DePaul Law Review

Volume 56
Issue 3 *Spring 2007: Symposium - Ties That Bind: Family Relationships, Biology, and the Law*

Article 5

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INVISIBLE SCARS: THE NEUROBIOLOGICAL CONSEQUENCES OF CHILD ABUSE

*Debra Niehoff**

INTRODUCTION

Child abuse and neglect pose significant problems for health care professionals, social service agencies, police departments, and courts. According to the U.S. Department of Health and Human Services, 906,000 children were victims of abuse or neglect in 2003.[1] Some community-based surveys suggest that the actual number of victims may be three times higher when cases that were never reported to authorities are included.[2] Abuse and neglect are significant causes of childhood injury, accounting for approximately 1500 deaths per year.[3]

In addition to acute injuries, child maltreatment is associated with a wide range of long-term health problems. These problems include chronic physical disorders such as heart disease, obesity, and cancer, as well as psychiatric disorders.[4] One longitudinal study of individuals with a history of childhood abuse found that as many as 80% met the diagnostic criteria for at least one mental health condition by age twenty-one.[5] Foremost among these is posttraumatic stress disorder (PTSD), a condition first identified in combat veterans and characterized by hypervigilance, irritability, sleep disturbances, emotional numbing, an inability to relate to friends and family, and recurrent memories of the initiating trauma. Reported rates of PTSD in abused children range from 6.9% to 35%.[6] The lifetime prevalence rate of

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1. U.S. DEP'T OF HEALTH & HUMAN SERVS., CHILD MALTREATMENT 2003, at 21 (2005), *available at* http://www.acf.hhs.gov/programs/cb/pubs/cm03/cm2003.pdf.

2. National Child Abuse Statistics: Childhelp 2 (2005), *available at* http://www.childhelp.org/uploads/Gl/ci/GlciCz0RJ5B-BqEfR8Bh_w/STATS-2006.pdf.

3. *Id.* at 1.

4. Vincent J. Felitti et al., *Relationship of Childhood Abuse and Household Dysfunction to Many of the Leading Causes of Death in Adults: The Adverse Childhood Experiences (ACE) Study*, 14 AM. J. PREVENTIVE MED. 245, 251–52 & tbl.4 (1998).

5. Amy B. Silverman et al., *The Long-Term Sequelae of Child and Adolescent Abuse: A Longitudinal Community Study*, 20 CHILD ABUSE & NEGLECT 709, 715 tbl.2, 716 (1996).

6. *Compare* Esther Deblinger et al., *Post-traumatic Stress in Sexually Abused, Physically Abused, and Nonabused Children*, 13 CHILD ABUSE & NEGLECT 403, 405 (1989), *with* Richard

PTSD among individuals of all age groups who were abused as children has been estimated to be as high as 37.5%.[7] Rates of depression are comparable; for example, a 1997 study found that 30% of a group of 264 patients with a history of childhood abuse met criteria for a major depressive disorder.[8] Child abuse has also been implicated in the incidence of panic disorder, drug and alcohol abuse, attention-deficit/hyperactivity disorder, and eating disorders.[9] Perhaps the most troubling consequence of abuse, however, is the increased incidence of criminal behavior, including acts of violence, among individuals with a history of childhood abuse. A widely cited prospective study by Professors Cathy Widom and Michael Maxfield compared more than 900 children with a history of substantiated abuse or neglect with a control group that was matched with abuse victims by age, race, sex, and social class.[10] The study found that abused individuals were 1.8 times more likely than the control group to be arrested for a juvenile offense, 1.5 times more likely to be arrested as an adult, and 1.35 times more likely to be arrested for a violent crime.[11] A total of 21% of the study subjects who had been physically abused as children were arrested for violent offenses, compared to 14% of the matched controls.[12] An unexpected result was that neglect had almost as great an effect on subsequent behavior as the experience of physical abuse, in that 20% of those who experienced neglect were arrested for a violent crime.[13] Sadly, the victims of individuals with histories of abuse are often their own children. Studies of this "cycle of abuse" estimate that approximately one-third of abused children become abusive parents themselves.[14]

Widespread recognition of the impact of child abuse on emotional and social behavior has not resolved the question of whether abused children fare better when they are separated from violent and neglectful parents or when treatment efforts reunite them with their birth

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Famularo et al., *Psychiatric Comorbidity in Childhood Post Traumatic Stress Disorder*, 20 CHILD ABUSE & NEGLECT 953, 956 (1996).

7. Cathy Spatz Widom, *Posttraumatic Stress Disorder in Abused and Neglected Children Grown Up*, 156 AM. J. PSYCHIATRY 1223, 1225 tbl.1 (1999).

8. Bruce E. Wexler et al., *Physical and Sexual Abuse During Childhood and Development of Psychiatric Illnesses During Adulthood*, 185 J. NERVOUS & MENTAL DISEASE 522, 523 fig.1 (1997).

9. Silverman et al., *supra* note 5; Martin H. Teicher, *Wounds That Time Won't Heal: The Neurobiology of Child Abuse*, 2 CEREBRUM 50 (2000).

10. Cathy Spatz Widom & Michael G. Maxfield, *A Prospective Examination of Risk for Violence Among Abused and Neglected Children*, 794 ANNALS N.Y. ACAD. SCI. 224 (1996).

11. *Id.* at 229.

12. *Id.* at 231 tbl.3.

13. *Id.*

14. Cathy Spatz Widom, *The Cycle of Violence*, 244 SCIENCE 160, 160 (1989).

families. Policies over the last four and a half decades have alternately favored either the removal of children from abusive homes or reunification with their families, often on the basis of social and political concerns rather than on an objective assessment of the long-term medical, social, and economic consequences of these choices.[15] Nor has our knowledge of the effects of abuse answered the troubling question of what role, if any, a history of abuse should play in the treatment of violent offenders. Childhood maltreatment is often introduced as a mitigating factor during criminal trials in an effort to secure a more lenient sentence for a violent offender, based on the argument that the experience of abuse has damaged the capacity to self-regulate behavior.[16] Conversely, the fact that the same studies reporting an association between childhood abuse and violence also note that a majority of abused children do not become adult criminals has been frequently cited by critics as evidence that calls for leniency based on past maltreatment constitute an "abuse excuse"—a ploy on the part of perpetrators to avoid assuming responsibility for their actions.[17]

Victims of abuse, the institutions charged with protecting them, and the criminal justice system would be better served if child welfare laws, policies, sentencing guidelines, and treatment approaches were informed by a better understanding of the impact of abuse and neglect on the human brain. The brain is, of course, the biological organ responsible for the generation and regulation of behavior. Over the last three decades, both animal studies and clinical research on human abuse victims have demonstrated that the nervous system is highly sensitive to stress and trauma during the first years of life, and that abuse need not involve an actual physical injury to do lasting damage to the developing brain. Furthermore, trauma-induced aberrations in neural structure and function are essentially corruptions of fundamental neural mechanisms evolved to prepare the individual for survival in dangerous or capricious environments, and they are not erased by maturation. They continue to influence the interpretation of, and response to, emotionally significant events and relationships long after children part ways with their abusive parents. Bones mend and bruises fade, but the harm done to the brain by the experience of violence leaves enduring scars that, while invisible to the casual observer,

15. *See, e.g.*, A HISTORY OF CHILD WELFARE (Eve P. Smith & Lisa A. Merkel-Holguín eds., 1996); Kasia O'Neill Murray & Sarah Gesiriech, A Brief Legislative History of the Child Welfare System, http://pewfostercare.org/research/docs/Legislative.pdf (last visited May 29, 2007).

16. *See, e.g.*, SAUNDRA DAVIS WESTERVELT, SHIFTING THE BLAME: HOW VICTIMIZATION BECAME A CRIMINAL DEFENSE (1998); Paul Litton, *The "Abuse Excuse" in Capital Sentencing Trials: Is It Relevant to Responsibility, Punishment, or Neither?*, 42 AM. CRIM. L. REV. 1027 (2005).

17. *See, e.g.*, WESTERVELT, *supra* note 16; Litton, *supra* note 16.

have long-lasting implications for the health, well-being, and social functioning of the abuse victim.

II. Adaptation and Vulnerability: Why the Brain's Greatest Advantage Is Also a Liability

Change is a fundamental feature of life. From geological processes that span many generations to the vagaries of social relationships that present challenges on a daily basis, environmental caprice constantly rewrites the rules of engagement. Living organisms, including human beings, have had to adapt to these changes or face extinction. As a result, biological mechanisms that facilitate effective responses to environmental contingencies have proven essential to survival.

Perhaps the most obvious example of such a mechanism is the remodeling of the genome that underlies the process of natural selection.[18] Alterations to the sequence of the chemical bases that make up DNA—such as the substitution of one base for another, the accidental duplication of a gene, or the exchange of chromosome segments during cell division—result in fundamental changes to the proteins encoded by the affected genes. Although most of these accidents end in lethal malfunctions, some changes enhance survival and, hence, the opportunity to reproduce. These beneficial mutations are passed on to the next generation, "locking in" adaptations that have improved the fit between the organism and its environment.

