CHAPTER 1

The Developing Brain and Neural Plasticity: Implications for Normality, Psychopathology, and Resilience

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In recent years, the criticality of undertaking collaborations between scientists from diverse disciplines has increasingly been noted in the literature (Cicchetti & Blender, 2004; Cicchetti & Dawson, 2002; Pellmar & Eisenberg, 2000; Rodier, 2002). Two fields of inquiry that epitomize the movement toward interdisciplinary approaches to the investigation of brain-behavior relations in normality and psychopathology are neuroscience and developmental psychopathology (Cacioppo, Berntson, Sheridan, & McClintock, 2000; Cicchetti & Cannon, 1999a, 1999b; Cicchetti & Posner, 2005; Cicchetti & Tucker, 1994b; Cicchetti & Walker, 2001, 2003; Cowan & Kandel, 2001).

Several authors (Albright, Jessell, Kandel, & Posner, 2000; Cowan, Harter, & Kandel, 2000; Kandel & Squire, 2000) have described the unprecedented growth and achievements in the fields of neuroanatomy, neurochemistry, and neurophysiology that have taken place over the past half century. Despite the successes of research in these discrete areas, the present-day excitement engendered by neurobiological research emanates from the integration of several previously independent disciplines into one interdisciplinary intellectual framework known as neuroscience (Albright et al., 2000; Cowan et al., 2000; Kandel & Squire, 2000).

Cowan and colleagues (2000) reviewed the historical roots, as well as the twentieth-century phases of growth, of neuroscience. In the latter part of the nineteenth and the early decades of the twentieth centuries, a number of landmark discoveries occurred, each of which made a significant contribution to one or another of the long-established disciplines of neuroanatomy or neurophysiology. However, Cowan et al. (2000) note that none of these discoveries transcended traditional disciplinary boundaries, the defining feature of the contemporary field of neuroscience.

Kandel and Squire (2000) concluded that the modern cellular science of the nervous system was based on two fundamental discoveries: the neuron doctrine and the ionic hypothesis. Wilhelm His's description of the axon as an outgrowth from the immature nerve cell was an important step toward the formulation of the neuron doctrine. Evidence revealing that there was a discontinuity from neuron to neuron emanated from four scientific areas—embryology, histology, physiology, and pathological anatomy. The demonstration by Spanish neuroscientist Ramon y Cajal (1959) that nerve fibers have terminal structures that contact with other nerve cells but do not fuse with them—that they are contiguous rather than continuous—provided critical support for neuronal development. Ramon y Cajal established the neuron doctrine after demonstrating that the brain was composed of discrete cells called neurons that were thought to serve as elementary signaling units. In Ramon y Cajal's time, investigations of neurogenesis were conducted in the field of histology. In contemporary neuroscience, the focus has been on the molecular and cellular mechanisms involved in neuronal development. The ionic hypothesis, proffered by Alan Hodgkin, Andrew Huxley, and Bernard Katz in the late 1940s, explained the resting and action potentials of nerve cells in terms of the movement of specific ions, thereby enabling the nervous system to be comprehended in terms of physiochemical principles common to all of cell biology (Kandel & Squire, 2000).

The 1950s and 1960s witnessed the integration of neuroanatomy, neuropharmacology, neurochemistry, and behavioral science into neuroscience (Cowan et al., 2000). In early 1978, the inaugural issue of the *Annual Review of Neuroscience* was published, heralding the next phase of a multidisciplinary approach to the nervous system: the emergence of molecular neuroscience, the application of recombinant DNA technology and molecular genetics to neurobiological problems, and the unification, within a common intellectual framework, of neuroscience with the rest of the biological sciences (Ciaranello et al., 1995; Lander & Weinberg, 2000).

The emergence of molecular neuroscience enabled the field of neuroscience to surmount the intellectual barricades that had separated the study of brain processes, couched firmly in neuroanatomy and electrophysiology, from the remainder of the biological sciences, based more in biochemistry and cellular and molecular biology (Alberts et al., 1994; Cowan et al., 2000; Kandel & Squire, 2000). Kandel and Squire (2000) concluded that the modern molecular era of developmental neuroscience began in 1956 when Levi-Montalceni and Cohen isolated nerve growth factor (NGF), the first peptide growth factor to be discovered in the nervous system. The third phase in the evolution of neuroscience as a discipline, cognitive neuroscience, occurred during the 1980s and was marked by its incorporation of the methods of cognitive psychology, thereby bringing together the investigation of mental activity with the biology of the brain (see Gazzaniga, 2004; Kandel & Squire, 2000; Nelson & Bloom, 1997; Posner & DiGirolamo, 2000).

Similar to the historical growth witnessed in neuroscience, Cicchetti (1990) described developmental psychopathology as a new discipline that is the product of an integration of various disciplines, including genetics, embryology, neuroscience, epidemiology, psychoanalysis, psychiatry, and psychology, the efforts of which had previously been separate and distinct. Multiple theoretical perspectives and diverse research strategies and findings have contributed to developmental psychopathology. In fact, contributions to this field have come from virtually every corner of the biological and social sciences (Cicchetti & Sroufe, 2000).

GOALS OF THIS CHAPTER

Because developmental psychopathology and neuroscience share fundamental principles, the connection between neuroscience and developmental psychopathology can provide a compelling framework to support the study of normal and abnormal neurobiological development. In this chapter, we examine neurobiological development in normal and illustrative high-risk conditions and mental disorders. Moreover, we review relevant findings on neural plasticity and their potential contributions to the understanding of psychopathology and adaptive functioning. Additionally, we discuss the neurobiological correlates of, and contributors to, resilient adaptation. Finally, we conclude with a discussion of future work that can advance knowledge and inform prevention and intervention efforts in this area.

PRINCIPLES OF DEVELOPMENTAL NEUROSCIENCE AND DEVELOPMENTAL PSYCHOPATHOLOGY

One of the central tenets of the discipline of developmental psychopathology—that the study of normality and pathology are mutually informative—also is embraced by developmental neuroscientists (see, e.g., Cicchetti, 1990; Goldman-Rakic, 1987; Johnson, 1998). Developmental psychopathologists and developmental neuroscientists both emphasize the importance of understanding normal developmental patterns so that we can begin to investigate the ways in which deviant development may eventuate (Cicchetti & Posner, 2005). In addition, a firm knowledge base of normative biological and psychological developmental processes is essential to establish operational criteria for resilient functioning in individuals who have experienced significant adversity (Luthar, Cicchetti, & Becker, 2000).

Moreover, scientists in these two fields have long argued that one can gain valuable information about an organism's normal functioning by studying its abnormal condition (Cicchetti, 1984, 1990; Luria, 1980; Sroufe, 1990). Furthermore, developmental psycholopathologists and neuroscientists both contend that the investigation of "experiments of nature" can affirm, challenge, and augment existing etiological theories of normal and abnormal developmental processes (Cicchetti, 2003; O'Connor, 2003).

Nearly half a century ago, the embryologist Paul Weiss enunciated a view that foreshadows present-day thinking on the importance of examining the interrelation between normal and abnormal development: "Pathology and developmental biology must be reintegrated so that our understanding of the 'abnormal' will become but an extension of our insight into the 'normal,' while . . . the study of the 'abnormal' will contribute to the deepening of that very insight. Their common problems should provide foci for common orientation, so that, as they advance in joint directions, their efforts may supplement and reinforce each other to mutual benefit" (Weiss, 1961, p. 50).

Scientists within the field of neuroscience have a long history of investigating pathological phenomena to elucidate the nature of normal developmental processes (see Cicchetti, 1990, for an illustrative review). Some contemporary exemplars from neuroscience regarding how the study of atypical conditions can enhance our understanding of basic normal developmental processes include: the investigation of human microcephaly to gain insight into normal neurogenesis (Woods, 2004); the conduct of molecular genetic studies of human brain malformations in order to aid in the discovery of molecules that regulate central nervous system neuronal migration (Ross & Walsh, 2001); and neuropsychological investigations that demonstrate distinctive developmental differences following early damage to diverse areas of the prefrontal cortex and that support the critical role that the prefrontal cortex plays in the ongoing maturation of socioemotional, cognitive, and moral development (Diamond, Prevor, Callender, & Druin, 1997; Eslinger, Flaherty-Craig, & Benton, 2004).

THE BRAIN AS A DYNAMIC, SELF-ORGANIZING DEVELOPMENTAL SYSTEM

In present-day neuroscience, information in the brain is viewed as being represented and processed by distributed groups of neurons that maintain a functional interconnection based on experiential demands rather than by a strictly predetermined scheme (Black & Greenough, 1992; Courchesne, Chisum, & Townsend, 1994; Johnson, 1998). Because levels of organization and processes are reciprocally interactive, it is difficult, if not impossible, to impute ultimate causation to one level of organization over another (Cicchetti & Cannon, 1999a; Thelen & Smith, 1998).

It has become increasingly clear that the investigation of developmental processes, typical and atypical, often necessitates the simultaneous examination of individuals utilizing a multiple-levels-of-analysis approach (Cicchetti & Blender, 2004; Cicchetti & Dawson, 2002; Cicchetti & Toth, 1991; Gottlieb, Wahlsten, & Lickliter, 1998; Pellmar & Eisenberg, 2000; Thelen & Smith, 1998). In keeping with the historical tradition of prior systematizers in the field (Engel, 1977; McHugh & Slavney, 1986), *explanatory pluralism* and *methodological pluralism* have been considered to be the most suitable approaches to comprehend the nature of mental disorder (Cacioppo et al., 2000; Cicchetti & Dawson, 2002; Ghaemi, 2003; Kendler, 2005; Richters, 1997). Neuroscientists increasingly have shifted their emphasis from investigating molecules, membranes, and single neurons and tracts to examining complex neural systems (Edelman, 1987; Kandel, 1998; Thelen & Smith, 1998). In these more contemporary theoretical conceptualizations of brain-behavior relations, the brain is viewed as operating in a plastic and dynamic, self-organizing fashion, and as being less constrained by predetermined "localized" boundaries than previously thought (Cicchetti & Tucker, 1994a; Finger, 1994).

