

The long-term costs of traumatic stress: intertwined physical and psychological consequences

ALEXANDER C. MCFARLANE

Centre for Military and Veterans' Health, University of Adelaide, Level 2/122 Frome Street, Adelaide, South Australia, 5000 Australia

The gradual emergence of symptoms following exposure to traumatic events has presented a major conceptual challenge to psychiatry. The mechanism that causes the progressive escalation of symptoms with the passage of time leading to delayed onset post-traumatic stress disorder (PTSD) involves the process of sensitization and kindling. The development of traumatic memories at the time of stress exposure represents a major vulnerability through repeated environmental triggering of the increasing dysregulation of an individual's neurobiology. An increasing body of evidence demonstrates how the increased allostatic load associated with PTSD is associated with a significant body of physical morbidity in the form of chronic musculoskeletal pain, hypertension, hyperlipidaemia, obesity and cardiovascular disease. This increasing body of literature suggests that the effects of traumatic stress need to be considered as a major environmental challenge that places individual's physical and psychological health equally at risk. This broader perspective has important implications for developing treatments that address the underlying dysregulation of cortical arousal and neurohormonal abnormalities following exposure to traumatic stress.

Key words: Post-traumatic stress disorder, allostasis, kindling, hypertension, heart disease

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One of the greatest challenges to the field of traumatic stress has been the observation that many individuals who coped at the time of their traumatic exposure became unwell at a later date.

This observation was particularly challenging in the context of World War I and World War II because the prevailing psychopathological theories at the time did not have a clear rationale for this phenomenon and led to considerable stigmatization of disabled veterans (1). The later emergence of disability in veterans was attributed to compensation neurosis, pre-existing personality disorder, and suggestibility (2). Furthermore, with the blossoming of the general life events stress literature, this pattern of morbidity was not consistent with the prevailing views about high levels of acute distress that progressively ameliorated with time (3, 4). The life events literature which reached its zenith in the 1960s and 1970s focused on notions such as brought-forward time, and emphasized that there was generally a window of approximately six months following which a life event stress could lead to the onset of disorder (5). Delayed onset post-traumatic stress disorder (PTSD) was seen as inconsistent with this conclusion about the window of effect of stressful life events (6).

A primary question has been about how a model of psychopathology could account for this lingering and delayed impact of extreme adversity. Prevailing psychoanalytic constructs and later learning theory did not readily provide an answer to this question. Many significant observations in the context of the depression literature have not been readily adapted by the field of traumatic stress until recent links through the research concerning the relevance of child abuse to depression (7).

This paper explores the evidence about the delayed effects of traumatic stress and their cumulative burden on psychological and physical health. An underlying psychopathological model is summarized and its potential implications for treatment are discussed.

THE RELATIONSHIP BETWEEN ACUTE STRESS DISORDER AND PTSD

The relation between acute post-traumatic symptoms and the emergence of PTSD is an issue of considerable theoretical and clinical importance. There is now a significant body of research documenting that the majority of people who develop PTSD do not initially meet the diagnostic criteria for an acute stress disorder (8). In contrast, the majority of those who have an acute stress disorder are likely to display subsequent PTSD.

A number of longitudinal studies of accident victims have demonstrated that it is only with the passage of time that the level of symptoms crosses a threshold sufficient to warrant a clinical diagnosis (9-13). A similar phenomenon was found in a study of severely injured US troops who were assessed at one month, 4 months and 7 months. This study demonstrated that 78.8% who had a disorder at 7 months did not attract a diagnosis at one month (14). Further support for the delayed emergence is the finding from the screening of military populations that symptoms increase in the first six months following deployment (15,16). Additional adversity, conflict or stress plays a role in the later emergence of psychopathology (17). Hence, in a significant number of individuals, PTSD is a disorder that is not initially manifest in the aftermath of the trauma. Rather, there is a progressive escalation of distress or a later emergence of symptoms, particularly in military and emergency service personnel. A related construct is delayed onset PTSD.