Despite its fundamental importance to the evolution of life on earth, change at the level of the genome is not sufficient to meet all of the challenges encountered in an unpredictable world. For one thing, the pace of genomic change is glacial. It takes place over the course of generations and is too slow to offset the day-to-day upheavals that occur over the course of a single lifetime. Moreover, responses to these more immediate and pressing needs must be customized, for no two individuals encounter the same constellation of circumstances, even if they live in the same time and place. Survival, therefore, requires a second way to adapt to environmental demands, a mechanism that provides the additional flexibility needed to deal rapidly with problems that vary from individual to individual.

The evolution of the nervous system provides this second form of flexibility. This tissue, which is specialized to detect events in the outside world and interpret them in the context of experience, uses this information to guide the selection of appropriate behavioral re-

18. *See generally* Bruce Alberts et al., Molecular Biology of the Cell 453–65 (4th ed. 2002).

sponses. Rather than waiting for DNA to catch up with changing conditions, an organism with a nervous system takes action. Furthermore, the adaptable nervous system also features built-in mechanisms that enable the individual to remember an action, the event that provoked it, the immediate circumstances, and its final outcome. Consequently, organisms with a nervous system both react and anticipate, facilitating their responses to familiar problems.

But the freedom to reinvent oneself is not without risk. Tissues with the greatest capacity to regenerate—like the skin or the epithelial cells lining the digestive tract—pay for their ability to replace worn out, dead, or injured cells with an increased vulnerability to cancer, the result of mutations incurred during successive rounds of cell division. Similarly, a nervous system malleable enough to accommodate every contingency can be waylaid by the very flexibility that makes it so valuable. The brain's ability to change in response to experience allows us to learn a language, perfect new motor skills, build and maintain social relationships, and acquire basic necessities. Unfortunately, this flexibility also chronicles adversity with the same fidelity and attention to detail. The lessons learned from traumatic experiences can be life-saving or self-defeating. When memories of past perils intrude on the present and cause benign stimuli to be misconstrued as threats, reactions that were once adaptive become inappropriate, injurious, and even dangerous.

III. COMMUNICATION AND ITS CONSEQUENCES

The adult human brain contains about one hundred billion cells, known as neurons, which differ widely in size and shape but are composed of the same three structural elements: the cell body, the dendrites, and the axon. The cell body houses the nucleus containing the neuron's DNA. The dendrites, a crowning arbor of short processes, receive signals from other neurons. The axon, a single taproot of a process, may vary in length from a fraction of a millimeter to more than three meters and transmits signals to the dendrites of one or more neurons.[19]

Every function carried out by the brain is the result of a collaboration of thousands of neurons, organized in groups that reside in distinct brain regions, each of which makes a unique contribution to the task at hand. For example, the recognition and characterization of emotionally significant stimuli, the retention and retrieval of emotional memories, and the regulation of emotional behavior are the col-

19. *See generally* PRINCIPLES OF NEURAL SCIENCE (Eric R. Kandel et al. eds., 4th ed. 2000).

lective responsibility of the limbic system, a group of structures located deep within the brain, and the frontal lobes of the overlying cerebral cortex.

Two critical nodes in this emotional circuit are the amygdala and the prefrontal cortex. The amygdala is an ovoid aggregation of neurons located deep in the temporal lobe that swells out from the side of the brain. Processes that originate in brain regions associated with senses like vision and hearing, visceral sensation, endocrine function, memory, meaning, and judgment converge in the amygdala, which uses this wealth of information to coordinate reflexive responses to emotional stimuli. For example, the amygdala is activated by threatening facial expressions, pictures of disturbing events, and emotionally charged words.[20] Information from neurons in the brain stem responsible for the physical sensations associated with fear and other strong emotions is used by the amygdala to assign emotional value to previously neutral stimuli, which will speed retrieval of the memory of that experience in the future. The prefrontal cortex, the part of the cerebral cortex located at the very front of the brain, is central to the top-down processing needed to formulate internal representations of goals and organize the voluntary actions necessary to achieve them. The contribution of the prefrontal cortex is especially important when the best course of action is not obvious, or when inputs from different sources conflict (e.g., hearing an angry outburst and the moral proscription against injuring another).[21] The orbitofrontal and ventromedial sectors lying close to the midline and along the lower surface of the prefrontal area respond to expressions of anger and have reciprocal connections with the amygdala. This line of communication enables the prefrontal cortex to suppress inappropriate behavioral responses, such as violent actions, or tone down distressing feelings of anxiety or sadness.

The process of neural communication begins with an action potential, an electrical impulse that begins near the cell body and travels the length of the axon, speeded by an insulating layer of a fatty substance called myelin. But axons and dendrites are not contiguous. As a result, neurons in one part of the brain's emotional circuitry must have a way to transmit the information encoded in the action potential across the gaps that separate them from neurons in other parts of the brain. This task is accomplished by chemical signals called neurotransmit-

20. Richard J. Davidson et al., *Dysfunction in the Neural Circuitry of Emotion Regulation—A Possible Prelude to Violence*, 289 SCIENCE 591, 591 (2000).

21. *Id.*; Earl K. Miller & Jonathan D. Cohen, *An Integrative Theory of Prefrontal Cortex Function*, 24 ANN. REV. NEUROSCIENCE 167 (2001).

ters, acting within the confines of a specialized junction known as a synapse. The neurotransmitter is stored near the axon terminal in sacs, or vesicles, anchored to a protein gridwork on the presynaptic side of the junction. When an action potential reaches the terminal, these vesicles merge with the cell membrane and turn inside out, disgorging their contents into the synapse. The neurotransmitter seeps across the gap and binds to receptor proteins clustered on the postsynaptic side of the synapse, like a key sliding into a lock. Neuroscientists have identified two types of these receptors. One regulates the opening and closing of specialized channels to alter the flow of charged particles, converting the chemical signal back into an electrical one. The other couples the binding of neurotransmitter signals to the activation of a second protein (an effector) that triggers a cascade of biochemical reactions culminating in a molecular response with lasting consequences for the "listener" neuron. For example, the activation of the signaling pathway may prompt the cell to add receptors to the synapse or activate an enzyme that decreases receptor affinity for the neurotransmitter, in effect improving or blunting the neuron's "hearing acuity." Or it may stimulate a transcription factor, a protein switch with the power to turn genes on or off, increasing or decreasing levels of the corresponding proteins. Because proteins are the molecules used to build and operate cells, changes in protein levels will lead to changes in the structure and function of the neuron. Changes in synaptic "strength" related to the density and sensitivity of receptors, together with changes to neuronal architecture or physiology related to alterations in gene expression, create an enduring physical record of the experience originally responsible for the neural activity. This record is as tangible as a written transcript of a conversation between two people.

Both the capacity for change and the ability to remember are products of the mechanisms that enable neurons to communicate with one another. Based on experiments in simplified laboratory models, neurobiologists have proposed that the chronicle of the past, which is written into the fabric of the brain by intracellular signaling mechanisms, represents the cellular basis of learning and memory. For example, Columbia University scientist Eric Kandel and his colleagues conducted studies on the sea slug *Aplysia*, an invertebrate with a nervous system containing only 20,000 neurons. They linked the sensitization of the gill reflex that occurs in response to an unpleasant tactile stimulus—a brief electric shock—to a series of molecular changes in sensory neurons: alterations to pores in the cell membrane that regulate the flow of charged particles, prolonging the action potential; an

increase in the number of available vesicles containing a neurotransmitter; and the activation of the transcription factor CREB-1, a precursor to changes in gene expression and protein synthesis that generate the building materials to construct additional synapses.[22] A comparable pattern has been observed in the mammalian brain using small pulses of electrical current in place of an actual sensory stimulus to trigger neural activity in thin sections of brain tissue. This form of sensitization, known as long-term potentiation, occurs in two phases, each associated with a characteristic event.[23] Following a brief period of electrical stimulation, receptors for the neurotransmitter glutamate are relocated from storage sites in the dendrite to the relevant synapse and increase synaptic strength by enhancing the response to future bursts of glutamate. This is the so-called early phase. Protracted stimulation leads to the emergence of a late phase, in which the activation of CREB-1 and the subsequent surge in protein synthesis trigger the elaboration of spines along the dendrites, which serve as platforms for the formation of new synapses.

Recent studies have demonstrated that this remodeling of synapses and dendrites in the wake of experience, which neurobiologists refer to as neural or synaptic plasticity, is not limited to instrumental learning in simple organisms or the "learning" simulated by repeated electrical stimulation.[24] Experiments based on a paradigm known as fear conditioning show that such changes also occur during emotional learning, where they preserve the memory of frightening events.[25] Fear conditioning, which involves a variation on the famous experiments of Pavlov, pairs the delivery of an otherwise innocuous tone with an electric shock. A laboratory rat needs to hear the tone and experience the shock only a few times before the sound alone is enough to make it cower; its heart pounds and its blood pressure soars. The emergence of the conditioned fear response is accompanied on a cellular level by a sequence of events in the amygdala that are reminiscent of the changes that occur during long-term potentiation. Glutamate receptor proteins are transferred from intracellular

22. Eric R. Kandel, *The Molecular Biology of Memory Storage: A Dialogue Between Genes and Synapses*, 294 SCIENCE 1030 (2001).

