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Discrete and Recurrent Traumatization in PTSD: Fear vs. Anxious Misery

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As noted in a report from the VA National Center for PTSD (Consensus Conference Recommendations for Veteran Treatment of PTSD and Comorbid TBI: updated 2010): "No screening instruments available can reliably make the diagnosis [*of PTSD*]; the gold standard remains an interview by a skilled clinician." That is, unlike for most medical disease entities, we currently do not have good quantitative, biological symptom measures that can help the clinician define the pathology of PTSD and assure reliable diagnosis, serve as efficient prognostic tools, and provide better targets for treatment. This circumstance is also true for the other anxiety and mood disorder diagnoses, many of which are frequently comorbid with PTSD.

The above consideration has recently prompted a National Institute of Mental Health (NIMH) initiative—Research Domain Criteria (RDoC) (e.g., Insel & Cuthbert, 2009; Sanislow et al., 2010)—to define for research purposes promising domains of study that are not constrained by traditional diagnostic categories. The aim is to develop measures that might serve as endophenotypes to better relate to emerging data in genetics and clinical neuroscience.

Consistent with this program, we have undertaken psychophysiological study of the full range of anxiety spectrum disorders, evaluating reflex outputs from the brain's fear/defense circuitry, and assessing a current sample of over 500 treatment-seeking anxiety patients and community controls (Lang & McTeague, 2009). These participants complete a structured clinical interview establishing DSM-IV diagnoses along with a battery of questionnaire measures. In a subsequent session emotional imagery of both standard arousing events and personally relevant fear memories are evoked and autonomic and somatic measures are recorded.

Of particular interest in this assessment is the potentiated probe startle reflex evoked during imagery, a response readily measured by the magnitude of its first component—the eyeblink. Startle potentiation is mediated by the brain's fear/defense circuit—as defined over several decades of infrahuman neuroscience research (e.g., Kapp & Pascoe, 1986; Kapp, Pascoe, & Bixler, 1984; LeDoux, 1987; Sarter & Markowitsch, 1985). Circuit activation begins when the lateral and basolateral nuclei of the amygdala receive threat-relevant information from sensory/memory systems. These nuclei project to the amygdala's central nucleus and the bed nucleus of the stria terminalis (a subregion of the extended amygdala), which in turn project to a variety of hypothalamic sites, the central gray, facial motor nucleus, and brainstem target areas, initiating a range of defensive reflexes that evolved to counter imminent threats to survival (cf. Lang & Davis, 2006). Importantly, the

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amygdala and bed nucleus of the stria terminals also project to the central pontine site of the startle circuit, increasing the magnitude of the startle reaction during threat/fear states (Davis, Walker, Miles, & Grillon, 2010). Startle reactions are elicited by any abrupt sensory stimulus, and serve as a primitive escape response in many species. In the case of human fear, recording the startle response to a brief acoustic probe (e.g., 95 dB white noise) has provided a productive, cost-effective, and *non-invasive* measure of defensive neural activation.

Aversive hyperarousal and exaggerated startle are DSM-IV designated symptoms of PTSD, and case reports of returning veterans are replete with descriptions of profound and functionally disruptive startle responses to loud albeit mundane noises encountered in daily life (e.g., Shay, 1994). Laboratory evidence of exaggerated startle response and hyperarousal has also accumulated (e.g., Norrholm et al., 2011). However, it is apparent that heightened reactivity in PTSD is not always found and there is a dearth of startle research that considers accumulated trauma exposure or comorbid symptom constellations.

In a recent publication (McTeague et al., 2010) we reported results from our overall sample of over 500 treatment-seeking anxiety patients, specifically for those with PTSD as their principal (i.e., primary) disorder. As anticipated, when their idiographic trauma imagery was evoked, PTSD patients significantly exceeded control participants in startle reflex potentiation, autonomic responding, and facial muscle action; and though less pronounced, showed heightened reactivity to standard anger, panic, and physical danger imagery. However, when the group was divided, comparing patients who had suffered a single-incident catastrophic trauma with those who had experienced recurrent traumatic exposure, a dramatic difference was apparent. Patients whose posttraumatic stress resulted from a single, discrete trauma showed extreme startle potentiation to their fear memories, greater in magnitude than for any other anxiety diagnosis in the overall sample; in contrast, the patients who had experienced recurrent traumatization were among the least reactive and failed to show significant startle potentiation. The cumulatively traumatized patients also evidenced significantly more extensive comorbidity (major depression and anxiety disorders), longer enduring PTSD, and more severe scores on questionnaire measures of broad dysphoria and functional interference.