DELAYED ONSET PTSD

Delayed/late onset PTSD is defined in the DSM-IV (18) as a disorder meeting the diagnostic criteria for PTSD which is present after a post-trauma adjustment period of at least 6



months during which diagnostic criteria were absent or sub-threshold (19). From a theoretical point of view, these are likely to be individuals who have managed to contain their individual distress by adaptive means, but subsequent stresses and/or the natural progression of neurobiology have led to the manifestation of the symptoms. A recent review emphasized the confusion which has arisen from different definitions of delayed onset PTSD (20). For example, different interpretations of the concept include an individual who has had sub-syndromal symptoms that have subsequently crossed a threshold of clinical severity as well as an individual who has been asymptomatic and then at some later point developed the disorder.

The existence of this delayed form of PTSD emphasizes how a traumatic experience can apparently lie relatively dormant with an individual only to become manifest at some future point. Many unanswered questions remain about when and how this sub-clinical state is triggered into a full-blown syndrome of PTSD. However, increasingly the evidence would suggest that sub-clinical symptoms leave the individual at risk of progressive activation with further environmental stress or trauma exposure.

A related construct in the depression literature is how individuals who have had partial remission following treatment for an episode of a major depressive disorder are at significantly greater risk of a further recurrence (21). This vulnerability relates to the sensitivity of individuals with residual depressive symptoms to environmental triggers. The underlying neural structures that are sensitive to activation are the same that have been identified as being relevant to the aetiology of PTSD. For example, Ramel et al (22) highlighted that amygdala reactivity is an important issue in people with a history of depression in contrast to those without such a history. These results indicated that the amygdala plays an essential role in modulating mood congruent memory, particularly during the induction of sad states of mind in individuals who are vulnerable to depression.

In such individuals, the cognitive and neural processing of emotional information potentially contributes to the vulnerability for negative emotions and the onset of depressive episodes (23). Hence, there is a significant body of literature documenting that individuals who are primed in emotionally labile and sensitive states are at risk for the progressive intensification of further symptoms, particularly when these resonate with the environment. Hence, the presentation of delayed onset of PTSD is not a unique construct in mental health.

Furthermore, Hedtke et al (24) demonstrated that there is a cumulative effect of exposure to interpersonal violence in terms of PTSD, depression and substance abuse problems. The cumulative risk model highlights the ongoing interaction between prior stress exposure and subsequent life events. The severity of stresses that are experienced prior to and following a traumatic exposure have a significant impact on the incidence and severity of the condition (25). Hence, delayed onset PTSD is intimately involved with the

fact that individuals live in a dynamic environment in which traumatic events and other life stresses interact, with the progressive accumulation of risk.

A related question is whether a longer duration of repeated exposures to trauma in defined time periods carries a greater risk of PTSD, a question relevant to the military and police. The recent UK study of Rona et al (26) provides the first reliable data from the military addressing this question and suggests that the risk of PTSD is greater in those units that have had longer durations of deployment with less time to recuperate between deployments. This study highlights that PTSD is an emerging disorder where multiple traumatic events progressively increase the risk of occurrence.

THE ENDURING IMPACT OF TRAUMATIC MEMORY

The repeated recollection of traumatic memories is a central component of the phenomenological response to traumatic events. Freud highlighted the importance of traumatic memories in his first lecture with Breuer, suggesting that these were the “agent still at work” playing a central role in symptom onset and maintenance (27). Subsequently, modelling in epidemiological samples has highlighted how traumatic memories account for the relationship between exposure to traumatic events and the symptoms of hyperarousal and avoidance (28).

The triggering of these memories is also a consequence of fear conditioning mechanisms (29), and these serve to sustain and kindle the increased arousal that is central to the symptoms of PTSD (30). The disorder arises because some individuals are unable to progressively shut off the acute stress response, which is ubiquitous at times of exposure to such events. From a learning theory perspective, this process is seen as a failure of extinction or new learning in the aftermath of the fear conditioning. Rather, there is a progressive augmentation of the amplitude of the response to reminders.

TRIGGERING AND SENSITIZATION

A primary component of the symptomatology of PTSD is the re-experiencing or reliving of the traumatic memory, that has both elements of psychophysiological reactivation and psychological distress. A unique part of this condition is the repeated reactivation of the traumatic memory and the associated stress response with the attendant risk of the progressive augmentation of the reactivity of the individual (31). In fact, the suggestion has been made that in PTSD there is a failure of the retention and extinction of conditioned fear and that this is an acquired deficit in the condition (32).