23. Eric R. Kandel, *Cellular Mechanisms of Learning and the Biological Basis of Individuality*, *in* PRINCIPLES OF NEURAL SCIENCE, *supra* note 19, at 1247.

24. M.G. McKernan & P. Shinnick-Gallagher, *Fear Conditioning Induces a Lasting Potentiation of Synaptic Currents* in Vitro, 390 NATURE 607 (1997); Kerry J. Ressler et al., *Regulation of Synaptic Plasticity Genes During Consolidation of Fear Conditioning*, 22 J. NEUROSCIENCE 7892 (2002); Michael T. Rogan et al., *Fear Conditioning Induces Associative Long-Term Potentiation in the Amygdala*, 390 NATURE 604 (1997); Simon Rumpel et al., *Postsynaptic Receptor Trafficking Underlying a Form of Associative Learning*, 308 SCIENCE 83 (2005).

25. Joseph E. LeDoux, *Emotion, Memory and the Brain*, SCI. AM., June 1994, at 50.

stores to the synapse, resulting in an increase in the sensitivity of amygdala neurons. The expression of genes, particularly genes that encode proteins critical to synapse formation, is also altered.[26] The lesson that a certain sound portends discomfort has been absorbed, recorded, and linked to a defensive response by translating the experience into the movement of receptors and the synthesis of proteins, which forms a physical representation of a frightening event that can persist many months after the original trauma.

In the rat's native environment, fear conditioning facilitates the rapid recognition of sensory stimuli formerly associated with danger, so the animal can act swiftly to protect itself in the future. But behavior that improves the chances of survival in a dangerous environment can be counterproductive in more benign circumstances. In a cage where it receives no shocks at all, the rat's continued panic at the sound of the tone is unwarranted. When responses keyed to emotionally significant memories outlive their usefulness in this way, they are more likely to create problems than solve them.

A. Brain-Body Communication and Reaction to Stress

Neurons can communicate with the cells of other tissues as well as each other.[27] These exchanges also involve the secretion and interpretation of chemical-signaling molecules, including blood-borne substances known as hormones, which are responsible for regulating the physiological processes that maintain critical parameters such as body temperature, levels of glucose and oxygen, and the concentration of electrolytes within a narrow range of values compatible with life. Paradoxically, this internal stability, or homeostasis, is possible only because of allostasis—the inherent flexibility that allows functions such as heart rate and respiration to increase or decrease to counter potentially destabilizing events.[28] An encounter with an assailant, for example, triggers the familiar fight or flight response: heart and lungs work harder, energy stored in the form of fat and glycogen is mobilized to fuel active muscles, white blood cells are deployed to fend off infection after injury, and nonessential functions like reproduction are temporarily suspended. At the cost of temporarily increasing the burden on the heart and lungs, flooding the body with insulin, and consuming

26. McKernan & Shinnick-Gallagher, *supra* note 24; Ressler et al., *supra* note 24; Rogan et al., *supra* note 24; Rumpel et al., *supra* note 24.

27. BRUCE S. MCEWEN & HAROLD M. SCHMECK, JR., THE HOSTAGE BRAIN (1994).

28. Bruce S. McEwen, *Protection and Damage from Acute and Chronic Stress: Allostasis and Allostatic Overload and Relevance to the Pathophysiology of Psychiatric Disorders*, 1032 ANNALS N.Y. ACAD. SCI. 1 (2004).

energy reserves (an imposition physiologists refer to as allostatic load), these adjustments ensure that tissues vital to the escape effort receive sufficient amounts of oxygen and glucose during a period of greater demand.

Allostasis, the result of cooperation between the brain (which detects the threat) and the body (which responds to it) is coordinated by a battery of chemical signals, some secreted by the nervous system and others by the endocrine system.[29] These signals include the following: norepinephrine, a neurotransmitter secreted by the sympathetic nerves that innervate organs such as the heart; epinephrine, secreted by the adrenal gland; cytokines, which mediate the immune response; and the glucocorticoid hormone cortisol, a product (like epinephrine) of the adrenal glands. The control of cortisol secretion, however, involves both the brain and glands in an arrangement known as the hypothalamic-pituitary-adrenal (HPA) axis. The first member of this trio, the hypothalamus, is a wedge-shaped region located at the base of the brain. A slender cord of blood vessels ferries corticotrophin-releasing factor (CRF), a hypothalamic hormone, to the nearby pituitary gland, where it orders the pituitary to release a second hormone, adrenocorticotrophic hormone (ACTH), into the bloodstream. ACTH, in turn, prompts the adrenal glands to secrete cortisol.

Heart and lungs need to work overtime in an emergency. But when stress is chronic, the sustained elevations in heart rate and respiration place unnatural demands on these organs that can lead to disease. Similarly, cortisol, which is essential to maintaining glucose levels and organizing immune responses during an emergency, can promote the formation of atherosclerotic plaques, contribute to the development of type 2 diabetes, leach calcium from bone, or damage the brain with prolonged exposure. An important feature of stress-response mechanisms, therefore, is a system of checks and balances that curbs the production of alarm signals and restores body functions to resting values once the crisis has passed. Balancing the excitatory action of the sympathetic nerves, for example, are the parasympathetic nerves. Cortisol controls its own secretion, acting on receptors in the brain and the pituitary to reduce the production of CRF and ACTH, turning off the signal to the adrenal glands. Additional restraint is provided by the hippocampus, another element of the limbic system. Exquisitely sensitive to cortisol levels, the axons of hormone-activated hippocampal neurons project to the hypothalamus, where they inhibit the

29. *Id.*

secretion of CRF and turn off the neuroendocrine stress response at its source.

Like synaptic plasticity, the flexibility afforded by allostasis enables the organism to adapt quickly and efficiently to meet the challenges of a demanding environment. Just as fear can change the brain in lasting but potentially counterproductive ways, prolonged allostatic load can have a detrimental effect on the neuroendocrine system. Evolved to cope with acute emergencies, the effort needed to cope with chronic or recurrent stress taxes the regulatory mechanisms that are repeatedly called upon to restore the status quo. Stress researchers compare this struggle to maintain equilibrium in the face of protracted stress to the challenge of balancing a seesaw built to accommodate two five-year-old children with two five-ton elephants.

Bent too far and for too long, an overloaded seesaw will finally break. Similarly, overworked regulatory mechanisms will eventually malfunction. When this happens, levels of cortisol rise without falling again, spike at the slightest provocation, or remain at baseline levels regardless of what is happening in the environment.[30] Dysregulation of the HPA axis has been linked to the pathophysiology of disorders like heart disease and diabetes. In addition, abnormalities in cortisol secretion have been associated with a number of psychiatric disorders, particularly depression and anxiety, as well as violence. These conditions, exaggerated versions of normal fight or flight responses, can be thought of as "stress-response disorders"—behavioral manifestations of stress-induced damage to neuroendocrine mechanisms.

IV. BUILDING A BRAIN: OPPORTUNITIES, RISKS, AND THE ROLE OF EXPERIENCE

Adverse experiences can produce traumatic memories and tax stress-response mechanisms to the point of no return at any time in an individual's life, but the impact of the environment is felt most keenly in early childhood. During the prolonged course of human neural development, synaptic plasticity is aided and abetted by the way the developing brain uses experience to assist in the construction process. Over the course of development, billions of cells, synapses, and processes are generated and tested; the brain is more open to change and more vulnerable as a consequence.

Orienting billions of neurons and shepherding them through the process of locating and establishing synaptic connections with their

30. Bruce S. McEwen, *Protective and Damaging Effects of Stress Mediators*, 338 NEW ENG. J. MED. 171 (1998).

designated partners constitutes one of the most formidable challenges of development. Hardwiring each of the more than one hundred trillion connections in the adult nervous system would require a supercomputer-sized genome. Instead, like profligate creatures that lay thousands of eggs, only a fraction of which result in offspring fit enough to survive, the developing brain spawns an overabundance of neurons, axons, and synapses, pitting them against one another in a struggle for survival. Those that find their way and prove useful will emerge intact; the others will be ruthlessly eliminated.

Over half of the neurons generated early in development ultimately die—victims of an innate suicide program biologists call apoptosis.[31] Apoptosis turns newborn neurons into living time bombs, seeded with enzymes that will attack their DNA within days unless they locate the source of an essential growth factor—their partners—as quickly as possible.[32] Only those that reach the correct target within the allotted time are rewarded with enough elixir to deactivate the suicide program. Those that are too slow or wander off course will miss the cutoff and self-destruct. The magnitude of the carnage is staggering, but this "survival of the fittest" strategy is remarkably prudent, ensuring that every neuron is correctly lined up with the right partner without the need for a formal wiring diagram.

