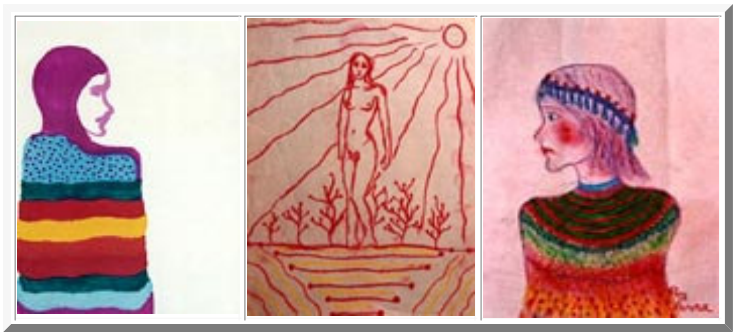

SCARS THAT WON'T HEAL: THE NEUROBIOLOGY OF CHILD ABUSE

Maltreatment at an early age can have enduring negative effects on a child's brain development and function

In 1994 Boston police were shocked to discover a malnourished four-year-old locked away in a filthy Roxbury apartment, where he lived in dreadfully squalid conditions. Worse, the boy's tiny hands were found to have been horrendously burned. It emerged that his drug-abusing mother had held the child's hands under a steaming-hot faucet to punish him for eating her boyfriend's food, despite her instructions not to do so. The ailing youngster had been given nomedical care at all. The disturbing story quickly made national headlines. Later placed in foster care, the boy received skin grafts to help his scarred hands regain their function. But even though the victim's physical wounds were treated, recent research findings indicate that any injuries inflicted to his developing mind may never truly heal.

Though an extreme example, the notorious case is unfortunately not all that uncommon. Every year child welfare agencies in the U.S. receive more than three million allegations of childhood abuse and neglect andcollect sufficient evidence to substantiate more than a million instances.

It is hardly surprising to us that research reveals a strong link between physical, sexual and emotional mistreatment of children and the development of psychiatric problems. But in the early 1990s mental health professionals believed that emotional and social difficulties occurred mainly through psychological means. Childhood maltreatment was understood either to foster the development of intrapsychic defense mechanisms that proved to be self-defeating in adulthood or to arrest psychosocial development, leaving a "wounded child" within. Researchers thought of the damage as basically a software problem amenable to reprogramming via therapy or simply erasable through the exhortation "Get over it."

New investigations into the consequences of early maltreatment, including work my colleagues and I have done at McLean Hospital in Belmont, Mass., and at Harvard Medical School, appear to tell a different story. Because childhood abuse occurs during the critical formative time when the brain is being physically sculpted by experience, the impact of severe stress can leave an indelible imprint on its structure and function. Such abuse, it seems, induces a cascade of molecular and neurobiological effects that irreversibly alter neural development.

Extreme Personalities

The aftermath of childhood abuse can manifest itself at any age in a variety of ways. Internally it can appear as depression, anxiety, suicidal thoughts or posttraumatic stress; it can also be expressed outwardly as aggression, impulsiveness, delinquency, hyperactivity or substance abuse. One of the

more perplexing psychiatric conditions that is strongly associated with early ill-treatment is borderline personality disorder. Someone with this dysfunction characteristically sees others in black-and-white terms, often first putting a person on a pedestal, then vilifying the same person after some perceived slight or betrayal. Those afflicted are also prone to volcanic outbursts ofanger and transient episodes of paranoia or psychosis. They typically have a history of intense, unstable relationships, feel empty or unsure of their identity, commonly try to escape through substance abuse, and experience self-destructive or suicidal impulses.

While treating three patients with borderline personality disorder in 1984, I began to suspect that their early exposure to various forms of maltreatment had altered the development of their limbic systems. The limbic system is a collection of interconnected brain nuclei (neural centers) that play a pivotal role in the regulation of emotion and memory. Two critically important limbic regions are the hippocampus and the amygdala, which lie below the cortex in the temporal lobe [see illustration on opposite page]. The hippocampus is thought to be important in the formation and retrieval of both verbal and emotional memories, whereas the amygdala is concerned with creating the emotional content of memory--for example, feelings relating to fear conditioning and aggressive responses.

