Introduction

The purpose of this chapter is to examine potential mechanisms underlying the well-documented, complex relationships between maltreatment in childhood and the subsequent development of psychopathology. Thousands of studies over the last fifty years have described various aspects of these relationships. Maltreatment in childhood increases risk for virtually every DSM-IV disorder, from autistic-spectrum disorders to schizophrenia to ADHD to major depression to substance abuse disorders. The mechanisms underlying this maltreatment related increase in risk of neuropsychiatric problems are undetermined. The key question addressed in this chapter is “How can abuse lead to psychopathology?” The perspective of the present chapter is neurodevelopmental. This “lens” provides significant insight about the sometimes confusing interrelationships between psychopathology, DSM-IV “diagnoses” and developmental trauma or neglect. A neurodevelopmental perspective is meant to compliment other theoretical and experimental views and can provide useful clues to the mechanisms underlying the origins of neuropsychiatric problems.

The primary premise of a neurodevelopmental perspective is that the human brain is the organ mediating all emotional, social, cognitive and behavioral functioning. Neuropsychiatric disorders and psychopathology, therefore, must involve altered functioning of systems in the brain. The specific nature of dysfunction (e.g., anxiety vs inattention vs affect regulation vs thought disorder) will be determined by which neural networks and brain areas are altered. The present chapter provides an overview of key neurodevelopmental processes and important neural networks which are impacted by abuse and suggests mechanisms which may underlie neuropsychiatric problems related to developmental maltreatment. The major conclusion of this chapter is that we can make plausible conclusions regarding the effects of abuse if we understand how these experiences impact the developing brain. Simply stated childhood trauma will result in alterations in the
systems in the brain which mediate the stress response and neglect will result in dysfunctions in the neural systems which do not receive appropriately timed, patterned repetitive stimulation.

Two major forms of maltreatment will reviewed in the present chapter: neglect and trauma. Though often co-occurring, these two types of maltreatment are distinctly different in the impact they have on the developing brain, and, therefore, will have differing impact on the development of psychopathology. Neglect, defined from a neurobiological perspective, is the absence of an experience or pattern of experiences required to express an underlying genetic potential in a key developing neural system. Trauma, from a neurobiological perspective, is an experience or pattern of experiences which activate the stress response systems in such an extreme or prolonged fashion as to cause alterations in the regulation and functioning of these systems. Both neglect- and trauma-related abnormalities in neurodevelopment would be predicted to cause significant psychopathology.

Abuse can have a negative impact on development in several ways. Maltreatment may be the primary mediator of psychopathology when these abnormal experiences directly alter developing neural systems; for example, trauma may cause post-traumatic stress disorder or neglect an attachment disorder. In addition, trauma or neglect may play an exacerbating or expressing role for neuropsychiatric syndromes in individuals with genetic vulnerabilities (e.g., major depression and schizophrenia). And finally, symptoms and problems caused by maltreatment can be disrupting factors for subsequent developmental opportunities (e.g., the disrupting impact of hypervigilance on academic experiences or of neglect-related attachment problems on social development). Often these secondary and tertiary effects are as devastating as the primary abuse-related pathology.

In order to better understand the potential mechanisms by which abuse can cause psychopathology it is crucial to consider the core processes and principles of neurodevelopment.

Neurodevelopment

The brain develops rapidly in utero and in the first years of life. During this time important molecular processes are taking place which, if disrupted, can result in abnormal organization and function. Depending upon the nature, timing and frequency of maltreatment, all of these processes can be impacted by chaos, threat, trauma and neglect.

Molecular Processes of Neurodevelopment

**Neurogenesis:** The vast majority of cell birth or neurogenesis takes place in utero. Few neurons are born after birth, although researchers have demonstrated neurogenesis in the mature brain (Gould, Reeves, Graziano, & Gross. 1999). Neurogenesis may be impacted by maternal substance use, most especially alcohol use and abuse during pregnancy. This can have a devastating impact on the fetal brain growth and result in profound psychopathology later in life (Bookstein et al., 2002).

**Migration:** As neurons are born and the brain grows, neurons move. It is the fate of some neurons to settle in the brainstem, others in the cortex, for example. Cortical cell
migration and fate mapping are some of the most studied processes in developmental neuroscience (Rakic, 1981; 1996). It is clear that both genetic and environmental factors play important roles in determining a neuron’s final location. Migration takes place primarily during the intrauterine and immediate perinatal period but continues throughout childhood and, possibly, to some degree into adult life. A host of intrauterine and perinatal insults – experiences such as infection, lack of oxygen, exposure to alcohol and various psychotropic drugs can alter migration of neurons and have profound impact on the expression of genetic potentials for a host of functions (see Perry, 1988).

**Differentiation:** Neurons can mature to thousands of unique structures, producing any of a hundred different neurotransmitters (e.g., norepinephrine, dopamine, serotonin, CRF or Substance P). Developing neurons change (differentiate) in response to chemical, often neurochemical, signals. Therefore, any experience that alters neurochemical, hormonal or micro-environmental signals (e.g., extreme activation of the stress-response) during development can change the ways in which certain neurons differentiate, thereby altering the functional capacity of the neural networks in which these neurons reside (e.g., Rutledge et al., 1974).

**Apoptosis:** More neurons born than are required to make a functional system. Redundant neurons, when unable to adequately “connect” into an active neural network, die (Kuan, Roth, Flavell, & Rakic. 2000). Neurons that make synaptic connections with others and have an adequate level of stimulation will survive; neurons with little activity resorb. This is an example of the important principle of activity-dependent development (see below). Obviously, under stimulation from neglect could increase apoptosis.

**Arborization:** As neurons differentiate, they send out one form of fiber-like receptive processes called dendrites. The density of these dendritic branches is related to the frequency and intensity of incoming signals. Arborization allows the neuron to receive, process, and integrate complex patterns of input. Dendritic density appears to be one of the most experience-sensitive physical features of a neuron (Diamond, Law, Rhodes, et al. 1966; Greenough, Volkmar, & Juraska. 1973).