Even after the competition for growth factors has weeded out superfluous and errant neurons, the number of axons, dendrites, and synapses far exceeds the needs of the adult nervous system.[33] This number is also whittled down to size using experience to differentiate the useful from the redundant.[34] Synapses that are actually put to use are retained; those that are never called upon are eliminated as unnecessary.[35] This pruning of superfluous processes spans more than two decades. In the cerebral cortex, for example, pruning begins in the visual and motor areas near the back and top of the brain and proceeds from back to front and laterally, ending in the prefrontal cortex, which is not fully mature until the early twenties.[36] At the same time surplus axons are being trimmed, those that remain are receiving a coat of insulating myelin. Myelination, which accounts for much of

31. DEBRA NIEHOFF, THE LANGUAGE OF LIFE: HOW CELLS COMMUNICATE IN HEALTH AND DISEASE 133–34 (2005).

32. *Id.*

33. L.C. Katz & C.J. Shatz, *Synaptic Activity and the Construction of Cortical Circuits*, 274 SCIENCE 1133, 1136–37 (1996).

34. *Id.*

35. *Id.*

36. Nitin Gogtay et al., *Dynamic Mapping of Human Cortical Development During Childhood Through Early Adulthood*, 101 PROC. NAT'L ACAD. SCI. 8174 (2004).

the increase in brain mass that occurs over the first five years of life and balances the loss of gray matter due to pruning, continues until approximately age fifty.[37]

Keying the retention of synapses to experience allows the developing brain to shape the nervous system to match conditions in the outside world. Similarly, the brain and endocrine system make use of postnatal experience to "program" the sensitivity of the HPA axis in accordance with the demands of the environment. Following the cataclysmic experience of birth, the HPA axis enters a period of quiescence, in which basal cortisol levels drop and the response to stress is temporarily blunted.[38] Over the next ten to fifteen years, the immature HPA axis uses experience to answer questions about the safety of the world, much as the immature immune system uses encounters with pathogens to answer questions about the optimal configuration of antibodies for fending off disease in the environment. The intensity and duration of neuroendocrine responses to a crisis are determined by the nature and severity of the stressors it encounters during this time. When experiences are largely positive, those answers are optimistic. But when negative experiences outweigh the positive—for example, when violence and neglect are a prominent aspect of family life—the lesson learned by the brain is that the world is dangerous, vigilance is imperative, and self-defense is a priority.

Studies of rats demonstrate how early life experience can program the adult sensitivity of the HPA axis.[39] In these studies, carried out during the first week of postnatal life, rat pups were removed from the nest and handled for a brief interval by the experimenters (a modestly stressful experience) or separated from their dams for several hours (a much more stressful experience). The two manipulations had opposing effects on the sensitivity of the HPA axis, and these adaptations colored responses to stressful events for the rest of the rats' lives. Handling led to resiliency. Pups treated in this way had a higher number of glucocorticoid receptors in the hippocampal region of the brain central to the feedback inhibition of cortisol secretion. As adults, these animals displayed tempered reactions to stressful events. For example, they secreted less cortisol in response to being restrained. In

37. Elizabeth R. Sowell et al., *Mapping Continued Brain Growth and Gray Matter Density Reduction in Dorsal Frontal Cortex: Inverse Relationships During Postadolescent Brain Maturation*, 21 J. NEUROSCIENCE 8819, 8826–29 (2001).

38. Wolfgang G. Sippell et al., *Plasma Levels of Aldosterone, Corticosterone, 11-Deoxycorticosterone, Progesterone, 17-Hydroxyprogesterone, Cortisol, and Cortisone During Infancy and Childhood*, 14 PEDIATRIC RES. 39 (1980).

39. Tie-Yuan Zhang et al., *Maternal Programming of Individual Differences in Defensive Responses in the Rat*, 1032 ANNALS N.Y. ACAD. SCI. 85 (2004).

contrast, rat pups separated from their mothers developed hypervigilant nervous systems in a perpetual state of near crisis. These animals experienced a significant decline in the density of glucocorticoid receptors in the hippocampus, an elevation in CRF levels in the hypothalamus, and impaired feedback control of hormone secretion. When restrained, they overreacted, producing more cortisol for a longer period of time than rats that were merely handled during infancy or control animals reared in undisturbed nests.

But young rats do not need outside interference from a human researcher to alter the development of the HPA axis—their own mother can do this. Rats enjoy an extended period of parental care; the time spent in the nest is an opportunity for their mothers to prepare them for life outside of the nest. Variations in maternal care during the nesting period, a function of the environmental conditions encountered by the mother, presage the state of affairs pups are likely to encounter outside of the nest, and they program the HPA axis accordingly.[40] Some female rats lick and groom their pups frequently; these mothers also tend to adopt an "arched-back" posture while nursing, in which they crouch over the pups, allowing them to move freely.[41] Such demonstrative mothers can afford to dote on their offspring. They are typically the dominant animals in the neighborhood and enjoy the right to build nests close to the best foraging sites. Their pups, like rat pups handled briefly on a regular basis, become resilient adults that react to stress in a measured fashion. Females that occupy a lower position in the hierarchy lead a more precarious existence on the outskirts of the neighborhood. Farther from food and closer to predators, these mothers engage in fewer bouts of grooming. Pups reared by them resemble those separated from their mothers. They have fewer glucocorticoid receptors, poorly regulated stress-responses, and higher cortisol levels. Given their circumstances, touchy stress-response mechanisms are an advantage, improving their chances of survival in an environment where resources are scarce, enemies are prevalent, and injury and disease are common. Their austere upbringing, a mirror image of the environmental adversity encountered by their mothers, is an excellent preparation for adult life.

By using early life experience to guide neural development, even an individual born into a dangerous environment has a chance of surviv-

40. *Id.* at 94–97.

41. *Id.* at 90.

ing. But when parental behavior is abusive rather than instructive, the ease with which the brain learns to be afraid can ruin a child's future.

V. THE MARK OF VIOLENCE

Over the last two decades, neurobiologists have extended their studies of adverse early life experiences from laboratory animals to abused children and adults with a history of abuse. This research has been aided immeasurably by the development of sophisticated neuroimaging techniques that not only reveal structural details with unprecedented clarity, but enable scientists to observe the brain in action by monitoring changes in regional cerebral blood flow or glucose utilization indicative of neural activity. Clinical studies confirm that exposure to stress early in life—specifically, to inadequate or abusive parenting—changes the emotional circuitry of the brain and the neuroendocrine mechanisms underlying allostasis in enduring and often compromising ways. Such stress-related aberrations are independent of any direct injury to the brain and have been documented even in the absence of overt clinical symptoms. This suggests that pathology alone is not an accurate indicator of the integrity of the nervous system following maltreatment.[42]

Biochemical measures of the magnitude and sensitivity of stress responses have demonstrated that abuse, like maternal separation or infrequent grooming, can program the HPA axis for a life of perpetual vigilance. Studies of abused children diagnosed with PTSD[43] or other emotional problems[44] found elevated levels of cortisol compared to control subjects with no history of abuse. Neglect has a similar impact on stress hormones; children reared in an orphanage under conditions of profound neglect and emotional deprivation also exhibited a significant elevation in cortisol levels over a twenty-four-hour period relative to controls.[45] Dysregulation of the HPA axis is not limited to abused children. Studies of adults with a prior history of abuse have also found abnormalities in cortisol secretion, documenting an in-

42. *See, e.g.*, J. Douglas Bremner, *Long-Term Effects of Childhood Abuse on Brain and Neurobiology*, 12 CHILD & ADOLESCENT PSYCHIATRY CLINICS N. AM. 271 (2003); Martin H. Teicher et al., *Developmental Neurobiology of Childhood Stress and Trauma*, 25 PSYCHIATRY CLINICS N. AM. 397 (2002); Martin H. Teicher et al., *The Neurobiological Consequences of Early Stress and Childhood Maltreatment*, 27 NEUROSCIENCE & BIOBEHAVIORAL REVS. 33 (2003) [hereinafter Teicher et al., *Neurobiological Consequences*].

43. Michael D. De Bellis et al., *Developmental Traumatology Part I: Biological Stress Systems*, 45 BIOLOGICAL PSYCHIATRY 1259 (1999).

44. Dante Cicchetti & Fred A. Rogosch, *The Impact of Child Maltreatment and Psychopathology on Neuroendocrine Functioning*, 13 DEV. & PSYCHOPATHOLOGY 783 (2001).

45. Megan R. Gunnar et al., *Salivary Cortisol Levels in Children Adopted from Romanian Orphanages*, 13 DEV. & PSYCHOPATHOLOGY 611, 623 (2001).

crease in the neuroendocrine response to trauma reminders. They also found a greater suppression of cortisol release in response to a pharmacological challenge with a synthetic analogue of cortisol; this suggests that both the initial response to stress and the feedback mechanisms had become hypersensitive.[46] As in the animal studies, stress-induced alterations to the sensitivity of the HPA axis following adversity in early life appear to persist long after the original trauma.

