Research Report

PTSD and traumatic stress
From gene to community and bench to bedside

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ABSTRACT
Individuals and communities are exposed to traumatic events, those that are accidents or naturally occurring and those that are intentional or human made. Although resilience is the expected response, for some, posttraumatic stress disorder may be the outcome. Brain models of PTSD require understanding the phenomenology of the disorder and the brain “breakdown” that occurs. Among several models, importantly, is the perspective that PTSD is a “forgetting” disorder. Other elements in the onset and triggers of PTSD can identify further models to examine at the bench. New studies of the 5-HT2A receptor, the glucocorticoid receptor, p11, mitochondrial genes and cannabinoids are bringing new perspectives to understanding brain function in PTSD. Effective treatments indicate areas for bench research on the mechanisms of the disorder.

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Exposure to a traumatic event, the essential element in the development of acute stress disorder (ASD) and posttraumatic stress disorder (PTSD), is a relatively common experience. Approximately 50%–70% of the U.S. population is exposed to a traumatic event sometime during their lifetime. However, only 5%–12% develop PTSD. In a nationally representative study of 5877 people aged 15–45 in the U.S., the National Comorbidity Study (NCS) (Kessler et al., 1995) found the lifetime prevalence of exposure to trauma to be 60.7% in men and 51.2% in women. In a nationally representative sample of women in the U.S., the National Women’s Study (NWS) (Resnick et al., 1993) found that 69.0% of women were exposed to a traumatic event at some time in their lives. Over a lifetime, most individuals are likely to be exposed to a traumatic event.

In 2005, an estimated 162 million people worldwide were affected by disasters (e.g., natural disasters, industrial and other accidents, and epidemics). Over 105 thousand people died and damages totaled over $176 million (World Health Organization, 2006). Earthquakes illustrate the burden of natural disasters. Worldwide, there are over 20,000 earthquakes a year and over 1300 per year are magnitude 5 or greater (National Earthquake Information Center: neic.usgs.gov/neis/eqlists/eqstats.html). Apart from causing death and
dislocation, disasters exert a substantial psychological burden on affected populations including PTSD, depression and substance abuse (Neria et al., 2007a). Disaster workers who respond to fires, earthquakes, hurricanes, plane crashes and other disasters are at high risk of PTSD as well (Benedek et al., 2007; Fullerton et al., 2004).

Human made disasters include war and terrorism. In the world today, more than 30 armed conflicts are occurring in 26 countries (Project Flowshares, 2008). Soldiers defending their nation as well as civilians exposed to war have high rates of PTSD (Hoge et al., 2004; Karam et al., 2008). Over 2 million children have been killed in war in the last decade and six million permanently disabled or injured (Ursano and Shaw, 2007). One and a half million people are displaced due to war and conflict in Uganda alone (Bolton et al., 2007).

Resilience is the expected response to traumatic events. However, some suffer the psychological stress of the trauma exposure and develop distress, psychiatric illness, and exhibit health risk behaviors. In fact, after trauma exposure an altered sense of safety, increased fear and arousal, and concern for the future, can affect not only those who develop mental health problems but also those who continue to work and care for their families and loved ones (Ursano et al., 2007).

Interventions for disaster victims require rapid, effective and sustained mobilization of resources (Ursano and Friedman, 2006). Interventions must address individual care needs as well as sustaining the social fabric of the community (Ursano and Blumenfield, 2008). Psychiatric illness, distress and health risk behaviors must be addressed (Institute of Medicine, 2003; Raphael and Wooding, 2004). The medical care system, public health system and emergency response system must work together to meet the health care needs of a mass disaster and in particular the mental health care needs.

