Call #: QP376 .P7 V.167
Location: 4

ILL Number: 84961789

Patron: Jenson, Deborah

Journal Title: Progress in brain research.

Volume: 167 Issue: 
Month/Year: 2008
Pages: 217-28

Article Info: Brewin, Chris R; What is it that a neurobiological model of PTSD must explain?

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CHAPTER 15

What is it that a neurobiological model of PTSD must explain?

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Abstract: PTSD is a complex disorder that involves far more than a fear response, and cannot be explained by a simple conditioning model. Both individual vulnerability and specific reactions during and after the trauma are involved in maintaining the disorder. A consideration of risk factors implicates the experience of being "overwhelmed" at the time of the trauma, accompanied by possible downregulation of the prefrontal cortex. Also important are reactions to symptoms post-trauma and specific strategies adopted to manage symptoms, such that there is a continuing inability to process trauma memories. An analysis of the characteristic forms of autobiographical memory in PTSD implicates two memory systems, one predominantly image-based and one predominantly verbal. These systems are likely to be differentially impacted by hormonal responses to extreme stress, leading to an imbalance in the representation of trauma in the two systems. Exposure to trauma reminders leads to retrieval competition between the two sets of memories, with retrieval of verbal memories able to inhibit inappropriate amygdala responses. Evidence to support this analysis is described, drawing on experimental studies of memory for trauma and a meta-analysis of memory for emotionally neutral information in PTSD. The implications for neurobiological studies of PTSD are discussed.

Keywords: PTSD; stress; memory; amygdala; hippocampus

Posttraumatic stress disorder (PTSD) is a condition that may occur following an overwhelming event that typically involves actual or threatened death or injury. The symptoms consist of the re-experiencing of the event in the form of intrusive memories or nightmares, avoidance of reminders of the event, emotional numbing, and a permanent state of high arousal. In order to evaluate the potential contribution of neurobiological research to the understanding of PTSD it is necessary to summarize the current state of knowledge about clinical features of this disorder, its risk factors, and the psychological mechanisms that contribute to its onset and maintenance. This information will provide a useful benchmark with which to gauge the strengths and weaknesses of a neuroscience perspective, and to assess those areas in which it is likely to make an important contribution.

Clinical features of PTSD

It is clear that PTSD is associated with overwhelming stress, but is not defined by exposure to overwhelming stress. The majority of individuals exposed to extreme stress do not develop PTSD. In this respect PTSD is similar to other psychiatric
disorders in that onset of a particular episode tends to follow a stressor but is more likely to do so in vulnerable individuals. PTSD requires a diathesis-stress model in which aspects of event exposure interact with individual characteristics and response patterns (Brewin, 2003). Similarly, the traumatic memories of individuals with PTSD are different from the memories of non-sufferers: once an initial period of adjustment has passed, memory characteristics are less a function of the event than of the individual who has experienced it (Brewin, 2007).

PTSD symptoms also have in common with the symptoms of other psychiatric disorders that they are not in themselves abnormal, but are commonly experienced in the immediate aftermath of a traumatic event. What defines the disorder is not the unique nature of the symptoms, but their frequency, longevity, and the associated impairment. Further, PTSD symptoms overlap to a large extent with those characteristic of other conditions associated with exposure to stress, such as bereavement and depression. In both these conditions there tends to be a spontaneous intrusion of memories that the individual tries to avoid, ruminate thoughts, social withdrawal and emotional numbing, and arousal symptoms including lack of concentration, irritability, and sleeplessness.

Although traumatic events are defined by the DSM-IV as generating extreme fear, helplessness, and horror, it is a mistake to think that PTSD is just a disorder of fear. Studies have shown that other emotions, such as anger, are as common or more common than fear (Reynolds and Brewin, 1999). The whole question of the relationship between PTSD and emotions needs to be considered separately in terms of onset and maintenance, and a variety of different causal pathways and psychological mechanisms may be relevant. For example, shame appears to be important in determining the longitudinal course of the disorder (Andrews et al., 2000). Thus there is a significant degree of overlap between PTSD and other disorders in emotions as well as symptoms.