Using electroencephalography (EEG), proton magnetic resonance spectroscopy, and imaging procedures such as magnetic resonance imaging (MRI) and positron emission tomography (PET), scientists have found striking evidence that trauma can also alter the course of brain development. In children, developmental alterations have been reported in both community samples and children diagnosed with PTSD and other disorders. Neuroanatomical and functional changes have also been documented in studies of adults who were abused as children, suggesting that the effect of trauma on brain development is as persistent as its effect on the HPA axis.

Given the importance of the hippocampus in the regulation of stress responses, it is not surprising that trauma has an impact on the structure and function of this brain region. Neuroimaging studies of combat veterans with PTSD provided the first evidence of a link between the experience of trauma and differences in brain morphology. These studies documented a reduction in the volume of the hippocampus of PTSD victims relative to controls. Similar results have been reported in imaging studies of adults with a history of abuse and trauma-related psychiatric disorders. One study not only reported a reduction in the volume of the left hippocampus, but also found that the magnitude of this reduction could be correlated with psychiatric symptoms and the degree of disruption in neuroendocrine feedback control.[47] Professor J. Douglas Bremner and his colleagues, using PET scanning, also found evidence of functional deficits in the hippocampus in women with a history of childhood sexual abuse. Specifically, they found a significant reduction in the activity of the hippocampus during a ver-

46. J.D. Bremner et al., *Cortisol Response to a Cognitive Stress Challenge in Posttraumatic Stress Disorder (PTSD) Related to Childhood Abuse*, 28 PSYCHONEURONENDOCRINOLOGY 733 (2003); Bernet M. Elzinga et al., *Higher Cortisol Levels Following Exposure to Traumatic Reminders in Abuse-Related PTSD*, 28 NEUROPSYCHOPHARMACOLOGY 1656 (2003); Murray B. Stein et al., *Enhanced Dexamethasone Suppression of Plasma Cortisol in Adult Women Traumatized by Childhood Sexual Abuse*, 42 BIOLOGICAL PSYCHIATRY 680 (1997).

47. M.B. Stein et al., *Hippocampal Volume in Women Victimized by Childhood Sexual Abuse*, 27 PSYCHOL. MED. 951 (1997).

bal memory task.[48] This finding is noteworthy because the hippocampus is known to play a critical role in memory storage and retrieval as well as in the regulation of stress responses.

Because the hippocampus is disproportionately sensitive to cortisol, the observed effects of abuse on the structure and function of the hippocampus may be mediated in part by recurrent or persistent exposure to high levels of cortisol caused by the dysregulation of the HPA axis. In laboratory animals, elevated cortisol levels have been associated with a variety of adverse consequences for hippocampal neurons, including the atrophy of dendrites, the breakdown of cellular repair processes that mitigate the effects of oxidative stress, and even death. Furthermore, patients with Cushing's disease—an endocrine disorder characterized by the overproduction of cortisol as a result of a hypothalamic, pituitary, or adrenal tumor—experience reductions in hippocampal volume that can be directly correlated to cortisol concentrations: the higher the level of stress hormone, the greater the volume reduction in the hippocampus.[49] Similar neurotoxic effects may also underlie hippocampal atrophy in abuse victims.

In contrast to the results in adults with PTSD and a history of abuse, three imaging studies of abused children and adolescents, one of which dealt specifically with children who had PTSD, did not find evidence for the reductions in hippocampal volume seen in adults.[50] One explanation for this discrepancy is that the adaptations triggered by the experience of abuse may set in motion a sequence of events, including reexposure to anxiety in the form of traumatic memories, that has a cumulative effect on the developing hippocampus and finally reaches a detectable level of damage in adulthood. Alternatively, differences in hippocampal volume may not be a direct result of abuse, but a risk factor for the persistence of abuse-initiated PTSD symptoms into adulthood.[51]

Given the prominent role of the amygdala in fear conditioning, it is not surprising that imaging studies have also documented changes in this brain region following abuse. Two studies reported reductions in amygdala volume. In one, a study of young adults with a history of recurrent sexual abuse, the damage was confined to the left amyg-

48. J. Douglas Bremner, *Structural Changes in the Brain in Depression and Relationship to Symptom Recurrence*, 7 CNS SPECTRUMS 129 (2002).

49. Michael D. De Bellis et al., *Developmental Traumatology Part II: Brain Development*, 45 BIOLOGICAL PSYCHIATRY 1271, 1281 (1999).

50. Victor G. Carrion et al., *Attenuation of Frontal Asymmetry in Pediatric Posttraumatic Stress Disorder*, 50 BIOLOGICAL PSYCHIATRY 943 (2001); De Bellis et al., *supra* note 49; Teicher et al., *Neurobiological Consequences*, *supra* note 42.

51. Carrion et al., *supra* note 50.

dala.[52] The other, a study of adult women, reported a decrease in volume for both left and right amygdala.[53] In addition, a study of fear conditioning in women who were sexually abused as children, using a paradigm similar to that used to provoke fearful reactions to an innocuous stimulus in laboratory animals, found an increase in blood flow to the amygdala during acquisition of the fearful response.[54]

Abuse and neglect also take a toll on the cerebral cortex, a brain region that remains susceptible to outside influences throughout its protracted period of development. The prefrontal cortex, one of the last cortical areas to mature, is especially vulnerable to the effects of adversity. In addition, the prefrontal cortex, like the hippocampus, has a high density of glucocorticoid receptors; as a result, it is also at risk from stress-induced elevations in cortisol.

Structural and functional imaging studies have demonstrated that the experience of abuse disrupts the normal development of the cerebral cortex. For example, using a spectroscopic technique that measures the relative concentration of N-acetyl aspartate and creatinine (a measure correlated with the density and integrity of neurons), Professor Michael De Bellis and his colleagues found evidence of neuronal loss and dysfunction in the prefrontal cortex and, specifically, in the anterior cingulate area of children and adolescents with PTSD subsequent to abuse.[55] Research also suggests that child abuse may interfere with the critical process of lateralization, in which the left and right sides of the cortex become specialized for particular functions.[56] Speech and language comprehension, for example, are localized in the left hemisphere, while prosody (the ability to understand the emotional and contextual aspects of language) is the province of the right hemisphere. In right-handed children, the left or dominant hemisphere is more developed than the right. A study that employed electroencephalography to compare left and right brain development in a group of right-handed, physically and sexually abused children

52. Teicher et al., *Neurobiological Consequences*, *supra* note 42.

53. Martin Driessen et al., *Magnetic Resonance Imaging Volumes of the Hippocampus and the Amygdala in Women with Borderline Personality Disorder and Early Traumatization*, 57 ARCHIVES GEN. PSYCHIATRY 1115, 1118 (2000).

54. J. Douglas Bremner et al., *Positron Emission Tomographic Imaging of Neural Correlates of a Fear Acquisition and Extinction Paradigm in Women with Childhood Sexual-Abuse-Related Post-traumatic Stress Disorder*, 35 PSYCHOL. MED. 791, 799 (2005).

55. Michael D. De Bellis et al., *N-Acetylaspartate Concentration in the Anterior Cingulate of Maltreated Children and Adolescents with PTSD*, 157 AM. J. PSYCHIATRY 1175, 1176–77 (2000).

56. Martin H. Teicher et al., *Preliminary Evidence for Abnormal Cortical Development in Physically and Sexually Abused Children Using EEG Coherence and MRI*, 821 ANNALS N.Y. ACAD. SCI. 160, 162 (1997).

found that the right hemisphere was more developed than the left.[57] More accurately, the right hemisphere resembled that of children with no history of abuse, while the development of the left hemisphere was significantly delayed.

Furthermore, information flow between the two specialized hemispheres may be impeded as a result of abuse-related deficits in the development of the corpus callosum—the large, heavily myelinated fiber tract that links the left and right sides of the brain. Animal studies have shown that high levels of glucocorticoid stress hormones retard the growth of myelin-producing cells, resulting in deficient myelination of axons. This effect is thought to be responsible for the decrease in the size of the corpus callosum observed following stressors like maternal separation. Similarly, imaging studies have noted a decrease in the size of the corpus callosum in abused or neglected children, particularly boys.[58]

Results of a study assessing left and right brain function in adults with a history of abuse confirm that damage to developmental processes like lateralization and the myelination of the corpus callosum can compromise the subsequent ability to coordinate the functions mediated by the two hemispheres.[59] Electrical activity in the brains of adults with a history of abuse was monitored during the recall of work-related or abuse-related memories. In control subjects, the left and right hemispheres were equally active during the performance of both recall tasks. Abused individuals, in contrast, displayed more activity in the left hemisphere during recall of the neutral memory, while the right was more active during recollection of an abusive episode. The experience of abuse, in other words, disrupted the normal integration of the emotional and cognitive aspects of information processing.

Finally, functional imaging studies in adults indicate that childhood abuse has long-lasting effects on the processing of emotional information by the cerebral cortex. These studies have documented a variety of aberrations in the activity of parts of the prefrontal cortex during emotionally provocative tasks. For example, Professor Lisa Shin and her colleagues used PET to examine regional blood flow in women with a history of abuse while they listened to a script dealing with an

57. *Id.* at 166–68.