The viewpoint that the nervous system is dynamic is not exclusively a product of modern neuroscientific principles.

For example, in *The Brain of the Tiger Salamander,* C. J. Herrick (1948) restated the point that he had made in several prior publications spanning from 1908 through 1933—namely, that in all phylogenetic investigations of morphogenesis, it is important to keep in mind the conservative factor of stable genetic organization and the more labile influence of the functional requirements. Herrick (1948) contended that any morphology that overlooked the dynamic factors of tissue differentiation in terms of physiological adaptiveness lacks something and is sterile.

Systems theory approaches have historical roots in the investigations of a number of eminent developmental psychobiologists whose work occurred in the 1930s through the 1960s (see, e.g., Kuo, 1967; Lehrman, 1953; Schneirla, 1957). In contemporary developmental psychobiology, the system viewpoint is represented most elegantly in the writings of Gilbert Gottlieb (1983, 1992; Gottlieb et al., 1998).

SELF-ORGANIZATION

One of the main principles of systems theory (von Bertalanffy, 1968) is that organisms exist in a state of disequilibrium (i.e., dynamic stability) and participate in and seek out stimulation, thereby playing an active role in the construction of their own development. Thus, organisms are capable of *self-organization*—a reorganization that alters a system in an adaptive fashion when it is subjected to new constraints.

Similarly, several historically prominent developmental theorists maintain that disequilibrium enables individuals to exhibit change and flexibility throughout ontogenesis (Piaget, 1971; Werner, 1957). Such nonequilibrated systems assume a number of special properties including the ability to self-organize into patterns and nonlinearity or sensitivity to initial conditions (Prigogine, 1978). Cicchetti and Tucker (1994a) suggested that the concept of self-organization might serve as one of the mechanisms whereby individuals function in a resilient fashion despite experiencing great adversity. Furthermore, Cicchetti and Tucker (1994a) conjectured that self-organization might be a mediator of neural plasticity throughout the life course.

In self-organizing brain development, some regions of the brain serve to stabilize and organize information for other areas, whereas other regions utilize experience to fine-tune their anatomy for optimal function (Singer, 1995). In this manner, individuals can use the interaction of genetic constraints and environmental information to self-organize their highly complex neural systems. Accordingly, each individual may follow a potentially unique and partly self-determined developmental pathway of brain building.

Fundamental mechanisms of self-regulation are provided by brainstem neuromodulatory projection systems (Cicchetti & Tucker, 1994a). With widespread projections to cortical and subcortical targets, the neuromodulator systems serve as focal control points for regulating neural activity. By directing neural activity, it is expected that the neuromodular systems of the developing brain direct the activity-dependent pruning of the synaptic architecture. Each neuromodular system appears to tune neural and behavioral activity in a specific way and this specificity of effect may have direct implications for the control of neural plasticity.

THE DEVELOPING BRAIN

Wilhelm His was perhaps the preeminent contributor to research on the histogenesis of the central and peripheral nervous systems in the nineteenth century. His's discoveries included finding that changes in the shape of cells were involved in the folding of tissues, such as the neural plate. His also discovered the neural crest and the origin of the peripheral nervous system, and demonstrated that cranial and spinal ganglia are formed by cells that migrate from the neural crest (Jacobson, 1991). Moreover, His found that nerve cells originate by mitosis of stem cells near the ventricle of the neural tube rather than in the cerebral cortex itself (Jacobson, 1991). Furthermore, the concept of cell migration in the vertebrate central and peripheral nervous systems was discovered by His, initially through his observations on the origins of the peripheral nervous system from the neural crest and subsequently by his discovery that neuroblasts migrate individually from the ventricular germinal zone to the overlying mantle layer of the neural tube (Jacobson, 1991).

In 1904, His published a monograph in which he summarized more than 3 decades of his experimental work on the development of the embryonic nervous system of humans. In this monograph, he delineated the basic principles of neurogenesis for vertebrates in general. His's ideas provide the framework for the vast majority of subsequent studies of the nervous system (Sidman & Rakic, 1982). The virtual identity of the neural plate and the neural tube in all vertebrates provided suggestive evidence for the operation of very similar mechanisms in central nervous system development throughout phylogenesis.

In subsequent years, important contributions have been made by a number of investigative teams that elucidated the extraordinary diversity, organizational complexity, and precision of connections between cells in the nervous system of both vertebrates and invertebrates. Among these

most prominent historical contributions to the early understanding of neural development were those of Ramon y Cajal in Madrid, Hochstetter in Vienna, and scientists at the Moscow Brain Institute (1935–1965) and the Carnegie Institute in Baltimore (1942–1962; see review in Sidman & Rakic, 1982).

Cowan (1979) concluded that in the development of any part of the brain, eight major stages can be identified: (1) the induction of the neural plate; (2) the localized proliferation of cells in different regions; (3) the migration of cells from the region in which they are generated to the places where they ultimately reside; (4) the aggregation of cells to form identifiable parts of the brain; (5) the differentiation (expression) of the immature neurons; (6) the formation of axonal pathways and synaptic connections with other neurons and the onset of physiological function; (7) the selective death of certain cells; and (8) the elimination of some of the connections that were initially formed and the stabilization of others. As Steingard and Coyle (1998) noted, these stages proceed in a stepwise fashion following a genetically encoded plan that is influenced by environmental events. Specifically, within each of these phases there are parallel processes of metabolic differentiation and maturation. Genes that take their regulatory cues from the immediate neurochemical (and experiential) environment regulate the onset and offset of each stage.

Moreover, each stage of brain development is dependent on the successful completion of the preceding stages. Alterations in these processes can eventuate in aberrant neural development, connectivity, or function (Rakic, 1996; Steingard & Coyle, 1998). In general, early disruption in the neurodevelopmental process is associated with a greater and more diffuse pathology (Nelson, 2000a; Volpe, 1995), while later disruptions in this process are associated with less severe pathology and more discrete neurological lesions (Steingard & Coyle, 1998). For example, if neuronal migration is disrupted, then abnormalities in cell position result. When this occurs, the neurons are said to be ectopic or heterotopic (Nowakowski, 1987). Likewise, delaying, extending, shortening, or blocking either the *progressive* (e.g., synaptogenesis and neuronal maturation) or *regressive* (e.g., cell death and synaptic pruning) events in the neurodevelopmental process exerts varying effects on structure-function relations, genetic regulatory processes, and on the emergence of later neurodevelopmental events that are dependent on earlier events (Keshavan & Hogarty, 1999; Nowakowski, 1987; Nowakowski & Hayes, 1999; Steingard & Coyle, 1998).

In 1939, Conel suggested that most cortical neurons in the human cerebrum were generated prenatally. More sophisticated marking of cells has enabled neuroscientists to permanently date DNA cell replication and thereby provide direct evidence and precise time of neuron data on the origin and termination of corticogenesis in primates (Johnson, 1997; Rakic, 1996, 2002a, 2002b). By utilizing the same marking of DNA replication technique in humans, we now know that humans develop their full complement of neurons mainly during the 4th, 5th, and 6th prenatal months (Rakic, 1981). The onset of corticogenesis in humans is approximately at 6 prenatal weeks (Rakic, 1996). Through a more sophisticated autoradiographic analysis, Sidman and Rakic (1982) confirmed His's earlier discovery that all neurons destined for the neocortex were produced in the proliferative zone near the cerebral ventricle.

In the proliferative zone, precursor cells divide asynchronously; their nuclei move from the ventricular surface to synthesize DNA and then return to the surface to undergo another mitotic cycle (Rakic, 1996). There are two proliferative sites: (1) the ventricular zone, which contributes to cell proliferation and division in phylogenetically older brain structures and (2) the subventricular zone, which contributes to cell proliferation and division in more recently evolved brain structures, such as the neocortex. These two proliferative zones generate separate glial and neuron cell lines and give rise to different forms of migration, the process whereby neuronal cell bodies are displaced from their last cell division in the proliferative zone to their final destination in the mature brain (Johnson, 1997; Rakic, 1988a, 1988b).

In 1874, His inferred the phenomenon of neuronal cell migration by analyzing the fixed brains of human embryos; however, more sophisticated autoradiographic techniques have led to the discovery of the underlying cellular and molecular mechanisms of migration (Hatten, 1999; Price & Willshaw, 2000; Sidman & Rakic, 1982). There are two types of cell migration: tangential and radial. In *tangential migration,* once cells are generated they are passively displaced and pushed further away from the proliferative zone by more recently born cells in a so-called "outside-in" gradient. This tangential form of migration occurs at later developmental stages of the prenatal brain and gives rise to brain structures, such as the thalamus, dentate gyrus of the hippocampus, and many regions of the brain stem. In contrast, in *radial migration,* the most recently born cell actively moves beyond previously generated cells to create an "inside-out" gradient. This radial form of migration is visible during early stages of prenatal brain development and is found in the cerebral cortex and in some subcortical areas that have a laminar (layered) structure.