Posttraumatic stress disorder is not uncommon following traumatic events from terrorism to motor vehicle accidents to industrial explosions (Breslau et al., 1991; Breslau et al., 2005). In its acute form, PTSD is like the common cold, perhaps experienced at some time in one’s life by nearly all. Some colds progress to pneumonia and may create substantial illness, impairment of function and be debilitating. Similarly, PTSD when it becomes chronic requires psychotherapeutic and/or pharmacological intervention. Importantly, PTSD is not the only trauma related disorder, nor perhaps the most common (Ursano et al., 2007; North et al., 1999; Norris et al., 2002).

PTSD can be diagnosed one month after exposure to a traumatic event, classically a life threatening event. PTSD includes symptoms of intrusive thoughts (e.g. nightmares, unwanted thoughts), avoidance of reminders of the traumatic event and numbing of emotional responses, and hyperarousal such as startle responses or physiological arousal. Prior to one month, ASD may be diagnosed. ASD has the same three symptoms as PTSD but also requires dissociative symptoms early after or at the time of the traumatic event. Dissociative symptoms include time distortion, i.e., the feeling that time has slowed down or speeded up, or that one is outside oneself looking at oneself or feeling detached and observing the traumatic event.

1. PTSD: models of brain change after an environmental event

Structural neuroimaging has demonstrated decreased size of the hippocampus in PTSD (Bremner et al., 1997a,b; Stein et al., 1997) and other brain regions (De Bellis et al., 1999). The hippocampal volume changes do not appear to be the result of the trauma exposure but rather a predisposing factor (Bonne et al., 2001; Gilbertson et al., 2002). Importantly numerous functional neuroimaging studies now implicate the amygdala (increased cerebral blood flow cfb), prefrontal cortex (decreased cfb) and the hippocampus in PTSD. The anterior cingulate is also often reported as abnormal in functional studies (Liberzon and Martis, 2006; Williams et al., 2006). A recent study has implicated the perhnial cortex as an index of probable resilience/recovery after trauma exposure (Osuch et al., 2008). Importantly, tissue studies of these areas are needed to verify neuroimaging findings and understand the cellular and genetic mechanisms involved in these circuits (Osuch et al., 2004).

One cannot assume that only some human aspects of traumatic stress can be modeled in animals—Perhaps the alternative is a better approach: the behaviors seen in animal models should be sought more diligently in human responses. Similarly the absence of some symptoms of PTSD in animals calls for understanding the genomic or proteomic differences that may explain this response pattern difference.

PTSD is a waxing and waning disorder—in this way more like Multiple Sclerosis than atherosclerosis. The disorder can come and go and be more or less present across a long period of time. Animal models rarely model such vacillation in symptoms. Similarly animal models of PTSD have rarely considered that everyone does not develop the traumatic response after the event (Kesner et al., 2009). Most animal stress studies examine the animals that show symptoms or behavioral changes after the stressor rather than the individual differences.

PTSD is also a “toxic exposure”, not only metaphorically but also in the stimuli (i.e. threat to life, exposure to death) that result in PTSD. The “toxic model” brings a number of questions into focus, in addition to being understandable to many non-scientists. Toxins have dose, duration and susceptible organs or functions. Is the toxicity of threat to life the same as the toxicity of witnessing death of a loved one? Are the dose, duration and response curve the same? What are the useful animal models of witnessing death?

PTSD may also be considered an “overuse” disorder e.g. the amygdala is “over used”. In this way, might it be an “inflammation” of an over used muscle and the “brain inflammatory response” is what we are seeing in PTSD. The cytokines of human csf may relate to this view of the PTSD story.

PTSD is above all a disorder of forgetting even more than of remembering. It is the inability to forget that leads to the pathology and suffering in PTSD. Forgetting is often overlooked or even avoided in clinical practice. Yet it is a critical component of recovery. If we could not “forget”, our brains would rapidly be cluttered with information and observations and perhaps limit our cognitive control functions for other activities (Kuhl et al., 2007).
Extinction is one avenue for examining “forgetting” (Myers and Davis, 2002; Quirk et al., 2000; Sharot et al., 2004). Extinction—which is an active process of new learning—is a potentially important mechanism for PTSD formation and also its treatment (Ressler et al., 2004). Is PTSD a deficit of synaptic plasticity underlying extinction or a deficit in the active process of reconsolidation of memory? Similarly, differences in brain regions in their response to reversal of cues (Morris and Dolan, 2004) indicating a threatening or painful state is no longer present may lead to new avenues of considering forgetting, extinction and the inability to recognize safety after exposure to threat.