58. *Id.* at 168–70.

59. Andrew C. Papanicolaou et al., *Convergent Evoked Potential and Cerebral Blood Flow Evidence of Task-Specific Hemispheric Differences*, 66 ELECTROENCEPHALOGRAPHY & CLINICAL NEUROPHYSIOLOGY 515 (1987).

abusive encounter.[60] Abuse victims who also had PTSD displayed an increase in blood flow to the orbitofrontal cortex, an area considered an extension of the limbic system with extensive connections to the amygdala, compared to those who had been abused but did not develop PTSD.[61] Other studies have reported changes in activity in the orbitofrontal and medial prefrontal cortex in response to traumatic memory recall or a task involving the recall of neutral or emotionally significant word pairs.[62]

VI. Behavioral Consequences of Abuse-Related Injury to the Nervous System

Child abuse is associated not only with the emergence of a number of psychiatric disorders (particularly PTSD, depression, borderline personality disorder, and dissociative disorders), but also with an increased risk of developing these conditions later in life. In addition, abuse increases the risk that victims will themselves become violent, either toward family members or other individuals. Clinical research on the neurobiological basis of anxiety, depression, and aggression has documented abnormalities in (1) the perception of threat, (2) the recognition of emotionally relevant stimuli, (3) the regulation of emotional behavior and inhibition of maladaptive or inappropriate behavioral responses, and (4) the feedback control of cortisol secretion.[63] These abnormalities correlate with the changes in brain structure, neural activity, and neuroendocrine responses described above in the studies of children and adults with a history of abuse or neglect. This overlap suggests that the neural consequences of childhood trauma can make important contributions to behavioral pathology and explain some of the symptoms common to disorders found in abuse victims.

A common thread running through all of these stress-related pathologies is HPA axis dysregulation, which is characterized by ab-

60. Lisa M. Shin et al., *Regional Cerebral Blood Flow During Script-Driven Imagery in Childhood Sexual Abuse-Related PTSD: A PET Investigation*, 156 Am. J. Psychiatry 575 (1999).

61. *Id.* at 580–83.

62. J. Douglas Bremner et al., *Neural Correlates of Declarative Memory for Emotionally Valenced Words in Women with Posttraumatic Stress Disorder Related to Early Childhood Sexual Abuse*, 53 Biological Psychiatry 879 (2003); J. Douglas Bremner et al., *Neural Correlates of Memories of Childhood Sexual Abuse in Women with or Without Posttraumatic Stress Disorder*, 156 Am. J. Psychiatry 1787 (1999).

63. Davidson et al., *supra* note 20; Jozsef Haller et al., *Mechanisms Differentiating Normal from Abnormal Aggression: Glucocorticoids and Serotonin*, 526 Eur. J. Pharmacology 89, 90 (2005); Eric J. Nestler et al., *Neurobiology of Depression*, 34 Neuron 13, 17 (2002); Rachel Yehuda et al., *Cortisol Regulation in Posttraumatic Stress Disorder and Major Depression: A Chronobiological Analysis*, 40 Biological Psychiatry 79 (1996).

normalities in the magnitude, duration, or timing of cortisol secretion. Hypercortisolemia (an abnormal elevation in cortisol), disruptions in the normal diurnal pattern of cortisol secretion (e.g., evening cortisol levels in depressed patients are lower than in individuals who are not depressed),[64] and reductions in the number and sensitivity of glucocorticoid receptors have been documented in depression.[65] In addition, approximately half of the depressed patients failed to suppress cortisol production in response to a challenge dose of the synthetic hormone dexamethasone; this result is consistent with a defect in feedback control mechanisms.[66] Although some studies of stress hormones in PTSD show a similar elevation in cortisol levels, the predominant finding is a seemingly paradoxical reduction in basal cortisol, accompanied by a concomitant increase in hormone receptors and increased suppression of cortisol secretion in response to the dexamethasone challenge.[67] Repeated sampling of cortisol levels over a twenty-four-hour period, however, demonstrated that superimposed on the abnormally low basal level of cortisol is a volatile diurnal pattern characterized by dramatic oscillations in cortisol, rather than the leisurely ebb and flow found in individuals who do not have PTSD.[68] Depression and PTSD, therefore, may represent two different manifestations of a common failure to distinguish legitimate threats from false alarms and adjust to stress responses accordingly. In depression, an overactive HPA axis responds too vigorously and for too long; in PTSD, it responds too often. Both of these patterns have been documented in abuse victims.[69]

The neurotoxic effect of repeated or chronic exposure to cortisol has been implicated in the atrophy of the hippocampus observed in victims of child abuse, individuals with PTSD subsequent to other types of trauma, and patients with recurrent depression. Damage to the hippocampus, a region critical to declarative memory, can result in a variety of memory deficits. Such deficits are common complaints of those who suffer from both depression and PTSD.[70] Stress-related at-

64. McEwen, *supra* note 30.

65. Rachel Yehuda, *Sensitization of the Hypothalamic-Pituitary-Adrenal Axis in Posttraumatic Stress Disorder*, 821 ANNALS N.Y. ACAD. SCI. 57, 62 (1997).

66. *Id.* at 63.

67. *Id.* at 65.

68. *Id.*

69. *See, e.g.*, Bremner et al., *supra* note 46; Cicchetti & Rogosch, *supra* note 44; De Bellis et al., *supra* note 43; Elzinga et al., *supra* note 46; Gunnar et al., *supra* note 45; Stein et al., *supra* note 46.

70. J. Douglas Bremner et al., *Deficits in Short-Term Memory in Posttraumatic Stress Disorder*, 150 AM. J. PSYCHIATRY 1015, 1017 (1993); J. Wolfe & L.K. Schlesinger, *Performance of PTSD Patients on Standard Tests of Memory*, 821 ANNALS N.Y. ACAD. SCI. 208, 212 (1997); Rachel

rophy of the hippocampus may play a prominent role in this memory dysfunction, as well as in amnesia for the factual details of the precipitating trauma.[71]

HPA dysregulation has also been linked to two distinct patterns of violent behavior, which are associated with two types of malfunction in the neuroendocrine response to stress.[72] Exaggerated responses to stress are characteristic of episodic, impulsive violence associated with a high degree of emotional arousal; this behavior is typified by the "hothead" who lashes out in response to some trivial provocation but is often remorseful afterward. Conversely, violent individuals classified as antisocial or psychopathic rarely express regret for their actions; these individuals exhibit blunted responses to stress indicative of a more fundamental and wide-ranging defect in the emotional circuitry that diminishes the capacity for empathy and impedes social learning. In both cases, the alteration in stress responses has transformed fighting back—an adaptive response—into violence. In hostile aggression, the perpetrator overreacts to a nonexistent threat; in antisocial violence, the perpetrator ignores the very real threat of injury, imprisonment, or even death.

Research on the relationship between the experience of violence early in life and dysregulation of the HPA axis also offers a new perspective on the concept of an intergenerational cycle of violence. The recurrence of child abuse in families has often been attributed to social learning processes that emphasize the importance of parents as role models. Abused children, according to this line of thinking, observe and then copy the abusive behavior, or, more generally, they come to think of the parent-child relationship as adversarial. Recent animal studies, however, suggest that learning at the cellular level, in the form of adaptations to neuroendocrine mechanisms induced by defective parenting, may play as important a role to the transmission of violent behavior as the cognitive and social dimension of learning.

In rats, the offspring of low-grooming mothers, programmed for a life of exaggerated vigilance, also groom their own pups infrequently. But if they are transferred from their birth mother to the nest of a

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Yehuda et al., *Learning and Memory in Combat Veterans with Posttraumatic Stress Disorder*, 152 AM. J. PSYCHIATRY 137 (1995).

71. J. Douglas Bremner et al., *Magnetic Resonance Imaging-Based Measurement of Hippocampal Volume in Posttraumatic Stress Disorder Related to Childhood Physical and Sexual Abuse—A Preliminary Report*, 41 BIOLOGICAL PSYCHIATRY 23 (1997); Yvette I. Sheline et al., *Depression Duration but Not Age Predicts Hippocampal Volume Loss in Medically Healthy Women with Recurrent Major Depression*, 19 J. NEUROSCIENCE 5034 (1999).

72. DEBRA NIEHOFF, THE BIOLOGY OF VIOLENCE: HOW UNDERSTANDING THE BRAIN, BEHAVIOR, AND ENVIRONMENT CAN BREAK THE VICIOUS CIRCLE OF AGGRESSION (1999).

high-grooming mother, they not only exhibit well-regulated stress responses as adults, they also become high-grooming mothers, suggesting that the sensitivity of the stress response and mothering behavior go hand in hand.[73] This concept has been demonstrated even more clearly in primates, and has been specifically tied to parental abuse. Observers of rhesus monkeys living in captive social groups have documented the abuse of infants in this species: approximately 5% to 10% of infant monkeys are bitten, dragged, crushed, thrown, or trampled by their mothers. These abusive mothers are not especially aggressive in their social interactions with peers. Once they abuse one infant, however, they typically turn into "serial offenders" who consistently abuse other youngsters as well.