My McLean colleagues Yutaka Ito and Carol A. Glod and I wondered whether childhood abuse might disrupt the healthy maturation of these brain regions. Could early maltreatment stimulate the amygdala into a state of heightened electrical irritability or damage the developing hippocampus through excessive exposure to stress hormones? We reasoned further that hippocampal harm or amygdaloid overexcitation could produce symptoms similar to those experienced by patients with temporal lobe epilepsy (TLE), which sporadically disrupts the function of these brain nuclei. During TLE seizures, patients remain conscious while experiencing a range of psychomotor symptoms brought on by electrical storms within these regions. Associated effects include the abrupt onset of tingling, numbness or vertigo; motor-related manifestations such as uncontrollable staring or twitching; and autonomic symptoms such as flushing, nausea or the "pit in your stomach" feeling one gets in a fast-rising elevator. TLE can also cause hallucinations or illusions in any of the five senses. It is not unusual, for instance, for one afflicted with this condition to experience Alice-in-Wonderland-like distortions of the sizes or shapes of objects. Disconnected feelings of déjà vu and mind-body dissociation are also common.

Abuse-Driven Brain Changes

To explore the relation between early abuse and dysfunction of the limbic system, in 1984 I devised a checklist of questions that assess the frequency with which patients experience TLE-related symptoms. In 1993 my co-workers and I reported results from 253 adults who came to an outpatient mental health clinic for psychiatric evaluation. Slightly more than half reported having been abused physically or sexually, or both, as children. Compared with patients who reported no ill-treatment, average checklist scores were 38 percent greater in the patients with physical (but not sexual) abuse and 49 percent higher in the patients with sexual (but not other physical) mistreatment. Patients who acknowledged both physical and sexual abuse had average scores 113 percent higher than patients reporting none. Maltreatment before age 18 had more impact than later abuse, and males and females were similarly affected.

In 1994 our McLean research team sought to ascertain whether childhood physical, sexual or psychological abuse was associated with brain-wave abnormalities in electroencephalograms (EEGs), which provide a more direct measure of limbic irritability than our checklist. We reviewed the records of 115 consecutive admissions to a child and adolescent psychiatric hospital to search for a link. We found clinically significant brain-wave abnormalities in 54 percent of patients with a history of early

trauma but in only 27 percent of nonabused patients. We observed EEG anomalies in 72 percent of those who had documented histories of serious physical and sexual abuse. The irregularities arose in frontal and temporal brain regions and, to our surprise, specifically involved the left hemisphere rather than both sides, as one would expect.

Our findings dovetailed with a 1978 EEG study of adults who were victims of incest. The study's author, Robert W. Davies of the Yale University School of Medicine, and his team had found that 77 percent exhibited EEG abnormalities and 27 percent experienced seizures.

Subsequent work by other investigators using magnetic resonance imaging (MRI) technology has confirmed an association between early maltreatment and reductions in the size of the adult hippocampus. The amygdala may be smaller as well. In 1997 J. Douglas Bremner, then at the Yale University School of Medicine, and his colleagues compared MRI scans of 17 adult survivors of childhood physical or sexual abuse, all of whom had posttraumatic stress disorder (PTSD), with 17 healthy subjects matched for age, sex, race, handedness, years of education, and years of alcohol abuse. The left hippocampus of abused patients with PTSD was, on average, 12 percent smaller than the hippocampus of the healthy control subjects, but the right hippocampus was of normal size. Not surprisingly, given the important role of the hippocampus in memory function, these patients also scored lower on verbal memory tests than the nonabused group.

In 1997 Murray B. Stein of the University of California at San Diego also found left hippocampal abnormalities in 21 adult women who had been sexually abused as children and who had PTSD or dissociative identity disorder (also called multiple personality disorder, a condition thought by some researchers to be common in abused females). Stein determined that in these women the volume of the left
hippocampus was significantly reduced but that the right hippocampus was relatively unaffected. In addition, he found a clear correspondence between the degree of reduction in hippocampus size and the severity of the patients' dissociative symptoms. In 2001 Martin Driessen of Gilead Hospital in Bielefeld, Germany, and his colleagues reported a 16 percent reduction in hippocampus size and an 8 percent reduction in amygdala size in adult women with borderline personality disorder and a history of childhood maltreatment.