The area-specific features in the human adult neocortex are not evident in the immature cortical plate; rather, they emerge gradually over ontogenesis (Rakic, 1988b). The cells of the neocortex are not committed to differentiate the area-specific architectural and connectional features that distinguish neocortical areas in the adult at the time the neocortical plate is assembled during embryogenesis (Nowakowski, 1987; Sidman & Rakic, 1982; Steingard & Coyle, 1998). There are two primary models of cortical area differentiation that have been put forward in the literature (Johnson, 1997). Rakic (1988a, 1988b) has proposed the *protomap* hypothesis, a model whereby future cytoarchitectonic areas are thought to be genetically specified in the neuroepithelium and recapitulated in the developing cortical plate by a point-to-point migration along a radial glial scaffolding. In this "radial unit hypothesis," Rakic (1988a, 1988b) contends that the neuroepithelium is genetically programmed to generate area-specific cohorts of cortical plate neurons and that the relative positions and sizes of areas of the cerebral cortex are prespecified. Rakic's protomap hypothesis applies the same mechanisms of development to areas throughout the cerebral cortex (Johnson, 1997; O'Leary, 1989). Although the programmed emergence of discrete, cytoarchitectonic areas requires an interaction with thalamocortical afferents, the capacity of developing cortical plate neurons to differentiate features normally associated with other areas is conceived as being restricted by their commitment to specific area plates.

A contrasting viewpoint of cortical area differentiation, the *protocortex* model, has been proposed by O'Leary (1989; see also Johnson, 1997, 1998). The protocortex model emphasizes the role of epigenetic influences and applies only to the development of neocortical areas. According to the protocortex model, the neocortical epithelium is not genetically programmed to generate cortical plate cells that are committed to a particular areal fate. Rather, it is hypothesized that the neurons of the neocortical plate have the potential to develop the range of features associated with diverse neocortical areas. The differentiation of the neurons into area-specific connections and architecture requires inputs from thalamic (experiential) afferents to each region (Johnson, 1997; O'Leary, 1989).

In sum, despite their differing emphases, both the protomap and protocortex models recognize contributions from genetic and epigenetic mechanisms in the differentiation of neocortical areas as well as a vital role for thalamocortical afferents in this process. Original to the protocortex model (O'Leary, 1989) is the fact that molecular differences are thought to exist throughout the neocortex and contribute to the process of areal differentiation. Numerous investigations suggest that afferent inputs, especially thalamocortical afferents, have a fundamental role in regulating the differentiation of area-specific features (see Johnson, 1997). Thus, from the viewpoint of the protocortex model, normal cortical development is believed to enable a considerable amount of cortical plasticity. Cortical regions are capable of supporting a number of different types of representations depending on the nature of their input (Johnson, 1999).

Rakic (1996) discussed that, in the neocortex of the rhesus monkey, synaptogenesis and synapse elimination occur simultaneously and at an equal rate in all cortical regions (see also Goldman-Rakic, Bourgeois, & Rakic, 1997). Conversely, because there are known regional differences in neurobiological development, including timing of maximum brain growth, dendritic arborizations, and myelination of cortical afferents and efferents (Huttenlocher & Dabholkar, 1997; Thompson & Nelson, 2001), it is not surprising that concurrent synaptogenesis does not occur in humans. The prefrontal cortex is the last region to develop (Huttenlocher, 1994, 2002). Thus, competition between and correlated activity within neural networks drives the selective stabilization of some neural connections at the expense of others and leads to the normal parcellation of neural systems into specific structural and functional units (Courchesne et al., 1994).

The normal brain develops from a network of few elements, infrequent interactions among elements, less stability, and less structural and functional differentiation, to one of additional elements, more intricate interactions among elements, greater stability, and increased structural and functional parcellation and specialization (see, e.g., J. W. Brown, 1994; Cicchetti & Tucker, 1994a; Courchesne et al., 1994). In Chapter 3, this *Handbook,* this volume, magnetic resonance imaging studies are reviewed to present a picture of normal and abnormal brain structural development over time.

EXPERIENCE AND BRAIN DEVELOPMENT

One outgrowth of systems theorizing has been a growing acceptance of the viewpoint that neurobiological development and experience are mutually influencing (Cicchetti & Tucker, 1994a; Eisenberg, 1995; Kandel, 1998; Nelson & Bloom, 1997). For example, it has been demonstrated that, just as gene expression alters social behavior (Young, Nilson, Waymore, MacGregor, & Insel, 1999), so, too, do social experiences exert actions on the brain by feeding back on it to modify gene expression and brain structure, function, and organization (Francis, Diorio, Liu, & Meaney,

1999; Kandel, 1998). Relatedly, changes in the brain may directly exert effects on mental functioning. Conversely, alterations in mental processing can causally affect brain functioning (Bolton & Hill, 1996; Edelman, 2004).

The concept that experience can modify brain structure can be traced back at least to the writings of Cajal (see Cajal, 1913/1959), who, despite his belief that the connections that occurred between neurons unfolded according to a definite plan (i.e., the principle of connection specificity), asserted that the strength and effectiveness of these neuronal connections were not predetermined and that they could be altered by experience (Kandel & Squire, 2000). Likewise, D. O. Hebb (1949) believed that experience could alter brain structure and function and made this viewpoint a central feature of his neuropsychological theory (see Posner & Rothbart, 2004).

In current perspectives, experience is broadly construed to include not only external social and psychological events but also, for example, internal events, such as the effects of psychopathology, trauma, abuse, or injury; the actions of hormones; and the consequences of development and aging (Boyce et al., 1998; Cicchetti & Walker, 2003). For example, an investigation revealed that early life experiences could affect neurogenesis in adulthood. Mirescu, Peters, and Gould (2004) demonstrated that early adversity affects the regulation of adult neurogenesis in the hippocampus. Specifically, rats who experienced maternal deprivation when they were pups did not display the normal decrease in cell proliferatin and immature neuron production in the dentate gyrus. This finding was observed despite the fact that these rats had normal hypothalamic-pituitary-adrenal (HPA) axis activation. These results provide suggestive evidence that early adverse experience inhibits structural plasticity via a hypersensitivity to glucocorticoids and impairs the ability of the hippocampus to respond adaptively to stress that occurs in adulthood. Research with humans has similarly demonstrated that adverse early experiences may lead to the development of abnormal brain structures and functioning and sensitize developing neural networks to stressful experiences (Gunnar, 2000). Work with Romanian orphans and with children who have been abused or neglected early in life also has revealed anomalies in their brain structure and functioning (Cicchetti & Curtis, in press; Cicchetti & Rogosch, 2001a, 2001b; DeBellis, 2001; Gunnar, Morison, Chisholm, & Schuder, 2001; S. W. Parker & Nelson, 2005b; Pollak, Cicchetti, Klorman, & Brumaghim, 1997). Furthermore, it has been shown that alterations in gene expression induced by learning and by social and psychological experiences produce changes in patterns of neuronal and synaptic connections and, thus, in the function of nerve cells (Kandel, 1998, 1999; Post, Weiss, & Leverich, 1994). Such neuronal and synaptic modifications not only exert a prominent role in initiating and maintaining the behavioral changes that are provoked by experience but also contribute to the biological bases of individuality, as well as to individuals being differentially affected by similar experiences, regardless of their positive or negative/adverse valence (Cicchetti & Rogosch, 1996; Depue & Collins, 1999; Kandel, 1998).

Mechanisms of Neural Plasticity

Although brain development is guided and controlled to some extent by genetic information (Rakic, 1988a, 1998), a not insignificant portion of brain structuration and neural patterning is thought to occur through interaction of the child with the environment (Greenough, Black, & Wallace, 1987; Nelson, 1999; O'Leary, 1989). As eloquently expressed by Torsten Weisel (1994): "genes controlling embryonic development shape the structure of the infant brain; the infant's experience in the world fine tunes the pattern of neuronal connections underlying the brain's function. Such fine-tuning . . . must surely continue through adulthood" (p. 1647). Relatedly, Nelson (1999) asserted that the fine-tuning of the biological and behavioral systems that occurs beyond the early years of life is more subtle and protracted than that which is manifested in infancy. Moreover, Nelson (1999) stated that the "dramatic changes that occur in the brain long after the child's second or third birthday are in large measure brought about by the experiences the child has with his or her environment" (p. 237).

Recognizing that mechanisms of plasticity are integral to the very anatomical structure of cortical tissue, and that they cause the formation of the brain to be an extended malleable process, neuroscientists and developmental psychopathologists are presented with new avenues for understanding the vulnerability and protective aspects of the brain as contributors to the genesis and epigenesis of psychopathology and resilience (Cicchetti & Tucker, 1994a). Because the mechanisms of neural plasticity cause the brain's anatomical differentiation to be dependent on stimulation from the environment, it is now clear that the cytoarchitecture of the cerebral cortex also is shaped by input from the social environment. Since the human cerebral cortex is only diffusely structured by a genetic plan, and since the eventual differentiation of the cortex is highly reactive to the individual's active coping and "meaning making" in a particular environment, it is very likely that both abnormal and resilient outcomes following the experience of significant adversity would encompass a

diverse range of neural, synaptic, and associative networks that are the physiological underpinnings of many possible individual psychological organizations (cf. Cicchetti & Tucker, 1994a; Curtis & Cicchetti, 2003). As Luu and Tucker (1996) have articulated: "To understand neuropsychological development is to confront the fact that the brain is mutable, such that its structural organization reflects the history of the organism. Moreover, this structure reflects both what is most important to the organism and what the organism is capable of at that particular time" (p. 297). Cortical development and organization should no longer be viewed as passive processes that solely depend upon genetics and environmental input. Rather, corticogenesis and organization should be conceived as processes of self-organization guided by self-regulatory mechanisms (Cicchetti & Tucker, 1994a).