**Synaptogenesis:** The most experience-sensitive feature of a neuron is the synapse. Developing neurons send out fiber-like processes which become axons and synapses. A continuous dynamic of synaptic neurotransmission regulates the activity chains of neurons that allow all brain function. Neurons, during development, find and connect with the appropriate target neurons. This process is guided by certain growth factors and cellular adhesion molecules that attract or repel a specific growth cone to appropriate target neurons. Furthermore this process is influenced by neurotransmission; altering levels of dopamine while nigrostriatal cells are developing will alter receptor expression and synaptogenesis (Wainwright et al.,1995). During the first eight months of life there is an eight-fold increase in synaptic density while the developing neurons in the brain are “seeking” their appropriate connections (Huttenlocher. 1979; 1994). This explosion of synaptogenesis allows the brain to have the flexibility to organize and function with a wide range of potential. Due to the rapid and important neural changes taking place in this first year, this is also a time of remarkable vulnerability to trauma and neglect.

**Synaptic sculpting:** The synapse is a dynamic structure. With continuous, but episodic release of neurotransmitter, occupation of receptors, release of growth factors, shifts of ions in and out of cells, laying down of new microtubules and other structural molecules, the synapse is continually changing. A key determinant in this synaptic sculpting process is the activity of neurotransmission. When there is a consistent active process of
neurotransmitter release, synaptic connections will be strengthened with actual physical changes that make the pre- and postsynaptic neurons grow closer together, making neurotransmission between these two neurons more efficient. When there is little activity, the synaptic connection will dissolve. Synaptic sculpting is a “use it or lose it” process (see below). Dynamic synaptic sculpting continues though the entire life cycle; however the rate of sculpting decreases with age. This powerful activity-dependent process appears to be the molecular basis of learning, memory and, therefore, at the core of neurodevelopment.

Myelination: Specialized glial cells wrap around axons and, thereby, create more efficient electrochemical transduction down the neuron. This allows a neural network to function more rapidly and efficiently, thereby allowing more complex functioning (e.g., walking depends upon the myelination of neurons in the spinal cord for efficient, smooth regulation of neuromotor functioning.) The process of myelination begins in the first year of life but continues in many key areas throughout childhood with a major burst of myelination in key cortical areas taking place in adolescence. Final myelination of key cortical tracts can take place as late as age 30.

The neurodevelopmental processes described above are sensitive to “signals” from neurotransmitters, neuromodulators, neurohormones, ions, growth factors, cellular adhesion molecules and other morphogens. Disruption of the pattern, timing or intensity of these cues can lead to abnormal neurodevelopment and psychopathology. The specific psychopathology will depend upon the timing of the insult (e.g., was the insult in utero during the development of the brainstem or at age two during the active development of the cortex), the nature of the insult (e.g., is there a lack of sensory stimulation from neglect or an abnormal persisting activation of the stress response from trauma?), the pattern of the insult (i.e., is this a discreet single event, a chronic experience with a chaotic pattern or an episodic event with a regular pattern?). Experience, good and bad, literally becomes the neuroarcheology of the individual’s brain (see Perry, 2001a).

The effects of abuse, then, will be very dependent upon the state of development of the child, and, of course the stage of neurodevelopment. Several key principles help explain the key findings of developmental maltreatment.

Principles of Neurodevelopment

Nature and Nurture: Neurodevelopment is a product of genetic potential and how that potential is expressed as function of the timing, nature and pattern of experience. Genetic differences in key neural factors have been demonstrated that may be related to the functioning of the stress-response systems, for example (Caspi et al., 2002). Yet the way these genetic vulnerabilities are expressed remain sensitive to developmental experiences of trauma (Caspi et al., 2003).

The impact of experience on neurodevelopment shifts during development. In the just fertilized ovum, chemical processes that are driving development are genetically-determined sequences of molecular events. By birth, however, the brain has developed to the point where environmental cues mediated by the senses play a major role in neural differentiation, arborization, and synaptogenesis, helping create functional neural networks. By adolescence, the majority of the changes that are taking place in the brain of that child are determined by experience, not genetics. The languages, beliefs, cultural practices, and
complex cognitive and emotional functioning (e.g., self esteem) by this age are primarily experience-based.

**Sequential Developmental:** The brain develops in a sequential and hierarchical fashion; organizing itself from least (brainstem) to most complex (cortical areas). These different areas develop, organize and become fully functional at different times during childhood. At birth, for example, the brainstem areas responsible for regulating cardiovascular and respiratory function must be intact for the infant to survive, and any malfunction is immediately observable. In contrast, the cortical areas responsible for abstract cognition are not fully functional until adult life.

This is important in understanding the role of the stress-response neural systems in shaping future neurodevelopment. As described in detail below, the monoamine neurons originating in the brainstem and diencephalon (present by birth) send direct connections into all other brain areas (Figure 1). If these systems are poorly organized or dysregulated themselves, they can dysregulate and disorganize higher parts of the brain. The “higher” more complex areas (e.g., limbic and cortical) have not yet organized. The final organization of these important areas (and all of the functions mediated by these areas) will be influenced by the pattern, intensity and nature of stimulation coming from these adrenergic, noradrenergic, serotonergic and dopaminergic neurons.

Trauma will result in profound alterations in the pattern of activation in these stress-mediating neural systems; which in turn will result in patterned, repetitive neuronal activation in a distributed and diverse set of brain systems, influencing the organization and function of these higher brain areas; the result can be compromised function and psychopathology. Traumatic stress, for example, can impact cortically-mediated (e.g., cognition), limbic-mediated (e.g., affect regulation), diencephalic-mediated (e.g., fine motor regulation, startle response) and brainstem-mediated (e.g. heart rate, blood pressure regulation) functioning.

Each brain area will have its own timetable for development. The neurodevelopmental processes described above will be most active in different brain areas at different times and will, therefore, either require (critical periods) or be sensitive to (sensitive periods) organizing experiences (and the neurotrophic cues related to these experiences). The neurons for the brainstem have to migrate, differentiate and connect, for example, before the neurons for the cortex.

