Childhood Posttraumatic Stress Disorder: A Review of Neurobiologic Sequelae

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Each year an alarmingly high number of children are exposed to severe psychological trauma. Stressors range from single-episode acute traumas to chronic ongoing and repetitive traumas. Examples of the former include accidents, natural and manmade disasters (earthquakes, fires, hurricanes, tornadoes, and floods) and crimes (eg, kidnapping, rape, or assault). Examples of the latter include exposure to childhood maltreatment (sexual and physical abuse and neglect), chronic illnesses, living in war zones (such as Cambodia, Beirut, and Bosnia), and exposure to ongoing family- and community-based violence. Although phenomenologic studies suggest there are many similarities between posttraumatic stress symptomatology in adults and children, there also seem to be important differences. First, it appears that traumatized children are more likely than adults to develop posttraumatic stress responses. In a meta-analysis of more than 2000 children from 34 separate samples of traumatized children (including preschoolers, school-aged children, and adolescents), an average 36% of youngsters were diagnosed with posttraumatic stress disorder (PTSD) compared with an average 24% of traumatized adults (based on more than 3000 adults from five samples).[1] Second, children exhibit a wider range of posttraumatic symptoms that differ according to the type of stressor experienced, age of the child,[3] cognitive ability at the time of the trauma (including ability to appraise danger),[4] level of family functioning and support,[2,5] and number of secondary adversities encountered after the trauma.[4] In addition to the core symptoms of PTSD (intrusion, avoidance, and hyperarousal), trauma in a developing child can affect a variety of emotional and behavioral functions such as attention span, affect regulation , impulse control, sense of future orientation, and even personality.

Traumatic stress appears to have a greater impact on children than adults because of its capacity to disrupt normal stages of childhood development. For example, sexual abuse occurring in latency-aged children may alter the timing and course of puberty.[6] Further, other forms of maltreatment, such as emotional abuse and neglect, can affect multiple stages of development, typically beginning in infancy and often extending into adolescence. Likewise, exposure to chronic community violence often persists throughout a child's formative years.[7]

Animal studies with rodents[8] and monkeys[9] have shown that the type, timing, and predictability of stress can influence the development of neuroendocrine systems and brain structures. There are certain "critical periods" during which small environmental insults can exert disproportionately large effects on neurobiologic systems. From a structural standpoint, certain cortical and subcortical structures such as the hippocampus, amygdala, prefrontal cortex, and corpus callosum may be preferentially affected.[10] Functionally, early stress and trauma conceivably can affect many neurotransmitter systems, including the catecholaminergic, dopaminergic, serotonergic, and GABAergic systems, and multiple neuroendocrine axes,

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including the hypothalamic-pituitary-adrenal (HPA) axis, the hypothalamic-pituitary-thyroid (HPT) axis, the hypothalamic-pituitary-growth hormone (HPGH) axis, and the hypothalamic-pituitary-gonadal (HPGN) axis.[11]

Despite the widespread prevalence of childhood trauma and its serious psychological, medical, and legal ramifications, there has been relatively little empirical research on neurobiologic alterations caused by chronic stress and violence in children. This article reviews some of what is known about the neurobiology of PTSD in children by focusing on the following areas: (1) early childhood trauma and the developing brain; (2) dysregulation of catecholamine systems, including the startle response; and (3) dysregulation of the HPA axis. Each of these topics will be covered in detail in other articles in this edition of *Psychiatric Annals* so a brief summary of these findings in adults with PTSD will be presented followed by the findings in children. Finally, some directions for future research are discussed.

EARLY CHILDHOOD TRAUMA AND THE DEVELOPING BRAIN

The brain is a relatively plastic organ whose final structure and function are determined by a complex interplay of genetic and environmental factors. There are progressive maturational changes in brain structure from infancy to adolescence with four stages, or periods, of major structural brain development. These periods include: (1) early childhood (birth to 4 years), (2) late childhood (6-10 years), (3) puberty, and (4) mid-adolescence.[12] These stages of structural brain growth and cortical reorganization correspond with developmental changes in cognitive, emotional, and psychological function and might represent periods of increased stress-related vulnerability for children.