Black, Jones, Nelson, and Greenough (1998) have described brain development as a complex scaffolding of three types of neural processes: gene driven, experience expectant, and experience dependent. Black et al. (1998) conceptualized *gene-driven processes* as being largely insensitive to experience. Gene-driven processes serve to guide the migration of neurons, to target many of their synaptic connections, and to determine their differentiated functions. To protect the development of the brain, much of the basic organization of most nervous systems is thought to be relatively impervious to experience. The recalcitrance to environmental influences during embryonic development was termed *canalization* by Waddington (1966). Black and colleagues (1998) note that this canalization process can be either helpful (e.g., the minimization of experiential effects on embryogenesis can aid survival) or harmful (e.g., in cases of genetic diseases, prenatal brain development proceeds along a maladaptive pathway that is largely resistant to any therapeutic interventions).

Experience-expectant processes correspond roughly to critical or "sensitive" periods and take place in early age-locked sensory system development (Greenough & Black, 1992; Greenough et al., 1987). During experience-expectant periods, the brain is primed to receive particular classes of information from the environment. The brain builds an overabundance of synapses that are then pruned back by experience to a selectively retained subset (Huttenlocher, 1990; Huttenlocher & Dabholkar, 1997). The pruning of synapses appears to be initiated by competitive interactions between neuronal connections such that inactive neural connections are eliminated and synapses that are most actively mediated by experience are selectively maintained (Greenough et al., 1987). In human embryology, the pruning process applies to neurons, whereas postnatally it applies predominantly to synapses (Edelman, 1987). In the absence of behavioral and neural activity, cells do not die and circuits do not become pruned in an adaptive way that aids the organism in adapting to the demands of its environment.

Experience-expectant neural plasticity is usually embedded in a developmental program and requires appropriate timing and quality of the information stored for brain development to be normal. Abnormal experience or deprivation during experience-expectant development may exert enduring deleterious effects on brain and behavioral epigenesis (Black et al., 1998). Experience-expectant neural plasticity varies widely across brain systems, eventuating in highly specialized alterations that occur as a function of the timing and nature of the modified experience and the brain systems involved (Bavelier & Neville, 2002). Variations in experience-expectant neural plasticity take place as a function of a number of existing factors, including: (1) differences in the temporal expression of receptors that are necessary for synaptic plasticity; (2) differences in the molecular factors that control the development of various neural pathways; and (3) differences in the degrees of exuberant or redundant early connectivity (Bavelier & Neville, 2002).

In later development, synaptogenesis seems to be generated in response to events that provide information to be encoded in the nervous system. This *experience-dependent* synapse formation involves the brain's adaptation to information that is unique to the individual (Greenough & Black, 1992; Greenough et al., 1987). Because all individuals encounter distinctive environments, each brain is modified in a singular fashion. Experience-dependent synaptogenesis is localized to the brain regions involved in processing information arising from the event experienced by the individual. Unlike the case with experience-expectant processes, experience-dependent processes do not take place within a stringent temporal interval because the timing or nature of experience that the individual engages or chooses cannot be entirely and dependably envisioned. An important central mechanism for experience-dependent development is the formation of new neural connections in contrast to the overproduction and pruning back of synapses often associated with experience-expectant processes (Greenough et al., 1987). Because experience-dependent processes can occur throughout the life span, social interactions, psychotherapy, and pharmacotherapy have the capacity to exert a palliative influence on brains that are afflicted with disorders (Black et al., 1998; Cicchetti, 1996; Cicchetti &

Posner, 2005; Cicchetti & Sroufe, 2000; Cicchetti & Walker, 2001; Goldapple et al., 2004; Mayberg, 2003).

Neural Plasticity: Historical Aspect

In the denouement to his treatise entitled *Degeneration and Regeneration of the Nervous System,* Cajal declared: "Once development is completed, the sources of growth and regeneration are irrevocably lost. In the adult brain, nervous pathways are fixed and immutable; everything may die, nothing may be regenerated" (Cajal 1913/1959, p. 750).

After over a decade of innovative and meticulous research in which he investigated whether the brain was capable of regeneration in animals with injuries to the spinal cord, the cerebellum, or the cerebral cortex, Cajal proclaimed that "the vast majority of regenerative processes described in man are ephemeral, abortive, and incapable of completely and definitely repairing the damaged pathways" (Cajal, 1913/1959, p. 750). Since Cajal's early work, it has been known that there is some axonal regeneration subsequent to spinal cord injury; however, in the experimental conditions that Cajal designed, regeneration was limited and, therefore, not believed to have any functional significance (Stein & Dawson, 1980). Cajal's assertions served as the prevailing dogma for a large portion of the twentieth century. The widespread belief put forward by neuroscientists was that because no new neuron generation was deemed possible, rewiring of existing connections, dendritic branching, and elimination of synaptic connections were the only ways whereby neural plasticity could occur.

It was not until the 1970s that regenerative capacity was demonstrated in the adult mammalian brain. Two types of growth were found to occur in response to nerve injury (Stein & Dawson, 1980). The first is *regenerative sprouting,* a process whereby when the axons of cells are cut and the distal portion begins to degenerate, the remaining stump, including the cell body, begins to form growth cones and regenerate new terminals. In the second, known as *collateral symmetry,* a number of cells innervating a given structure are destroyed and their terminals degenerate. However, the remaining intact cells begin to grow additional new terminals (sprouting) that innervate the target area evacuated by the damaged neurons. As such, the degenerated inputs are replaced by terminals arriving from intact neurons.

In 1975, the eminent neuropsychologist Hans-Lucas Teuber declared that if one is going to have brain damage, then it would be preferable to have it early rather than late in life. Teuber based his conclusion on the findings of Margaret Kennard's experiments on the long-term effects of brain damage in monkeys of different ages. Kennard (1938) discovered that damage to the adult nervous system resulted in more deleterious and less reversible effects than similar brain damage inflicted during early development. The field's acceptance of the so-called "Kennard principle" led to the belief that little reorganization of function could occur after injury to the mature mammalian nervous system and that most structure-function relations were permanently established during the early years of life. In fact, Teuber's (1975) own studies with humans revealed that improvement in traumatic head injury cases was substantially greater when the brain damage had taken place in an early developmental period. However, scientists in the field had differing interpretations of Teuber's belief that brain damage that occurred later in development would exert more disruptive effects than damage originated earlier in life. Critics noted that the results of the experimental data of Teuber and his contemporaries in the field could be interpreted to indicate that the maturational status of the nervous system at the time of injury must be considered in any explanation of recovery or sparing of function after early brain damage (Stein & Dawson, 1980). Commentators on the aforementioned body of work reasoned that if subjects were tested at a time when the substrate for a particular function had not yet developed, then the function would appear to have been compensated when, in fact, it had never been lost (Isaacson, 1975). Depending on the location of the lesion and the precise timing of the injury, the developing brain can suffer from far more neuronal degeneration than that evidenced in the mature brain. For example, excessive amounts of excitatory amino acids, such as glutamate, produce much more severe lesions in the immature brain than in the adult brain. Thus, there are a number of instances in which early brain damage can be viewed as more disastrous than later brain damage because early lesions often result in the formation of anomalous circuitry and neural pathways as well as reduction in brain size (Black et al., 1998; Isaacson, 1975; Steingard & Coyle, 1998).

Kolb, Forgie, Gibb, Gorny, and Rowntree (1998), in their programmatic enrichment studies on brain plasticity and behavior in rats after brain injury, found that enriched experience could have varying effects upon the brain at different ages. They reported discovering compensatory changes in brain plasticity following brain injury that are similar in kind to those observed when animals learn from experience. Kolb and colleagues (1998) found that experience alters the synaptic organization of the cortex and that these changes in synaptic organization are associated with behavioral changes. The similarity between plastic changes

in the brain in response either to injury or to experience suggests that it is conceivable that there may be basic mechanisms of synaptic change in the mammalian cortex that are used in many forms of neural plasticity (see also Kolb, 1995).

Accordingly, it appears that there are not any simple rules that govern whether neural plasticity occurs following lesions in early life. Most of the early neuropsychological models of the effects of brain lesions were based on work with patients, were predominantly focused on brain localization, and were couched within unidirectional models of causality (i.e., brain lesions were believed to affect behavior, but not vice versa). These early models did not take into account the dynamic interplay that occurs among brain regions and the bidirectional impact that brain and behavior exert upon each other. Modern-day research, conducted predominantly, but not exclusively, with animals, provides suggestive evidence that the mammalian central nervous system possesses much greater potential for producing new neurons and repairing damaged areas than has heretofore been thought (Cicchetti & Tucker, 1994a, 1994b; Curtis & Cicchetti, 2003).

In the developing organism, studies conducted with a variety of species also have revealed that positive or negative early life experiences can modify both brain structure and function. For example, Sur and colleagues (Sur, Garraghty, & Roe, 1988; Sur, Pallas, & Roe, 1990) trained adult ferrets, who had one hemisphere rewired at birth, to discriminate between auditory and visual stimuli that were presented to the normal hemisphere. The results of these experiments provide support for the functional equipotentiality of cortical mapping. Specifically, the findings in the Sur, Garraghty, et al. (1988) and Sur, Pallas, et al. (1990) investigations demonstrate that it is possible to rewire sensory inputs to the thalamus such that processing of auditory stimuli takes place in the primary visual cortex and vice-versa; that is, the cortical field that usually mediates vision could attain a functional organization capable of processing sound, and the cortical field that usually mediates audition could attain a functional organization capable of processing sight.