Despite the fact that phobic symptoms are often part of PTSD, the disorder is unlike a simple phobia. In phobia, anxiety is only present when the individual is confronted with their feared situation. In PTSD, by contrast, there is a sense of continuing, current threat that leads to a permanent state of arousal (Ehlers and Clark, 2000). This sense of threat may be present even though the individual accepts that it is logically impossible for the trauma to happen again. PTSD is also associated with much more profound changes to sufferers’ sense of identity than in phobia: It is not unusual for patients to feel strongly that they have been changed irrevocably by their experiences and that they can no longer see the world in the same way (Brewin, 2003). This often goes along with wide-ranging changes to their social relationships.

It has also been argued that PTSD is distinguished from other disorders by two main symptoms, flashbacks and traumatic nightmares. Both symptoms involve the repeated reliving of the traumatic event, often in a stereotyped way. The concept of reliving is as yet poorly understood, and it is commonplace for emotional memories, for example in depression, to contain an element of repetition and recognition of the original emotions. What appears to differentiate flashbacks from these common intrusions of memories is that they involve the sense that events are happening again in the present. This distortion in the sense of time is an aspect of dissociation, a term that refers to a variety of ways in which the usually integrated functions of consciousness, memory, identity, or perception of the environment may be disrupted. For example, speeding up or slowing of subjective time, feelings of numbness and detachment, or out-of-body experiences, are common during and after traumatic events. In extreme cases traumatized individuals may become totally absorbed in their memories and unable to apprehend events in the environment. This kind of phenomenon has not been described in depressive disorders, where intrusive memories tend to be experienced as belonging in the past, like ordinary autobiographical memories.

**Insights from risk factors**

Risk factor research has been summarized in two recent meta-analyses (Brewin et al., 2000; Ozer et al., 2003). Background factors, such as greater socioeconomic disadvantage, prior trauma, adverse parenting, prior psychopathology, and a family history of psychopathology, are risk factors for PTSD just as they are for most psychiatric conditions. There have been several longitudinal studies indicating that lower intellectual ability confers some risk, or alternatively that greater intellectual ability confers a degree of protection. A recent twin study suggests that this effect is accounted for by verbal rather than non-verbal abilities (Gilbertson et al., 2006). These factors only account for a relatively small amount of the variance, however.

A second set of risk factors describes responses during the traumatic event (peri-traumatic factors). High stressor intensity, particularly subjectively experienced intensity as measured through a perceived threat to life or extreme fear, helplessness, or horror, is strongly related to risk of later PTSD. A sense of mental defeat, as having given up any attempt to control the outcome, is a related phenomenon that also acts as a risk factor (Ehlers et al., 2000). Dissociation is also well established as a risk factor. This is interesting, as dissociation might be expected to interfere with encoding of the traumatic events into memory. Indeed, some theories have assumed that PTSD involves enhanced encoding of traumatic material and have even predicted that greater dissociation should protect against PTSD for this reason (Tryon, 1999).

A third set of risk factors involves processes that occur post-trauma and that may interfere with normal adaptation. Ehlers and Clark’s (2000) cognitive model of PTSD maintenance describes numerous factors that have now been shown to predict a worse outcome, including negative appraisals of the trauma, of people’s actions, and of the perpetrator’s own symptoms, and inappropriate coping strategies such as avoidance, thought suppression, and adoption of safety behaviors (see Brewin and Holmes, 2003, for a review).

Consistent with the major psychological theories of PTSD, disruption and fragmentation of narrative memories of the trauma also appears to be a risk factor for the development of the disorder. This has been shown in two longitudinal studies, one measuring narratives as early as 1 week post-trauma (Halligan et al., 2003; Jones et al., 2007). Narratives characterized by repetition of utterances and the presence of non-consecutive chunks were associated with more severe PTSD at 3 months. Additionally, disorganization in narrative memories is associated with peri-traumatic dissociation. These findings are compelling, but it should be noted that they depend on having independent blind raters categorize the content of patients’ narratives. Attempts to have patients rate disorganization in their own narratives, or to use computer programs to index this, have often failed to find a relationship between PTSD and memory disorganization.