On the other hand, when Michael D. De Bellis and his colleagues at the University of Pittsburgh School of Medicine carefully measured MRI images of the hippocampus in 44 maltreated children with PTSD and 61
healthy control subjects in 1999, they failed to observe a significant difference in volume.

My McLean colleagues Susan Andersen and Ann Polcari and I obtained similar results in our recently completed volumetric analysis of the hippocampus in 18 young adults (18 to 22 years of age) with a history
of repeated forced sexual abuse accompanied by fear or terror, who were compared with 19 healthy age-matched controls. Unlike in previous studies, the control subjects were not patients but were recruited
from the general public and had fewer mental health problems. We observed no differences in hippocampal volume. Like Driessen's group, however, we did find a 9.8 percent average reduction in the size of
the left amygdala, which correlated with feelings of depression and irritability or hostility. We asked ourselves why the hippocampus was smaller in abused subjects in studies from Bremner's, Stein's and Dreissen's groups but normal in De Bellis's and in our own investigations. Of the several possible answers, the most likely is that stress exerts a very gradual influence on t he hippocampus, so adverse

effects may not be discernible at a gross anatomical level until people get older.

Moreover, animal studies by Bruce S. McEwen of the Rockefeller University and Robert M. Sapolsky of Stanford University had previously demonstrated the marked vulnerability of the hippocampus to the ravages of stress. Not only is the hippocampus particularly susceptible because it develops slowly, it also is one of the few brain regions that continues to grow new neurons after birth. Further, it has a higher density of receptors for the stress hormone cortisol than almost any other area of the brain. Exposure to stress hormones can significantly change the shape of the largest neurons in the hippocampus and can even kill them. Stress also suppresses production of the new granule cells (small neurons), which normally continue to develop after birth.

Experiments with rats by Christian Caldji, Michael J. Meaney of McGill University and Paul M. Plotsky of Emory University have shown that early stress reconfigures the molecular organization of these regions.
One major result is the alteration of the protein subunit structure of GABA receptors in the amygdala [see illustration on next page]. These receptors respond to gamma aminobutyric acid, the brain's primary
inhibitory neurotransmitter, and GABA attenuates the electrical excitability of neurons. Reduced function of this neurotransmitter produces excessive electrical activity and can trigger seizures. This discovery provides an elegant molecular explanation for our findings of EEG abnormalities and limbic irritability in patients with childhood abuse.

Left-Side Problems

The effect on the limbic system was only the most expected consequence of childhood trauma. We were intrigued, however, by our earlier observation that ill-treatment was associated with EEG abnormalities
in the left hemisphere. This inspired us to examine the effect of early abuse on the development of the left and right hemispheres. We chose to use EEG coherence, a sophisticated quantitative analysis method that provides evidence about the brain's microstructure--its wiring and circuitry. Conventional EEG, in contrast, reveals brain function. The EEG coherence technique accomplishes its task by generating a mathematical measure of the degree of cross-correlation among the elaborate neuronal interconnections in the cortex that process and modify the brain's electrical signals. In general, abnormally high levels of EEG coherence are evidence of diminished development among these neuron interchanges.

Our research team used this technique in 1997 to compare 15 healthy volunteers with 15 child and adolescent psychiatric patients who had a confirmed history of intense physical or sexual abuse. Coherence measures showed that the left cortices of the healthy control subjects were more developed than the right cortices, a result that is consistent with what is known about dominant hemisphere anatomy--that is, right-handed people tend to be left-cortex dominant. The maltreated patients, however, were notably more developed in the right cortex than the left, even though all were right-handed and hence
left-dominant. The right hemispheres of abused patients had developed as much as the right hemispheres of the control subjects, but their left hemispheres lagged substantially behind. This anomalous result
showed up regardless of the patient's primary diagnosis. And although the effect extended throughout the entire left hemisphere, the temporal regions were most affected, which suppor ted our original hypothesis.

The left hemisphere is specialized for perceiving and expressinglanguage, whereas the right hemisphere specializes in processing spatial information and in processing and expressingemotions--particularly negative emotions. We had wondered whethermistreated children might store their disturbing memories in the righthemisphere and whether recollecting these memories mightpreferentially activate the right hemisphere.