Studies show that rhesus monkeys can be induced to become foster parents. An infant born to an abusive mother, for example, can be removed from the birth mother and given to a nonabusive mother to rear; conversely, an infant born to a nurturing mother can be cross-fostered to a known abuser. By comparing the behavior of females reared by their birth mothers to those reared by adoptive mothers, researchers at the University of Chicago were able to confirm the intergenerational recurrence of abusive behavior and to establish that this transmission was not due to purely genetic factors.[74] In this study, sixteen female infants, of which seven were natural daughters and nine were adoptees born to nonabusive mothers, were raised and abused by their mothers. Nine of these abused infants subsequently abused their own offspring.[75] In contrast, none of the sixteen female infants reared by nurturing mothers were abused, and none became abusers themselves.[76] Moreover, a follow-up study revealed that the continuation of abusive patterns of behavior in female monkeys abused as infants could be correlated with alterations in their cortisol levels as a result of their own abuse.[77] Compared to control monkeys with no prior history of abuse and no record of injuring their own infants, cerebrospinal fluid drawn from abusive rhesus mothers that had been abused by their own mothers contained significantly higher amounts of CRF, the hypothalamic hormone triggering the cascade that culminates in the secretion of cortisol. Like rat pups reared by

73. Zhang et al., *supra* note 39.

74. Dario Maestripieri, *Early Experience Affects the Intergenerational Transmission of Infant Abuse in Rhesus Monkeys*, 102 PROC. NAT'L ACAD. SCI. 9726, 9728 (2005).

75. *Id.*

76. *Id.*

77. Dario Maestripieri et al., *Neurobiological Characteristics of Rhesus Macaque Abusive Mothers and Their Relation to Social and Maternal Behavior*, 29 NEUROSCIENCE & BIOBEHAVIORAL REVS. 51, 52 (2005).

low-grooming mothers, abused monkeys had nervous systems programmed by parental mismanagement to remain in a continuous state of hypervigilance. Confronted with the demands of caring for an infant, such mothers appear to easily lapse into behavioral patterns more appropriate to the dangerous environment they knew when they were young than those suited to interactions with a helpless infant.

The amygdala and the prefrontal cortex represent important nodes in a network of brain regions that not only regulate the HPA axis, but also figure prominently in the perception of threat, the response to social cues (such as facial expressions) that characterize emotionally significant interactions with others, and the conscious ability to moderate or suppress negative emotions. As a result, trauma-related adaptations observed in the amygdala and cerebral cortex may also contribute to symptoms of disorders like depression and PTSD. Increased activation of the amygdala during fear conditioning, for example, may reflect supersensitivity to stimuli underlying excessive anxiety. Disruption of the normal process of lateralization, coupled with shrinkage of the corpus callosum, may compromise the ability to integrate thought and emotion, reducing "top-down" control over excessive emotional reactions. Alterations in the activity of the prefrontal cortex during exposure to emotionally provocative stimuli may similarly reveal aberrations in the ability to control fearful or gloomy reactions to such stimuli. Failure to regulate emotional responses has also been linked to excessively aggressive responses, particularly the impulsive, angry form of violent behavior.[78]

VII. GENES, EXPERIENCE, AND RESILIENCE

Psychopathology and criminal violence are not inevitable consequences of childhood abuse, nor do individuals abused as children invariably repeat the sins of their parents. The lifetime prevalence of PTSD among those with a history of childhood maltreatment, for example, has been reported to be 37.5%.[79] The study by Widom and Maxfield found convincing evidence of an association between abuse and subsequent violent behavior, yet the overwhelming majority of abuse victims monitored over a period of more than two decades—79% of those who experienced physical abuse, 80% of those who experienced neglect, and 91% of those who experienced sexual abuse—were never arrested for a violent offense.[80] Similarly, research on the

78. *See* Davidson et al., *supra* note 20.
79. Widom, *supra* note 7, at 1225 tbl.1.
80. Widom & Maxfield, *supra* note 10, at 231 tbl.3.

transmission of abusive behavior has demonstrated that although most abusive parents were abused themselves as children, the converse is not true; approximately two-thirds of abuse victims do not abuse their own children.[81] Even animal research on abuse indicates that the experience of violence early in life does not inexorably lead to pathological behavior: of the sixteen infants reared by abusive female rhesus monkeys, seven (i.e., more than 40%) did not repeat the abusive behavior with their own offspring.[82]

Research suggests that resiliency is not an accident, nor do some children simply "get over it," managing somehow to rise above their upbringing. Rather, the likelihood that neural adaptations to abuse will culminate in neuropathology is determined by the cumulative effect of all the environmental and biological variables that impinge on the developing brain. This includes not only the abuse itself, but also factors that act to exacerbate or moderate its impact. Children have no control over these factors, any more than they can affect the course of synaptic plasticity or the consequences of allostatic overload.

Not surprisingly, the probability of pathology following childhood trauma—not only abuse, but also the exposure to events such as acts of terrorism and natural disasters—escalates with the increasing frequency and severity of the trauma.[83] The developmental stage of the victim constitutes another important determinant, as does gender, the nature of the abuse, and the relationship between perpetrator and victim. Other environmental influences are protective. Having a source of social support, particularly within the family, appears to moderate the impact of abuse and is associated with more positive outcomes.[84]

In addition to circumstantial and environmental influences, recent studies of naturally occurring differences (polymorphisms) in genes encoding brain proteins have found evidence that some children may be inherently more vulnerable to early life stress. This vulnerability is the result of the impact of these genetic differences on the baseline sensitivity to emotional stimuli.[85] From a biological perspective, no

81. Widom, *supra* note 14, at 160.

82. Maestripieri et al., *supra* note 77.

83. Rachel Yehuda & Steven E. Hyman, *The Impact of Terrorism on Brain, and Behavior: What We Know and What We Need to Know*, 30 NEUROPSYCHOPHARMACOLOGY 1773, 1777 (2005).

84. Robin Malinosky-Rummell & David J. Hansen, *Long-Term Consequences of Childhood Physical Abuse*, 114 PSYCHOL. BULL. 68 (1993); Yehuda & Hyman, *supra* note 83.

85. S.M. Brown et al., *A Regulatory Variant of the Human Tryptophan Hydroxylase-2 Gene Biases Amygdala Activity*, 10 MOLECULAR PSYCHIATRY 884 (2005); Zhe-Yu Chen et al., *Genetic Variant BDNF (Val66Met) Polymorphism Alters Anxiety-Related Behavior*, 314 SCIENCE 140 (2006); Ahmad R. Hariri et al., *Serotonin Transporter Genetic Variation and the Response of the Human Amygdala*, 297 SCIENCE 400, 401 (2002).

child is born a "blank slate." Naturally occurring, individual variations in receptor proteins, neurotransmitter-synthesizing enzymes, proteins that remove or break down signaling molecules to terminate transmission, or intracellular-signaling proteins that couple the binding of signal and receptor to biological responses change the tenor of neuron-to-neuron conversations about emotionally significant events. As a consequence, they set the stage for how individuals will perceive and react to the same experience from the very youngest of ages. Such differences are no more than another attempt to meet the environment head on. In the context of a normal, nurturing family environment, they influence personality, but do not lead to pathology. In the context of an abusive environment, however, they cause the nervous system to respond to adversity in a more extreme fashion.

A recent analysis of polymorphisms in the 5-HTT gene, which encodes the serotonin transporter responsible for terminating the action of the neurotransmitter serotonin, illustrates how genotype influences the reactivity of the amygdala to fearful stimuli.[86] The 5-HTT gene comes in two common versions (alleles) distinguished by differences in the promoter region of the gene—the docking platform for proteins that regulate gene expression. The so-called short variant (designated "s") produces less of the serotonin transporter. As a consequence, serotonin lingers in the synapse, increasing the duration of its influence on serotonin receptors, including receptors in the amygdala. The study in question used functional magnetic resonance imaging (fMRI) to compare individuals with two copies of the long variant (designated "l") of the 5-HTT gene (one from each parent) to those with at least one copy of the short variant, while they completed a task that involved matching pictures of angry or fearful faces.[87] Those heterozygous (s/l) or homozygous (s/s) for the short variant exhibited more activity in the right amygdala than those homozygous for the long variant (l/l), indicating that genetically determined differences in serotonin signaling mechanisms altered the perception of fear.[88]

Furthermore, a study of gene-environment interactions found that polymorphism in the 5-HTT gene, and the underlying variation in vulnerability implied by its effect on emotional sensitivity, influenced the outcome of exposure to stress early in life—specifically, the stress imposed by child abuse.[89] Again, study subjects were divided into three

86. Hariri et al., *supra* note 85.

87. *Id.* at 401.

