

Neurobiological sequelae of childhood trauma: post-traumatic stress disorders in children

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Traumatic events can have a profound and lasting impact on the emotional, cognitive, behavioral and physiological functioning of an individual. These adverse effects have been described in combat veterans since the Civil War (DaCosta 1871, Bury 1918, Frazer and Wilson 1918, Dobbs and Wilson 1960 Birkhimer et al. 1985, Bleich et al. 1986). Only recently, however, has the distinct trauma-associated syndrome characterized by prominent affective symptoms (dysphoria, irritability, anxiety) and a 'hyperactive' sympathetic nervous system (Horowitz et al. 1980, Brende 1982) been called Post-Traumatic Stress Disorder (DSM-III, PTSD). The symptoms of PTSD fall into three clusters; 1) recurring intrusive recollection of the traumatic event such as dreams and 'flashbacks', 2) persistent avoidance of stimuli associated with the trauma or numbing of general responsiveness and 3) persistent symptoms of increased arousal characterized by hypervigilance, increased startle response, sleep difficulties, irritability, anxiety and physiological hyperreactivity. While described originally in combat veterans, a high percentage of rape victims, sexual abuse victims, survivors of natural or manmade disasters, and witnesses to violence also experience symptoms of PTSD (e.g., Terr 1983, Blanchard et al. 1983, Boehlein et al. 1985, McLeer et al. 1988). The largest group of victims of these traumatic events are children.

The present chapter will review childhood PTSD with specific focus on neurobiological sequelae of childhood trauma and present some preliminary evidence of altered functioning of brainstem catecholamine systems in childhood PTSD. In specific, it is hypothesized that the abnormal patterns of catecholamine activity associated with prolonged 'alarm reactions' induced by traumatic events during infancy and childhood can result in altered development of the central nervous system (CNS). Furthermore, it is hypothesized that this altered development includes a 'dysregulated' brainstem which in turn results in a host of signs and symptoms related to abnormal brainstem functioning, including altered cardiovascular regulation, affective lability, behavioral impulsivity, increased anxiety, increased startle response and sleep abnormalities. Finally, early life experience is discussed, in context of childhood trauma, as an 'expresser' of genetic predispositions.

THE SCOPE OF CHILDHOOD TRAUMA

PTSD has been described in survivors of sexual abuse (Conte 1985, Browne and Finkelhor 1986), victims of violence (Boehnlein et al. 1985), witnesses to violent acts (Eth and Pynoos 1985), survivors of natural disasters (McFarlane 1987), survivors of catastrophic accidents (Martini et al. 1990), and burn victims (Perry et al. 1987) among others. While no epidemiological data regarding childhood PTSD are available, conservative estimates can be

made based upon the incidence of traumatic events in the childhood population. Conservative estimates of childhood sexual abuse suggest an incidence of 200,000 new cases each year (Finkelhor, 1984). Maltreatment of children (physical, emotional or sexual abuse) is estimated to exceed 1.5 million children per year (National Incidence Study, US Dept Health/Human Services, 1988). Prevalence values for sexual (roughly 10-35 %) and physical abuse (5-15 %) vary (see Conte 1985, Greenwood 1990) but even with conservative estimates (there are approximately 65 million children in the United States below the age of 16), the number of children exposed to one of these severe traumas is 9.5 million. In addition to being victims of, children are often witnesses to, violence; Eth and Pynoos (1985) have estimated that approximately 3 million children each year witness violence in their homes. Each year thousands of children survive natural or man-made disasters and traumatizing medical problems such as burns. Taken together, a conservative estimate of children currently at risk for PTSD exceeds 15 million, and grows, as traumatized children carry their scars to adulthood and new children are traumatized each year. It is estimated that 15 % of Vietnam Veterans (1.5 million people) suffer PTSD (Helzer 1987), yet if one assumes that only 10 % of the children traumatized since 1964 develop symptoms (a very conservative estimate) there would be 4.5 million 'veterans' of childhood with PTSD. Despite the scope of this serious public health problem relatively little research has been dedicated to this area. Some critical initial steps towards understanding the effects of childhood trauma, descriptive and clinical studies, have been carried out, however.

THE CLINICAL PICTURE: CHILDHOOD PTSD

Clinical descriptive studies of PTSD in children have been pioneered by Dr. Lenore Terr (Terr 1983). While fitting roughly into the three main clusters described above, the symptoms of PTSD in children present a more confusing diagnostic picture for the clinician, often appearing as Attention Deficit Hyperactivity Disorder, Conduct Disorders, anxiety disorders and affective disorders (Terr 1991).

Over the last two years childhood PTSD has been the focus of study at the Center for the Study of Childhood Trauma in Chicago. A number of interesting observations have been made regarding the clinical picture of childhood PTSD. In the population at the Center, co-morbid DSM III-R diagnoses were seen in 85 % of the children with PTSD. In many cases the only clear distinguishing features of PTSD were 1) documented history of a severe traumatic event(s), 2) exacerbation of symptoms with re-exposure to trauma-specific stimuli and 3) autonomic nervous system hyperarousal. These three features were noted in children that exhibited psychotic, anxiety and affective symptoms as well as symptoms of disordered conduct (often aggressive or sexualized, dependent upon the original trauma). One of the more interesting groups we have identified is a set of children severely traumatized during the first 3 years of life, resulting in an apparent post-traumatic pervasive developmental delay. In almost all cases the children do not understand their symptoms as being related to their history of trauma and often, especially in the children abused before age 4, cognitive recall of the trauma is not present. In this regard, it is easy to see how the diagnosis of PTSD is under reported in children -- a child presents with any array of psychiatric symptoms with no understanding or recall of traumatic events in their early life, often with an adult caretaker who is unaware of (e.g., sexual abuse), or unwilling (e.g., physical abuse) to give, history regarding the trauma. A very consistent physical finding in these children, however, is autonomic nervous system (ANS) hyperarousal.