To test this hypothesis, Fred Schiffer worked in my laboratory at McLean in 1995 to measure hemispheric activity in adults during recall of a neutral memory and then during recall of an upsetting early memory. Those with a history of abuse appeared to use predominantly their left hemispheres when thinking about neutral memories and their right when recalling an early disturbing memory. Subjects in the control group used both hemispheres to a comparable degree for either task, suggesting that their responses were more integrated between the two hemispheres.

Because Schiffer's research indicated that childhood trauma was associated with diminished right-left hemisphere integration, we decided to look for some deficiency in the primary pathway forinformation exchange between the two hemispheres, the corpus callosum.In 1997 Andersen and I collaborated with Jay Giedd of the National Institute of Mental Health to search for the posited effect. Togetherwe found that in boys who had been abused or neglected, the middleparts of the corpus callosum were significantly smaller than in the control groups. Furthermore, in boys, neglect exerted a far greater effect than any other kind of maltreatment. In girls, however, sexual abuse was a more powerful factor, associated with a major reduction in size of the middle parts of the corpus callosum. These results were replicated and extended in 1999 by De Bellis. Likewise, the effects of early experience on the development of the corpus callosum have been confirmed by research in primates by Mara M. Sanchez of Emory.

**Our latest finding had its roots in the seminal studies of Harry F. Harlow of the University of Wisconsin-Madison. In the 1950s Harlow compared monkeys raised by their mothers with monkeys reared by wire
or terrycloth surrogate mothers. Monkeys raised with the surrogates became socially deviant and highly aggressive adults. Working with Harlow, W. A. Mason of the Delta Primate Center in Louisiana discovered that these consequences were less severe if the surrogate mother was swung from side to side. J.W. Prescott of the NationalInstitute of Child Health and Human Development hypothesized that this
movement would be conveyed to the cerebellum, particularly the middle part, called the cerebellar vermis, located at the back of the brain just above the brain stem. Among other functions, the vermis modulates
the brain-stem nuclei that control the production and release of the neurotransmitters norepinephrine and dopamine. Like the hippocampus, this part of the brain develops gradual ly and continues to create
neurons after birth. It has an even higher density of receptors for stress hormones than the hippocampus, so exposure to such hormones can strongly affect its development.**

Abnormalities in the cerebellar vermis have recently been reported to be associated with various psychiatric disorders, including manic-depressive illness, schizophrenia, autism and attention deficit/hyperactivity disorder. These maladies emerge from genetic and prenatal factors, not childhood mistreatment, but the fact that vermal anomalies seem to sit at the core of so many psychiatric conditions suggests that this region plays a critical role in mental health.

Dysregulation of the vermis-controlled neurotransmitters norepinephrine and dopamine can produce symptoms of depression, psychosis and hyperactivity as well as impair attention. Activation of the

dopamine system has been associated with a shift to a more left hemisphere-biased (verbal) attentional state, whereas activation of the norepinephrine system shifts attention to a more right hemisphere-biased (emotional) state. Perhaps most curiously, the vermis also helps to regulate electrical activity in the limbic system, and vermal stimulation can suppress seizure activity in the hippocampus and amygdala.

R.G. Heath, working at Tulane University in the 1950s, found that Harlow's monkeys had seizure foci in their fastigial nuclei and hippocampus. In later work with humans, he found that electrical stimulation of the vermis reduced the frequency of seizures and improved the mental health in a small number of patients with intractable neuropsychiatric disorders. This result led my colleagues and me to speculate whether childhood abuse could produce abnormalities in the cerebellar vermis that contributed to psychiatric symptoms, limbic irritability and gradual hippocampal degeneration.

To begin to test this hypothesis, Carl M. Anderson recently worked in tandem with me and with Perry Renshaw at the Brain Imaging Center atMcLean. Anderson used T2-relaxometry methods, a new MRI-based functional imaging technique we developed. For the first time, we can monitor regional cerebral blood flow at rest without the use of radioactive tracers or contrast dyes.

When the brain is resting, the neuronal activity of a region closely matches the amount of blood that area receives to sustain this activity. Anderson found a striking correlation between the activity in the cerebellar vermis and the degree of limbic irritability indicated by my TLE-related question checklist in both healthy young adult controls and young adults with a history of repeated sexual abuse.

At any level of limbic symptomatology, however, the amount of blood flow in the vermis was markedly decreased in the individuals with a history of trauma. Low blood flow points to a functional impairment in the activity of the cerebellar vermis. On average, abused patients had higher checklist scores presumably because their vermis could not activate sufficiently to quell higher levels of limbic irritability.