Disruptions of experience-dependent neurochemical signals during early life may lead to major abnormalities or deficits in neurodevelopment. Disruption of critical neurodevelopmental cues can result from 1) lack of sensory experience during sensitive periods (e.g., neglect) or 2) atypical or abnormal patterns of necessary cues due to extremes of experience (e.g., traumatic stress, see Perry, 2001a; 2001b). This has implications for understanding psychopathology related to maltreatment. In the development of socio-emotional functioning, early life nurturing appears to be critical, for example. If this is absent for the first three years of life and then a child is adopted and begins to receive attention, love and nurturing, these positive experiences may not be sufficient to overcome the malorganization of the neural systems mediating socio-emotional functioning.

**Activity-dependent Neurodevelopment:** The brain organizes in a use-dependent fashion. Many of the molecular processes in neurodevelopment are activity dependent. In the developing brain, undifferentiated neural systems are critically dependent upon sets of
environmental and micro-environmental cues (e.g., neurotransmitters, cellular adhesion molecules, neurohormones, amino acids, ions) in order for them to appropriately organize from their undifferentiated, immature forms (Lauder, 1988; Perry, 1994) (Perry & Pollard, 1998). Lack, or disruption, of these critical cues can alter the neurodevelopmental processes of neurogenesis, migration, differentiation, synaptogenesis - all of which can contribute to malorganization and diminished functional capabilities in the specific neural system where development has been disrupted. This is the core of a neuroarcheological perspective on dysfunction related adverse childhood events (Perry, 2001b).

These molecular cues that guide development are dependent upon the experiences of the developing child. The quantity, pattern of activity and nature of these neurochemical and neurotrophic factors depends upon the presence and the nature of the total sensory experience of the child. When the child has adverse experiences – loss, threat, neglect, and injury – there can be disruptions of neurodevelopment that will result in neural organization that can lead to compromised functioning throughout life (see below). Healthy organization of neural networks depends upon the pattern, frequency and timing of key experiences during development. Patterned, repetitive activity changes the brain. Chaotic, episodic experiences out of sync with the developmental stage of the child create chaotic, developmentally-delayed dysfunctional organization.

If a child is neglected – if he or she hears fewer words, has fewer relational opportunities, has less physical comfort and love – the rapidly organizing networks in the brain which mediate language, social affiliation and attachment will not receive sufficient patterned, repetitive activation to develop normally. The result is a neglect related set of deficits. The deficit will be in the domains where the neglect occurred (see Perry 2002).

Sensitive and Critical Windows: Due to sequential and activity-dependent development of the brain there are times when a given developing neural system is more sensitive to experience. In healthy development, that sensitivity allows the brain to efficiently organize in response to the unique demands of a given environment. If the child’s is born into a hunter-gatherer clan in New Guinea as opposed to a suburban English family, for example, different genes can be expressed, and different neural networks can be organized to best fit that family, culture and environment. This sensitivity, for most functions, passes with time. Acquisition of language with full fluency after a certain age becomes more difficult; formation of key relational and attachment capacities after the first five years of life becomes difficult if these initial years were characterized by disorganized, absent or abusive primary caregivers.

Sensitive periods are different for each brain area and neural system, and therefore, for different functions. The sequential development of the brain and the sequential unfolding of the genetic map for development mean that the sensitive periods for neural system (and the functions they mediate) will be when that area is most actively organizing. The brainstem must organize key systems by birth; therefore, the sensitive period for those brainstem-mediated functions is during the prenatal period. A variety of in utero experiences may influence the development of the key stress-mediating neurotransmitter systems which originate in the brainstem. For example, prenatal exposure to psychoactive drugs may disrupt normal development of the brainstem catecholamines (Perry, 1988). In animal models, brief prenatal and perinatal stress can cause altered development of hippocampal organization and the hypothalamic-pituitary-adrenal axis which remain altered throughout life (Plotsky and Meaney, 1993; Shors et al., 1990). The neocortex, in contrast,
has systems and functions organizing throughout childhood and into adult life. The sensitive periods for these cortically mediated functions are likely to be very long.

The primary clinical implication of this is that early childhood trauma or maltreatment has disproportionate capacity to cause significant dysfunction in comparison with similar trauma or neglect later in life (see Rutter et al., 1998; Rutter et al., 1999). Children are more vulnerable to trauma and neglect that adolescents and adults. The younger a child is, the more likely they are to have enduring and pervasive problems following trauma and neglect. Neglect in the first years of life can have devastating impact even if a child is removed from the neglectful environment (Perry 2002; Perry, 2005). The longer a child remains in a neglectful environment, the more vulnerable they become (e.g., Rutter et al. 1998; 1999; O’Connor et al. 2000; Perry, 2005).

The major consequence of these principles of brain development is that the organizing brain of an infant or young child is more malleable to experience than a mature brain. While experience may alter the behavior of an adult, experience literally provides the organizing framework for an infant and child. Because the brain is most plastic (receptive to environmental input) in early childhood, the child is most sensitive to experience at this time – both good and bad.

The Neurodevelopmental Impact of Neglect

Deprivation during the sensitive period of a given neural system will result in insufficient patterned, repetitive activity to stimulate adequate organization. The deprived developing neural network will have altered neural microarchitecture which may include cell migration, synaptogenesis, dendritic sprouting. The result is a neural system less functionally capable. This deprivation – neglect – can take multiple forms. In some rare cases, a single domain of functioning is primarily impacted. Our clinical group has worked with several children raised with cognitive stimulation, physical and emotional warmth but physically restrained for multiple years and, therefore, unable to sit, stand or walk. Most neglect takes the form of chaotic, mis-timed, inconsistent experience related to the isolation, personal chaos, incompetence, ignorance, domestic violence, substance abuse or psychopathology of the primary caregiver. This can manifest as delays in motor, self-regulatory, affective and cognitive functioning. A common manifestation of this form of neglect is in speech and language acquisition; if the infant or toddler hears few words, the developing speech and language systems will be impacted (Huttenlocher et al., 2002); the result is impaired speech and language.

The earlier and more pervasive the neglect is, the more devastating the developmental problems for the child. Indeed, a chaotic, inattentive and ignorant caregiver can produce pervasive developmental delay (PDD; DSM IV-R) in a young child (Rutter, Andersen-Wood, Beckett, et al. 1999). Yet the very same inattention for the same duration if the child is ten will have very different and less severe impact than inattention during the first years of life.