This review has emphasized the variety of processes shown to be associated with PTSD, and it is important to be open to the possibility that there are alternative pathways leading to the disorder. For example, many PTSD patients exposed to trauma stimuli experience an increase in heart rate (Pitman et al., 2000), and there is evidence that increased heart rate immediately post-trauma predicts the likelihood of developing PTSD (Shalev et al., 1998; Bryant et al., 2000). Some individuals with PTSD, on the other hand, respond to trauma stimuli with dissociative reactions, a type of response that has on several occasions been linked to reductions in heart rate (Giffin et al., 1997; Koopman et al., 2004). Likewise, longitudinal studies of trauma survivors suggest that those who experience high levels of dissociative symptoms initially, and those who have high levels of reexperiencing and arousal, are both at risk for PTSD but that they form non-overlapping groups (Brewin et al., 1999). These contrasting patterns have been related to the experience of alternative behavioral responses to threat (flight/fight versus freezing) that are thought to possess different biologic substrates (Nijenhuis et al., 1998).

**Explaining flashbacks and nightmares: sensory versus verbal memory**

In order to explain why traumatized individuals experience vivid involuntary memories while at the same time having difficulty in deliberately retrieving coherent narrative memories, clinicians
have from the end of the 19th century onwards argued for the existence of parallel verbal and sensory memories of trauma (see Brewin, 2003, for a review). Verbal memories require high levels of cortical processing, resulting in them being contextually within the autobiographical memory system, whereas sensory memories receive less in the way of higher processing and are stored as isolated images devoid of context. Metcalfe and Jacobs (1998) outlined evidence that high levels of stress may simultaneously impair the operation of brain structures supporting autobiographical memory (e.g., the prefrontal cortex and hippocampus), while simultaneously facilitating the operation of brain structures such as the amygdala that support image-based memories.

In the most recent incarnation of this approach, the dual representation theory of PTSD, Brewin (Brewin et al., 1996; Brewin, 2003) discusses in some detail how image-based ("situationally accessible") forms of memory can be retrieved automatically by trauma cues and how the lack of contextual coding results in the brain responding as though the trauma occurred again in the present. In this theory a prerequisite for the development of flashbacks as well as the poor quality of intentional recall is enhanced encoding of situationally accessible trauma memories coupled with impaired encoding of the same material into the autobiographical ("verbally accessible") memory system. This preferential encoding may be a product of peri-traumatic dissociation and the prefrontal cortex temporarily going "off-line" in response to a level of stress that exceeds the individual's coping abilities. Over the next days and weeks flashbacks provide an opportunity for this material to receive additional conscious processing and to be re-encoded into verbally accessible memory. The additional information provided by this form of memory enables the brain to classify the trauma as having happened in the past and inhibits the retrieval of corresponding sensory memories. Thus imbalances in encoding into the two memory systems can be naturally corrected in a relatively short space of time, allowing defensive arousal to subside.

In PTSD, however, dual representation theory suggests that normal adaptation does not occur because this process of re-encoding never takes place. The high levels of behavioral and cognitive avoidance characteristic of the disorder result in intrusive sensory images not being consciously attended to. Corresponding verbally accessible memories remain impoverished and never contain sufficient information about critical retrieval cues to enable them to inhibit the intrusions. As a result exposure to reminders of the trauma continues to elicit the intrusion of unwanted sensory memories accompanied by high levels of emotion and perceived threat, shortly to be followed by secondary consequences such as depression and social withdrawal.