On reviewing the available evidence, Rauch et al (33) have suggested that in PTSD there is an exaggerated amygdala response which underpins the excessive acquisition of fear associations and the expression of fear responses. A corresponding deficit of frontal cortical functioning plays a cen-





tral role in mediating extinction. There is also a deficit in the appreciation of the context of safety, which is related to hippocampal function.

The central mechanism is the process of sensitization to the subtle reminders of traumatic memories as well as exposure to prior and future traumatic events. This process of reactivity to minor cues, which very frequently goes unrecognized, serves to progressively increase and exacerbate the reactivity of the dysfunctional individual (34). This leads to an interaction between the individual's distress, psychophysiological reactivity, and the neurohormonal response at the time of the traumatic event. In discussing this question, it is important to recognize that some traumas in combat and policing are not the equivalent of a single traumatic event such as being in a motor vehicle accident. Combat and emergency service work involves repeated activations of the fear and stress systems that are then prone to present as future dysregulation over time.

Individuals who develop PTSD have been found to have a progressive evolution of dysfunction as described above (30). Progressively, they react to the presence of potential threat with greater amplitude or intensity and ultimately develop a generalized overreactivity to a range of stimuli in their civilian and military environments that remind them of the traumatic event. This cycle of increasing reactivity to a widening range of cues in their environment serves to further reinforce the distress response. This pattern is not unique to PTSD and has been highlighted in depression as having a critical role in early episodes (35).

Elzinga and Bremner (36) have further characterized the role of the noradrenergic system in the enhanced encoding of the emotional memories and fear-conditioning in individuals who develop PTSD. The failure of the normal neurotransmitter inhibitory mechanisms that quell the stress response appears to be important in the progression of the individual's distress into a full blown post-event or post-traumatic stress disorder. According to Miller (37), childhood trauma increases the risk of adult psychopathology because of the same process of sensitization (7). Shalev (38) has highlighted that this process is also intimately integrated into the person's social and cultural setting. He states that traumatic events are followed by "a critical period of increased brain plasticity, during which irreversible neuronal changes may occur in those who develop PTSD". He also emphasizes the importance of group cohesion, marital discord, and leadership skills as mediating factors.

Fear conditioning, kindling, and sensitization contribute to the manner in which repeated activation of the fear memories, in PTSD, leads to the emergence of spontaneous intrusive memories (39). In depression, a similar process predisposes an individual to negative affective appraisal and increasingly depressed mood. There is an emerging medical scientific literature indicating that pharmacological agents may be able to modify these responses (40).

The measurement of the startle response can objectively characterize the sensitization that occurs in the fear and

alarm response in PTSD. Increased heart rate in response to sudden loud tones is an abnormality that emerges following traumatic exposure (41,42). This increased reactivity suggests the role of fear conditioning and the impact of the environment following the event. The acquisition of an increased startle response was not related to the severity of the event or the initial intensity of the symptoms. These observations are consistent with the model of progressive neuronal sensitization and increasing heart rate reactivity over the subsequent six months to trauma exposure. This pattern of increased reactivity is also observed in relation to innocuous and aversive stimuli in a conditioning experiment where increased autonomic reactivity was demonstrated to both types of stimuli (43). Once conditioned, those with PTSD had reduced extinction to conditioned responses.

PTSD is only one of the outcomes that have been associated with trauma exposure. The emergence of multiple physical symptoms also has a strong association, and the consensus opinion is that these syndromes are indicative of a general reflection of distress. The underlying mechanisms of these disorders have been related to similar mechanisms of sensitization noted in those with PTSD (44). In parallel, multiple traumas have an accumulative effect on physical health which appears to be independent of the development of PTSD (45).

PHYSICAL MORBIDITY ASSOCIATED WITH TRAUMATIC STRESS

There is longstanding interest in the effects of stress on health, due to the strain that it places on the adaptive capacity of individuals, which thereby leads to an increased risk of disease.

The effects of stress on the hypothalamic pituitary adrenal axis (HPA) and the autonomic nervous system have long been studied and the regulation of these systems has been referred to as "allostatic load". This refers to the wear and tear on the body in response to repeated cycles of stress. This phenomenon has the potential to be manifest in various ways, influenced by the interaction with other personal and environmental risk factors for disease. Hence, the physiological dysregulation that underpins allostasis represents a final common pathway to disease that can be manifest in various ways.