Studies of the neurodevelopmental impact of neglect are not as common as those on the effects of trauma. Both animal studies, descriptive reports with severely neglected children and some recent studies with adopted children following neglect which document some aspects of the neurodevelopmental impact of neglect.
Animal Studies: Hubel and Weisel’s landmark studies on development of the visual system using sensory deprivation techniques helped define the concepts of critical and sensitive period (Hubel & Wiesel. 1963). In hundreds of other studies, extremes of sensory deprivation (Hubel & Wiesel. 1970; Greenough, Volkmar, & Juraska. 1973) or sensory enrichment (Greenough & Volkmar. 1973; Diamond, Krech, & Rosenzweig. 1964; Diamond, Law, Rhodes, et al. 1966) have been studied. These include disruptions of visual stimuli (Coleman & Riesen. 1968), environmental enrichment (Altman & Das. 1964; Cummins & Livesey. 1979), touch (Ebinger. 1974; Rutledge, Wright, & Duncan. 1974), and other factors that alter the typical experiences of development (Uno, Tarara, Else, & et.al. 1989; Plotsky & Meaney. 1993; Meaney, Aitken, van Berkal, Bhatnagar, & Sapolsky. 1988).

These findings generally demonstrate that the brains of animals reared in enriched environments are larger, more complex and functional more flexible than those raised under deprivation conditions. Relationships between experience and brain cytoarchitecture have demonstrated a relationship between density of dendritic branching and the complexity of an environment (Diamond & Hopson. 1998). Rats raised in environmentally enriched environments have higher density of various neuronal and glial microstructures, including a 30% higher synaptic density in cortex compared to rats raised in an environmentally deprived setting (Bennett, Diamond, Krech, & Rosenzweig. 1964; Altman & Das. 1964). Animals raised in the wild have from 15 to 30% larger brain mass than their offspring who are domestically reared (Darwin. 1868; Rohrs. 1955; Rohrs & Ebinger. 1978; Rehkamper, Haase, & Frahm. 1988).

Animal studies suggest that critical periods exist during which specific sensory experience was required for optimal organization and development of the part of the brain mediating a specific function (e.g., visual input during the development of the visual cortex). While these phenomena have been examined in great detail for the primary sensory modalities in animals, few studies have examined the issues of critical or sensitive periods in humans. What evidence there is would suggest that humans tend to have longer periods of sensitivity and that the concept of critical period may not be useful in humans (Perry, 2006). Yet altered emotional, behavioral, cognitive, social and physical functioning has been demonstrated in humans following specific types of neglect. For obvious ethical reasons, most of these findings come from descriptive clinical rather than experimental studies.

Neglect in Early Childhood: The majority of clinical reports on neglect have focused on institutionalized children or feral children. As early as 1833, with the famous Kaspar Hauser, feral children had been described (Heidenreich. 1834). Hauser was abandoned as a young child and raised from early childhood (likely around age two) until seventeen in a dungeon, experiencing relative sensory, emotional and cognitive neglect. His emotional, behavioral and cognitive functioning was, as one might expect, very primitive and delayed.

In the early forties, Spitz described the impact of neglectful caregiving on children in foundling homes (orphanages). Most significant, he was able to demonstrate that children raised in fostered placements with more attentive and nurturing caregiving had superior physical, emotional and cognitive outcomes (Spitz. 1945; Spitz. 1946).

Dennis (1973) described a series of findings from children raised in a Lebanese orphanage. These children were raised in an institutional environment devoid of individual attention, cognitive stimulation, emotional affection or other enrichment. Prior to 1956 all of these children remained at the orphanage until age six, at which time they were
transferred to another institution. Evaluation of these children at age 16 demonstrated a mean IQ of approximately 50. When adoption became common, children adopted prior to age 2 had a mean IQ of 100 by adolescence while children adopted between ages 2 and 6 had IQ values of approximately 80 (Dennis. 1973). This graded recovery is consistent with the known principles of neurodevelopment described above; the older a child was at time of adoption, (i.e., the longer the child spent in the neglectful environment) the more pervasive and resistant to recovery were the deficits.

Money and Anneclilo (1976) reported the impact of change in placement on children with psychosocial dwarfism (failure to thrive). In this preliminary study, 12 of 16 children removed from neglectful homes recorded remarkable increases in IQ and other aspects of emotional and behavioral functioning. Furthermore, they reported that the longer the child was out of the abusive home the higher the increase in IQ. In some cases IQ increased by 55 points.

A more recent report on a group of 111 Romanian orphans (Rutter & English and Romanian Adoptees study team. 1998; Rutter, Andersen-Wood, Beckett, et al. 1999) adopted prior to age two from very emotionally and physically depriving institutional settings demonstrate similar findings. Approximately one half of the children were adopted prior to age six months and the other half between six months and 2 years old. At the time of adoption, these children had significant delays. Four years after being placed in stable and enriching environments, these children were re-evaluated. While both groups improved, the group adopted at a younger age had a significantly greater improvement in all domains. As a group, these children were at much greater risk for meeting diagnostic criterion for autism-spectrum disorder, a finding that sheds light on the evolving relationships between early life trauma, neglect and subsequent development of severe neuropsychiatric problems including psychotic disorders and schizophrenia (Read et al., 2001).

These observations are consistent with the clinical experiences of the ChildTrauma Academy working with maltreated children for the last fifteen years. During this time we have worked with more than 1000 seriously children. We have recorded increases in IQ of over 40 points in more than 60 children following removal from neglectful environments and placed in consistent, predictable, nurturing, safe and enriching placements (Perry, 2005). In a group of 200 children under the age of 6 at time of removal, significant developmental delays were seen in more than 85% of the children. The severity of these developmental problems increased with age, suggesting, again, that the longer the child was in the neglectful environment - the earlier and more pervasive the neglect - the more indelible and pervasive the deficits.

Neurobiological Findings
All of these reported developmental problems – language, fine and large motor delays, impulsivity, disorganized attachment, dysphoria, attention and hyperactivity, and a host of others described in these neglected children – are caused by abnormalities in the brain. Despite this obvious statement, very few studies have examined directly any aspect of neurobiology in neglected children. One early clue in humans On autopsy, the brain of Kasper Hauser (see above) was notable for small cortical size and few, non-distinct cortical gyri – all consistent with cortical atrophy (Simon, 1978).