Importantly PTSD can also be considered a "breakdown" of our usual neural functions. Engineering models are often built around the concept of “failure mode analysis”, that is, “How can we break the machine? How does it breakdown?” Breakdown is not the same as function. It draws our attention to the neurobiology that may be least redundant, most subject to interference or disruption. How our “forgetting system” may breakdown is intrinsically a different question from how does it function.

If PTSD is the failure to recover (rather than the onset of disease), what is the breakdown that has occurred? Perhaps some aspect of our “immunological” response to traumatic stress has not operated sufficiently or perhaps at all? The contribution of identification with the dead ("It could have been me. It could have been my child") as a cognitive risk factor for development of PTSD (Ursano et al., 1999, 1992) indicates a failure of a normally adaptive and health promoting cognitive mechanism, identification. We most often think of identification as growth promoting. PTSD from this perspective is an autoimmune disorder — a normal mechanism usually growth enhancing and protective (e.g. identification) is causing disease. Identification with the aggressor and the Stockholm syndrome are additional examples of identification gone awry. Why in high stress settings is identification likely or possibly able to induce pathological neurobiological and psychological changes?

Alternatively, might our human cognitive process of identification, be an aspect of mirror neuron activity? (Oberman et al., 2007; Buccino and Amore 2008; Nummenmaa et al., 2008). Identification appears to be a one of the neural systems that supports cognitive up-regulation of emotion—both negative and positive. Medial prefrontal regions (BA32) have been implicated in regulation of emotion related to focusing on personal relevance of negative emotions (Ochsner et al., 2004). In these studies the participants imagined themselves or their loved one as the central figure in the situation. This is in contrast to cognitions related to altered anticipation of future events which recruit lateral prefrontal regions. Thus different cognitive approaches to traumatic stimuli may involve different neurocircuitry and modulate amygdala response in different ways.

2. Understanding the basics: recent work at the bench

A number of animal models are potentially helpful in studying PTSD (Ursano et al., 2008) in one animal model of PTSD, exposure of experimental animals to an intense stress protocol such as restraint/tail shock, can produce abnormal-
stress-induced psychiatric symptoms. For example, 5-HT2A receptor-mediated behaviors are readily blunted by footshock and forced swim stress (Izumi et al., 2002; Pericic, 2003). Inescapable stress induces a decrease in 5-HT2A receptor expression in the hippocampus (Dwivedi et al., 2005; Wu et al., 1999), amygdala (Wu et al., 1999) and hypothalamus (Dwivedi et al., 2005; Petty et al., 1997; Wu et al., 1999). The decrease of 5-HT2A receptors in the hypothalamus and hippocampus appears to be specifically associated with behavioral depression after exposure to stress (Dwivedi et al., 2005). Taken together, these findings suggest stress-induced disturbance of central 5-HT2A receptor signaling may contribute to the occurrence of stress-induced psychiatric symptoms.

Pharmacological intervention with more specific newer generation 5-HT2A receptor antagonists may prevent the impairment in the function of 5-HT2A receptors, and thus prevent the stress-induced alterations in neuronal functions of the amygdala, hypothalamus and brain regions that are associated with the clinical manifestation of PTSD.