Evidence for dual representations of trauma
Experimental studies of intrusions

In order to test hypotheses about intrusive trauma memories being supported by a sensory memory system, Holmes et al. (2004) had healthy volunteers as though the trauma occurred again in the present. In this theory a prerequisite for the development of flashbacks as well as the poor quality of intentional recall is enhanced encoding of situationally accessible trauma memories coupled with impaired encoding of the same material into the autobiographical ("verbally accessible") memory system. This preferential encoding may be a product of peri-traumatic dissociation and the prefrontal cortex temporarily going "off-line" in response to a level of stress that exceeds the individual's coping abilities. Over the next days and weeks flashbacks provide an opportunity for this material to receive additional conscious processing and to be re-encoded into verbally accessible memory. The additional information provided by this form of memory enables the brain to classify the trauma as having happened in the past and inhibits the retrieval of corresponding sensory memories. Thus imbalances in encoding into the two memory systems can be naturally corrected in a relatively short space of time, allowing defensive arousal to subside.

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Verbal and visual memory capacity in PTSD

The theory suggests that PTSD is likely to be associated with impaired verbal memory but a well-functioning sensory memory system. In order to test whether there are general deficits in verbal memory that apply even to emotionally neutral material, Brewin et al. (2007) recently conducted a meta-analysis of verbal and visual memory functioning in PTSD. The analysis summarized investigations that compared a PTSD group diagnosed according to the DSM with healthy controls on their performance on standardized memory tests. They found 27 relevant studies that included a total of 812 controls and 660 individuals with PTSD arising from a variety of different trauma types. PTSD was associated with impaired memory functioning generally and, consistent with dual representation theory, patients' verbal memory was significantly worse than their visual memory. These differences could not be explained by potential confounding factors such as trauma exposure, general intellectual ability, head injury, or substance abuse. The analysis does not tell us whether these neuropsychological differences predate the onset of PTSD, whether they are a result of PTSD, or both. Relevant evidence is provided in a study by Gilbertson et al. (2006) of combat veterans and their identical twins who were not exposed to combat. By comparing the performance of veterans with and without PTSD, and their non-exposed co-twins, it is possible to distinguish the consequence of combat exposure and PTSD from familial vulnerability factors that increase or decrease the risk of disorder. Gilbertson et al. reported that the identical co-twins of PTSD combat veterans, who had neither combat exposure nor PTSD themselves, showed a similar pattern to their PTSD brothers in having poorer verbal memory. They suggested that better neuropsychological functioning in these areas acted as a source of pre-existing resilience when veterans were later faced with traumatic events. Consistent with the results of the meta-analysis, they found no evidence that poorer visual memory was associated with PTSD symptoms or acted as a risk or resiliency factor.

Experimental studies of PTSD

Hellawell and Brewin (2004) described the difference between flashbacks, involving a marked sense of reliving events in the present, and ordinary memories to people with PTSD and then had them write a detailed narrative of their traumatic event. At the completion of the narrative participants retrospectively identified periods of writing during which they experienced each of the two types of memory. All the participants reported recognizing and being able to distinguish between the two types of memory as they wrote about their trauma, but there was great individual variation in how many reliving periods they identified, how long these lasted, and where in the narrative they occurred.

Consistent with prediction, during parts of the narrative involving reliving they used more words describing seeing, hearing, smelling, tasting, and bodily sensations, as well as more verbs and references to motion, than they did during ordinary memory sections. Fear, helplessness, horror, and thoughts of death, all reactions associated with the traumatic moments themselves, were prominent during the reliving sections. In contrast, emotions associated with later appraisals and interpretations of the events, such as sadness and anger, were more prominent during the ordinary memory sections. These data support the argument that reliving is not just a function of extreme emotion,
but of specific emotions such as fear that occur at the moment of trauma (see also Reynolds and Brewin, 1999, for evidence supporting a specific relationship between fear and reliving).