Teicher and colleagues[13] have postulated that early abuse can affect both the pattern and degree of cortical development. Using a measure of electroencephalopathy (EEG) that they term "EEG coherence," Teicher and colleagues compared EEG patterns in 15 children with histories of severe sexual and physical abuse to 15 matched control subjects. Abused children had greater left hemispheric coherence than control subjects but comparable right-sided hemispheric coherence. The authors postulated that early abuse might delay maturation of the corpus callosum, the large myelinated tract that connects the right and left cortical hemispheres thereby affecting the lateralization of EEG coherence. Consistent with their hypothesis, MRI records of 51 pediatric inpatients admitted to McLean Hospital were blindly reviewed and the volume of the corpus callosum was calculated. Both physical abuse and neglect, but not sexual abuse, were associated with volumetric reductions in certain regions of the corpus callosum. These findings were more pronounced in boys. In a separate study, Giedd and colleagues[14] also reported volume reduction in boys with attention deficit hyperactivity disorder (ADHD) but in a different region of the corpus callosum. These MRI findings might help to understand the reported relationship between PTSD and comorbid ADHD.[15]

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Catecholamines

In adults with PTSD, an accumulating number of psychophysiological, neuroendocrine, and pharmacologic challenge studies have demonstrated increased responsivity of the sympathetic nervous system that is detectable under conditions of stress. Compared with healthy control subjects, combat veterans with PTSD have been reported to have greater increases in blood pressure and heart rate when exposed to visual and auditory reminders of trauma,[16] increased 24-hour urine epinephrine and norepinephrine excretion,[17] decreased platelet alpha-2 adrenergic receptor number,[18] decreased basal cAMP and basal adenyl cyclase levels,[19] increased reactivity to sodium lactate,[20] and increased behavioral, cardiovascular, and peripheral biochemical responses as well as decreased cerebral metabolism to the alpha-2 receptor antagonist yohimbine hydrochloride.[21]

In traumatized children, a number of studies suggest that alterations in sympathetic nervous system responsivity resemble the alterations seen in traumatized adults. Perry and colleagues[22] have speculated that the early dysregulation of catecholamine systems may lead to problems in cardiovascular regulation, anxiety, modulation of affect and impulse control, and impairments in attention and concentration. Using cardiovascular lability as a physiological correlate of brain stem catecholaminergic dysregulation, Perry and coworkers studied 34 children who met criteria for PTSD secondary to chronic childhood abuse. Eighty-five percent of subjects had a resting tachycardia greater than 94 beats per minute. Following an orthostatic challenge where the child was supine for 9 minutes and then rose and remained standing for the next 10 minutes, two patterns of heart rate changes emerged. The first pattern consisted of a higher than control basal heart rate and a dramatic overshoot of heart rate on standing with a slow return to a baseline rate. The second pattern consisted of a normal increase in heart rate with a sluggish return to baseline.[22] It further has been hypothesized that for children, sus-

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tained elevated levels of circulating catecholamines might have the additional effect of influencing neuronal differentiation, migration, synaptic proliferation (sprouting), and neuronal loss (pruning).[23]

In two studies of 24-hour urine catecholamine excretion, Debellis and colleagues[24,25] reported differences between traumatized children and healthy control subjects. In the first study, 24-hour urine catecholamine and metabolite levels were compared between 12 sexually abused girls, aged 8-15 years, and nine healthy control subjects. Only one of the subjects met the criteria listed in the *Diagnostic and Statistical Manual* III-R for PTSD. Elevated levels of metanephrine, vanillylmandelic acid, homovanillic acid, and total catecholamines (the sum of norepinephrine, epinephrine, and dopamine) were excreted by girls with histories of sexual abuse. After controlling for height, the strongest developmental covariate, homovanillic acid remained significantly elevated in the sexually abused girls whereas there were trends toward greater excretion of VNA, MN, and total cathecolamines. In the second study, child subjects meeting diagnostic criteria for PTSD (n = 9) were compared with children meeting criteria for overanxious disorder (n = 7) and with healthy control subjects (n = 14).[25] Preliminary results reveal that the PTSD group excreted significantly greater amounts of epinephrine than the other two groups. There were no differences between groups in urinary norepinephrine or dopamine excretion. These two studies suggest that childhood maltreatment may lead to dysregulation of catecholamine systems.