2.2. Glucocorticoid receptors and the formation of traumatic memories

Activation of glucocorticoid receptors (GR) has long been associated with stress and traumatic memory. A classic and well characterized response to stress and trauma is activation of the hypothalamic pituitary adrenal (HPA) axis resulting in increased release of cortisol into the blood stream (de Kloet et al., 1999; McEwen, 2007). This cortisol feeds back onto all cells in the body including neurons. The glucocorticoid response is complex as cortisol levels are raised in response to psychological and physical ‘stress’ as well as other non stressful situations (Kim and Diamond, 2002). Therefore GR is not simply a stress receptor but rather, as described by McEwen, a receptor involved in the promotion of adaptation and well being or “allostasis” (McEwen, 2007).

A significant body of work links the cortisol response to the development of PTSD. However, this evidence has been mixed. Yehuda et al. (2006) found that cortisol levels were significantly lower in Vietnam veterans with PTSD than controls as well as individuals involved in motor vehicle accidents, compared to their respective controls (Yehuda et al., 1998; Delahanty et al., 2003); Similar results have been found in other studies (see Yehuda et al., 2002; Yehuda et al., 2004; Pfeffer et al., 2007). However, not all studies report this (Lindauer et al., 2006). Moreover, in a meta-analysis of cortisol in PTSD victims Meewisse et al. (2007) found evidence that across 37 studies, there was no significant difference in cortisol levels between individuals with PTSD and those without PTSD. Nonetheless a significant body of evidence from animal studies demonstrates that GR activation has significant effects on neuron structure, synaptic transmission and especially on the consolidation of fearful and stressful memories. As above, our animal models are telling us something that has not yet been understood in human disease. But perhaps the animals “have it right” and we have not yet understood the particular manifestation of this neurobiology in the human more complex model.

Activation of GR has significant effects on the brain structure and function. A growing body of literature describes the effects of GR activation on dendrite structure, synaptic transmission and plasticity, and the modulation of memory (Kim and Diamond, 2002; McEwen, 2007). Corticosterone, the rat analogue of cortisol, acts on mineralocorticoid receptors (MR) at lower concentrations and at GR at higher concentrations (McEwen, 2007, de Kloet et al., 2008). Activation of MR and GR modulate memory in animals (de Kloet et al., 1999; Roozendaal,1999; McEwen, 2007) and humans (De Quervain et al., 2003; Buchanan and Loovallo, 2001). For example, in the fear motivated active avoidance paradigm, application of a GR agonist into the amygdala enhances memory retention of the fearful stimuli. Likewise, infusing the same area with GR antagonist impairs fear memory consolidation (Roozendaal,1999; McEwen and Roozendaal, 2002).

Consistent with the role of GR in memory consolidation, chronic stress has been shown to increase memory of a cue and context in an amygdala dependent fear memory paradigm (Conrad et al., 1999). Moreover, stress has also been shown to increase anxiety in animal models (Vyas et al., 2002). This increase in anxiety also corresponded to an increase in amygdala neuron dendrite size (Vyas et al., 2002). Some of these effects have been shown to be dependent upon GR. Recently, Mitra and Sapolsky (2008) found that direct infusion of corticosterone in to the amygdala promoted dendrite hypertrophy. GR has also been shown to directly regulate synaptic transmission in a non genomic modulation (de Kloet et al., 2008). These examples testify to the range of cellular and behavioral change mediated GR, and speak to the importance of understanding their cellular mechanisms in order to understand the relationship between stress and traumatic memory.

The cellular mechanisms of how GR exert wide ranging effects on neurons are not fully understood. However accumulating evidence suggests that GR may activate a range of cellular changes from regulation of gene transcription to modulation of ionic membrane channels (McEwen, 2007; de Kloet et al., 2008; Johnson et al., 2005). As a transcription factor, intracellular corticosterone activated GR homodimers translocated to the nucleus where they act on a wide range of genes. These include genes encoding for proteins involved in neuron structure and synaptic transmission (Datson et al., 2001; Morsink et al., 2006, Chameau et al., 2007, Zhang et al., 2008a,b). Additionally membrane GR (mGR) may rapidly regulate a range of synaptic functions by acting directly at the synapse (Johnson et al., 2005; Tasker, 2006; de Kloet et al., 2008; McEwen, 2007). Evidence indicates that mGR may inhibit both NMDA receptor and voltage gated Ca2+ currents at post synaptic sites (French-Mullen, 1995; Liu et al., 2007). Furthermore, mGR has been localized at the post synaptic density (PSD) of excitatory synapses (Johnson et al., 2005), providing direct evidence to support a synaptic localization and function for the mGR. These data suggest that mGR acting either via the genome or directly at the synapse itself may potentially regulate learning and memory during times of stress.