As part of this study, Hellawell and Brewin (2002) investigated whether flashbacks were predominantly image-based, using visuospatial resources, and ordinary memories predominantly verbal. They reasoned that if flashbacks use visuospatial resources, then they should interfere with performance on other tasks that also made visuospatial demands but not interfere with unrelated tasks. So, while participants with PTSD were writing their narratives, they were stopped on two occasions, once when they were in a reliving phase and once when they were in an ordinary memory phase, and made to carry out two tasks. One task, trail-making, involved visuospatial abilities and the other, counting backwards in threes, involved more verbal abilities. The results showed that trailmaking performance was much worse when participants had been halted during a reliving phase of their narrative than when they had been halted during an ordinary memory phase, whereas counting backwards in threes was adversely affected to an equal extent in both phases. This supports the idea that there is a qualitative difference between flashbacks and ordinary memories.

A possible neural substrate for trauma memories

Within the declarative memory system concerned with conscious knowledge of facts and events the hippocampus appears to be specialized for the learning of context (including temporal context; Kesner, 1998), and for learning relational properties among stimuli. It is thought to be crucial in binding together the various elements of an episode to make a coherent and integrated ensemble. Eichenbaum (1997) proposed that the hippocampus encodes separate stimulus elements and the relations between them such that the representations can be utilized flexibly and accessed in a variety of ways. It has also been suggested that the hippocampal system is particularly associated with memories of conscious experience (Moscovitch, 1995).

From the perspective of dual representation theory it would appear that hippocampal processing is likely to be a critical aspect of verbally accessible (narrative) memories that form the basis of deliberate appraisal and communication concerning the trauma (Brewin, 2001, 2005). The hippocampus is highly sensitive to stress, being well supplied with receptors that are occupied by stress hormones. A wealth of animal studies confirm that severe stress impairs hippocampal function and memory performance, and there is a corresponding literature in humans. This demonstrates impaired paired explicit memory performance associated with raised levels of glucocorticoids, adrenal steroid hormones that are released after stressful experiences, in the context of naturally occurring conditions or experimental treatments (Alderson and Novack, 2002). Acutely elevated levels of glucocorticoids have been found to be associated with impaired memory and reduced blood flow in areas of the medial temporal lobe adjacent to the hippocampus (de Quervain et al., 2003). At present it is unclear whether high levels of stress hormones impair the consolidation of memories, their retrieval, or both.

Importantly, studies reveal that mild to moderate levels of stress have opposite effects to severe stress on memory function. This has been related to the levels of occupancy of different types of receptor in the hippocampus. At low levels of stress there is heavy occupancy of mineralocorticoid receptors and low-to-moderate occupancy of glucocorticoid receptors. Memory impairments appear to be associated with the high levels of occupancy of glucocorticoid receptors that are associated with severe stress (Alderson and Novack, 2002; Kim and Diamond, 2002; Sapolsky, 2003). At present it is unclear whether reduced hippocampal function in PTSD is primarily related to the effects of severe stress, to pre-existing vulnerabilities, or both.

Whereas explicit memory is associated with the hippocampus, the various forms of implicit memory (e.g., priming, fear conditioning) do not appear to have any particular locus in the brain. The involuntary memories that are characteristic of PTSD may be considered to be related to implicit memory, in that they share the characteristics of being automatically retrieved in a predictable, cue-driven manner, and being hard to control. They are unlike normal examples of implicit memory, however, in that they possess explicit trauma-related content that is immediately recognized by the person experiencing them. In the dual representation theory of PTSD, both flashbacks and fear conditioning are considered to be products of the situationally accessible memory system.

It is possible for fear-relevant information to reach the amygdala via a number of different routes, independently of the hippocampus. For example, the visual areas of the inferior temporal cortex, which are involved in the late stages of sensory processing, project strongly to the amygdala. The pathway from the thalamus to the amygdala has a less sophisticated processing capacity and would be capable of transmitting lower level sensory features of frightening situations. Memories formed in these ways would not be open to deliberate recall, but could be accessed automatically by reminders, particularly perceptual features, similar to those recorded in the fear memory.

As noted by several authors (Metcalf and Jacobs, 1998; Elzinga and Brenner, 2002), high levels of stress appear to have very different effects on the hippocampus and the amygdala. For example, the same stress experience produces dendritic atrophy and debranching in the hippocampus at the same time as producing enhanced dendritic arborization in the amygdala (Yuas et al., 2002, 2003). Thus, sensory or situationally accessible memories (such as flashbacks) could be enhanced at the same time as narrative or verbally accessible memories were impaired.