Particularly in the context of post-deployment syndromes, the link to musculoskeletal symptoms has become a focus of increasing interest. Equally, the role of allostatic load has come to be seen as an important risk for coronary arterial disease and its antecedent risk factors. However, the intermediary role of PTSD has not been the focus of particular interest in explaining these relationships until recently. The emerging body of evidence, which coincides with the real prevalence of PTSD in studies such as the National Comorbidity Survey Replication (46), suggests that physiological dysregulation associated with PTSD may play a central mediating role in a range of conditions.





PTSD AND PSYCHOSOMATIC SYNDROMES

Andreski et al (47) reported that, of all the psychiatric disorders, PTSD is the one with the strongest relationship with somatization and particularly medically unexplained pain. Although there is substantial literature relating somatization to PTSD, this body of knowledge is seldom referred to in the broader literature about somatization, which has largely focused on the role of depression and anxiety (48-52). Particularly in the light of more recent epidemiological studies which suggest the previous underestimation of the prevalence of traumatic events and PTSD in many settings, there is a greater need to focus on the possible role of trauma in populations with medically unexplained symptoms (53).

There has been an increasing recognition of a shared pattern of symptoms and aetiology between whiplash, fibromyalgia, irritable bowel, chronic fatigue and PTSD. In particular, disorders of the HPA axis have been identified in all these disorders (54,55), where the shared dysfunction appears to be an enhanced negative feedback of the axis. Such stress-induced changes have been associated with major impacts on neurogenesis and brain functioning (56,57). A recent prospective study has suggested that this dysfunction of the HPA axis plays an important role in the onset of chronic widespread musculoskeletal pain in a general population sample (58). McEwen's model of allostasis has focused on the temporal lobe and the changes induced by cortisol at the times of stress exposure (56). Whilst focusing on the importance of this process in PTSD, persistent pain has also been associated with stress-like induced alterations of hippocampal neurogenesis and gene expression (59).

Sensitization is a critical process in the onset of pain syndromes and also in PTSD, as outlined above. The exposure to environmental triggers to the traumatic memory structure plays a critical role in the emergence and progressive escalation of an individual's distress across time, which includes somatic dimensions. This complex biological process emerges in the weeks and months following the event, involving the interaction between the individual's distress and the neuro-hormonal response at the time of the traumatic event (34).

The central role of the amygdala in the kindling in PTSD has much in common with the phenomena of windup of C fibre evoked pain (60). The centrality of this process has been suggested in both fibromyalgia and chronic fatigue (61,62).

Similar patterns of sensitization and modified pain sensitivity have been characterized in irritable bowel syndrome (63,64). The shared neurobiological abnormalities in these conditions are a further argument in favour of a generalized stress response syndrome underpinning multiple complaints. Furthermore, this has been associated with a modified autonomic function, that is also thought to play an important role in the pain response in fibromyalgia patients, individuals with neck and shoulder pain, and irritable bowel disorder (65), and has been found to be present also in individuals absent from work with a stress related illness (66).

THE RELATIONSHIP BETWEEN HYPERTENSION AND PTSD

A number of studies have suggested that PTSD has a direct relationship with the risk of developing hypertension. A study of a probability sample from the US National Comorbidity Survey examined the interaction between PTSD and major depression as determinants of hypertension. It concluded that PTSD was related to hypertension, independent of depression, and that this finding could possibly explain the elevated rates of cardiovascular disease associated with PTSD (67). This specific relationship explains the high prevalence rate of hypertension identified amongst refugee psychiatric patients (68).

O'Toole and Catts (69) examined an epidemiological sample of Australian Vietnam veterans, aiming to explore the relationship between the physical health consequences of combat trauma exposure and PTSD. Hypertension was one of the conditions that was found to be associated with PTSD, both before and after controlling for potential confounds. In PTSD, it has been recognized that exposure to traumatic triggers leads to increased blood pressure, heart rate, and sympathetic activation of sweating in the hands (70). This abnormality has a significant degree of specificity for PTSD (71). This is consistent with the observation that in PTSD there is increased activity of the sympathetic nervous system, and in particular hyperfunction of the central noradrenergic system (72).