Galvin and colleagues[26] have provided a separate line of evidence linking early maltreatment to disturbances of catecholamine systems. The authors compared dopamine beta hydroxylase (DBH) levels, an enzyme involved in the conversion of dopamine to norepinephrine, in psychiatrically hospitalized boys who had experienced early abuse and neglect and in psychiatric control subjects. DBH levels were significantly lower in boys who had histories of early maltreatment with onset before 72 months. The authors hypothesize that at developmentally critical times maltreatment overstimulates the catecholamine system. This results in initial surges of catecholamines followed by a downregulation of enzyme activity and low levels of peripheral DBH activity.

Two treatment studies provide further evidence for alterations in catecholamine systems.[22,27] Clonidine is an alpha-2 adrenergic receptor partial agonist that acts through both presynaptic and postsynaptic inhibition. It has been used to treat aggressive children and to treat children with comorbid ADHD and Tourette's syndrome. In an open-labeled study of clonidine for the treatment of 65 traumatized children over a 10-week period, Perry[22] found that 60 of 65 subjects had significant improvements in their psychiatric symptoms. Initial improvements were seen in the domains of sleep, irritability, distractibility, and hypervigilance (cluster D symptoms or symptoms of heightened arousal). Later improvements, over the 10-week course, were seen in peer relationships and school performance. Physiologic lability also decreased with a significant drop in basal heart rate. In another open-labeled study of propranolol, a beta-adrenergic blocker, Famuluaro[27] reported an improvement in 11 children with PTSD over a 5-week trial. Improvements were noted in aggressive behavior, agitation, exaggerated startle, insomnia, fearfulness, and loss of control. Our research group is presently conducting a 10-week, double-blind, placebo-controlled trial of clonidine in children with PTSD. We are assessing baseline measures of noradrenergic responsivity such as urinary catecholamines, heart rate, blood pressure, and plasma MHPG at the start and at the end of treatment to determine if clonidine modifies catecholaminergic function in traumatized children and if these neurobiologic changes are associated with response.

STARTLE RESPONSE

The startle response in animals (measured as a flexor motor response to a sudden stimulus) is similar to the startle response in humans (measured as the magnitude of a reflex eye blink).[28] It has been linked to hyperarousal or "cluster D" PTSD symptoms and preclinical studies suggest that it is a useful correlate of noradrenergic activity (see the article by Morgan and colleagues pp 430-434). The startle reflex also has been used to examine some aspects of attention by assessing the impact of prestimulation on its amplitude. Sensory events presented at various times before the startle-eliciting stimuli can either facilitate or enhance the startle response. Startle modulation differs in children and adults. Normal preschoolers do not show prepulse-induced startle inhibition, but they do demonstrate exaggerated prepulse-induced startle facilitation.[29] In the only published study to date of the startle response in children with PTSD, Ornitz and Pynoos[30] compared six children who witnessed a schoolyard sniper attack with age-matched control subjects. Children with PTSD exhibited a significantly reduced level of age-related prepulse inhibition of their startle response suggestive of chronic alteration in their PPI activity. This is not a finding specific to PTSD because PPI deficits

have been noted in enuretic boys,[31] children with comorbid ADHD and Tourette's syndrome,[32] and individuals at risk for schizophrenia.[33]