Sur and colleagues (Sharma, Angelucci, & Sur, 2000) also have demonstrated that, in ferrets whose retinal projections were routed into their auditory pathway, visually responsive neurons in the "rewired" auditory cortex, just as is the case with neurons in the primary visual cortex, were characterized by orientation modules—groups of cells that share a preferred stimulus orientation. Although the orientation tuning of neurons within the "rewired" auditory cortex was comparable to the tuning of cells in the primary visual cortex, the orientation map was less orderly. Thus, the findings of this investigation reveal that sensory afferent activity profoundly influences diverse components of cortical circuitry.

Finally, the long-held assumption that neural reorganization following injury was restricted to the period of infancy, with only modest neural reorganization possible in the child and adult, has been challenged through research with humans. Results from a number of investigations suggest that reorganization of cortical pathways can occur in the brains of older children and adults (see, e.g., Merzenich, 1998; Merzenich et al., 1996; Tallal et al., 1996). Although the majority of these neural changes to date have been demonstrated in work on sensory or motor pathways (see, e.g., Aglioti, Bonazzi, & Cortese's, 1994, work on phantom lower limb as a perceptual marker of neural plasticity), existing research provides suggestive evidence that cognitive systems (i.e., language) can reorganize beyond infancy (see, e.g., Merzenich et al., 1996; Tallal et al., 1996; also see discussions in Johnson, 1999). Thus, it is becoming quite clear that under certain conditions at least some regions of the brain can incorporate the signature of experience into the structure, function, and organization of the brain.

The process of neural plasticity is influenced by a number of neurotransmitters and growth factors. These growth factors, including nerve growth factor and brain-derived neurotrophic factor, stimulate a variety of cellular effects at the structural and functional levels that eventuate in the promotion of survival and differentiation of responsive neurons. Adaptive alterations in neuroarchitecture may occur throughout life as new synapses form, old ones disintegrate, and new neurite outgrowth occurs. The discovery of brain behavioral plasticity can make important contributions to the understanding of development through demonstrating that neural representations are dynamic processes. Moreover, experimental results that provide evidence of plasticity can give critical insights into the actual processes through which neurobiological development occurs.

Recovery of function following brain injury can be characterized as a maturational process in which the brain is thought to cause the formation of new structures via specialized mechanisms that were triggered by the injury (i.e., *causal epigenesis;* see Johnson, 1999). This viewpoint involves the restriction of fate—that is, biological tissue that initially had many possibilities for subsequent specialization throughout development is reduced to a subset of these possibilities by the injury. In contrast, according to Gottlieb's (1992) *probabilistic epigenesis* framework, brain plasticity may be conceived as a fundamental and inherent

property of the developing brain. From this viewpoint, plasticity is conceptualized as allowing the neural system to retain a number of options for specialization even after brain injury. This process is influenced by neural activity rather than by molecular markers. In humans, neurobiological development is a more prolonged process than in animals, extending well into postnatal life (Nelson & Bosquet, 2000; Spear, 2000; Thompson & Nelson, 2001). Critical aspects of neurobiological development occur after middle childhood (Dahl, 2004; Giedd, 2004; Spear, 2000). Therefore, some degree of functional specialization in the cerebral cortex is likely to be influenced by the child's interaction with the postnatal environment (Johnson, 1999; Johnson et al., 2005). The extremely long juvenile period (neotony) in humans may have evolved, in part, for the primary purpose of shifting cortical specification from genetic to epigenetic control (Cicchetti & Tucker, 1994a).

During the past several decades, scientific research has begun to reveal that, within certain limits, forms of neural plasticity may take place throughout epigenesis and are not limited to early development (Cicchetti & Tucker, 1994b; Hann, Huffman, Lederhendler, & Meinecke, 1998; Kandel & Squire, 2000). The cortex, in fact, appears to be capable of organizational changes throughout the life course of the organism (Cicchetti & Tucker, 1994a; Jacobs, van Praag, & Gage, 2000). For example, Thatcher's (1992, 1994, 1997) work on the development of electroencephalogram (EEG) coherence in humans suggests that cortical organization proceeds in stages that are repeated cyclically over development. Each stage of cortical organization reflects the ongoing and dynamic shaping of cortical circuitry throughout an individual's life span. These periods of EEG coherence are thought to represent rapid synaptic growth within functionally differentiated neural systems. Neural plasticity involves the genetically driven overproduction of synapses and the environmentally driven maintenance and pruning of synaptic connections.

Neuroscientists conceive plasticity as being reflective of anatomic, chemical, or metabolic changes in the brain. Nelson (2000b) stated that neuroanatomic changes illustrate the ability of existing synapses to alter their activity through sprouting new axons, regenerating old ones, or by elaborating their dendritic surfaces. Thus, for example, loss of fibers in an area of the cortex (e.g., the corpus callosum) may eventuate in a reduction of synapses in the affected area that is subsequently compensated for by an influx of thalamic synapses into the vacated space that reestablishes communication between the hemispheres. Nelson (2000b) also defined neurochemical plasticity as the ability of synapses to alter their activity through augmenting the synthesis of neurotransmitters or enhancing the response of the postsynaptic receptor to the neurotransmitter. Additionally, Nelson (2000b) delineated fluctuations in cortical and subcortical metabolic activity, for example, at the site of an injury, as another possible sign of neural plasticity.

In most mammalian brain regions, neuronal birth and migration take place during a discrete period of prenatal development, followed several days later by cell death (Rakic, 1988a, 1996, 1998). In contrast, the granule cells of the dentate gyrus in the hippocampus, olfactory bulb, and cerebellum are generated predominantly during the postnatal period (Gould & Cameron, 1996). In addition, stem cells that reside in specialized niches in the brain of adult mammals continuously generate new neurons. The neurons in mammalian brains are born in two germinal regions: the subventricular zone (SVZ) and the subgranular zone (SGZ). The SVZ generates olfactory bulb neurons and the SGZ of the hippocampal formation gives rise to granule neurons of the dentate gyrus (Doetsch & Hen, 2005).

In the early adult, approximately 1% of the total olfactory bulb interneurons are added each day. Approximately 50% of these adult-generated olfactory bulb interneurons die within 15 to 45 days after their birth, after they have developed elaborate dendritic morphology and spines. In contrast to their neurogenesis, the early cell death that characterizes the adult-generated olfactory system is activity dependent. Because olfactory cues are critical for survival, the function of the newly born olfactory neurons may be to help enhance olfactory discrimination (Petreanu & Alvarez-Buylla, 2002). Interestingly, environments that are olfactory enriched enhance the length of time that adult-generated olfactory neurons survive. The increased life span of these neurons also is accompanied by improved performance on olfactory memory tasks; however, it is not known whether the improved performance was due to the newly generated neurons or to existing cells exhibiting enhanced activity (Rochefort, Gheusi, Vincent, & Lledo, 2002). Moreover, these adult-born immature neurons have electrophysiological properties that differ from those of old neurons. The unique excitability and connectivity properties may exert distinct functional consequences on the processing of olfactory information (Doetsch & Hen, 2005).

Approximately 85% of dentate gyrus neurons are generated postnatally; however, their production begins during the embryonic period (Gould & Cameron, 1996). A large population of cells reaches the dentate gyrus without undergoing final division; these precursor cells remain in the dentate gyrus and become the source of granule neurons born in the postnatal period. Granule cells are excitatory

neurons that utilize glutamate as their primary neurotransmitter. A growing body of investigations indicates that excitatory input plays a prominent role in the formation of many neuronal populations.

In fact, in the mature central nervous system pools of progenitor cells appear to proliferate and migrate well into adulthood. For example, Kempermann, Kuhn, and Gage (1998) discovered that neurogenesis continues to occur in the dentate gyrus of senescent mice and can be stimulated when the mice are placed in an enriched environment. Kempermann et al. (1998) found that neurogenesis declined with increasing age; however, stimulation of adult and aged mice by changing from regular housing to an enriched environment that provided opportunities for social interaction, physical activity, and exploration brought about an increased number of survival cells. Furthermore, animals residing in enriched environments had more of their cells differentiate into neurons than did mice housed in standard conditions. These findings suggest that the new neurons were generated in the hippocampal area and that neural plasticity can take place in the aging brain in mice.

Likewise, Gould, Tanapat, McEwen, Flugge, and Fuchs (1998) discovered that new neurons are produced in the dentate gyrus of adult monkeys. Moreover, these investigators found that a single exposure to a socially stressful condition (i.e., a resident intruder unfamiliar adult male conspecific) inhibits the proliferation of granule cell precursors. Cortisol and glucocorticoids control the rate of the development of these new neurons, and it is clear that the existing neurons are not merely reorganizing their connections. Furthermore, the mature central nervous system continues to express an array of molecules that are required for the formation of neuronal networks during embryonic development (e.g., neurotrophic growth factors, embryonic forms of cell adhesion molecules, axon-guidance molecules). The presence of these molecules suggests that the degree of potential network remodeling in the mature central nervous system may be more extensive than generally thought (Lowenstein & Parent, 1999). Thus, although there is currently no unequivocal evidence that the fully developed central nervous system continues to generate new neurons and glial cells everywhere, progenitor cells with the potential to produce new cells are prevalent throughout the mature mammalian central nervous system (Gage, 2000; Lowenstein & Parent, 1999).

Two factors, adrenal steroids and excitatory input, have been identified that regulate the proliferation, migration, and survival of granule neurons during the postnatal period through adulthood. In general, increases in adrenal steroid levels or NMDA receptor activation diminish the rate of cell proliferation, whereas decreases in adrenal steroid levels or NMDA receptor activation increase the rate of cell production. These results also suggest that decreased neurogenesis associated with increased corticosteroid levels may contribute to age-related memory deficits. Moreover, the finding that the neuronal precursor population in the dentate gyrus remains stable into old age, but that neurogenesis is slowed by high levels of adrenal steroids, suggests that these memory deficits may be reversible (Cameron & McKay, 1999). Gould (1999) also reported that activation of serotonergic receptors enhanced neurogenesis in the adult mammalian dentate gyrus. Because adult-generated hippocampal neurons are affected by, and conceivably involved in, learning and memory (Gould, Beylin, Tanapat, Reeves, & Shors, 1999), serotonergic agonists that stimulate granule cell production may prevent memory deficits.