Conclusions: implications for a neurobiological model of PTSD

The results of existing data from structural and functional imaging studies of PTSD show some consistency, for example in increased amygdala activation coupled with hypoactivation of the medial prefrontal cortex, but also a high degree of variability, for example with respect to hippocampal activation (Hull, 2002; Shin et al., 2005a; Francati et al., 2007) that has the potential to impede progress in this area. Research into the clinical features, risk factors, and psychological mechanisms associated with PTSD has a number of important implications for designing better and more tightly focused studies, and reducing this variability. Among the most obvious are the findings concerning the high incidence of comorbidity, the role of maintenance as well as onset processes, the different pathways to the development of PTSD, and the existence of different forms of memory.

Given the overlap in symptoms between PTSD and other disorders, the use of comparison groups needs to be reconsidered. It is already accepted as good practice to include a control group of individuals who have been exposed to similar traumatic events without ever developing PTSD, in order to rule out the possibility that observed group differences are simply due to trauma exposure. Most neuroimaging studies, however, do not include comparison groups suffering from other disorders such as depression (see Shin et al., 2005a, for a review). This means that the interpretation of structural and functional differences between PTSD patients and controls. For example, the interpretation of studies showing reduced hippocampal volume in PTSD is complicated by studies with similar findings in patients selected for major depressive disorder (Neumeister et al., 2005; Slayam et al., 2006). The fact that it is the persistence of PTSD symptoms that is pathological, rather than their form, also has important implications. It suggests that neurobiological differences between PTSD patients and controls are as likely to reflect differences in the way individuals have adapted or responded to having symptoms as they are to reflect differences in their initial response to trauma. This is particularly important given that the vast majority of neuroimaging studies, for example, have been conducted on samples with very chronic PTSD (Shin et al., 2005a). PTSD is associated with the use of well-marked behavioral and cognitive strategies including avoidance, thought suppression, and the adoption of safety behaviors. It is these habitual responses that may be detected by functional imaging studies of patients exposed to
trauma stimuli, for example in the script-driven imagery paradigm.

Risk factor research has identified the importance of processes that operate before, during, and after traumatic events, with the latter two sets of processes accounting for most of the variance. This suggests that neurological studies conducted at encoding (in healthy volunteers exposed to experimental stress) or immediately posttrauma (e.g., on admission to an emergency room) are essential to disentangle the two sets of effects. Further, there will be value to studies that focus more intensively on the first 2-3 weeks posttrauma, when high levels of initial symptoms subside in most exposed individuals but not in the subset who go on to develop PTSD. Shafee (2003), for example, has described how during this period a process of increasing sensitization differentiates those who fail to recover. Sensitization refers to systematic changes in normal thresholds of stimulus discrimination and responding, illustrated for example by a slowly developing abnormal startle response. There are also specific emotional states that may only develop posttrauma and yet have been shown to predict a worse outcome. It will be important to correct the over-emphasis on emotions present at encoding (such as fear) in favor of emotions present during recovery (such as anger and shame).

Risk factor research has also drawn attention to the possibility that there is more than one pathway to the development of PTSD, involving acute reactions characterized either by excessive arousal and high heart rate, or by dissociation and lowered heart rate. Both routes have received independent support from experimental research either with PTSD patients or healthy volunteers. Apart from alerting researchers to the possible existence of subgroups of PTSD patients demonstrating different forms of pathology, these data underscore the importance of individual differences, for example in response to tasks in the laboratory such as being exposed to trauma reminders. These different reactions are likely to be associated with alternative patterns of neural as well as psychophysiological responses. Lanius and colleagues, for example, reported that individuals with a history of sexual abuse evidenced different kinds of responses to script-driven imagery, some experiencing reliving and increased heart rate while others experienced a dissociative response. They went on to analyze differential patterns of neural activation (Lanius et al., 2002) and interregional brain activity co-variations (Lanius et al., 2005) in these groups.