Many factors appear to be important in the development of PTSD following trauma -- the nature of the trauma, the degree to which body integrity is threatened, the family support system following a trauma, among others (see Eth and Pynoos 1985). We observed two important

factors which appeared to play a role in the specific set of symptoms a given child will exhibit following trauma: 1) family history of psychiatric disorder and 2) age at which trauma occurred. Consistent with diathesis-stress models of mental illness, we observed that, in general, if an individual had a family history of schizophrenia, the symptoms expressed following childhood trauma included some pre-psychotic and psychotic range symptoms, if affective or anxiety disorders were in the family history, the expressed symptoms were mood and anxiety disorders, and if there was a strong history of alcoholism and sociopathy, symptoms were more conduct disorders. All of this was superimposed on a developmental matrix such that severe trauma occurring before age 4 resulted in a much higher probability of pre-psychotic and psychotic symptomatology. On the other hand, children with a stable first three years of life but traumatized later in childhood tended to have more affective and anxiety symptoms similar to those observed in adult PTSD (Perry et al, submitted). These observations may shed light on recent studies suggesting a relationship between childhood sexual and physical abuse and borderline personality disorder (Ogata et al. 1990). In this regard we have found the same ANS hyperarousal and down-regulated platelet alpha-2 adrenergic receptors in borderline personality disorder (Southwick et al., 1990a, 1990b) as we observed in adult PTSD (Perry et al. 1987, Perry 1988, Perry et al. 1990).

This complex clinical picture complicates neurophysiological research in childhood PTSD. Indeed, most of the useful clinical research which informs the future directions of this field has not been performed within the conceptual framework of PTSD, a DSM III-R diagnostic entity. Much of the important descriptive work comes from studies of the effects of sexual or physical abuse (e.g., Browne and Finkelhor 1988, Dodge et al. 1991) and of early life loss as a predisposing feature for affective disorders (e.g., Brier et al. 1987; 1988). Despite a relative abundance of clinical descriptive studies from these areas, we know very little about the pathophysiology underlying the many physical signs and symptoms of childhood PTSD (Ornitz and Pynoos 1990). Studies of the neurobiology of PTSD in adults which suggest altered functioning of catecholamines (this volume) provide direction for studies in children. Involvement of CNS catecholamines in the pathophysiology of childhood PTSD is not surprising considering the key role they play in the stress response (Murberg 1990).

CATECHOLAMINES AND STRESS

In 1914 Walter B. Cannon first coined the phrase "fight or flight" to describe the body's appropriate response to a stressful stimuli. When an individual is exposed to real or perceived danger, a series of complex, interactive neurophysiological reactions occur in the brain, the autonomic nervous system, the hypothalamic-pituitary adrenocortical (HPA) axis and the immune system. These responses evolved to provide the critical total body mobilization required for the individual to survive a life-threatening danger. In the initial phases, first labeled 'the alarm reaction' and the 'stage of resistance' by Hans Selye in 1936, portions of the brain involved in arousal, attention and concentration become activated, resulting in hypervigilance to the danger with a decrease in attention to less pressing environmental stimuli -- a soldier in the midst of a fire fight, for example, may not know he has been wounded until the end of the fight.

The neurophysiology of the 'alarm reaction' has been studied extensively in man and in animal models (see Selye 1936, Stone 1975, Stone 1988, Murberg et al. 1990). Acute 'stress' is associated with a variety of physiological responses including the activation of the HPA axis with a concomitant peripheral release of ACTH, epinephrine and cortisol, a significant increase in centrally-controlled peripheral sympathetic nervous system tone, and the 'activation' of a variety of neurochemical systems in the CNS. One of the most critical of these systems is the noradrenergic nucleus in the locus coeruleus (Korf 1976). This region controls noradrenergic tone and activity throughout the midbrain and in important forebrain areas including the cortex

(Foote et al. 1983). The LC has been shown to be critical in many regulatory functions including the regulation of affect, 'irritability', locomotion, arousal, attention and startle (Korf 1976, Foote et al. 1983, Andrade and Aghajanian 1984, Bhasharan and Freed 1988). Another key neural system in the brain, also an adrenergic/noradrenergic system is the ventral tegmental nucleus (V.T.N.) which is involved in regulation of the sympathetic nuclei in the pons/medulla (Moore and Bloom 1975). Both the L.C. and the VTN nuclei have adrenergic receptors which are involved in modulation of the adrenergic or noradrenergic afferentation and efferent outflow (Perry et al. 1983, Vantini et al. 1984). The critical role of CNS catecholamines and their receptors is discussed in detail elsewhere (Giller et al. 1990, Murberg 1990, Perry 1988, Perry et al. 1990), for the present discussion it is sufficient to know that acute stress results in an increase in LC and VTN activity.

The neurophysiological activation seen during acute stress is usually rapid and reversible. When the stressful event is of a sufficient duration, intensity, or frequency, however, these changes are not reversible. Stress induced 'sensitization' occurs-- the neurochemical systems mediating the stress response (e.g., LC noradrenergic systems) change, becoming more 'sensitive' to future stressful events. The molecular mechanisms underlying this phenomenon are not well understood but likely are related to changes in receptor sensitivity following transiently increased neurotransmitter activity, similar to what is seen in cocaine sensitization (Kalivas and Duffy 1989, Kleven et al. 1990) The major increases in catecholamine activity seen during the stress response result in increased receptor stimulation and intracellular receptor-mediated signals. In turn, these changes in intracellular second and third messenger result in altered gene expression of a variety of important structural and regulatory proteins including receptor/effector systems (see Kandel and Schwartz 1982, Goelet and Kandel 1986). Finally, the altered expression of these proteins alters the responsivity of the catecholamine systems mediating stress. It is this altered responsivity which can be related to the hypervigilance, increased startle, affective lability, anxiety, dysphoria, increased SNS activity and reactivity seen in PTSD (see Krystal et al. 1989; Perry et al. 1990a).