Cells that divide in adulthood do not die soon thereafter. Thus, the cell death that occurs in adulthood does not simply remove cells that were generated incorrectly in adulthood. In fact, because granule neurons that generate in adults survive for at least 1 month and form connections, it is likely that their addition to the granule cell layer has significant functional consequences. In a study that has generated a great deal of controversy in the literature, Gould et al. (1999) discovered that stress does not alter the survival of recently produced neurons in the dentate gyrus. Accordingly, young (immature) adult-generated hippocampal cells may make them uniquely qualified to form synaptic connections rapidly and to participate in the transient storage of information. Furthermore, Gould, Beylin, et al. (1999) found that in order for learning to further enhance the number of new hippocampal neurons, the animal must be engaged in a task for which this brain region is essential. In addition, Gould, Reeves, Graziano, and Gross (1999) discovered that in adult macaque monkeys new neurons are added to the prefrontal, posterior parietal, and inferior temporal cortex. These investigators stated that these new neurons most likely originated in the subventricular zone and then migrated through white matter tracts to the neocortex, where they extended axons. Gould and colleagues hypothesized that the new neurons added to these regions of association cortex might play a role in such functions. Moreover, Gould, Reeves, et al. (1999) conjectured that these immature neurons, which continue to be added on adulthood, are capable of undergoing rapid structural changes and thereby serve as a substrate for learning and memory.

In a subsequent investigation, Gould, Vail, Wagers, and Gross (2001) compared the production and survival of adult-generated neurons and glia in the dentate gyrus, pre-

frontal cortex, and inferior temporal cortex. These investigators found that there were many more cells produced in the dentate gyrus than in either of the two neocortical association areas. Furthermore, a greater percentage of cells in the dentate gyrus expressed a neuronal marker than was the case for cells in either of the neocortical areas. Additionally, Gould and colleagues (2001) discovered that there was a decline in the number of cells approximately 9 weeks after they had been labeled, suggesting that some percentage of the adult-generated new cells may have a transient existence. It is believed that the short-lived nature of these newly generated neurons may make them particularly suited to play a role in learning and memory processes (cf. Gould, Tanapat, Hastings, & Shors, 1999).

The finding of neurogenesis in the neocortex of the adult primate by Gould and her colleagues (1999; Gould, Vail, et al., 2001) astonished the scientific world because, since the writings of His and Cajal, the brain has been considered to be a nonrenewable organ comprised of fully differentiated neurons (Jacobson, 1991; Rakic, 2002b). As previously noted, numerous investigations have found that adult neurogenesis in mammals only occurs unambiguously in the granule cells of the dentate gyrus and the olfactory bulb (Carleton, Petreanu, Lansford, Alvarez-Buylla, & Lledo, 2003; Gage, 2000; Kornack & Rakic, 2001b; Rakic, 1998). Not surprisingly, a number of methodological critiques of the findings of Gould, Reeves, et al. have appeared in the literature (Kornack & Rakic, 2001a; Korr & Schmitz, 1999; Nowakowski & Hayes, 2000; Rakic, 2002a, 2002b). Consequently, the conclusion put forth by some of the great systematizers in the history of developmental neurobiology, that nerve cells that subserve the highest cortical functions are irreplaceable under typical conditions, appears to continue to garner strong support from contemporary neurobiologists.

Neurobiological Pathways to Psychopathology

Just as we described with respect to normal brain development, abnormal neurobiological development also is a dynamic, self-organizing process. However, unlike the case for normal neurobiological development, the final product of abnormal brain development includes a substantial measure of misorganization (Courchesne et al., 1994). Perturbations that occur during brain development can potentiate a cascade of maturational and structural changes that eventuate in the neural system proceeding along a trajectory that deviates from that generally taken during normal neurobiological development (Cicchetti & Tucker, 1994a; Courchesne et al., 1994; Nowakowski & Hayes, 1999). Early stressors, either physiological or emotional, may alter the neurodevelopmental processes of networks, in turn generating a cascade of effects through subsequent developmental periods, conceivably constraining the child's flexibility to adapt to new challenging situations with new strategies rather than with old conceptual and behavioral prototypes (Cicchetti & Tucker, 1994a; Gunnar, 2000; Sanchez, Ladd, & Plotsky, 2001). Accordingly, early psychological trauma may eventuate not only in emotional sensitization (Maughan & Cicchetti, 2002; Rieder & Cicchetti, 1989) but also in pathological sensitization of neurophysiological reactivity (Pollak, Cicchetti, & Klorman, 1998).

Accordingly, abnormal perturbations at one stage of brain development hinder the creation of some new structures and functions, distort the form of later-emerging ones, make possible the construction of ones that normally never become manifest, and/or limit the elaboration and usage of structures and functions that had appeared earlier (Courchesne et al., 1994; Steingard & Coyle, 1998). Eventually, successively more complex, specialized, and stable abnormal neural network configurations and operations develop that differ greatly from antecedent ones (Courchesne et al., 1994). Abnormal competition between, and abnormal correlated activity within, undamaged, as well as damaged, neural networks can drive the abnormal elimination of some connections and neural elements (e.g., remote loss) and the abnormal selective stabilization of others (e.g., aberrant connections are retained or created; Courchesne et al., 1994). Such early developmental abnormalities may lead to the development of aberrant neural circuitry and often compound themselves into relatively enduring forms of psychopathology (Arnold, 1999; Cicchetti & Cannon, 1999b; Nowakowski & Hayes, 1999).

Children whose gene-driven processes construct a disordered brain are likely to experience the world in a vastly different fashion than children who do not have such a strong genetic predisposition (Black et al., 1998). Genes often exert different functional roles in divergent cell types at varying developmental periods (Alberts et al., 1994; Lewin, 2004). Consequently, defects in such genes may trigger a cascade of change that is not confined to a particular neural structure, functional system, or behavioral domain. Even if the subsequent experience-expectant and experience-dependent processes are unimpaired, the experience distorted by the neuropathology is not likely to be appropriately utilized (Black et al., 1998). Thus, children with genetically constructed abnormal brains must have their environments tailored to their specific deficits. If such environmental modifications are not introduced, then these children's subsequent experience-expectant and experience-dependent processes manifest additional aberrations and development

proceeds on an even more maladaptive pathway. Pathological experience may become part of a vicious cycle, as the pathology induced in the brain structure may distort the child's experience, with subsequent alterations in cognition or social interactions causing additional pathological experience and added brain pathology (Cicchetti & Tucker, 1994a). Because experience-expectant and experience-dependent processes may continue to operate during psychopathological states, children who incorporate pathological experience during these processes may add neuropathological connections into their developing brains instead of functional neuronal connections (Black et al., 1998).

Social Experience and Brain Development and Functioning

Empirical evidence gleaned from research with rodents and nonhuman primates has demonstrated that the experience of traumatic events early in life can alter behavioral and neuroendocrine responsiveness, the morphological characteristics of the brain, and the activation of genes associated with negative behavioral and neurobiological outcomes (Sanchez et al., 2001). Moreover, the results of animal studies reveal that early traumatic experiences may exert a harmful impact on the normative developmental processes, which have been shown to be associated with long-term alterations in coping, emotional, and behavioral dysregulation; responsiveness of the neuroendocrine system to stressful experiences; brain structure; neurochemistry; and gene expression (Cicchetti & Walker, 2001; Gunnar et al., 2001). Additionally, research has discovered that depriving rodent infants of adequate social and physical stimulation from their mothers' influences the responsivity of the hypothalamic pituitary-adrenal axis to stressors in later life (Levine, 1994; Meaney et al., 1996). Furthermore, research with rodents has revealed that naturally occurring variations in maternal care alter the expression of genes whose function is to regulate behavioral and endocrine responses to stress, as well as to modify synaptic development in the hippocampus (Meaney, 2001). In particular, stressors that are imposed on mothers have been shown to increase stress reactivity in their rodent offspring. Thus, quality of parental care is a mediator of the impact that adverse environmental conditions have on neural development in rodents.

Children who are endowed with normal brains may encounter a variety of negative experiences that exert a deleterious effect on neurobiological structure, function, and organization, and contribute to distortions in the way in which these children interpret and react to their worlds (Pollak et al., 1998). In this Handbook, Chapter 4, Volume 3 (Cicchetti & Valentino, 2006), the effect of child maltreatment on the structure and function of neurobiological systems was reviewed. We do not wish to restate the details of the neurobiological studies conducted to date, which demonstrate that different components of brain structure and function, each representing fairly distinct neural systems, are negatively affected by experiencing child maltreatment. Work on acoustic startle, neuroendocrine regulation, event-related potentials (ERPs), and neuroimaging have revealed that the various stressors associated with child maltreatment exert harmful effects on numerous interconnected neurobiological systems. Moreover, the neurobiological development of maltreated children is not affected in the same way in all individuals. Finally, not all maltreated children exhibit anomalies in their brain structure or function. Accordingly, it appears that the effects of maltreatment on brain microstructure and biochemistry may be either pathological or adaptive. Finally, because research with rodents and nonhuman primates has revealed that social experiences, such as maternal care giving behaviors, maternal deprivation, and maternal separation, affect gene expression, as well as brain structure and function (Kaufman & Charney, 2001; Meaney et al., 1996; Sanchez et al., 2001), it is highly probable that child maltreatment affects the expression of genes that impact brain structure, as well as basic regulatory processes (Caspi et al., 2002; Cicchetti & Blender, 2004; Kaufman et al., 2004).

