, the acoustic startle response, and the 24-hour urinary neurohormone profile. This is a short list; hopefully it will be lengthened and fortified by future research.

## 11. WHERE SHOULD WE DIRECT FUTURE RESEARCH ON THE CLINICAL PHARMACOLOGY OF PTSD?

We have mentioned several suggestions for future research on PTSD, including clinical pharmacological issues. We wish to emphasize several additional points.

Clinical reports concerning military and disaster trauma indicate that clinical interventions within the first 24–72 hours of traumatic exposure, such as critical incident stress debriefing, may not only result in rapid symptom relief but may also prevent the later development of PTSD. We believe that acute pharmacological intervention may achieve similar results. There is clearly a need to identify drugs that, when administered shortly after acute exposure to traumatic events, will prevent autonomic instability and the encoding of horrific traumatic memories.

Treatment of established cases of PTSD with adrenergic antagonists (such as clonidine and propanolol) and agents that reduce panic attacks (tricyclic antidepressants and monomine oxidase inhibitors) has been disappointing, since even the most successful trials have achieved only modest symptomatic relief. Preliminary trials with selective serotonin reuptake inhibitors (SSRIs) have been promising, as have an array of case reports and open trials with other drugs. Our major concern in this regard is the low number of randomized clinical trials with PTSD patients. This is a crucial area of research that has not received appropriate attention.

From a theoretical perspective, there are several classes of drugs that would be particularly interesting to test in the treatment of PTSD. These include novel peptidergic (CRH, neuropeptide Y (NPY)) antagonists, allosteric modulators of the *N*-methyl-D-aspartate (NMDA) receptor, and certain anticonvulsant medications. These choices are suggested by preclinical research findings.

It is important to emphasize that we are entering a new period in the treatment of PTSD, one in which rationally-based therapeutic interventions may be envisioned. It is imperative that we focus on carefully executed, randomized clinical trials that are based on clearly stated hypotheses.

## 12. HOW CAN WE UNDERSTAND, FROM A NEUROBIOLOGICAL PERSPECTIVE, THE FACT THAT PTSD IS USUALLY ASSOCIATED WITH AT LEAST ONE OTHER COMORBID PSYCHIATRIC DISORDER?

As with most other psychiatric disorders, PTSD rarely occurs in "pure form," but is most often associated with other DSM-III-R diagnoses. In view of the considerable symptom overlap between PTSD and other diagnoses, comorbidity may reflect an artifact of a nosological system that cannot make fine distinctions between different disorders based on phenomenology alone. On the other hand, it may indicate that there is a common pathophysiology underlying a number of distinct psychiatric disorders that may exhibit different clinical presentations. The only thing that is not in doubt is that phenomenology cannot take us much further. The key to distin-

guishing true comorbidity from apparent comorbidity lies in biological research. Only when we understand the differences and similarities between various psychiatric diagnoses in terms of underlying pathophysiology will we be able to put the clinical question of comorbidity in its proper context. At that time, we may be able to move to hypothesis-driven research on intervention strategies and treatment approaches that are informed by a pathophysiological understanding of the psychiatric disorder(s) in question.

## 13. WHAT SHOULD BE THE FUTURE AGENDA FOR RESEARCH ON PTSD?

We have addressed this question throughout this chapter. The field is wide open, since we are really only now entering the realm of contemporary PTSD research, despite the long history of the disorder. The following list summarizes areas that we believe are of importance to our understanding of PTSD. Since stress is so pervasive, and affects all of us in various ways, it is likely that the benefits derived from PTSD research will not be limited to PTSD. We anticipate that the findings derived from studies of the following areas will have wide relevance to a large number of conditions:

a. further exploration of basic neurobiological and psychological mechanisms known to play a central role in the stress response;
b. greater emphasis on theory-driven research derived from important animal models in this field;
c. intensification of efforts to understand the pathophysiology of PTSD;
d. application of laboratory paradigms to psychobiological diagnostic protocols;
e. greater emphasis on randomized clinical tests of drugs in the current pharmacopoeia, as well as initiatives to test new classes of drugs that are suggested by extrapolation from basic stress research;
f. attention to the impact of traumatic stress and PTSD on physical health.

It is our hope that this book will serve as a starting point from which to implement this research agenda during the next few years. We hope that clinical researchers will investigate questions about PTSD from the broader perspective of coping and adaptation, and that their research initiatives will be driven by theoretical considerations. We also hope that basic biobehavioral scientists will test laboratory paradigms that are informed by clinical observations and questions.

In closing, we wish to emphasize that PTSD is a widespread and prevalent disorder. The diagnosis of PTSD is frequently missed. Current treatment strategies for PTSD have generally been attempts at symptomatic relief, with rather poor outcomes. However, with the rapid advances in treatment strategies, aimed at treating symptoms, acutely intervening to ameliorate or retard the emergence of subsequent symptoms, or actively engaging in preventive approaches, it is imperative that PTSD be appropriately diagnosed and that persons at risk be identified. More clinical training is needed. More recognition is needed regarding PTSD's profound long-term effects on brain function. Future success with regard to improved recognition and treatment will require ongoing collaboration between neuroscientists, clinicians, public policy makers, and the community at large. We hope that this book is a start in that direction.