Collectively these data indicate that activation of GR affects neuron structure and memory during stress. Understanding the direct synaptic target of the adrenal stress response holds potential for understanding unique aspects of the physiological basis of stress and identifying potential
targets for therapeutic intervention in anxiety and traumatic stress disorders. Changes in endogenous cortisol or GR themselves continue to be a subject of investigation in PTSD research. Data from animal research continue to indicate that GR are powerful modulators of neuron behavior associated with stress and trauma.

The gene target and protein products of the genomic GR are only beginning to be identified and characterized. Recent evidence identifies that at least one gene target plays an important role in the regulation of neurotransmission.

3. From the bench to the bedside — biomarkers and stress test

Translational research should be a two-way street. Basic scientists provide clinicians with potential biomarkers for PTSD diagnosis and treatment. Clinical researchers provide observations about the relationships between the biomarker and symptoms of PTSD that stimulates basic investigations. For example, we found that P11 mRNA level was positively correlated with the scores of HAMD-17, CDTS-F and CDTS-S in the PTSD subjects. This clinical observation provides a new window to search for the relationships between the marker and certain symptoms in PTSD. This information is critical in the development of a tool to predict or evaluate the symptoms of PTSD. Therefore translational research is a powerful process that drives the clinical research engine. This research strategy could strengthen and accelerate PTSD clinical research, and also enhance translating new knowledge between clinic and bench.

Converging evidence from family, twin, and molecular genetic studies suggest a role for genetic influences in the etiology of PTSD (Koenen et al., 2008). As in most genetic studies these often are small samples and require replication. Family studies demonstrate an increased risk for PTSD in first-degree relatives of PTSD patients (Sack et al., 1995). Twin studies have identified three relevant areas of genetic influence: the risk of trauma exposure, the development of PTSD, and the existence of comorbidity (Nugent et al., 2008).

Zhang et al. recently demonstrated differential expression of P11, a member of the S-100 protein family, in the peripheral blood mononuclear cells of patients with PTSD, major depression (MD), bipolar disorder (BP), and schizophrenia (SCZ), and controls. In a small clinical sample, Comings et al. (1996) demonstrated that a dopamine D2 receptor (DRD2) variant in linkage disequilibrium with the D2A1 allele confers an increased risk to PTSD, and the absence of the variant confers a relative resistance to PTSD. Recently, Kilpatrick et al. (2007) found that the low expression variant of the serotonin transporter gene 5-HTTLPR increased the risk of post-hurricane PTSD, but only under the conditions of high hurricane exposure and low social support. Elizabeth and colleagues found that four SNPs in the FKBP5 locus significantly interacted with the severity of child abuse to predict the level of adult PTSD symptoms after correcting for multiple testing (Binder et al., 2008). In this study there were no main effects of the SNPs on PTSD symptoms and no significant genetic interactions with the level of non-child abuse trauma as a predictor of adult PTSD symptoms. These results suggest a potential FKBP5 gene-childhood environment interaction important for the development of adult PTSD, in that individuals with these SNPs are at greater risk to develop PTSD with specific childhood environmental stressors.