Often, the investigation of a system in its smoothly operating normal or healthy state does not afford the opportunity to comprehend the interrelations among its component systems (see, e.g., Caviness & Rakic, 1978; Chomsky, 1968). Because pathological conditions enable scientists to isolate the components of the integrated system, investigation of these nonnormative conditions sheds light on the normal structure of the system. We next discuss Autism and neurodevelopmental aspects of Schizophrenia as illustrations of how the examination of brain development in mental disorder could provide insights into normal neurobiological processes.

CONTRIBUTION OF BRAIN DEVELOPMENT IN ATYPICAL POPULATIONS TO FURTHERING INSIGHTS INTO TYPICAL NEUROLOGICAL PROCESSES

Autism

Autism is a pervasive developmental disorder characterized by impairments in social communication and inter-

action, a wide range of cognitive and executive functioning deficits, and behavioral stereotypes (American Psychiatric Association, 1994). Over 60 years ago, Kanner (1943), who originally devised the term Autism, suggested that Autism represented a biological dysfunction that reduced the capacity of children to form emotional contact with people. However, a short time later, Kanner revised his conceptual thinking on the etiology of Autism and, along with many others, came to view it as environmentally caused, often believed to be a result of emotionally distant, rejecting parents (Bettelheim, 1967). Fortunately, more recent formulations concerning the etiology of this disorder have emphasized its probable neurobiological and genetic basis (e.g., Courchesne, 1987; Rodier, 2002).

Many neurobiological theories concerning Autism have tended to focus on possible abnormalities of individual brain structures as underlying the observed behavioral and neuropsychological symptoms observed in Autism. A range of theories focused on dysfunction of the brain have implicated abnormalities in nearly every brain system. For example, some theories have been based on animal models of medial temporal lobe dysfunction (e.g., Bachevalier, 1996; Bachevalier & Loveland, 2003), while others have emphasized abnormalities in brain structures, such as the amygdala (e.g., Baron-Cohen et al., 2000), hippocampus (e.g., DeLong, 1992), frontal cortex (e.g., Damasio & Maurer, 1978), and cerebellum (e.g., Courchesne, 1997), as well as other cortical and subcortical regions as fundamental to the etiology of Autism. Until recently, etiological formulations of Autism have failed to take into account the impact of developmental processes and the probable interconnected nature of multiple brain systems at multiple levels of analysis.

Many of the conceptualizations of neural-structural abnormalities underlying the behavioral manifestations of Autism have been based on data obtained through neuropsychological assessment of children with Autism. Such assessments have consistently demonstrated deficits in discrete areas of cognition and executive functioning. One such commonly observed deficit is in attentional functioning, whereby speed of orienting to and processing novel stimuli is reduced in those with Autism (e.g., Akshoomoff, Courchesne, & Townsend, 1997; Townsend, Harris, & Courchesne, 1996), as well as the ability to shift attention (e.g., Wainwright-Sharp & Bryson, 1993). Generally, however, individuals with Autism have been found to have widespread executive functioning impairments that are perhaps a result of the more fundamental attentional deficits found with this disorder (Ozonoff, 2001). Detailed analyses of individual components of executive functioning in those with Autism by Ozonoff and colleagues (2001) have revealed that individuals with Autism exhibit impairments in cognitive flexibility (Ozonoff, Strayer, McMahon, & Filoux, 1994), but do not show deficits in inhibiting responses (Ozonoff & Strayer, 1997) or in working memory functioning. In addition, Frith (2001) has proposed a somewhat controversial etiological theory of Autism linking deficits in theory of mind ("mind blindness") to abnormalities in a network of brain regions, including the medial prefrontal cortex, areas in the temporal-parietal region, and the temporal poles, all of which are active in nonautistic individuals during theory of mind tasks.

Courchesne and his colleagues have begun to formulate a developmentally based theory of Autism, built upon empirical evidence derived from an examination of the neurodevelopmental course of the whole brain, and in particular the cerebellum and its interconnections with many different brain structures. Across many studies with varying methodologies, the most consistent brain structural abnormality in individuals with Autism occurs in various sites within the cerebellum and limbic system structures (Carper, Moses, Tigue, & Courchesne, 2002). The vast majority of postmortem studies have reported cerebellar pathology, while structural magnetic resonance imaging (MRI) studies consistently find evidence of hypoplasia in the cerebellum (see Courchesne, 1997, for a comprehensive review). The most common postmortem pathology of the cerebellum is a reduction in the number and size of Purkinje neurons (e.g., Bailey et al., 1998; Fatemi et al., 2000; Kemper & Bauman, 1998). Additionally, volumetric MRI studies have consistently indicated reduced size of one or another subregion of the cerebellar vermis (Carper & Courchesne, 2000; Hashimoto et al., 1995). In sum, the strongest and most consistent neuroanatomical evidence points to structural abnormalities in the cerebellum.

However, there is not a clear consensus in the Autism literature concerning the relevance of cerebellar anomalies for a disorder primarily characterized by cognitive, social, and emotional deficits, given the prevailing view that the cerebellum is primarily involved in motor function. But evidence has pointed to cerebellar involvement in a number of cognitive and emotional functions (e.g., G. Allen, Buxton, Wong, & Courchesne, 1997; Gao et al., 1996; Paradiso, Andreasen, O'Leary, Arndt, & Robinson, 1997; Xiang et al., 2003). Thus, a more current, broad view of the role of the cerebellum in overall neurobehavioral functioning creates a more reasonable scenario for implicating abnormalities in this structure as having a central underlying role in Autism.

A functional MRI (fMRI) study of the cerebellum revealed different patterns of cerebellar activation during a simple motor task (pressing a button with the thumb) in a

sample of young adults with Autism compared to a nonautistic control group (G. Allen, Muller, & Courchesne, 2004). In the group with Autism, areas of the cerebellum predicted to be involved in the task exhibited more activation than observed in the control group, and areas of the cerebellum not expected to be associated with this simple motor task were activated in the group with Autism but not in the control group. The investigators concluded that the pattern of functional activation found strongly suggested that the observed functional differences were a reflection of the anatomic abnormalities (i.e., reduced cerebellar volume) found in the persons with Autism.

These authors hypothesize that many of the motor deficits commonly seen in individuals with Autism (e.g., balance problems, abnormal gait) may be related, at least in part, to both anatomical and functional abnormalities of the cerebellum. In addition, there also is evidence that cerebellar pathology can bring about a wide range of cognitive and affective deficits (G. Allen & Courchesne, 1998). In fact, one published case study reported on a child who, after surgical resection of a cerebellar tumor, exhibited behaviors after the surgery that were highly characteristic of classic symptoms of Autism, such as gaze aversion, social withdrawal, and stereotyped movements (Riva & Giorgi, 2000).

Although the neuroanatomical and neurofunctional evidence point to a clear association between cerebellar abnormalities and the behavioral manifestation of Autism, the mechanism involved remains unknown. One primary reason is that the general functional properties of the cerebellum in normal brains remain unknown to a large extent. Some preliminary evidence points to anticipatory motor deficits, given increasing evidence that the cerebellum appears to have a role in preparing many neural systems to which it maintains connections (e.g., attention, motor, affect, language) for shifts or alterations in neural responsiveness (G. Allen et al., 2004). G. Allen et al. hypothesize that the cerebellum may accomplish this task by making predictions about what might happen next based on prior learning and may alter responsiveness in the particular neural system(s) needed in upcoming moments. Thus, function in these diverse cognitive realms is not abolished in those with Autism, but lacks in coordination due to a preparatory deficit.

Another strong neuroanatomical finding in individuals with Autism is abnormal developmental changes in overall brain volume. Courchesne and colleagues have shown that brain volume of those children later diagnosed with Autism appeared to be normal at birth (according to neonatal head circumference records), but by age 2 to 4 years, volumetric MRI data indicated that 90% of the children with Autism had a larger than average brain volume compared to nonautistic children (Courchesne et al., 2001). The observed excessive brain size was due primarily to increased white matter volume in the cerebellum and cerebrum (Courchesne et al., 2001).

Further, a study by Courchesne, Carper, and Akshoomoff (2003) has yielded evidence that there is an increased rate of growth of the brain in infants who later were diagnosed with Autism compared to those who were not, as reflected by measurements of head circumference (HC). Although HC was similar in all infants enrolled in the study during the first few months of life, those who later developed Autism exhibited a marked accelerated rate of increase in HC beginning several months after birth. On average, between birth and 6 to 14 months of age, HC increased from the 25th percentile to the 84th percentile (Courchesne et al., 2003). This increase in HC was associated with greater cerebral and cerebellar volume in these children by 2 to 5 years of age. It is striking that brain size in young children with Autism reaches its maximum by ages 4 to 5 years (Courchesne et al., 2001). Average overall maximum brain size in children with Autism is statistically equivalent to that achieved by healthy children (approximately 1350 mL), but is achieved, on average, 8 years sooner than in normally developing, healthy children (Courchesne et al., 2001). However, in adolescence and adulthood, brain size of those with Autism does not differ from that of nonautisitc individuals (Aylward, Minshew, Field, Sparks, & Singh, 2002).