CATECHOLAMINES AND DEVELOPMENT

In the adult, with a mature brain, the increases in catecholamine activity associated with the stress response may result in sensitization. In the developing brain, however, neurotransmitters and hormones play key roles in neuronal migration, differentiation, synaptic proliferation and overall brain development (Lauder 1988) and, therefore, the tremendous increases in neurotransmitter activity seen with severe or prolonged stress would be expected to have a significant impact on brain development.

While each neuron, indeed each cell, in an individual's brain contains the same genetic material, each expresses a slightly different portion. As the brain develops, neurons divide, migrate, and differentiate in response to 'microenvironmental' cues, which confer information to, and direct specific differentiation of, the cell. Each neuron's unique structural, biochemical and functional character, then, is a function of the its unique environmental history -- the specific pattern, timing and quantity of these microenvironmental cues. Some of the most important of these cues are receptor-mediated signals from neurotransmitters and hormones. Indeed, catecholamine cues during development are important in determining critical functional properties of mature neurons, including the density of neurotransmitter receptor (e.g., Miller and Friedhoff 1988, Perry et al. 1990b). Alterations in the pattern, timing and quantity of catecholamine (or any critical neurotransmitter system) activity during development might be expected to result in altered development of catecholamine receptor/effector systems and the functions mediated, in part, by these systems. A trauma-induced prolonged stress response is likely to result in an abnormal pattern, timing and intensity of catecholamine activity in the

developing brain. The development of the human brain continues beyond birth and its development remains vulnerable to the abnormal patterns of neurotransmitter and hormone activity seen following trauma. Young children victimized by trauma are at risk for developing permanent vulnerabilities -- permanent changes in neuronal differentiation and organization. In this regard, childhood PTSD is a developmental disorder.

It appears that there are developmental phases during which an individual is most vulnerable to traumatic stressors. This most vulnerable period occurs during the development of the complex stress-mediating CNS systems, including the catecholamines. It is likely that the functional capabilities of the CNS systems mediating stress in the adult are determined by the nature of the 'stress' experiences during the development of these systems, i.e., in utero, during infancy and childhood (Perry, 1988; Perry et al., 1990). A number of fascinating studies in animals demonstrate the exquisite sensitivity of the developing CNS to stress (see Suoumi 1986). In rats exposed to perinatal handling stress major alterations in the ability of the rat to 'learn' and to respond appropriately to stressors are seen later in life (Weinstock et al. 1988). The most interesting aspect of these studies is that exposure to unpredictable stress resulted in deficits while exposure to consistent, daily stress resulted in 'improved' or superior behavior -- these animals were 'resilient'. One can speculate on equivalent 'controlled' or daily stress and uncontrollable, non-scheduled stressors in the development of a human. An infant who is allowed to have an 'optimal' degree of frustration, one who can control, during rapprochement, his own optimal degree of 'tension, anxiety' (i.e., stress) and return to mother for comfort, is one whose developing CNS is establishing an appropriate neurochemical milieu for the development of a flexible, maximally-adaptive physiological apparatus for responding to future stressors. A child who is reared in an unpredictable, abusive or neglectful environment (see Spitz and Wolfe 1946) will likely have evoked in his developing CNS a milieu which will result in a poorly organized, 'dysregulated' CNS catecholamine system. One would hypothesize that such an individual would be susceptible to the development of more severe signs and symptoms when exposed to psychosocial stressors through the course of their life.

Some studies in humans suggest this is the case. Increased psychiatric symptoms and disorders are observed in adults who have severe, unpredictable early life stressors (Brown and Harris 1977, Lloyd 1980, Rutter 1984). A provocative study by Breier and co-workers (1988) reported the effects of parental loss during childhood on the development of psychopathology in adulthood. They examined a number of adults who had suffered a parental loss during childhood and found that the subjects with psychiatric disorders and symptoms had significant biological and immunological changes related to early parental loss relative to control groups. The authors concluded that early parental loss (a traumatic event) accompanied by the lack of a supportive relationship subsequent to the loss (an external stress reducing factor) is related to the development of adult psychopathology.

If the early life trauma results in an abnormal pattern of stress-mediating neurotransmitter and hormone and this abnormal set of cues alters development of CNS catecholamine systems in an adverse fashion, this should be manifest when examining functions putatively mediated by these CNS catecholamines (see Moore and Bloom 1989). In specific, one would predict a host of abnormalities related to catecholamine regulation of affect, anxiety, arousal/concentration, impulse control, sleep, startle, and autonomic nervous system regulation, among others. Clearly the clinical symptoms of PTSD support altered functioning in many of these domains. The next sections of this chapter will review some of our preliminary investigations of the pathophysiology of severe chronic childhood PTSD.

STUDIES IN CHILDHOOD PTSD

Over the last two years, a variety of studies have been in progress at the Center for the Study of Childhood Trauma. While multiple groups of children with PTSD have been studied, the present chapter will discuss our studies with the severe chronic PTSD group. All of the children in this group have been victims of severe, repeated trauma (usually physical or violent sexual abuse or both) typically occurring during the first five years of life. Diagnosis was made using a modification of the Structured Interview for Post Traumatic Stress Disorder (Davidson et al 1990). It was hypothesized that since this group experienced trauma early in development, major disruptions of brainstem organization/development would be more easily observed.

PLATELET ALPHA-2 ADRENERGIC RECEPTORS IN CHILDHOOD PTSD

Alpha-2 adrenergic receptors, both pre- and postsynaptic, play important roles in mediating the effects of the catecholamine systems of the LC and VTN (Perry et al. 1983, Vantini et al. 1984) and thereby mediating both acute and chronic stress (see U'Prichard and Kvetnansky 1980, Stone et al. 1975, Stone 1988). Over the last few years, we have demonstrated down-regulated and desensitized platelet alpha-2 adrenergic receptors in combat veterans with PTSD (Perry et al. 1987, Perry 1988, Perry et al 1990). We have been able to demonstrate that, using this marker, we can track the overall 'tone' of the sympathetic nervous system (Perry 1988, Perry et al. 1990, Southwick et al 1990a, 1990b). This indirect method has been useful in examining regulation and dysregulation of the brainstem catecholamine systems involved in the regulation of the SNS.