Hypothalamic Pituitary Adrenal Axis

The hypothalamic pituitary adrenal axis is one of the major biologic systems that coordinates the mammalian response to stress. This axis and its relation to stress and PTSD is reviewed in the article by Southwick and colleagues in this issue (pp. 436-442). Adults with depressive disorders, particularly those patients with features of melancholia, show HPA axis dysfunction characterized by primary hypercortisolemia.[34] There also is considerable evidence for HPA axis dysfunction in adults with PTSD, although the nature of the dysfunction in PTSD appears to be markedly different from that in melancholic, unipolar depression. Findings in patients with PTSD have included decreased basal 24-hour urinary cortisol in most[35,36] but not all studies[37]; decreased 24-hour plasma cortisol levels with increased circadian signal to noise ratio[38]; increased numbers of lymphocyte glucocorticoid receptors[39,40]; supersensitivity to the suppressant effects of a low dose of dexamethasone[40,41]; a blunted ACTH response to ovine CRF[42]; a heightened ACTH response to metyrapone[43]; and increased cerebrospinal fluid (CSF) levels of CRF and somatastatin.[44] When these findings are considered together, it appears that individuals with PTSD may exhibit enhanced reactivity and negative feedback inhibition of the HPA axis.

There have been few studies of HPA axis regulation in adolescents and children. The majority have compared youngsters with depression with healthy control subjects or with patients with other psychiatric disorders. In these studies, prepubertal children and adolescents with major depression have not consistently demonstrated the same neuroendocrine abnormalities as their adult counterparts.[44-47] For example, studies have not shown differences in total 24-hour urinary cortisol,[44] baseline plasma cortisol, or 24-hour diurnal variation of plasma cortisol[45] compared with healthy control subjects. Furthermore, they have not consistently shown escape from suppression to the standard 1-mg dose of dexamethasone.[46,47] However, the possible effects of an early trauma history and/or presence of PTSD have not been considered factors in the comparisons of depressed youngsters and nondepressed control subjects.

A recent study of prepubertal depressed children by Kaufman and colleagues[48] took such factors into account. CRF stimulation tests were performed in prepubertal, depressed children with histories of early childhood abuse. The depressed children with histories of early abuse who were currently experiencing chronic adversity (such as marital strife, emotional abuse, or poverty) showed greater peak, total, and net ACTH secretion but no difference in cortisol secretion following the CRF challenge when compared with (1) depressed children with histories of abuse and no current adversity, (2) depressed, nonabused children, and (3) healthy control subjects. In contrast, DeBellis and colleagues[49] report that 13 sexually abused girls, aged 9 to 15 years, had significantly lower basal and exogenous CRF-stimulated ACTH levels but comparable total 24-hour urinary cortisol and CRF-stimulated cortisol measures compared with 13 nonabused control subjects. Of note, all of the girls in this study were living in relatively stable households at the time of the study and were not experiencing ongoing stress.

Despite the few studies focused on the neurobiology of psychological trauma in children and adolescents, the rates of trauma and PTSD in children are alarmingly high.

Other measures of HPA axis functioning that have been studied in traumatized children include baseline salivary cortisol and cortisol reactivity to daily stress and to the challenge of low-dose dexamethasone. Over a 1-month period, Hart and colleagues[50] collected daily morning salivary cortisol levels in maltreated preschoolers and compared their mean cortisol levels and fluctuations in cortisol values with a comparison group of preschoolers from socially disadvantaged families who had not been maltreated. For each morning of the study period, teachers simultaneously rated the children's social behaviors and interactions (social competence). Cortisol reactivity was positively correlated with social competence scores and negatively correlated with shy and inhibited behavior. Maltreated preschoolers displayed blunted fluctuations in their daily cortisol levels and this diminished responsivity was correlated with impaired social competence as noted by their teachers. Salivary cortisol levels were also measured in response to the administration of a low dose (0.5 mg) of dexamethasone in 37 adolescents from two cities in Armenia hit by the 1988 earthquake.[51] Five years after the disaster, adolescents who lived closer to the epicenter had more PTSD symptoms and showed significantly lower baseline cortisol levels and greater afternoon suppression of salivary cortisol by dexamethasone. Of note, only youngsters with high levels of intrusive PTSD symptomatology demonstrated altered aspect HPA axis functioning. The authors suggest that persistent re-experiencing phenomena may serve as an ongoing source of stress that affects HPA axis function. Alternatively, youngsters who have an enhanced sensitivity to this synthetic glucocorticoid may be predisposed to develop re-experi-

encing symptoms. Prospective, longitudinal studies of traumatized children are needed to understand the long-term neurobiologic impact of trauma and posttraumatic stress disorder on normal childhood development.