3.1. P11

Translational research offers the opportunities for discoveries to effectively bring the benefit of bench findings to PTSD subjects. The study of P11 is one example of translational research on PTSD. P11 has been associated with the regulation of the 5HT1B and 5HT4 receptors. In studies of PTSD, P11 has been examined in three steps; identifying P11 in animal models of PTSD and in PTSD post mortem human brain prefrontal cortex, studying the function of the protein and examining p11’s utility as a biomarker in clinical samples. The initial studies, carried out using post mortem brain and an PTSD animal model used Western blot, quantitative real time PCR and microarray techniques. P11 was found to be over-expressed in the prefrontal cortex (PFC) area 46 of PTSD post mortem brain, an area associated with PTSD (Zhang et al., 2008a). A rat model of PTSD, inescapable shock, which shows PTSD like behavioral disturbances, was then examined. Using DNA microarray and quantitative real time PCR in this animal model, p11 was found to be up-regulated in the prefrontal cortex of these rats. Thus in this animal model of PTSD p11 protein over-expression similar to that seen in the post mortem prefrontal cortex of PTSD patients was found.

To study the function or mechanism of p11 in PTSD, molecular research was carried out. Dexamethasone (Dex), a synthetic glucocorticoid, was found to up-regulate p11 expression in SH-SY5Y cells through glucocorticoid response elements (GREs) within the p11 promoter. This response can be attenuated by either a glucocorticoid receptor antagonist, RU486, or mutating two of the three glucocorticoid response elements (GRE2 and GRE3) in the p11 promoter. This work supports the conclusion that PTSD is associated with increased p11 expression and that the p11 is regulated by glucocorticoids through GREs within the p11 promoter.

To translate these findings into a clinical tool, p11 was examined as a potential peripheral biomarker for PTSD. P11 mRNA levels in the PBMCs of patients with and without PTSD were assessed. P11 was down regulated in patients with PTSD, and it was up-regulated in bipolar (BP) and major depressive disorder (MDD) patients (Zhang et al., 2008b). Further research is now needed to confirm and extend the diagnostic utility and pathogenetic implications of p11 in larger clinical samples.

3.2. Mitochondrial genes

A second example of translational research (Su et al., 2008) is in recent studies identifying PTSD-specific mitochondrial gene targets. This was the first study to examine mitochondrial genes using human post mortem brain tissue from PTSD patients. Mitochondria are the principal energy source of cells that convert nutrients into energy. Mitochondrial dysfunctions are increasingly recognized as key components in stress-related mental disorders. The molecular markers associated
with mitochondrial functions underlying the pathogenesis of PTSD are poorly understood.

Using a 3rd generation mitochondria gene chip containing 1159 genes, researchers examined gene changes in the tissue of six post mortem PTSD patients compared to a control group of six well matched post mortem patients without PTSD. Results revealed specific gene expression patterns that distinguish the PTSD patients from the control subjects. If confirmed, these gene changes may be useful in PTSD diagnosis as well as in developing potential treatments.

3.3. Cannabinoids

The mechanisms by which exposure to traumatic events leads to the development of behavioral and psychological symptoms including posttraumatic stress disorder (PTSD) and substance abuse are complex and multifactorial ranging from genetic and epigenetic predisposing factors to the impact of interpersonal and social systems on stress responses. There is a significant body of research showing that the psychological effects of traumatic events are cumulative (Milliken et al., 2007; Williams et al., 2007) but there is limited information on effects of repeated exposure to trauma. There is evidence that these stress-related disorders are related to changes in brain structure and function especially in key areas associated with stress responses.

Recent studies have shown that the endogenous cannabinoids may be involved in traumatic stress-induced emotional behavior. The endogenous cannabinoid system is involved in a wide variety of physiological functions including pain, appetitive behaviors, addictions, motor control, emotion (e.g. Iversen, 2003) and may play a critical role in stress-induced emotions and the etiology of PTSD in response to severe or chronic stress. The endocannabinoids are found in brain areas associated with both stress and anxiety responses as well as those linked to alcohol and drug abuse which may help explain the increased risk of substance abuse in chronic stress and resulting PTSD or depression.