Figure 1

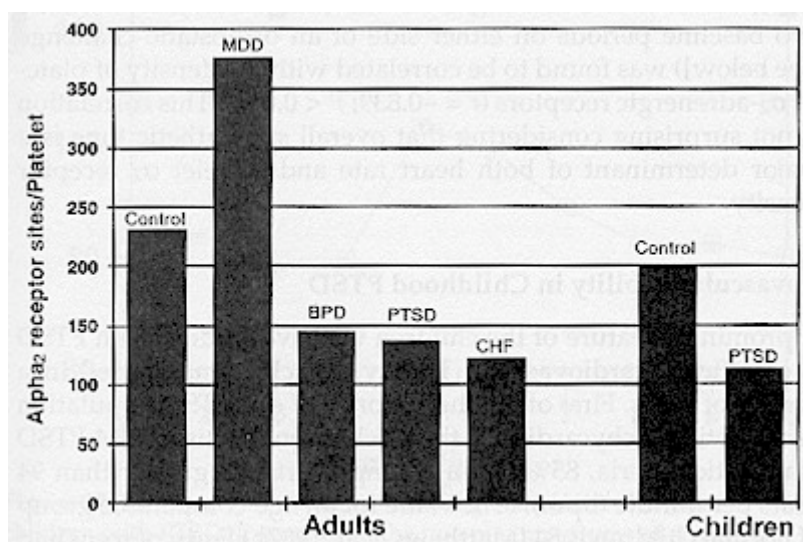


Figure 1. Platelet alpha-2 adrenergic receptor binding sites in childhood PTSD. Alpha-2 receptor sites were measured using standard methods (Perry 1988) and comparison of these values were made across a variety of disorders. These values are all from our laboratory and adult values summarize findings reported previously (Perry 1987; Perry 1988; Perry et al. 1990, Southwick et al. 1990a, 1990b). Groups include; adult control (n=24), major depression (MDD, n=8), borderline personality disorder (BPD, n=14), adult PTSD (n=25), congestive heart failure (CHF, n=23), children control (n=14), childhood PTSD (n=8).

We performed an initial pilot study using these peripheral receptor measures in childhood PTSD (Perry et al, submitted). Platelet alpha-2 adrenergic binding sites were measured in a small group (n = 8) of children (mean age = 11.1, range 9-13) with PTSD using standard

methodologies (Perry 1988). When compared with an age comparable control group, the PTSD group had fewer total binding sites (Fig 1). This is similar to our observations in adult PTSD. Down regulated peripheral adrenergic receptors is not unexpected. This likely reflects down regulation in the presence of 'higher than control' circulating catecholamine associated with the hyperreactive SNS seen in PTSD (Kosten et al. 1986).

These receptor measures are relatively invasive and difficult to employ for longitudinal studies in already traumatized children. We elected to seek other measures for our larger studies. Since the goal was to examine potential dysregulation of brainstem catecholamines, we elected to utilize simple measures which, in part, are regulated by brainstem catecholamines -- autonomic regulation of heart rate. We first demonstrated a relationship between a baseline heart rate measure and platelet alpha-2 receptor density. Using the children with PTSD and the controls from the preliminary receptor studies (Fig 1), an estimate of resting heart rate (obtained by the mean of two baseline periods on either side an orthostatic challenge, see below) was found to be correlated with the density of platelet alpha-2 adrenergic receptors ($r=-0.839$; $p<0.001$). This correlation is not surprising considering that overall sympathetic tone is a major determinant of both heart rate and platelet alpha-2 receptor density.

CARDIOVASCULAR LABILITY IN CHILDHOOD PTSD

A prominent feature of the children we have studied with PTSD is significant cardiovascular lability. This is manifested in a variety of ways. First of all, the majority of our PTSD population has a resting tachycardia. Of the 34 children meeting PTSD diagnostic criteria, 85 percent had a resting heart rate greater than 94 bpm, (the value for an age-comparable group of normal children is 84: Matthews et al. 1987). Forty percent had resting rates above 100 bpm.

Figure 2

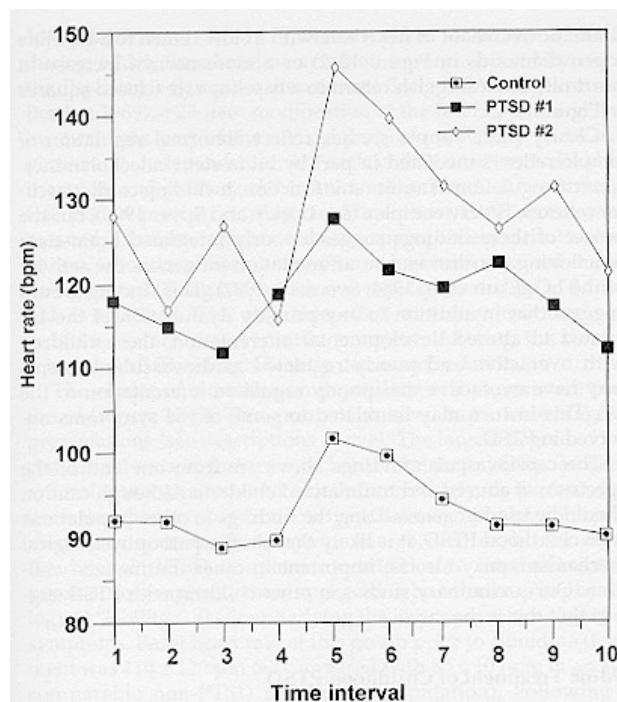


Figure 2. Heart rate changes following orthostatic challenge in children with PTSD. Examples of the two major patterns of change in heart rate observed in children with severe chronic PTSD. Heart rate was monitored each 2 minutes for 20 minutes. During the first 4 time intervals children were resting quietly in a supine position;

after 9 minutes (4.5 time intervals) children stood up and remained standing for the duration of the challenge period. A control pattern is illustrated by the open squares (non-PTSD, psychiatric disordered child, age 11.4). The two PTSD patterns are generally described by higher than control basal rate and 1) a dramatic overshoot of heart rate with a slow return to a baseline (closed squares) or 2) a more normal increase in heart rate but a sluggish return to a baseline rate (closed diamonds).