In a parallel vein, psychological studies have drawn attention to the existence of different forms of intrusive cognition that may underlie specific symptoms and that may interact to determine outcome. This implies that researchers need to develop strategies that enable them to focus more explicitly on individual symptoms rather than on PTSD as a whole. Ousch et al. (2001), for example, investigated the correlation between regional cerebral blood flow and the intensity of flashbacks. Researchers need pay more attention to individual responses to trauma stimuli, script-driven imagery, etc. These may elicit a variety of responses including rumination, ordinary remembering, flashbacks, thought suppression, or dissociation, all of which may correspond to distinct patterns of neural activity. Also, neurobiological models may need to consider in more detail how to model interactions between different areas of the brain. A good example of this is the existing work showing an inverse association between activation of the amygdala and prefrontal cortex (Shin et al., 2005b; Francazi et al., 2007).

Acknowledgments

The author’s research is supported by the Wellcome Trust.

References


**Discussion: Chapter 15**

SHALEV: Looking into the nature and origin of intrusive recollections is extremely important to the understanding of PTSD. For me they also occur in response to the incongruence and grotesqueness of the experience, which takes us beyond the fight/flight sequence paradigm. Relating this to work in basic science, there is evidence that exposure to species-specific 'grotesque' stimuli can evoke, in some animal species, a sequence of first attending to the aversive stimulus and second avoiding it. (Hebb, D.O. 1946; The nature of fear. Psychol. Rev., 53: 259–276; Humphrey, N.K. and Keeble, G.R. 1974; The reaction of monkeys to 'fearsome' pictures. Nature, 251: 502–502.) This sequence of attending/avoiding might be analogous to the sequence of intrusive recollections and their avoidance in PTSD. I would argue that stressful events do not become traumatic unless they include an element of incongruity—or otherwise unacceptable, shocking or unimaginable novelty. Stern's book "The Buffalo Creek Disaster" (Random House, 1977, pp. 46–47), for example, describes survivors who were satisfied to have struggled and pulled themselves out of the sliding mud, but then became extremely distressed as they saw other survivors—women and children—being swept away in the water. For me, this marks the boundary between stressful (fight/flight) and potentially traumatic (incongruous novelty) experience. Animal models of dealing with similarly incongruous novelty might teach us about this part of PTSD.

BREWIN: I think this is a very important point. Not enough attention has been paid to the content of intrusive images in PTSD. There is a difference between horror and fear for example, and we really have no idea about how reactions involving these two emotions are similar or different. Sometimes in a life threatening event it is almost as though a curtain between life and death gets torn aside, even if only for a second, and the person gets a glimpse of some terrifying other world involving their own death which they may never have to contemplate. Is that the same as the sort of grotesqueness that someone might experience at seeing a burned body in a car? I think there are some very interesting questions here that will take us further.

YEHUDA: It is a discussion question for later, but I think that this whole idea of the utility of studying a symptom in isolation of the syndrome is questionable. I also wonder if it is useful to study something that occurs in normals, and call it a symptom because it reminds us of a similar phenomenon that occurs in someone who is impaired. Somehow the occurrence of a faulty memory process in the context of an illness seems like something different completely because it is embedded within the larger syndrome, and therefore may reflect something quite different. I don't think we bridge the gap between basic and clinical neuroscience this way, I think we widen it.

BREWIN: I agree with you it is important to be cautious, and we have certainly thought about this issue a lot. What has impressed us about our data from the analogue studies of trauma is that the same risk factors that have been identified in clinical studies came out as predictive in the non-clinical samples as well. So it seems to us there are concrete grounds to argue that analogue studies may be useful in developing our knowledge.