Our group has examined various aspects of neurodevelopment in neglected children ((Perry & Pollard. 1997; Perry, 2005). Globally neglected children had smaller the frontal-occipital circumference, a measure of head size and in young children a reasonable
measure of brain size. Neuroimaging demonstrated that 64.7% of the brain scans were abnormal in the children with global neglect and 12% in children following chaotic neglect. The majority of the findings were "enlarged ventricles" or "cortical atrophy" (Figure 2). Once removed from the neglectful settings, recovery of function and relative brain-size were observed. The degree of recovery over a year period however was inversely proportional to age in which the child was removed from the neglecting caregivers. The earlier in life and the less time in the sensory-depriving environment, the more robust the recovery (Perry, 2005).

In the study of Romanian orphans described above, the 38% had FOC values below the third percentile (greater than 2 SD from the norm) at the time of adoption. In the group adopted after six months, fewer than 3% and the group adopted after six months 13% had persistently low FOCs four years later (Rutter & English and Romanian Adoptees study team. 1998; O’Connor, Rutter, & English and Romanian Adoptees study team. 2000). Strathearn (2001) has followed extremely low birth weight infants and shown that when these infants end up in neglectful homes they have a significantly smaller head circumference at 2 and 4 years, but not at birth. This is despite having no significant difference in other growth parameters.

Studies from other groups report similar altered neurodevelopment in neglected children. Teicher has reported altered corpus callosum development in neglected children (Teicher et al., 2004). Altered brain-related measures (e.g., salivary cortisol) have been demonstrated in children adopted following neglect (Gunnar et al., 2001). Chugani and colleagues have demonstrated decreased metabolic activity in the orbital frontal gyrus, the infralimbic prefrontal cortex, the amygdale and head of the hippocampus, the lateral temporal cortex and in the brainstem in a group of Romanian orphans (Chugani, et al., 2001).

Neurodevelopmental Impact of Trauma

The brain’s stress mediating systems are widely distributed; involve brain and the autonomic nervous system as well as neuroendocrine and neuroimmune responses. Clearly stress-related neural networks permeate the entire brain. The capacity, then, of a use-dependent alteration in the organization and functioning of neural systems involved in dozens of functions could easily take place with prolonged activation. The specific nature of which of these myriad systems becomes altered depends upon the specific nature of the threat response in any given circumstance.

The human brain is continually sensing, processing, storing, perceiving and acting in response to information from the external and internal environments. This continuous monitoring is process is especially sensitive to input that may indicate threat. These “worlds” – external as ‘sensed’ by our five senses and internal as ‘sensed’ by a set of specialized neurons throughout the body (e.g., glucose or sodium sensitive neurons) – are always changing. Our physiology and neurophysiology are characterized by a continuous process of modulation, regulation, compensation, activation – all designed to keep our body’s systems in some state of equilibrium or homeostasis. Whenever the incoming information from either inside or outside the body alter this homeostasis (Perry and Pollard, ) or indicate similarity to a pattern of activity previously associated with a threat (Perry, ),
the brain initiates compensatory, adaptive responses to re-establish homeostasis or to take the necessary actions to survive.

Sequential Processing of Threat Related Neural Activity

This process begins when our senses transform forms of energy (e.g., light, sound, pressure) into patterned activity of sensory neurons. The first ‘stops’ for sensory input from the outside environment (e.g., light, sound, taste, touch, smell) and from inside the body (e.g., glucose levels, temperature) are the lower, ‘regulatory’ areas of the brain (see later). These neural patterns of activity created by sensory input first come into the brain separately – visual input comes into one nuclei, auditory another, olfactory another and so on. The “first stops” for primary sensory input are in lower parts of the brain that are incapable of conscious perception.

Brainstem and Diencephalon

Neural input from our senses directly connects to the lower areas of the CNS in the brainstem, diencephalon and hypothalamus. For example, our internal organs directly relay information to the amygdala and locus coeruleus directly or through the nucleus paragigantocellularis and nucleus tractus solitaries (Elam et al., 1986; Nauta and Whitlock, 1956; Saper, 1982). Other primary sensory input from visual, auditory, tactile and olfactory systems directly connect into these lower brain nuclei where the process of sorting, integrating, interpreting, storing (if appropriate) and responding to these incoming signals begins.

These brainstem and diencephalic nuclei project to the thalamus which begins the process of integrating this information, relaying sensory information to the primary sensory receptive areas of the cortex. These primary sensory regions project to adjacent cortical association areas. A feedback process involves projections from key cortical areas back to the lower parts of the brain; visual, auditory and somatosensory cortical association areas send projections to the hippocampus, amygdala, orbitofrontal cortex, entorhinal cortex, and cingulate gyrus and other brain structures. This reciprocal processing allows the brain to sort, process and “act” on the threat related signals from the body and the external world.

The Reticular Activating System: Key to this entire process is the role of an array of important neurotransmitter networks; the monoamine systems; epinephrine, norepinephrine, dopamine and serotonin – have key nuclei (clusters of cell bodies) which send direct axonal projections to virtually all other areas of the brain and lower to influence the autonomic neurons which leave the brain and directly influence heart, lung, gut, skin and the rest of the organs of the body. Collectively this network has been referred to as the reticular activating system.

The reticular activating system (RAS) is a network of ascending, arousal-related neural systems in the brain that consists of locus ceruleus noradrenergic neurons, dorsal raphe serotonergic neurons, cholinergic neurons from the lateral dorsal tegmentum, and mesolimbic and mesocortical dopaminergic neurons, among others. Much of the original research on arousal, fear, and response to stress and threat was conducted using various lesion models of the reticular activating system (Moore and Bloom, 1979). The reticular activating system appears to be an integrated neurophysiological system involved in arousal, anxiety, and modulation of limbic and cortical processing (Munk et al., 1996). Working together, the brain-stem monoamine systems in the reticular activating system
provide the flexible and diverse functions necessary to modulate stress, distress and trauma. A key component of the RAS is the locus coeruleus.