This lability was even easier to see following a simple orthostatic challenge ([Fig 2](#)). In this simple procedure, a child was supine for 9 minutes, during which time a baseline heart rate was established. At 9.5 minutes, the child stood up and remained standing for another 10 minutes. Heart rate was monitored throughout this procedure. Two general patterns of heart rate change following orthostatic challenge were seen (see [Fig 2](#) legend). In general, the two PTSD patterns are generally described by higher than control basal rate and 1) a dramatic overshoot of heart rate with a slow return to a baseline (closed squares in [Fig 2](#)) or 2) a more normal increase in heart rate but a sluggish return to a baseline rate (closed diamonds in [Fig 2](#)).

Clearly these simple studies reflect abnormal regulation of simple autonomic nervous system reflexes mediated, in part, by brainstem catecholamines. Central regulation of autonomic function, including cardiovascular reflexes, is very complex (see Loewy and Spyer 1990) but the power of these findings suggest poorly integrated brainstem functioning. Cardiovascular afferentation influences the activity of the LC (Elam et al 1984, Svensson 1987) -- this would suggest that, in addition to any primary dysfunction of the LC related to altered developmental afferentation, these children with overactive and poorly regulated cardiovascular systems may also give overactive and poorly regulated afferentation to the LC. This in turn may be related to some of the symptoms observed in PTSD.

The cardiovascular findings above are from one end of the spectrum of abused and traumatized children. While caution should be used in generalizing the findings to other populations with childhood PTSD, it is likely that similar pathophysiological mechanisms may also be important in other traumatized children. Our preliminary studies in other children with PTSD suggest that this is the case.

CLONIDINE TREATMENT OF CHILDHOOD PTSD

The receptor and cardiovascular evidence above suggested that one of the key features of our PTSD population were overactive (increased sympathetic tone) and over-reactive, poorly regulated (exaggerated orthostatic responses) brainstem catecholamine systems. For this reason, an open trial of clonidine was carried out. Clonidine is an alpha-2 adrenergic receptor partial agonist. It acts via a combination of pre-synaptic inhibition and post-synaptic alpha-2 receptors, some on important sympathetic nuclei, which may be the mechanism by which it is an effective antihypertensive medication. In limited open trials, clonidine has been found to be effective in adult PTSD (Kolb et al. 1984) .

Seventeen children with PTSD (13 male, 4 female; mean age 10.4, range 6.0 -14.2) were drug free for at least four weeks during which time baseline symptoms were assessed by using the Psychiatric Symptom Assessment Scale, a 23 item modification of the Brief Psychiatric Rating Scale. As part of the clinical program, a weekly PSAS was performed, independently, by each child's teacher, individual therapist and primary child care worker. For the four week, drug-free period prior to starting clonidine these PSAS scores were meaned. Clonidine was started after appropriate physical exam, lab work and consents had been obtained. Initial dosage was 0.05 mg bid and rapidly titrated up to 0.1 mg bid as tolerated. The only side effect of any significance

was sedation, which was typically transient. Altering schedule to 0.05 qid significantly decreased sedation.

Figure 3

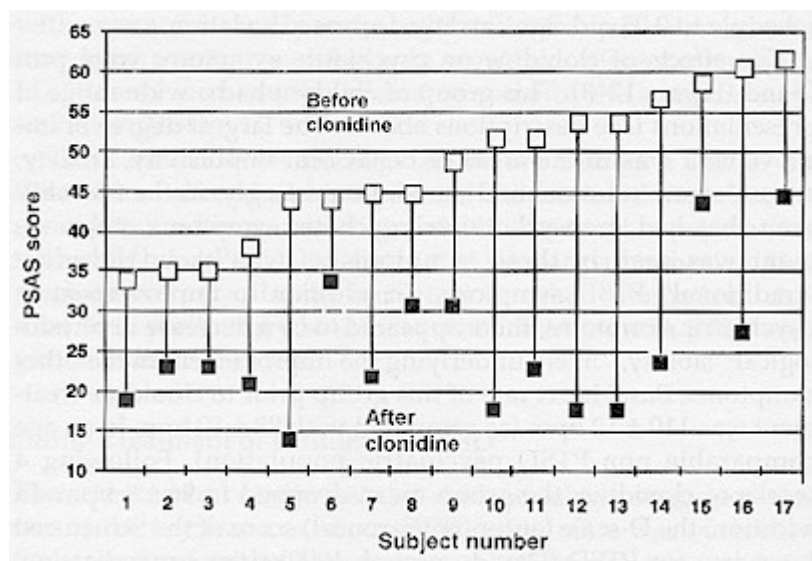


Figure 3. The effects of clonidine on psychiatric symptoms in childhood PTSD. Seventeen children with severe chronic PTSD received clonidine (dose range: 0.05 bid to 0.1 mg tid) for a four week period. Prior to and during this time weekly assessments of symptoms were made independently by teacher, individual therapist and primary child care worker using the Psychiatric Symptom Assessment Scale (PSAS). Values represent means of these three independent assessments from the two weeks prior to (open squares) and the fourth week (closed squares) of clonidine treatment.