A US population study of hypertensive individuals looked at the impact of the September 11, 2001 attacks. Whilst these patients did not have a particularly high level of exposure, in the two months following the terroristic attacks they had an increase between 1.7 and 3.3 mm of mercury of systolic blood pressure compared with a similar period in 2000. Hence, at a population level, individuals who are suffering from hypertension are at risk of increases in blood pressure as a consequence of exposure to stressful events (73).

This body of evidence indicates that there is a link between PTSD and the risk of hypertension. This is an important development, as it indicates that the failure to specifically look at the relationship between PTSD and hypertension in earlier studies has led to confusion about the link between stress and coronary heart disease. For example, the Australian National Heart Foundation in 2003 suggested that there was no strong or consistent evidence for a causal association between chronic life events, work stress, patterns of hostility/anxiety disorders or panic disorder and coronary heart disease. The intermediary role of PTSD in this relationship is an important link (74).

HYPERLIPIDAEMIA

Lipid metabolism is an area of importance to the risk of vascular disease. A study of Brazilian police officers demonstrated that officers with PTSD had significantly higher lev-





els of total cholesterol and triglycerides (75). A study from Croatia compared patients with combat related PTSD and a control group consisting of patients with major depressive disorder (76). In this study, lipid profiles consisting of cholesterol, LDL, HDL, and triglycerides were assessed. The groups were matched for age and body mass index (BMI). The individuals with PTSD had higher mean levels of cholesterol, LDL-C, and triglycerides and lower HDL-C than the control group. The arteriosclerotic index was higher in the PTSD than the control group. These results were taken to conclude that patients with combat related PTSD had a higher risk of arteriosclerosis (76-78). It is probable these findings will generalize to other populations.

THE RELATIONSHIP BETWEEN OBESITY AND PTSD

Obesity is associated with an increased risk for several diseases, including cardiovascular disease. Vieweg et al (79), using a national database, documented a significantly increased BMI in individuals with PTSD, not affected by the decade of life. It was concluded that PTSD may be a risk factor for being overweight. This relationship has also been found in clinical samples (80).

A population study of young adults in Germany (81) examined the relationship between a PTSD diagnosis and having a BMI greater than 30. In the 10-year follow-up of this sample from childhood, obesity was predicted by an antecedent subthreshold or full blown PTSD, with an odds ratio of 3, amongst men but not women. This relationship has not been universally identified, and a series of complexities influencing it should be acknowledged. However, a further population sample in New Zealand did find an association between PTSD and obesity (odds ratio 2.64) (82).

In a study of police officers, the relationship between PTSD symptoms and metabolic syndrome was examined. Metabolic syndrome was deemed to be present if an individual had 3 or more components among obesity, elevated blood pressure, reduced high density lipoprotein (HDL cholesterol), elevated triglycerides and abnormal glucose. The officers with severe PTSD had 3 times the rate of metabolic syndrome of the lowest PTSD severity category (83).

THE RELATIONSHIP BETWEEN PTSD SYMPTOMS AND CORONARY HEART DISEASE

The US Department of Veterans' Affairs has conducted a normative aging study (84). The sample, including men who had completed two scales for PTSD, was recruited in 1990. The men were followed up and the incidence of coronary heart disease occurring up to May 2001 was assessed. For each standard deviation increase in the level of post-traumatic symptoms, the men had an attributed relative risk of 1.26 for non-fatal myocardial infarction and fatal coronary heart disease combined and 1.21 for all coronary heart dis-

ease outcomes. The importance of this study is that it indicated that the level of post-traumatic symptoms, rather than the PTSD diagnosis itself, is associated with an increased risk of coronary heart disease. These results were maintained after controlling for depressive symptoms.

While hypertension, hyperlipidaemia and obesity are risk factor associations that could link PTSD to heart disease, this could also relate to the exaggerated catecholamine response to trauma related triggers. It has been demonstrated in a variety of settings that catecholamines may lead to injury of the lining intimal endothelium of the coronary arteries, leading to the development of atherosclerosis (85,86). Kubzansky et al (84) concluded that "exposure to trauma and prolonged stress not only may increase the risk of serious mental health problems but are also cardiotoxic".