In brief, the two subgroups represented distinctly different symptom complexes—PTSD secondary to a single, discrete trauma appears as a focused fear disorder in which the brain's defense circuit is intact, but hyper-active in response to trauma-related cues; in cumulatively traumatized patients, however, the brain's normal fear/defense circuit appears to be dysfunctional.

Epidemiological studies of anxiety and mood disorder comorbidity (Krueger & Markon, 2006) have emphasized a core internalizing dimension comprised of two classes of disorders, fear and anxious-misery/distress. Phobic disorders are classified as fear disorders whereas generalized anxiety disorder, dysthymia, and depression are characterized by pervasive distress and better captured by an anxious-misery factor. PTSD has been more closely associated with the latter dimension (Cox, Clara, & Enns, 2002), although Watson (2005) has qualified these results, pointing out that it is a less robust indicator of anxious-misery than the other disorders. That is, as suggested by the physiological response differences to fear imagery, the conventional PTSD diagnosis encompasses patients with a clear fear diathesis as well as patients with the more complex diathesis of chronic anxious/misery.

Of particular pertinence to our returning servicemen and women, those PTSD patients in our sample showing impaired defensive engagement endorsed the most pervasive anxious-

misery, reporting a history of repeated trauma exposure that long pre-dated their index trauma and often included sustained interpersonal victimization (e.g., childhood physical and/or sexual abuse). That individuals with cumulative developmental trauma are at risk for the worst post-deployment adjustment has been well established across theaters of operation (Dedert et al., 2009; Fritch, Mishkind, Regerm, & Gahm, 2010; Kulka et al., 1990). These individuals often experience a coalescence of somatic and psychiatric difficulties such as substance abuse, chronic, pain, and traumatic brain injury (TBI) (Dedert et al., 2009; Hoge et al., 2008). Our objective data further suggests that dysfunctional emotional engagement may also contribute to their poor treatment outcome and intractable functional limitations.

Returning to the goals of the NIMH RDoC project, we have observed that features (e.g., chronicity, comorbidity) predicting defensive impairment in PTSD, are also apparent in other principal anxiety and mood disorders (Lang & McTeague, 2009; McTeague et al., 2009; McTeague, Lang, Laplante, & Bradley, 2011). As such, considering the often complicated and highly comorbid presentation in returning service personnel, psychophysiological measures could be useful irrespective of the primary clinical complaint, easing the conventional emphasis on dichotomous diagnostic criteria, and augmenting the interview in improving estimates of prognosis and treatment planning.

In summary, the implications of these data are several:

1. Foremost, there is a great need for basic brain research that addresses the function/structure/connectivity in the emotional circuits mediating the pathology of anxiety and mood disorder. While there have been many functional neuroimaging studies of PTSD (Hughes & Shin, 2011), there is a dearth of data in which the ubiquitous comorbidities and the effects of prolonged stress are directly considered. The Department of Defense could well join with the NIMH RDoC project encouraging for research purposes, a search for neuroscience biomarkers of pathology unconstrained by the categories of current diagnostic practice.
2. The data suggest that the sustained stress of cumulative trauma has a profoundly debilitating effect on brain function and behavior. Furthermore, repeated warzone deployment, TBI incidence, and high psychiatric comorbidity are likely associated with this syndrome. In our sample, childhood abuse was frequent among recurrently traumatized civilian patients. In military patients a trauma history, including pre-service events, is equally important to optimize prognosis and determine treatment.
3. The effectiveness of prolonged exposure (Foa, Hembree, & Rothbaum, 2007) and other treatments aimed at extinguishing the patient's exaggerated fear response is clearly effective in helping patients recover from discrete trauma exposure. The treatment of PTSD consequent to cumulative trauma, however, represents a significant challenge. As these data suggest, when the brain's fear memory circuit is compromised, the reflex physiology of fear is not readily accessed for extinction.

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