The effects of clonidine on psychiatric symptoms were profound ([Fig 3](#)). This group of children had a wide range of presentations (see descriptions above). Largest degree of improvement was in the areas of behavioral impulsivity, anxiety, arousal, concentration and mood. Interestingly, in the few children that had pre-psychotic or psychotic symptoms, improvement was seen in these symptoms as well as the more 'traditional' PTSD symptoms. In addition to improvement in psychiatric symptoms, there appeared to be a decrease in physiological 'lability', likely underlying the improvement in the other symptoms. Basal heart rate of this group prior to clonidine treatment was $110 + 12$ (as compared to $88 + 10$ in an age comparable non-PTSD psychiatric population). Following four weeks of clonidine, the group mean dropped to $96 + 8$. In addition, the D-scale (autonomic arousal) score of the SI-PTSD (Davidson et al 1990) prior to medication, $15.3 + 4$, dropped to $6 + 3$. Overall, clonidine treatment, in this population, significantly improved the signs and symptoms of childhood PTSD.

This observed pharmacologically-induced decrease in arousal symptoms suggests that alpha-2 adrenergic receptors play a pivotal role in mediating the signs and symptoms of PTSD in this group of severely traumatized children. The role of the alpha-2 receptor in regulating the LC and VTN is well known (Perry et al. 1983, Vantini et al. 1984). The capacity of clonidine to modulate and 'buffer' LC and VTN activity is related to its special qualities as a partial agonist. In physiological systems, a partial agonist can act as both an agonist and as an antagonist depending upon the system's tonic activity -- if the tonic activity falls below a certain level, the partial agonist will act by stimulating unoccupied receptors thereby increasing agonism; when

the tonic activity becomes too high, the partial agonist will compete with the endogenous agonist for the receptor sites and **decrease** activity of the system by virtue of lower intrinsic activity than the full agonist neurotransmitter. In this way, clonidine activates some parts of the noradrenergic terminal areas and prevents over reactivity in others. The summed effect is to help poorly regulated brainstem catecholamine systems work in a more organized, efficient fashion, thereby decreasing symptoms related to dysregulation of the brainstem.

IMPLICATIONS AND FUTURE DIRECTIONS

Severe trauma during childhood can have a devastating effect on the development the brain and all functions mediated by this complex organ -- emotional, cognitive, behavioral and physiological. In many cases the sequelae of childhood trauma present with signs and symptoms similar to adult PTSD, often they present with very different symptoms. The concept of childhood PTSD must be considered within the broader concept of the diathesis-stress model of mental illness. The diathesis-stress model suggests that a predisposition (genetic or developmental) for a specific psychiatric disorder exists which can be differentially expressed in an individual depending upon the degree of 'biopsychosocial' stressors. The concept of PTSD loses meaning if we consider all of the effects of childhood trauma as part of this 'disorder'. Indeed, it is clear that early life trauma/stress plays an important role an expresser of genetically-determined vulnerabilities to a variety of neuropsychiatric disorders, including schizophrenia (e.g. Garmezy 1978), major depression (Lloyd 1980) and Tourette's syndrome (Leckman et al. 1990). It is important to study childhood trauma/stress as an expresser of genetic vulnerabilities to medical conditions, as well, (Coddington 1972a, 1972b) including cardiovascular diseases such as essential hypertension, sudden cardiac death or cardiac dysrhythmias. Associations between stress during childhood and adolescence and the development of cardiovascular disease have been made for many years (see Boyce and Chesterman 1990). It is interesting to note that associations have also been made between vulnerability to affective disorders and cardiovascular disease. Early life stress/trauma is a common link between many associated medical and psychiatric conditions -- including neuroimmunological, cardiovascular and neuroendocrine. This is not surprising considering the critical role of development in determining final phenotype (and therefore function) of all physiological functioning in the adult.

For a number of reasons, the long term effects of childhood trauma remain relatively unexplored. In part this has been due to a variety of complex clinical and social issues, some of which are being addressed at present by multidisciplinary research teams working closely with the state and local social agencies involved in providing services for these unfortunate children. With the high incidence of sexual abuse, physical abuse and violence in our society, the need to understand these complex issues is ever pressing. The study of traumatized children and the long term effects of trauma provides an important conceptual starting point from which to study the developmental nature of all psychiatric illness and, hopefully, to develop new and effective therapeutic and preventative interventions.

REFERENCES

- Andrade R, Aghajanian GK: Locus coeruleus activity in vitro: Intrinsic regulation by a calcium-dependent potassium conductance but not alpha-2 adrenoceptors. J Neurosci 4:161-70, 1984
- Bhaskaran D, Freed CR: Changes in neurotransmitter turnover in locus coeruleus produce by changes in arterial blood pressure. Brain Res Bull 21: 191-199, 1988