88. *Id.*

89. Avshalom Caspi et al., *Influence of Life Stress on Depression: Moderation by a Polymorphism in the 5-HTT Gene*, 301 SCIENCE 386 (2003).

groups on the basis of 5-HTT genotype: homozygous for the long variant (l/l), homozygous for the short variant (s/s), and heterozygous, with one copy of each variant (l/s).[90] The incidence of fourteen stressful life events, including a history of child abuse, was determined for each of the three groups and compared to the incidence of major depression. The results showed that the risk of depression was greatest among those who experienced high levels of stress and also had a copy of the short variant of the 5-HTT gene.[91] In addition, genotype specifically altered the risk of depression following childhood abuse.[92] Individuals in the s/s group (two copies of the short allele) who had a history of severe maltreatment had a 63% risk of depression, while individuals in the l/l group (two copies of the long variant) had only a 30% risk on average, even if they had been abused.[93]

Data from the same cohort also revealed an interaction between abuse and a second genetic polymorphism in the etiology of antisocial behavior, including violent behavior.[94] This polymorphism controls the expression of the gene for another neural protein responsible for "turning off" neurotransmission, the enzyme monoamine oxidase (MAO), which metabolizes the signaling molecules norepinephrine, dopamine, and serotonin.[95] In boys with a variant of the MAO gene that resulted in high enzyme activity, the incidence of conduct disorder, antisocial personality disorder, and the number of arrests for violent acts was independent of documented evidence of maltreatment; abused boys were no more violent than those with no history of abuse.[96] In contrast, maltreatment significantly increased the risk of antisocial and violent behavior among boys with a low activity variant of the gene. These individuals, who constituted only 12% of study subjects, accounted for 44% of convictions for a violent offense.[97]

Polymorphisms in genes for 5-HTT and MAO are not defects or mutations that "cause" pathology. Their potential to influence the development of conditions like depression or violence depends on the permissive or moderating effect of environmental circumstances that bring out the best or the worst in the genotype. The authors of the Dunedin studies suggest that these options have been maintained as

90. *Id.* at 387.
91. *Id.*
92. *Id.*
93. *Id.* at 388 fig.2.
94. Avshalom Caspi et al., *Role of Genotype in the Cycle of Violence in Maltreated Children*, 297 SCIENCE 851 (2002).
95. *Id.* at 851.
96. *Id.* at 852–53.
97. *Id.* at 853.

part of the human genome because they confer advantages in extreme circumstances and "probably act to promote organisms' resistance to environmental pathogens," toxic influences that include traumatic experiences.[98] Originally an advantage, a sensitive nervous system and an abusive environment are now an incendiary combination.

VIII. Implications for the Legal and Social Response to Child Abuse

Staying safe is a biological imperative as compelling as finding food or reproducing. The odds of surviving hostile encounters with enemies were significantly improved by the evolution of a nervous system capable of detecting threats and coordinating effective responses such as hiding, running away, and fighting back. This defensive enterprise results from the collective effort of a network of interconnected brain regions, including subcortical structures of the limbic system and parts of the prefrontal cortex with extensive connections to these structures, acting in concert with the neuroendocrine mechanisms that coordinate physiological and psychological responses to stress. Cellular mechanisms that translate experience into enduring adaptations to this neural circuitry shape the nervous system in accordance with the unique challenges facing every individual and maximize the chances of survival in any environment.

Violence can turn this capacity for adaptation—normally a seminal advantage—into a tragic liability. This is particularly true during the first years of life, when the brain is the least developed and most vulnerable. Childhood abuse and neglect corrupt the process of shaping the brain in response to the environment in fundamental ways. Moreover, trauma-induced alterations to brain structure and function, or the sensitivity of the HPA axis, are not transient events; they can persist long after the original trauma. As a consequence, they can compromise physical and mental health in the immediate aftermath of abuse and also affect the long-term health and well-being of the abused individual. Even abusive experiences with no obvious emotional sequel can do lasting damage by sensitizing the nervous system so that the individual overreacts to subsequent stress. Consequently, victims of maltreatment remain at increased risk for developing stress-response disorders like depression and PTSD. They may survive their abusive childhoods only to break down in the aftermath of some fu-

98. Caspi et al., *supra* note 89, at 389; *accord* Caspi et al., *supra* note 94. These two studies were part of the Dunedin Multidisciplinary Health and Development Study, a prospective-longitudinal analysis of physical and mental health outcomes in a cohort of more than 1000 New Zealand children.

ture catastrophe. American society pays a high price for the chronic mental health problems and criminal behavior of abuse victims. A 2001 report by Prevent Child Abuse America estimated that the indirect costs of child abuse, including expenditures by law enforcement and the judicial system, productivity losses attributable to unemployment and underemployment, special education services, and health care costs at more than $69 billion per year.[99]

The longer a child remains in an abusive environment, the greater the probability that stress will leave an enduring impression on the brain. Protective intervention is essential from a neurobiological, as well as social and moral, point of view. Yet inherent in the debate over the best way to achieve this goal is the unfortunate recognition that, in many cases, all of the available options have significant drawbacks. Removing the child in question from the home obviously negates the risk of further abuse by family members, but does not automatically ensure the child's safety. Abuse and neglect also occur in foster care. One study, for example, found that rates of physical abuse were three times higher and rates of sexual abuse two times higher among children in foster care than those in the general population. In addition, the results of researchers like Michael Meaney suggest that separating children from biological parents is a trauma in and of itself, with potential effects on the long-term sensitivity of stress responses. Family unification avoids the stress of separation, unless it entails extracting children from a foster home where they have spent an extended period of time and developed quasiparental relationships with caretakers. Furthermore, reunification is a calculated risk, because it returns the child to an environment that has already proven unsafe. The end result is often a devil's bargain, an uneasy compromise in which cash-strapped child welfare authorities are forced to settle on the alternative that seems least harmful, rather than on a solution that guarantees the safety, continuity, and serenity critical to proper development of a nervous system prepared to cope—instead of capitulate—in the face of life's inevitable misfortunes.

Moreover, the sad fact is that by the time abuse draws the attention of authorities, the nervous system is likely to have already begun to outfit itself for a life on the edge. Experiences incorporated into the fabric of the brain, research shows, are difficult to eradicate, raising the question of whether any intervention can reverse this damage. The good news, however, is that the inherent flexibility of the brain

99. PREVENT CHILD ABUSE AMERICA, TOTAL ESTIMATED COST OF CHILD ABUSE AND NEGLECT IN THE UNITED STATES 3 (2001), *available at* http://www.preventchildabusenj.org/documents/index/cost_analysis.pdf.

makes rewriting neural history unnecessary. Neural plasticity does not end with maturity; as long as neurons continue to traffic in the chemical language that underlies synaptic plasticity, the capacity for change will remain. As a result, damage that may not be reversible can be circumvented, and a brain programmed to survive in a hostile world can adapt to living in less perilous circumstances. But two conditions must be satisfied. First, the current situation must, in fact, be less dangerous; the nervous system cannot reconsider its defensive stance if the individual is subjected to additional trauma. Second, new learning requires new input. A more accurate view of the world, the skill to correctly gauge the intentions of others, and more appropriate responses to emotionally charged stimuli cannot be willed into place. They must be consciously taught and reinforced.

The larger society, however, must learn that adaptations retain their potency for a long time. But given a familiar confluence of circumstances, these "trauma reminders" can provoke powerful responses that challenge even the most committed efforts at self-control. Such lapses should not be misconstrued as an excuse for unacceptable behavior, but as an illustration of how, in the words of Emory University neuroscientist Michael Kuhar, "your brain can push you around," because the synaptic mechanisms evolved specifically to keep such lasting records of hazards have invested the circumstances surrounding terrifying responses with a life or death value.[100]

The best intervention is to prevent child abuse in the first place. Research analyzing the effectiveness of a range of abuse prevention programs has revealed significant benefits for two strategies in particular: home visitation programs designed to identify at-risk mothers and provide them with social support and practical advice on childcare, and community-based programs that provide multiple services to families, including health care, educational initiatives, and social services.[101] The efficacy of home visitation is particularly noteworthy and may reduce the risk of physical abuse in half. Children that are the product of such programs show demonstrable improvements in behavioral outcomes, such as arrest records, consistent with a developmental trajectory undistorted by excessive stress. Prevention is an unpopular concept in some circles, criticized as being too difficult to implement or too expensive. But given the long-term costs of abuse

100. Conversation with Michael J. Kuhar, Candler Professor of Pharmacology & Chief of Neuroscience, Yerkes Nat'l Primate Research Ctr. of Emory Univ., in Atlanta, Ga. (Oct. 2006).

101. Peter Fonagy, *Early-Life Trauma and the Psychogenesis and Prevention of Violence*, 1036 ANNALS N.Y. ACAD. SCI. 181 (2004).

to both victims and society, effective early intervention programs appear well worth the investment.

The biological consequences of abuse do not obviate personal responsibility, but we are responsible as well. If we want to improve the welfare of children, reduce the burden of stress-induced health problems, and break the cycle of violence, we must commit to protecting children from abuse and neglect—the "environmental pathogens" that threaten the integrity of their developing nervous systems. Failure to make such a commitment will threaten their future mental and physical health, their ability to cope, and the safety and well-being of many future generations to come.