In pilot studies we have found changes in endocannabinoid activity in brain regions associated with stress responses and with addiction. We also have indications of sex differences with the female rat endocannabinoid system more responsive to stress as consistent with increased rates of cannabis preference and increased risk of PTSD in female humans. We are currently working to validate and extend these findings in an animal model of repeated stress by measuring stress behaviors and brain changes in male and female rats. We believe our findings will offer new information on mechanisms of PTSD and drug abuse with the ultimate goal of developing better therapeutic interventions for these disorders.

3.4. Stress test for PTSD?

Stress testing is used in medicine to identify individuals at risk, disease onset, monitoring disease progression and response to treatment and to identify type/location of organ injury (e.g. rhythm disturbance and location vs MI). These same goals are applicable to PTSD to include potentially identifying the location of injury i.e. prefrontal cortex, amygdala, hippocampus etc. Considering the classic stress test for cardiac disease, what would a “stress test” for posttraumatic stress disorder mean? Knowing some of the brain pathology that is emerging as the basis of PTSD, can we look forward to being able to define a “prefrontal cortex amygdala inhibition impairment disorder”? Or a “hippocampal extinction impairment disorder”?

For myocardial infarction the stress test physiologically challenges the individual/organism and elicits evidence of early or past disease processes that may not be evident in the resting state. Can we imagine a similar test for PTSD? This could provide early detection, prediction of disease risk, or screening for those “at risk” for PTSD perhaps because of pre-existing genotype or past psychological exposures or conditions.

Neuroimaging under specific tasks could provide a model to think of this future possibility. Immediately after exposure to trauma, a stress test could be used for early detection, protection from further progression, prevention of disease onset or identifying necessary interventions to restore health and resilience. During the disease phase, it could be used for tracking, progression monitoring, and response to treatment. Finally, determining recovery from disease could also serve as a useful application of such an intervention. Thus a stress test would identify those at risk, disease onset, disease progression, response to treatment, assist in predicting disease trajectory and localize disease processes.

Implied in such an exploration would be a definition of “normal” functioning during stress, and that we can measure physical, psychological and cognitive baselines that would then give meaning to what the disease state or the “at risk” state might be. In animal models such a paradigm may imply that responses to predator stress, tail shock, swim test and physiological demand (forced running) may have different neurobiology’s. Examining the feasibility of such testing with goals of protection, treatment, and relapse prevention tells us why such testing is important, and that desired outcomes need not first be defined. Possible “first steps” for examination include neuroimaging, blood proteins (peptide y, p11), physiological responses, endocrine profiles, mitochondrial gene profiles, symptom patterns, and neuropsychological function.

The difference between biomarkers and a stress test is a matter of emphasis. Biomarkers are often seen as static. In addition the term biomarker does not capture the particular unique importance of examining subjects/animals while stressed as a key part of indexing disease and risk for PTSD. Perhaps the biomarker may not be evident at rest in PTSD. Under psychological, physical, or neurobiological challenge, we may find biomarkers not otherwise evident.

4. Treatment of PTSD

Effective treatments should also inform animal and human studies of the pathophysiology of PTSD. Strategies of Psychological First Aid are recommended as a first-line intervention for individuals with traumatic stress following traumatic events prior to development of any disorders. The principles of Psychological First Aid [SCCEO] are 1) Safety; 2) Calming 3) Connectedness both for instrumental (practical) and...
emotional support 4) Efficacy—including skills to respond as well as belief in ones ability to respond; and 5) Optimism/hope (Hobfoll et al., 2007). These evidence based principles direct early interventions for trauma exposed individuals. But they require further systematic evaluation. How to carry out traditional randomized trials for these early interventions is challenging.