The Locus Coeruleus: The locus coeruleus is involved in initiating, maintaining, and mobilizing the total body response to threat (Aston-Jones et al., 1986). A bilateral grouping of norepinephrine-containing neurons originating in the pons, the locus coeruleus sends diverse axonal projections to virtually all major brain regions and thus functions as a general regulator of noradrenergic tone and activity (Foote et al., 1983). The locus coeruleus plays a major role in determining the “valence,” or value, of incoming sensory information; in response to novel or potentially threatening information, it increases its activity (Abercrombie and Jacobs, 1987a; Abercrombie and Jacobs, 1987b). The ventral tegmental nucleus also plays a part in regulating the sympathetic nuclei in the pons/medulla (Moore and Bloom, 1979). Acute stress results in an increase in locus coeruleus and ventral tegmental nucleus activity and the release of catecholamines throughout the brain and the rest of the body. These brain-stem catecholamine systems (locus coeruleus and ventral tegmental nucleus) play a critical role in regulating arousal, vigilance, affect, behavioral irritability, locomotion, attention, and sleep, as well as the startle response and the response to stress (Levine et al., 1990; Morilak et al., 1987a; Morilak et al., 1987b; Morilak et al., 1987c).

Hypothalamus and Thalamus: Sensory thalamic areas receive input from various afferent sensory systems, and at this level, “feeling” begins. Although thalamic nuclei are important in the stress response, these regions have been studied primarily as “waystations” that transmit important arousal information from the reticular activating system neurons (e.g., locus coeruleus noradrenergic neurons) to key limbic, subcortical, and cortical areas involved in sensory integration and perception of threat-related information (Castro-Alamancos and Connors, 1996). The neuroendocrinological—and likely neuroimmunological—afferent and efferent wings of the threat response are mediated by hypothalamic and other anatomically related nuclei. Studies have demonstrated important roles for various hypothalamic nuclei and hypothalamic neuropeptides in the stress response in animals (Bartanusz et al., 1993; Miaskowski et al., 1988) (Rosenbaum et al., 1988), and humans (Young and Lightman, 1992).

The Limbic System

The central role of the subcortical network of brain structures in emotion was hypothesized by Papez (Papez, 1937) and elaborated by MacLean who coined the term limbic system. This sub-cortical network is responsible for a range of emotion- and relational-related functions. Among the key subcomponents of the limbic system are two brain areas known to be intimately involved in the stress response: the amygdala and hippocampus.

Amygdala: The amygdala has emerged as the key brain region responsible for the processing, interpretation, and integration of emotional functioning (Clugnet and LeDoux, 1990). Just as the locus coeruleus plays the central role in orchestrating arousal, the amygdala plays the central role in the brain in processing afferent and efferent connections related to emotional functioning (LeDoux et al., 1988; Pavlides et al., 1993b; Phillips and LeDoux, 1992b). The amygdala receives input directly from the sensory thalamus, the hippocampus (via multiple projections), the entorhinal cortex, and the sensory association...
and polymodal sensory association areas of the cortex as well as from various brain-stem arousal systems via the reticular activating system (Selden et al., 1991). The amygdala processes and determines the emotional valence of simple sensory input, complex multisensory perceptions, and complex cognitive abstractions, even responding specifically to complex socially relevant stimuli. In turn, the amygdala orchestrates the organism’s response to this emotional information by sending projections to brain areas involved in motor (behavioral), autonomic nervous system, and neuroendocrine areas of the CNS (Davis, 1992a; Davis, 1992b; LeDoux et al., 1988). In a series of landmark studies, LeDoux and colleagues demonstrated the key role of the amygdala in “emotional” memory (LeDoux et al., 1990). Animals, including humans, store emotional as well as cognitive information, and the storage of emotional information is critically important in both normal and abnormal regulation of anxiety. The “site” at which anxiety is perceived is the amygdala (Davis, 1992a). It is in these limbic areas that the patterns of neuronal activity associated with threat and mediated by the monoamine neurotransmitter systems of the reticular activating system—become an “fear.”

**Hippocampus:** This brain area is involved in the storage of various kinds of sensory information and is very sensitive to “stress” activation (Pavlides et al., 1993a; Phillips and LeDoux, 1992a; Sapolsky et al., 1984). The hippocampus appears to be critical in the storage and recall of cognitive and emotional memory (Selden et al., 1991). Any emotional state related to arousal or threat may alter hippocampal functioning, changing the efficiency and nature of hippocampal storage and retrieval. Threat alters the ability of the hippocampus and connected cortical areas to “store” certain types of cognitive information (e.g., verbal) but does not affect the storage of other types (e.g., nonverbal).

Hormonal signals affect heterogeneous corticosteroid nuclear receptors, i.e. type 1 (mineralocorticoid) or type 2 (glucocorticoid) in the hypothalamic-pituitary-adrenal (HPA) axis. Stressful life events such as isolation increase HPA axis activity (McEwen, 2001). The hippocampus, amygdala, and mPFC are limbic structures that are targets for and also modulate adrenal steroids. Glucocorticoids can result in neurotoxic damage to the hippocampus with suppression of neurogenesis (McEwen, 2001; Sapolsky, 2000). Exposure to stress results in release of corticotrophin releasing hormone (CRH), adrenocorticotropic hormone (ACTH), and cortisol via activation of the HPA axis. During periods of stress there is partial resistance to feedback inhibition of cortisol release and increase in plasma cortisol levels, in addition to a decrease in glucocorticoid receptors (Sapolsky and Plotsky, 1990). Glucocorticoid receptors are present in the brain in high density in areas relevant to stress and anxiety such as the hypothalamus, hippocampus, serotonergic and noradrenergic cell bodies on both neurons and glia. Based on animal studies, mineralocorticoid expression is high in limbic regions such as hippocampus, septum and amygdala (Reul and de Kloet, 1985; Veldhuis and De Kloet, 1982). Animal studies suggest that stress experienced during critical years of development can have long lasting effects on HPA axis. For instance, rats that experience in utero stress or early maternal deprivation have increased corticosterone concentrations when exposed to stress. Early postnatal stress is associated with changes in basal concentrations of hypothalamic CRH, mRNA, hippocampal glucocorticoid receptor mRNA, and median eminence CRH, in addition to the stress-induced CRH, corticosterone, and ACTH release (Levine et al., 1993a; Levine et al., 1993b; Stanton et al., 1988). Adults with PTSD and non-human primates with early adverse experiences have elevated CRH concentrations and decreased cortisol levels in the cerebrospinal fluid (Coplan et al., 1996). Finally a number of studies are indicating the crucial role of corticotrophin-releasing factor
(CRF) and the sensitivity of CRF receptors in mediating stress reactivity in humans (Kehne, 2007).