CONCLUSIONS AND FUTURE DIRECTIONS

To date there have been few studies focused on the neurobiology of psychological trauma in children and adolescents. However, thus far, among children with PTSD, it appears that alterations in sympathetic nervous system reactivity and HPA axis functioning basically parallel those seen in adults. In future neurobiologic studies it will be important to systematically assess PTSD and comorbid diagnoses with the use of structured clinical interviews. Reliable and valid instruments to measure type and severity of traumatic exposure also will be needed. Standardized assessment of family psychopathology and psychosocial risk factors for the development of PTSD will allow more meaningful interpretation of neurobiologic data. Fortunately, most of the salient findings of the neurobiology of PTSD can be derived from studies of a relatively noninvasive nature (urine, blood, or salivary measures and brain imaging)

Rates of trauma and PTSD in children are alarmingly high. A more informed understanding of the neurobiologic consequences of extreme stress and of the pathophysiology of PTSD in children should facilitate the development of more effective treatments.

REFERENCES

1. Fletcher KE. Childhood posttraumatic stress disorder. In: Mash EJ, Barkley RA, eds. *Child Psychopathology*. New York, NY: Guilford Publications, Inc; 1996:242-276.
2. Famularo R, Kinscherff R, Fenton T. Symptom differences in acute and chronic presentation of childhood posttraumatic stress disorder. *Child Abuse Negl.* 1991;14: 439-444.
3. Green BL, Korol M, Grace MC, et al. Children and disaster: age, gender and parental effects on PTSD symptoms. *J Am Acad Child Adolesc Psychiatry.* 1991;33:71-79.
4. Pynoos RS, Frederick CJ, Nader K, et al. Life threat and post traumatic stress in school-age children. *Arch Gen Psychiatry.* 1987;44:1057-1063.
5. Kaufman J. Depressive disorders in maltreated children. *J Am Acad Child Adolesc Psychiatry.* 1991;30:257-262.
6. Trickett PK, Putnam FW. Impact of child sexual abuse on females: towards a developmental, psychobiological integration. *Psychol Sci.* 1993;4:81-87.
7. Richters JE, Martinez P. The NIMH community violence project, I: Children as victims to violence. *Psychiatry.* 1993;56:7-21.
8. Ladd C, Owens M, Nemeroff C. Persistent changes in corticotrophin-releasing factor neuronal systems induced by maternal deprivation. *Endocrinology.* 1996;137: 1212-1218.
9. Coplan JD, Rosenblum LA, Gorman JM. Primate models of anxiety :longitudinal perspectives. *Psychiatr Clin North Am.* 1995;18:727-743.
10. Teicher MH, Ito Y, Glod C, Schiffer F, Gelbard H. Neurophysiological mechanisms of stress response in children. In: Pfeffer C, ed. *Severe Stress and Mental Disturbance in Children*. Washington, DC: American Psychiatric Association Press, Inc; 1996:59-84.
11. De Bellis MD, Putnam FW. The psychobiology of childhood maltreatment. *Child Adolesc Psychiatr Clin North Am.* 1994;3:663-678.
12. Ornitz EM. Developmental aspects of neurophysiology. In: Lewis M, ed. *Child and Adolescent Psychiatry: A Comprehensive Textbook*. Baltimore, MD: Williams and Wilkins; 1996:39-51.
13. Teicher MH, Ito Y, Glod A, et al. Preliminary evidence for abnormal cortical development in physically an sexually abused children using EEG coherence and MRI. In: Yehuda R, McFarlane AC, eds. *Psychobiology of Posttraumatic Stress Disorder. Ann NY Acad Sci.* 1997:160-175.