Well developed treatments are also available for PTSD. E.g., NICE, International Society of Traumatic Stress, the U.S. Department of Defense and Veterans Affairs and the American Psychiatric Association. The American Psychiatric Association Practice Guideline for the Treatment of Patients with PTSD was published in combination with treatment guidelines for patients with ASD (Ursano et al., 2004). The decision to publish these guidelines together was a substantial decision, reflecting the close relationship between these two disorders and the need for clinicians to consider both in a treatment plan.

The Workgroup conducted a comprehensive literature review to identify all randomized clinical trials as well as less rigorously designed studies. Keyword searches of MEDLINE (316 citations) and PILOTS (587 citations) were completed for the years 1966 to 2002. In addition the VA/DoD and ISTSS treatment guidelines were reviewed.

Each recommendation was coded for the level of endorsement: [I] recommended with substantial clinical confidence; [II] recommended with moderate clinical confidence; and [III] may be recommended on the basis of individual circumstances. Initial assessment was emphasized to include screening for trauma exposure and the importance of first interventions after trauma exposure including stabilization, supportive medical care and supportive psychiatric care and assessment [I]. Psychiatric management for all patients with PTSD (or ASD) includes safety, medical care, resources for self-care and recovery [I]. Treatment for comorbid disorders, ongoing assessment, increasing active coping with secondary adversities, education, managing physical health needs and functional impairments and coordinating care through collaboration with other clinicians are important [I].

No specific psychopharmacology was recommended for the prevention of PTSD. SSRIs are recommended as first-line medication treatment for PTSD [I]. Other antidepressants are also seen as beneficial [III]. Benzodiazepines are seen as possibly useful for anxiety and sleep but also may have negative effects on PTSD [III]. Second generation antipsychotic medications, anticonvulsants, adrenergic agonists and blockers are possibly helpful for specific symptoms [III].

Psychotherapeutic interventions recommended with evidence included cognitive behavior therapy (CBT) with exposure for the core symptoms of PTSD [I]. EMDR was also noted as effective [II], however, the mechanisms appear to be those of CBT rather than eye movements. Stress inoculation, imagery rehearsal and prolonged exposure techniques were suggested as possibly helpful for PTSD and associated symptoms such as anxiety and avoidance [II]. Psychodynamic psychotherapy was suggested as useful in addressing developmental, interpersonal and intrapersonal issues important to social, occupational and interpersonal function [II].

A recent APA review of the guidelines comments on the limited data on psychopharmacologic treatment of combat related PTSD; noted the promising findings of adjunctive agents to facilitate psychotherapy; the growing literature on prazosin for combat related nightmares; and the positive randomized clinical trials on cognitive processing therapy, prolonged exposure therapy and brief exposure therapy. Cognitive behavioral therapy (CBT) has been shown to be successful in preventing PTSD in those with ASD (Bryant et al., 2008).

5. Conclusion

Individuals and communities are exposed to a wide array of traumatic events. From motor vehicle accidents to natural and human made disasters, our psychological and brain responses show resilience, transient distress responses including change in emotional function, cognition, and health risk behaviors, and for some persons longstanding and disabling psychiatric illness. A constellation of symptoms may be present in sufficient intensity and duration to warrant the diagnosis of PTSD.

PTSD may be conceptualized in a number of ways including: 1) a response to a toxic exposure that becomes generalized and maladaptive, 2) failure in our “recovery” systems e.g. as an injury that results in a brain failure; and 3) a disorder of forgetting—or a failure of extinction learning. Animal models of behavioral changes in response to environmental stressors have led to a greater understanding of the molecular neuropathology of this disorder and to the exploration of the genetic basis of PTSD.

Current pharmacological and psychosocial treatments for PTSD target the neurocircuitry of fear-related learning, memory formation and extinction. Newer pharmacologic agents may speed response to psychosocial interventions precisely by expediting the process of extinction learning. As valid animal models of resilience to traumatic exposure are developed they may also lead to clarification of the genetics governing resilience in the face of traumatic exposure, to the identification of genetic biomarkers for PTSD and targets for therapeutic intervention.

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