Cortex

The quality and intensity of any emotional response, including anxiety, are dependent on subjective interpretation or cognitive appraisal of the specific situation eliciting the response (Maunsell, 1995; Singer, 1995). Most theories addressing the etiology of anxiety disorders focus on the process by which stimuli are “mislabeled” as being “threat” related, thereby inducing a fear response and anxiety in situations where no true threat exists. How individuals “cortically interpret” the limbic-mediated activity (i.e., their internal state) associated with arousal plays a major role in their subjective sense of anxiety (Gorman et al., 1989). Klüver-Bucy syndrome, which results from damage to or surgical ablation of the temporal lobes, is characterized by absence of fear in response to current and previously threatening cues (Kluver and Bucy, 1937). The general disinhibition characteristic of this syndrome suggests loss of the capacity to interpret incoming threat-related cues from lower brain areas.

Heterogeneity of Adaptive Responses to Threat: Hyperarousal and Dissociation

Individual responses to threat can vary tremendously. This is not surprising considering the vast distribution of neural functions which are available to the stress-response network. This network involves the entire brain, and, indirectly, the whole body. This allows the response to potential threat to be appropriate and proportional to the need. The specific adapatative changes taken by the brain to respond to the incoming threat-related signals will vary depending upon many factors; different elements of the widely distributed neural system will be recruited and others will be shut down to conserve energy and focus the body’s response to threat. Under normal circumstances (i.e., a normal stress-response capability), the responses are graded, proportional to the level of perceived threat; when the threat is mild, a moderate activation of key systems takes place; when extreme, intense and prolonged activation will occur. Further, adaptive responses to threat are specific to the nature of the threat; either preparing to flee or fight or preparing to be overwhelmed and injured. In cases of abnormal development or sensitivity of the stress-response systems (see later sections) the responses to potential threat are inappropriate and out of proportion; trauma can make the system over-active and overly reactive.

Two major, inter-related response patterns – hyperarousal and dissociative - have been described (Perry et al., 1995). The hyperarousal response has been well characterized; it was originally described as the fight or flight response (Cannon, 1914). As described above, incoming signals activate the locus coeruleus and through a cascade of neural activation recruiting key limbic and cortical areas to focus on, and respond to, the threat. These neural and neuroendocrine activations prepare the body to fight or flee. Cortisol and adrenaline course through the body; heart rate increases, glycogen is mobilized from muscles; all distracting information is tuned out.

However, when fighting or fleeing is not possible, the brain will recruit a different set of neural systems and utilize avoidant, dissociative adaptations. Dissociation is basically a mental mechanism by which one withdraws attention from the outside world and focuses on
the inner world. Dissociation may involve a distorted sense of time, a detached feeling that you are “observing” something happen to you as if it is unreal, the sense that you may be watching a movie of your life. In extreme cases, especially if the trauma is repetitive and painful (e.g., sexual abuse), the child may withdraw into an elaborate fantasy world where she may assume special powers or strengths. Like the alarm response, this “defeat” or dissociative response is graded. The intensity of the dissociation varies with the intensity and duration of the traumatic event.

The neurobiology of dissociation is related but somewhat different from that of the hyperarousal response. Both utilize the monoamine systems in the brainstem and diencephalon; but somewhat different elements of these complex networks. In animals, the ‘defeat’ response has a distinct neurobiology which is similar to dissociation response in humans. Indeed, the neurobiology and phenomenology of dissociation appears to most approximate the ‘defeat’ reaction described in animals (Henry, Stephens, and Ely, 1986; Heinsbroek, van Haaren, Feenstra, and Boon, 1991; Miczek et al., 1990). As with the hyperarousal/fight or flight response, dissociation involves brainstem-mediated CNS activation which results in increases in circulating epinephrine and associated stress steroids (Glavin, 1985; Henry, Liu, Nadra, Qian, Mormede, Lemaire, Ely, and Hendley, 1993; Herman, Guillonneau, Dantzer, Scatton, Semerdjian-Rouquier, and Le Moal, 1982). A major CNS difference, however, is that, in dissociation, vagal tone increases dramatically, decreasing blood pressure and heart rate (occasionally resulting in fainting) despite increases in circulating epinephrine. In addition, there appears to be an increased relative importance of dopaminergic systems, primarily mesolimbic and mesocortical (Kalivas, 1985; Kalivas, Richardson-Carlson, and Van Orden, 1986; Kalivas, Duffy, Dilts and Abhold, 1988; Abercrombie, Keefe, DiFrischia, and Zigmond, 1989). These dopaminergic systems are intimately involved in the reward systems, affect modulation (e.g., cocaine-induced euphoria) and, in some cases, are co-localized with endogenous opioids mediating pain and other sensory processing. These opioid systems are clearly involved in altering perception of: painful stimuli, sense of time, place and reality. Indeed, most opiate agonists can induce dissociative responses. Of primary importance in mediating the freeze or surrender dissociative response are endogenous opioid systems (Abercrombie and Jacobs, 1988).

For most children and adults, however, the adaptive response to an acute trauma involves a mixture of hyperarousal and dissociation. During the actual trauma, a child will feel threatened and the arousal systems will activate. With increased threat, the child moves along the arousal continuum. At some point along this continuum, the dissociative response is activated. This results in the host of protective mental (e.g., decreases in the perception of anxiety and pain) and physiological responses (decreased heart rate) that characterize the dissociative response.