Boscarino (87) studied a national random sample of 4,328 Vietnam veterans who did not have heart disease at baseline in 1985. The mortality due to heart disease from having PTSD had a hazard ratio of 2.25. When the effects of depression were controlled for, the degree of combat exposure made little difference to the results. The author concluded that "early age heart disease may be an outcome after military service among PTSD positive veterans". Again, this study emphasized that there is a specific risk for heart disease mortality associated with PTSD, but there is also a risk simply associated with an increased level of post-traumatic symptoms in individuals who do not reach the diagnostic threshold.

Another study carried out in former World War II prisoners of war found that prisoners with PTSD had a significantly increased risk of cardiovascular diseases, including hypertension and chronic ischemic heart disease, compared with individuals who had been prisoners of war but had not developed PTSD as well as non-prisoners (88).

In summary, the evidence from prospective studies is suggestive of a link between heart disease and PTSD.

CLINICAL IMPLICATIONS

The association between PTSD and a number of physical conditions emphasizes that the effects of traumatic stress are far reaching. There is the potential for a pervasive disruption of an individual's neurobiology and psychophysiology following exposure, and PTSD is only one end point. The association with cardiovascular risk factors and inflammatory markers indicates that exposure to traumatic stress leads to a general disruption of an individual's underlying homeostasis (89,90).

In essence, the internal physiological environment of an individual adapts to external demands. This dynamic regulatory process involves a continuous adaptation of physiology in response to environmental demand. When the body is repeatedly stressed, the consequent allostatic state has the capacity to disrupt an individual's health (91). For example, Karlamangla et al (92) looked at the longitudinal impact of allostatic load in the MacArthur studies of successful aging,



and found that those individuals whose allostatic load dropped over a 5 year period had a significantly lower risk of mortality.

Hence, the underlying acclimatization of an individual to an environment and the costs that this exerts on the body is critical to the maintenance of health from a psychological and physical perspective (93). Traumatic stress leads to a disruption of the glucocorticoid system, in concert with a range of other neuropeptides such as corticotrophin-releasing factor (CRF), beta endorphin, neuropeptide Y and the catecholamines. The impact of glucocorticoids on the amygdala and hippocampus as part of contextual fear conditioning is an essential component of allostatic adaptation (94).

TREATMENT IMPLICATIONS

At the present time, the treatment of PTSD focuses on cognitive behavioural therapy and the use of selective serotonin reuptake inhibitors (95). However, recommended treatments do not take into account the need to address the underlying instability of psychophysiology, particularly in the earlier periods following exposure. In this light, it is interesting that prazosin, an alpha-adrenergic antagonist, has been found to have a beneficial role in the treatment of PTSD (96), and that cortisol has been found in intensive care populations to have a protective effect against PTSD (97).

One treatment that may be of particular significance and requires systematic investigation is neurofeedback (98,99). There is now an established literature about abnormalities of quantitative EEG which suggest a significant disruption of cortical arousal in PTSD (100). Neurofeedback has been used in other disorders where there are demonstrated abnormalities of cortical activity. Particularly in populations at a significant risk for PTSD, such as military and emergency service groups, the use of this technique may be beneficial. Equally, the development of methods to modify the progressive augmentation of startle could help individuals to re-establish their psychophysiology to its baseline state. Recalibration may be easier prior to the development of a full-blown clinical disorder.

CONCLUSION

The progressive emergence of symptoms following traumatic stress exposure is a challenging concept and delayed onset PTSD has long been a controversial notion. However, there is an increasing body of literature demonstrating that a significant proportion of trauma victims do not have their maximal stressor response in the immediate aftermath of the event, but rather this progressively increases with time. In some individuals, the apparent adverse consequences of the stress exposure lie dormant for a long period of time before some intercurrent adversity leads to its manifestation.

Thus, it would appear that trauma exposure initiates a

process of disruption of an individual's internal psychophysiology that is then progressively sensitized and kindled with the repeated exposures to triggers. This pattern of increasing sensitivity to environmental load can also become manifest as hypertension, hyperlipidaemia, and obesity. There is now an established association between cardiovascular disease and PTSD.

Ultimately, major treatment advances in PTSD may arise from considering the broader disruption of these neurobiological systems by their repeated activation. This emphasizes that PTSD is not simply a psychosocial disorder, but one underpinned by a major neurobiological disruption.

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