14. Giedd JN, Castellanos FX, Casey BJ, Kozuch P, King AC, Hamburger SD, et al. Quantitative morphology of the corpus callosum in attention deficit disorder hyperactivity disorder. *Am J Psychiatry.* 1994;151:665-669.
15. Famuluaro R, Fenton T, Kinscherff R, Augustyn M. Psychiatric comorbidity in childhood post traumatic stress disorder. *Child Abuse Negl.* 1996;20:953-961.
16. Orr SP. Psychophysiologic studies of posttraumatic stress disorder. In: Giller EL, ed *Biological Assessment and Treatment of Posttraumatic Stress Disorder*. Washington, DC: American Psychiatric Press, Inc; 1990:136-160.
17. Kosten T, Mason J, Giller E, et al. Sustained urinary norepinephrine and epinephrine elevation in post-traumatic stress disorder. *Psychoneuroendocrinology.* 1987;12: 13-18.
18. Perry BD, Giller EL, Southwick SM. Altered platelet alpha-2 adrenergic binding sites in posttraumatic stress disorder. *Am J Psychiatry.* 1986;144:1511-1512.
19. Lerer B, Ebstein RP, Shistatsky M, Shemesh Z, Greenburg D. Cyclic AMP signal transduction in posttraumatic stress disorder. *Am J Psychiatry.* 1987;144:1324-1327.
20. Jensen CF, Keller TM, Peskind ER, et al. Behavioral and plasma cortisol responses to sodium lactate infusion in posttraumatic stress disorder. In: Yehuda R, McFarlane AC, eds. *Psychobiology of Posttraumatic Stress Disorder. Ann NY Acad Sci.* 1997:444-448.
21. Southwick SM, Krystal JH, Morgan CA, Johnson D, Nagy LM, Nicolau A, et al. Abnormal noradrenergic function on posttraumatic stress disorder. *Arch Gen Psychiatry.* 1993;50:266-274.
22. Perry BD. Neurobiological sequelae of childhood trauma: PTSD in children. In: Murberg M, ed. *Catecholamine Function in Posttraumatic Stress Disorder: Emerging Concepts*. Washington, DC: American Psychiatric Association Press, Inc; 1994:131-158.
23. Lauder JM. Neurotransmitters as morphogens. *Progr Brain Res.* 1998;73:365-388.
24. DeBellis MD, Lefter L, Trickett PK, Putnam FW. Urinary catecholamine excretion in sexually abused girls. *J Am Acad Child Adolesc Psychiatry.* 1994;33:320-327.
25. De Bellis MD, Baum AS, Birmaher B, Ryan ND. Urinary catecholamine excretion in childhood overanxious and posttraumatic stress disorders. In: Yehuda R, McFarlane AC, eds. *Psychobiology of Posttraumatic Stress Disorder. Ann NY Acad Sci.* 1997:451-455.
26. Galvin M, Ten Eyck R, Shekhar A, Stillwell B, et al. Serum dopamine beta hydroxylase and maltreatment in psychiatrically hospitalized boys. *Child Abuse Negl.* 1995;19:821-832.
27. Famularo R, Kinscherff R, Fenton T. Propranolol treatment for childhood posttraumatic stress disorder, acute type. A pilot study. *Am J Dis Child.* 1988;142:1244-1247.
28. Berg KM. Elicitation of acoustic startle in humans. Unpublished doctoral dissertation, University of Wisconsin, Madison; 1973.
29. Ornitz EM, Guthrie D, Kaplan AR, Lane SL, Norman RJ. Maturation of startle modulation. *Psychophysiology.* 1986;23:624-634.
30. Ornitz EM, Pynoos RS. Startle modulation in children with posttraumatic stress disorder. *Am J Psychiatry.* 1989;146:866-870.
31. Ornitz EM, Hanna GL, De Traversay J. Prestimulation-induced startle modulation in attention-deficit hyperactivity disorder and nocturnal enuresis. *Psychophysiology.* 1992;29:437-451.
32. Castellanos FX, Fine EJ, Kaysen D, et al. Sensorimotor gating in boys with Tourette's syndrome and ADHD: preliminary results. *Biol Psychiatry.* 1996;39:33-41.
33. Grillon C, Ameli R, Charney DS, Krystal J, Braff D. Startle gating deficits occur across prepulse intensities in schizophrenic patients. *Biol Psychiatry.* 1992;32:939-943.
34. Gold PW, Goodwin FK, Chrousos GP. Clinical and bio-