- Birkhimer LJ, DeVane CL, Muniz CE: Post-traumatic stress disorder: Characteristics and pharmacological response in the veteran population. Compr. Psychiatry 26:304-10, 1985
- Blanchard EB, Kolb LC, Pallmeyer TP, et al.: A psycho-physiologic study of post-traumatic stress disorder in Vietnam veterans. Psychiatr. Q. 54:220-28, 1983
- Bleich A, Siegel B, Garb R, et al.: Post-traumatic stress disorder following combat exposure: Clinical features and psychopharmacological treatment. Brit. J. Psychiatry 149:365- 69, 1986.
- Boehnlein JK, Kinzie JD, Ben R,et al., One year follow-up study of post-traumatic stress disorder among survivors of Cambodian concentration camps. Am. J. Psychiatry 142:956-59, 1985
- Boyce WT, Chesterman E Life events, social support, and cardiovascular reactivity in adolescence. J Dev Behav Pediatr 11: 105-111, 1990
- Breier A., Albus M., Pickar D., et al Controllable and uncontrollable stress in humans: alterations in mood, neuroendocrine and psychophysiological function. Am J Psychiatry, 144: 1419-1425, 1987
- Breier A, Kelsoe JR, Kirwin PD: Early parental loss and development of adult psychopathology. Arch Gen Psych 45: 987- 993, 1988.
- Brende JO: Electrodermal responses in post-traumatic syndromes. J Nerv Ment Dis 170:352-61, 1982
- Brown GW, Harris T, Copeland JR: Depression and loss. Br J Psych 130: 1-18, 1977
- Browne A, Finkelhor D Impact of child sexual abuse: a review of the literature. Psychol Bull 99: 66-77, 1986.
- Bury J.S.: Pathology of war neurosis. Lancet 1:97-99, 1918
- Cannon, W. B. The emergency function of the adrenal medulla in pain and the major emotions. Am J Physiol 3: 356-372, 1914
- Coddington RD The significance of life events as etiological factors in the diseases of children: I a survey of professional workers. J Psychosom Res 16: 7-18, 1972a
- Coddington RD The significance of life events as etiological factors in the diseases of children: II a study of the normal population. J Psychosom Res 16: 205-213, 1972b
- Conte JR The effects of sexual abuse on children: a critique and suggestions for future research. Victimology 10: 110-130, 1985
- Davidson JRT, Kudler HS, Smith RD Assessment and pharmacotherapy of posttraumatic stress disorder. In ***Biological Assessment and Treatment of Post-traumatic Stress Disorder***. Edited by Giller EL, Washington, DC , American Psychiatric Press Inc., 1990, pp 205-236
- DaCosta JM: On irritable heart: A clinical study of a form of functional cardiac disorder and its consequences. Am J Med Sci 61:17-52, 1871
- Dobbs D, Wilson WP, Observations on persistence of war neurosis. Dis Nerv Sys 21:40-46, 1960
- Dodge KA, Bates JE, Pettit, GS: Mechanisms in the cycle of violence. Science 250: 1678-1683, 1991
- Elam M, Svensson TH, Thoren P : Regulation of locus coeruleus neurons and splanchnic, sympathetic nerves by cardiovascular afferents. Brain Res 290: 281-87, 1984
- Eth S, Pynoos, RS (Eds) ***Post-traumatic Stress Disorder in Children***, Washington DC, American Psychiatric Press, 1985
- Finkelhor D ***Child Sexual Abuse*** The Free Press, New York, 1984
- Foote SL, Bloom FE, Aston-Jones G: Nucleus locus coeruleus: new evidence of anatomical and physiological specificity. Physiol Rev 63, 844-856, 1983
- Fraser F, Wilson RM: The sympathetic nervous system and the "irritable heart of soldiers." Br Med J 2:27-29, 1918

- Garmezy N Observations on high-risk research and premorbid development in schizophrenia. In ***The Nature of Schizophrenia*** Edited by Wynne LC, Cromwell , Matthysse S New York, Wiley, 1978
- Giller EL, Perry BD, Southwick S, et al., Psychoendocrinology of post-traumatic stress disorder. In ***Post-Traumatic Stress Disorder: Etiology, Phenomenology and Treatment***. Edited by Wolf ME, Mosnaim AD, Washington DC, American Psychiatric Press Inc, 1990, pp 158-170
- Goelet P, Kandel ER: Tracking the flow of learned information from membrane receptors to genome. Trend Neurosci 9:492-99, 1986
- Greenwood CL, Tangalos EG, Maruta T Prevalence of sexual abuse, physical abuse, and concurrent traumatic life events in a general medical population. Mayo Clin Proc 65: 1067-1071, 1990
- Helzer J, Robins L, McEvoy L Post traumatic stress disorder in the general population. N Engl J Med 317: 1630-1634, 1987
- Horowitz MJ, Wilner N, Kaltreder N, et al.: Signs and symptoms of post-traumatic stress disorder. Arch Gen Psych 37: 85-92, 1980
- Kalivas PW, Duffy P Similar effects of daily cocaine and stress on mesocorticolimbic dopamine neurotransmission in the rat. Biol Psychiatry 25: 913-928, 1989
- Kandel ER, Schwartz JH: Molecular biology of an elementary form of learning: modulation of transmitter release by cyclic AMP. Science 218: 433-443, 1982
- Kleven MS, Perry BD, Woolveron WL, Seiden, LS Effects of repeated injections of cocaine on D-1 and D-2 dopamine receptors in rat brain. Brain Res 532: 265-270, 1990
- Kolb LC, Burris BC, Griffiths S Propranolol and clonidine in the treatment of post traumatic stress disorders of war, In *Post Traumatic Stress Disorders: Psychological and Biological Sequelae*. Edited by van der Kolk BA, Washington, DC, American Psychiatric Press, 1984, pp 29-44
- Korf J: Locus coeruleus, noradrenaline metabolism, and stress. In: ***Catecholamines and Stress*** Edited by Usdin E, Kvetnansky R, Kopin, IJ, New York, Pergamon, 1976, pp 105-111
- Kosten TR, Mason JW, Giller EL, et al.: Sustained urinary norepinephrine and epinephrine elevation in post-traumatic stress disorder. Psychoneuroendocrinology 1986
- Krystal JH, Kosten T, Perry BD, et al.: Neurobiological aspects of post-traumatic stress disorder: review of clinical and preclinical studies. Behav Ther, 20: 177-193, 1989
- Lauder JM Neurotransmitters as morphogens. Progress in Brain Research, 73: pp 365-388, 1988.
- Leckman JF, Dolnansky ES, Hardin MT et al. Perinatal factors associated with tic severity in Tourette's syndrome. J Am Acad Child Adolesc Psychiatry 29: 220-226, 1990
- Lloyd C: Life events and depressive disorder reviewed: I. Events as predisposing factors. Arch Gen Psychiatry 37:529-535, 1980
- Loewy AD, Spyer KM (Eds) ***Central Regulation of Autonomic Functions***, New York, Oxford University Press, 1990
- Matthews KA, Rakaczky CJ, Stoney CM et al. Are cardiovascular responses to behavioral stressors a stable individual difference variable in childhood ? Psychophysiol 24: 464-473, 1987
- Martini DR, Ryan D, Nakayama D et al. Psychiatric sequelae after traumatic injury: the Pittsburgh regatta accident. J Acad Child Adolesc Psychiatry 29: 70-75, 1990
- McFarlane AC Posttraumatic phenomena in a longitudinal study of children following a natural disaster. J Am Acad Child Adolesc Psychiatry 26: 764-769, 1987
- McLeer SV, Deblinger E, Atkins MS, et al: Post-traumatic stress disorder in sexually abused children. J Am Acad Child Adolesc Psychiatry 27: 650-654, 1988
- Miller JC, Friedhoff AJ Neurotransmitter programming of receptor density during development Progress in Brain Res 73: 507-523, 1988