Whatever the adaptive response during a trauma, the key issue for subsequent psychopathology is how long these systems are activated. The longer and more intense the activation during the actual traumatic event (s), the more likely there will be molecular changes in the stress-response systems that lead to long-term functional changes. Trauma can cause alterations that lead to sensitized, dysfunctional neural networks; essentially the state of fear can become the persisting trait of anxiety. What were once adaptive neurobiological states can become, over time, maladaptive traits (Perry et al., 1995).

Trauma Alters Stress-Mediating Neural Networks
The clinical impact of traumatic stress on the developing child has been well documented. The simplest are the studies examining the development of obvious trauma-related psychopathology such as post-traumatic stress disorder (for review see; Perry, 1994; 2001b; Glaser, 2000; Teicher et al., 2002; DeBellis and Thomas, 2003; Bremner, 2003). The increased incidence of PTSD following trauma, the list of attenuating and exacerbating has been well documented. Table 1 summarizes the key factors which appear to be related to subsequent development of trauma-specific psychopathology.

Traumatic stress results in altered measures of brain function and in brain-mediated functioning in children. These include measures of hippocampal function, adrenergic receptor functioning, hippocampal and cortical structural development, cardiovascular functioning and emotional, social and behavioral functioning (Perry, 1998; Teicher et al., 1994; 1997; De Bellis et al., 1994; 1997; 1999a; 1999b, 1997; Scaer et al, 2001; Carrion et al., 2001; 2002a). Magnetic resonance imaging (MRI) has revealed reductions in hippocampus (Bremner et al., 1997; Stein et al., 1997; Bremner et al., 2003a), alterations in cerbellar vermis (Anderson, et al., 2002) and altered amygdala (Driessen et al., 2000; Schmahl et al., 2003) volumes as well as deficits in verbal declarative memory measured with neuropsychological testing among women who were sexually abused as children. Sexually abused girls demonstrate neuroendocrine abnormalities as adolescents (Putnam, 1998).

Functioning of monoamine systems in adults is influenced by developmental trauma (Perry, 1995; 2001a; 2001b). Further, developmental trauma appears to influence genetic expression of at least one potential genetic marker for depression. A study of a polymorphism for the promoter region of the serotonin transporter (5-HTT) gene found that childhood maltreatment increased the risk of depression in early adulthood for persons with the common “short” allele compared to persons with the long allele; the short allele is associated with lower transcriptional efficiency of the promoter (Caspi, 2003).

The most overwhelming evidence for the impact of developmental trauma on stress-related neural networks and their functioning comes from a retrospective epidemiological study of 17,000 adults. Over the last ten years the Adverse Childhood Experience (ACE) studies, have been reporting on increased risk of a host of emotional, social, behavioral and physical health problems following abuse and related traumatic experiences in childhood (Anda et al.1991; 2001; Dube et al., 2001a; 2001b; 2002a; 2002b; 2003a; 2003b; . These epidemiological findings converge with evidence from neurobiology about numerous effects of childhood stress on brain and physical systems (Glaser, 2000). These epidemiological studies examined the relationship between adverse childhood experiences including child abuse and a wide range of functioning in adult life. The findings are consistent with the view that developmental trauma impacts the stress-response systems, and, therefore, can have destructive impact on all of the neural systems and functions that are interconnected to this widely distributed network (see Fig. 1).

Among the ACE findings are a graded increase in risk (i.e., more abuse = more risk) for affective symptoms and panic attacks; for memory problems; for hallucinations; for poor anger control; for perpetrating partner violence; unhealthy sexual behavior (early intercourse, promiscuity, sexual dissatisfaction); suicide; substance abuse; alcohol use and abuse; smoking. In addition there is a significant increased risk for a range of physical health problems following child abuse. Risk for the major causes of death in adult life is increased following adverse childhood experiences (Felitti et al., 1998).
Taken together there is little doubt that developmental trauma alters key neural systems involved in mediating the stress response, and, thereby, results in a host of neuropsychiatric and related functional problems.

Summary

All of the major molecular processes involved in brain development can be impacted by abuse. With either neglect or trauma, the timing (the earlier in life the more impact), intensity, pattern and duration of the maltreatment can alter virtually every brain system and brain area. The result is that in any given child, the individual history of maltreatment results in a unique pattern of altered neural systems and resulting psychopathology. The result is that development maltreatment is the Great Impostor. Depending up the age, nature and pattern of maltreatment a child may develop symptoms that mimic dozens of traditional DSM-IV diagnoses from autism or ADHD or “learning disorder.” Further, developmental stressors may “express” underlying genetic vulnerabilities; a genetically-vulnerable child may develop a pathological phenotype while a hardier child may not.

This complexity poses a fundamental challenge to any attempts to create simple over-inclusive descriptive categories of psychopathology. Future classification of human psychopathology will need to incorporate a more neurodevelopmentally-informed perspective in order to accurately understand the mechanisms which underlie neuropsychiatric symptoms in a given child or adult. This more mechanism-focused classification would approximate the current model of diagnostic classification in other areas of medicine where there is a more direct connection between the disease process and the pathophysiology. The hope and the promise is that understanding the mechanisms underlying the psychopathology will lead to more effective interventions, and, ultimately, more important, changes in practice, programs and policy that will help prevent the development of abuse-related psychopathology.
Figure 1. Brain organization and monoamine systems: The human brain has a hierarchical organization. The multiple parallel systems in the brain are organized in various brain regions with the most simple in the brainstem and the most complex in the cortex. While somewhat simplified, it is clear that functional complexity correlates with the organizational complexity of the brain, with the most simple regulatory functions mediated by the lower less complex brainstem and the most complex functions - those functions that confer the most unique human properties - are in the cortex. The brainstem and diencephalic originating monoamine systems (DA: dopamine; NE: norepinephrine; 5-HT: serotonin) project up (and down) throughout the brain.
Fig. 2: Impact of neglect on brain development: These images illustrate the impact of neglect on the developing brain. The CT scan on the left is from a healthy three year old child with an average head size (50th percentile). The image on the right is from a three year old child following total global neglect during early childhood. The brain is significantly smaller than average and has abnormal development of cortical, limbic and midbrain structures.
Table 1. Risk and attenuating factors for the development of psychopathology following trauma.


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