chemical manifestations of depression: relation to the neurobiology of stress. *N Engl J Med.* 1988;319:413-420.
35. Mason JW, Giller El, Kosten TR, Ostroff RB, Podd L. Urinary free cortisol levels in post-traumatic stress disorder patients. *J Nerv Ment Dis.* 1986;174:145-149.
36. Yehuda R, Kahana B, Binder-Brynes K, Southwick SM, Mason JW, Giller EL. Low urinary cortisol in Holocaust survivors with posttraumatic stress disorder. *Am J Psychiatry.* 1995;152:982-986.
37. Pitman R, Orr SP. Twenty-four hour urinary cortisol and catecholamine excretion in combat related posttraumatic stress disorder. *Biol Psychiatry.* 1990;27:245-247.
38. Yehuda R, Teicher M, Trestman R, Levengood R, Siever L. Cortisol regulation in posttraumatic stress disorder and major depression: a chronobiological analysis. *Biol Psychiatry.* 1996;40:79-88.
39. Yehuda R, Boisoneau D, Mason JW, Giller EL. Relationship between lymphocyte and glucocorticoid receptor number and urinary free cortisol excretion in mood, anxiety and psychotic disorder. *Biol Psychiatry.* 1993;34:18-25.
40. Yehuda R, Boisoneau D, Lowy MT, Giller EL. Dose response changes in plasma cortisol and lymphocyte glucocorticoid receptors following dexamethasone administration in combat veterans with and without PTSD. *Arch Gen Psychiatry.* 1995;52:583-593.
41. Yehuda R, Southwick SM, Krystal JH, et al. Enhanced suppression of cortisol following dexamethasone administration in post traumatic stress disorder. *Am J Psychiatry.* 1993;150:83-86.
42. Yehuda R. Sensitization of the HPA axis in posttraumatic stress disorder. In: Yehuda R, McFarlane AC, eds. *Psychobiology of Posttraumatic Stress Disorder. Ann NY Acad Sci.* 1997:57-75.
43. Bremner JD, Licinio J, Darnell A, et al. Elevated CSF corticotropin releasing factor concentrations in posttraumatic stress disorder. *Am J Psychiatry.* 1997;154:624-629.
44. Dahl R, Ryan ND, Puig-Antich J, et al. 24-Hour cortisol measures in adolescents: a controlled study. *Biol Psychiatry.* 1991;30:25-36.
45. Puig-Antich J, Dahl R, Ryan ND, et al. Cortisol secretion in prepubertal children with major depressive disorder. *Arch Gen Psychiatry.* 1989;46:801-809.
46. Birmaher B, Dahl RE, Ryan ND, et al. The dexamethasone suppression test in adolescent outpatients with major depressive disorder. *Am J Psychiatry.* 1992;149:1040-1045.
47. Casat CD, Powell K. The dexamethasone suppression test in children and adolescents with major depressive disorder: a review. *J Clin Psychiatry.* 1988;49:390-393.
48. Kaufman J, Birmaher B, Perel J, et al. The corticotropin-releasing hormone challenge in depressed abused, depressed nonabused and normal control children. *Biol Psychiatry.* 1997;42:669-679.
49. De Bellis MD, Chrousos GP, Dorn LD, et al. Hypothalamic-pituitary-adrenal axis dysregulation in sexually abused girls. *J Clin Endocrinol Metab.* 1994;78:249-255.
50. Hart J, Gunnar M, Cicchetti D. Salivary cortisol in maltreated children: evidence of relations between neuroendocrine activity and social competence. *Development and Psychopathology.* 1995;7:11-26.
51. Goenjian AJ, Yehuda RY, Pynoos RS, et al. Basal cortisol, dexamethasone suppression of cortisol, and MHPG in adolescents after the 1988 earthquake in Armenia. *Am J Psychiatry.* 1996;153:929-934.