- Moore RY, Bloom FE: Central catecholamine neuron systems: anatomy and physiology of the norepinephrine and epinephrine systems. Ann Rev Neurosci 2: 113-153, 1979
- Murberg MM, McFall ME, Veith RC Catecholamines, stress and posttraumatic stress disorder. In ***Biological Assessment and Treatment of Post-traumatic Stress Disorder***. Edited by Giller EL, Washington, DC , American Psychiatric Press Inc., 1990, pp 27-65
- Murphy JK, Alpert BS, Willey ES et al. Cardiovascular reactivity to psychological stress in healthy children. Psychophysiol 25: 144-152, 1988
- Ogata SN, Silk KR, Goodrich S, et al. Childhood sexual and physical abuse in adult patients with borderline personality disorder Am J Psychiatry 147: 1008-1013, 1990
- Ornitz EM, Pynoos RS Startle modulation in children with post-traumatic stress disorder. Am J Psychiatry 147: 866-870, 1989
- Perry BD Placental and blood element neurotransmitter receptor regulation in humans: potential models for studying neurochemical mechanisms underlying behavioral teratology. Progress in Brain Research 73: 189-207, 1988.
- Perry BD, Stolk JM, Vantini G, et al. Strain differences in rat brain epinephrine synthesis and alpha-adrenergic receptor number apparent 'in vivo' regulation of brain alpha-adrenergic receptors by epinephrine. Science 221: 1297- 1299, 1983
- Perry BD, Southwick SM, Giller Jr EL Altered platelet alpha2- adrenergic receptor affinity states in post-traumatic stress disorder. Am J Psychiat 144: 1511-1512 , 1987
- Perry, B. D., Southwick, S. M., Giller, E. J. Adrenergic receptors in posttraumatic stress disorder. In ***Biological Assessment and Treatment of Post-traumatic Stress Disorder***. Edited by Giller EL, Washington, DC, American Psychiatric Press, 1990a, pp 87-115
- Perry BD, Wainwright MS, Won L et al. The influence of dopamine on dopamine receptor density in three dimensional tissue culture. Soc Neurosci Abstr 16: 646, 1990b
- Perry SW, Cella DF, Falkenberg J, et al. Pain perception in burn patients with stress disorders. J Pain Symptom Management 2:29-33, 1987
- Rutter M: Psychopathology and development: I. Childhood antecedents of adult psychiatric disorder. Australian and New Zealand J Psychiatry 18:225-34, 1984
- Sallis JF, Patterson TL, McKenzie TL et al. Stability of systolic blood pressure reactivity to exercise in young children. J Dev Behav Pediatr 10: 38-43, 1989
- Seyle H: A syndrome produced by diverse nocuous agents. Nature 196:32, 1936
- Southwick SM, Yehuda R, Giller EL, Perry, BD Altered platelet alpha-2 adrenergic binding sites in borderline personality disorders. Am J Psychiatry 147: 1014-1017, 1990a
- Southwick SM, Yehuda R, Giller EL, Perry, BD Altered platelet alpha-2 adrenergic receptor binding sites in major depressive disorder and borderline personality disorder. Psychiatry Res 34: 193-203, 1990b
- Spitz RA, Wolf KM: Anaclitic depression: An inquiry into the genesis of psychiatric conditions in early childhood, II. Psychoana. Stud Child 2:313-42, 1946
- Stone EA: Stress and catecholamines. In: A.J. Friedhoff (ed.), ***Catecholamines and Behavior 2: Neuropsychopharmacology***. New York: Plenum, 31-72, 1975
- Stone E: Stress and brain neurotransmitter receptors, in ***Receptors and Ligands in Psychiatry***. Edited by Sen AK, Lee T. New York, Cambridge Univ. Press, 400-423, 1988.
- Svensson TH: Peripheral, autonomic regulation of locus coeruleus noradrenergic neurons in brain: Putative implications for psychiatry and psychopharmacology. Psychopharmacology 92:1-7, 1987
- Suoumi SJ Genetic and maternal contributions to individual differences in rhesus monkey biobehavioral development. In: ***Psychobiological Aspects of Behavioral Development***, Edited by N. Krasnagor, New York: Academic Press, 1986, 397-420.

- Terr L: Chowchilla revisited: the effects of psychic trauma four years after a school-bus kidnapping. Am J Psychiatry 140: 1543- 1550, 1983.
 - Terr, LA: Childhood traumas: An outline and overview. Am J Psychiatry 148: 1-20, 1991
 - U'Prichard DC, Kvetnansky R: Central and peripheral adrenergic receptors in acute and repeated immobilization stress. In ***Catecholamines and Stress: Recent Advances***. Edited by E. Usdin E, Kvetnansky R, Kopin IJ, New York: Elsevier, North Holland Inc., 1980, pp 299-308
 - Vantini G, Perry BD, Gucchait RB et al Brain epinephrine systems: detailed comparison of adrenergic and noradrenergic metabolism, receptor number and in vivo regulation in two inbred rat strains. Brain Res 296: 49-65, 1984.
 - Weinstock M, Fride E, Hertzberg R: Prenatal stress effects on functional development of the offspring.
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