SECKEL: You started off with a fantastic premise, trying to bridge clinical science to basic science in order to formulate questions in a clinical model in a way that basic scientists might be able to address. One problem we've had in this meeting is that basic scientists have lovely models, but clinicians find they are poor facsimiles of the patients we see. And yet, those who see humans with disorders also tend poorly to analyze them in the context of the underpinning basic science of the brain. You describe what to a neuroscientist are 'black box' concepts: VAM and SAM. I wonder if you have thought about how these constructs that are quite hypothetical notions, might be formulated so that basic neuroscientists could address them. How are you going to come from your interesting position to talk to the basic scientists and say "let's construct an experiment?" I find myself concerned that we are in danger of making things even more inaccessible to each other rather than trying to bridge the gap, trying to discuss back and
forth from bench-to-bedside and from bedside-to-bench. In my view we need to be able to formulate questions and problems in ways that allow us to examine pathogenesis as a fundamental biological entity as well as very complex psychological constraints.

BREWIN: I don’t think that anybody has suggested that psychological constructs are anything but that, hypothetical. I would not want to claim that I am the person who can bridge this gap and somehow make this translation into basic science. What I’ve been trying to do in this talk is to identify what we as clinicians have observed about PTSD, and that is likely to be relevant to other scientists who are trying to understand the condition. The sort of model that I put forward was not designed to be tested by basic scientists, but rather to be informed by basic science, and particularly by what we know about the brain. The model is testable within the framework of cognitive psychology, but extending it further may depend on whether imagery processes, for example, are of interest to scientists who work with animals. It seems to me that in creating their models basic scientists may benefit from understanding in greater detail the clinical features of PTSD.

SECKEL: The point that I am making is that I think we are speaking two different languages. And there is difficulty in interaction, hampering translation which actually is the critical thing. We are in danger of developing a dualist view of PTSD, with the mind a ‘soul’, remote from genetics and cells and molecules that underlie disorders of body and brain. I find myself uncomfortable with this.

CHAPTER 16

Post-traumatic stress disorder in somatic disease: lessons from critically ill patients

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Abstract: Post-traumatic stress disorder (PTSD) is a well-recognized complication of severe illness. PTSD has been described in patients after multiple trauma, burns, or myocardial infarction with a particularly high incidence in survivors of acute pulmonary failure (Acute Respiratory Distress Syndrome) or septic shock. Many patients with evidence of PTSD after critical illness have been treated in intensive care units (ICUs). Studies in long-term survivors of ICU treatment demonstrated a clear and vivid recall of different categories of traumatic memory such as nightmares, anxiety, respiratory distress, or pain with little or no recall of factual events. A high number of these traumatic memories from the ICU has been shown to be a significant risk factor for the later development of PTSD in long-term survivors. In addition, patients in the ICU are often treated with stress hormones like epinephrine, norepinephrine, or cortisol. The number of the above-mentioned categories of traumatic memory increased with the totally administered dosages of catecholamines and cortisol, and the evaluation of these categories at different time points after discharge from the ICU showed better memory consolidation with higher dosages of stress hormones administered. Conversely, the prolonged administration of β-adrenergic antagonists during the recovery phase after cardiac surgery resulted in a lower number of traumatic memories and a lower incidence of stress symptoms at 6 months after surgery. Findings with regard to the administration of the stress hormone cortisol were more complex, however. Several studies from our group have demonstrated that the administration of stress doses of cortisol to critically ill patients resulted in a significant reduction of PTSD symptoms measured after recovery without influencing the number of categories of traumatic memory. This can possibly be explained by a cortisol-induced temporary impairment in traumatic memory retrieval that has previously been demonstrated in both rats and humans. ICU therapy of critically ill patients can serve as a stress model that allows the delineation of stress hormone effects on traumatic memory and PTSD development. This could also result in new approaches for prophylaxis and treatment of stress-related disorders.

Keywords: intensive care unit; critical illness; post-traumatic stress disorder; PTSD; catecholamines; glucocorticoids

Incidence of PTSD after critical illness

Post-traumatic stress disorder (PTSD) has been described as a consequence of serious medical conditions like myocardial infarction, cardiac surgery, hemorrhage and stroke, childbirth, miscarriage,