Together these findings suggest an intriguing model that explains one way in which borderline personality disorder can emerge. Reduced integration between the right and left hemispheres and a smaller corpus callosum may predispose these patients to shift abruptly from left- to right-dominated states with very different emotional perceptions and memories. Such polarized hemispheric dominance could cause a person to see friends, family and co-workers in an overly positive way in one state and in a resoundingly negative way in another--which is the hallmark of this disorder. Moreover, limbic electrical irritability can produce symptoms of aggression, exasperation and anxiety. Abnormal EEG activity in the temporal lobe is also often seen in people with a greatly increased risk for suicide and self-destructive behavior.

Adaptive Detriment

Our team initiated this research with the hypothesis that early stress was a toxic agent that interfered with the normal, smoothly orchestrated progression of brain development, leading to enduring psychiatric problems. Frank W. Putnam of Children's Hospital MedicalCenter of Cincinnati and Bruce D. Perry of the Alberta Mental Health Board in Canada have now articulated the same hypothesis. I have come to question and reevaluate our starting premise, however. Human brains evolved to be molded by experience, and early difficulties were routine during our ancestral

development. Is it plausible that the developing brain never evolved to cope with exposure to maltreatment and so is damaged in a nonadaptive manner? This seems most unlikely. The logical alternative is that exposure to early stress generates molecular and neurobiological effects that alter neural development in an adaptive way that prepares the adult brain to survive and reproduce in a dangerous world.

What traits or capacities might be beneficial for survival in the harsh conditions of earlier times? Some of the more obvious are the potential to mobilize an intense fight-or-flight response, to react aggressively to challenge without undue hesitation, to be at heightened alert for danger and to produce robust stress responses that facilitate recovery from injury. In this sense, we can reframe the brain changes we observed as adaptations to an adverse environment.

Although this adaptive state helps to take the affected individual safely through the reproductive years (and is even likely to enhancesexual promiscuity), which are critical for evolutionary success, it comes at a high price. McEwen has recently theorized that overactivation of stress response systems, a reaction that may be necessary for short-term survival, increases the risk for obesity, type II diabetes and hypertension; leads to a host of psychiatric problems, including a heightened risk of suicide; and accelerates the aging and degeneration of brain structures, including the hippocampus.

We hypothesize that adequate nurturing and the absence of intense early stress permits our brains to develop in a manner that is less aggressive and more emotionally stable, social, empathic and hemispherically integrated. We believe that this process enhances the ability of social animals to build more complex interpersonal structures and enables humans to better realize their creative potential.

Society reaps what it sows in the way it nurtures its children. Stress sculpts the brain to exhibit various antisocial, though adaptive, behaviors. Whether it comes in the form of physical, emotional or sexual trauma or through exposure to warfare, famine or pestilence, stress can set off a ripple of hormonal changes that permanently wire a child's brain to cope with a malevolent world. Through this chain of events, violence and abuse pass from generation to generation as well as from one society to the next. Our stark conclusion is that we see the need to do much more to ensure that child abuse does not happen in
the first place, because once these key brain alterations occur, there may be no going back.

MORE TO EXPLORE

Developmental Traumatology, Part 2: Brain Development. M.D. De Bellis, M.S. Keshavan, D.B. Clark, B.J. Casey, J.N. Giedd, A.M. Boring, K. Frustaci and N.D. Ryan in Biological Psychiatry, Vol. 45, No. 10, pages 1271-1284; May 15,1999.

Wounds That Time Won't Heal: The Neurobiology of Child Abuse. Martin H. Teicher in Cerebrum [Dana Press], Vol. 2, No. 4, pages 50-67; Fall 2000.

McLean Hospital: www.mcleanhospital.org/

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Inset Article

OVERVIEW / INSIGHT INTO CHILD ABUSE

*** Until recently, psychologists believed that mistreatment during childhood led to arrested psychosocial development and self-defeating psychic defense mechanisms in adults. New brain imaging surveys and other experiments have shown that child abuse can cause permanent damage to the neural structure and**
function of the developing brain itself.

*** This grim result suggests that much more effort must be made to prevent childhood abuse and neglect before it does irrevocable harm to millions of young victims. New approaches to therapy may also be indicated.**

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