Although the increases in brain volume are marked, the specific underlying cellular components of increased brain volumes are unknown to date. The increased volume found in children with Autism may potentially reflect abnormalities in any number of microstructural features, including excessive numbers of neurons and/or glial cells, excessive dendridtic arborization, and/or atypically large numbers of axonal connections (Courchesne et al., 2003). In addition, the cause of the increase in brain volume is not completely understood, but clearly reflects some type of dysregulation in one or more stages of brain developmental processes; however, it appears that the early transient period of brain overgrowth is an important underlying factor in the emergence of many of the behavioral symptoms seen in Autism. The observed overgrowth occurs during an important period of brain development when normative experience-dependent processes of neural plasticity are potentially at a maximum. This extended period of gradual axonal and dendritic growth and synapse refinement and elimination

appears to occur well into the 1st decade of postnatal life. In children with Autism, however, it appears that the physical growth of the brain is compressed into a relatively short period of time, that may in turn result in aberrantly rapid and disordered growth (Courchesne et al., 2003). Such a rapid pace of growth would not allow the normal process of experience-dependent neural plasticity to take place.

Observations of disturbances in normal neurodevelopmental processes in Autism have helped to refine theory and guide research concerning the underlying biological mechanisms of this pervasive developmental disorder. The accumulated (and still growing) knowledge on normal brain development has enabled investigators in Autism to differentiate the abnormal neurodevelopmental processes that appear to underly this disorder.

Ultimately, it appears that the key etiological feature of Autism is abnormality of the neurodevelopmental process across a wide spectrum of brain regions and networks. The emerging evidence increasingly points to abnormal regulation of brain growth in Autism, with pathological deviation from normative mechanisms underlying the typical progression through neurogenesis and synaptogenesis, followed by axon pruning and synapse elimination.

Despite the wide range of theoretical formulations and the relative paucity of consistent data pointing to a common underlying neurobiological "cause" of Autism, the study of this disorder provides an excellent example of the increasingly important role played by neuroscience in examining the potential biological contributors to a developmental disorder. Examining the evolution of theory and research in Autism also provides very useful information concerning the developmental trajectory of this disorder, and perhaps could provide insight into how the study of the development of the neural substrate underlying this disorder could inform the study of other disorders, as well as normal development. As we noted earlier, one of the fundamental tenets of developmental psychopathology is that the study of the development of disordered outcomes can be informed by an understanding of normal development (Cicchetti, 1984, 1990, 1993, 2003). Ideally, the study of normal and abnormal developmental sequelae can work in tandem to inform each other (Cicchetti, 1984, 1993; Sroufe, 1990). Autism is an excellent example of this principle at work. Also, the advances in our understanding of Autism have come as a result of close collaborations between behavioral and biological scientists working across multiple levels of analysis (Akshoomoff, Pierce, & Courchesne, 2002; Rodier, 2002). The success of such collaborative, cross-disciplinary efforts in the study of Autism, and the wealth of new knowledge that has emerged as a result, serve as an excellent example of the importance of a multidisciplinary, multiple levels of analysis approach to the study of neurodevelopmental disorders.

A View from Schizophrenia

Congruent with the theoretical principles of a developmental systems approach on brain development, it is expected that a dedifferentiation and disintegration would characterize the neurobiological and psychological development and functioning of individuals with mental disorders. Much of the contemporary research in the area of neurodevelopment and Schizophrenia owes a significant portion of its historical roots to the formulations of Emil Kraepelin (1919), who conceived of Schizophrenia as a deteriorating brain disease in its natural history, albeit with an onset in early adult life. Since the 1980s, when a resurgence of interest in initiating neurobiological studies in Schizophrenia took place, Kraepelin's viewpoint has been challenged and radically altered by advances from several levels of inquiry that point to a prenatal-perinatal origin of at least some of the brain abnormalities found in individuals with Schizophrenia (Cannon, 1998; Keshavan & Hogarty, 1999; Mednick, Cannon, Barr, & Lyon, 1991; Walker & DiForio, 1997; Weinberger, 1987). During the early 1980s, a number of investigations converged and all found evidence for increased ventricle size in persons with schizophrenic illness (Shenton et al., 2001). These enlarged ventricles were present at the onset of the illness and did not protract in size as the illness proceeded over time, even in prospective longitudinal studies. This finding suggested that a neurodegenerative process was not responsible for causing the illness.

The retrospective observations of Laura Bender (1947) and Barbara Fish (1957), as well as the follow-back study by Norman Watt (1972), in which a pattern of abnormalities in neurological and behavioral parameters dating back to childhood were found in adults with Schizophrenia, laid the seeds of the neurodevelopmental hypothesis of Schizophrenia (Marenco & Weinberger, 2000). Moreover, a number of longitudinal studies demonstrated that some degree of recovery was possible in some cases of Schizophrenia (Garmezy, 1970; Tsuang, Wollson, & Fleming, 1979; Zigler & Glick, 1986), thereby casting further doubt on the Kraepelinian viewpoint that Schizophrenia is a degenerative disease of early adulthood ("dementia praecox").

Similarly, prospective longitudinal high-risk offspring studies have revealed that behavioral antecedents of

Schizophrenia occurred before the disease. Fish (1977) demonstrated that a neurobiologic disorder exists in infants and children prior to the onset of more chronic forms of Schizophrenia. Fish's (1977) discovery of pandevelopmental retardation was considered an early marker of the inherited neurointegrative defect (i.e., schizotaxia) postulated to exist in Schizophrenia by Paul Meehl (1962). Importantly, Fish noted that the phenotypic manifestations of the neurointegrative defect change over epigenesis and that the signs of dysregulation of maturation are found in many developing systems. Specifically, Fish reported that the neurointegrative disorder present from infancy disrupted the normal timing, sequence, and overall organization of development. Moreover, in a landmark prospective longitudinal investigation, Fish, Marcus, Hans, Auerbach, and Perdue (1992) discovered that the infant offspring of schizophrenic mothers displayed greater lags in their motor development during infancy and that a number of these infants themselves went on to develop Schizophrenia or schizotypal personality disorders (see also the seminal work of Walker, Davis, & Gottlieb, 1991, in this regard).

Relatedly, Cannon, Rosso, Bearden, Sanchez, and Hadley (1999), in their epidemiological investigation of the Philadelphia cohort of the National Collaborative Perinatal Project, provide compelling evidence that adverse experiences during gestation and birth, as well as deviant cognitive, motor, and behavioral functioning during early childhood, are associated with an increased risk for Schizophrenia. In particular, these investigators demonstrated that the risk for Schizophrenia increases linearly with the severity of fetal oxygen deprivation. In prior neuroimaging studies of high-risk samples (Cannon, Mednick, Parnas, & Schulsinger, 1993; Cannon et al., 2002), a history of perinatal hypoxia was found to be associated with increased severity of a neuropathological indicator of Schizophrenia (i.e., ventricular enlargement) among individuals with an elevated genetic risk for the disorder, but not among controls at low genetic risk. Together, this evidence suggests that a genetic factor in Schizophrenia may render the fetal brain particularly susceptible to the effects of oxygen deprivation and encourages search for molecular mechanisms underlying this heightened neural vulnerability.

Cannon et al. (1999) also discovered that preschizophrenic individuals show evidence of cognitive, motor, and behavioral dysfunction during the first 7 years of life (cf. Walker, Davis, et al., 1991). Because there was not evidence of significant intraindividual decline during this period within any domain of functioning, the results argue against the view that a deteriorative neural process underlies these early phenotypic expressions of liability to Schizophrenia. Rather, the findings suggest that an increasing number of diverse phenotypic signs emerge with age as the various brain systems required for their expression reach fundamental maturity. Finally, because similar functional disturbances were observed in the unaffected siblings of the preschizophrenic cases, it would appear that these cognitive, motor, and behavioral disturbances are indicators of an inherited neural diathesis to Schizophrenia (cf. Walker & Diforio, 1997).

In addition to the early and more recent work with preschizophrenic infants and children that served as an impetus for modifying the Kraepelinian (1919) view of Schizophrenia, contemporary findings have contributed to the belief that the neurobiological foundations of Schizophrenia are established, at least in part, during the development of the brain. These include the following:

1. A number of prospective longitudinal investigations has discovered an association between prenatal and perinatal complications (e.g., fetal hypoxia) and an increased risk for the later development of Schizophrenia. These findings suggest that the adverse effects of obstetric complications on the developing fetal brain may play a role in the etiology of Schizophrenia.

   As Rakic (1988a, 1988b, 1996; Sidman & Rakic, 1982) and Nowakowski (1987; Nowakowski & Hayes, 1999) have concluded, during periods of rapid brain development in which neuronal migration is occurring and synaptic connections are formed the fetal brain is especially vulnerable. Exogenous teratogens, such as maternal influenza (Brown et al., 2004; Mednick, Machon, Huttunen, & Bonett, 1988) and maternal exposure to toxoplasmosis (Brown et al., 2005), along with obstetric complications, such as perinatal hypoxia (Cannon, 1998), in concert with the genetic predisposition to Schizophrenia, may exert dramatic effects on the regions of the brain experiencing the most rapid growth. Introducing birth complications and teratogens may also place the cortical connections being established and refined at increased risk for aberrant development.
2. A number of postmortem neuropathology studies has found evidence of heterotopic displacement of neurons in various regions of the brain, including the hippocampus and the frontal and temporal cortices. These findings suggest that there are disturbances of brain development in utero in many schizophrenics.
3. Disturbances in neurogenesis, neuronal migration and differentiation, synaptogenesis, neuronal and synaptic pruning (perhaps resulting in reduced synaptic connectivity; cf. McGlashan & Hoffman, 2000), and myelina-

tion, occurring at the cellular and molecular levels, suggest that Schizophrenia is a disorder that is instantiated in brain development (Arnold, 1999; Breslin & Weinberger, 1990; Weinberger, 1987).

For example, the laminar distribution of cortical neurons is displaced inward in Schizophrenia, indicating a defect in cortical organization, suggesting that the normal process of "inside-out" neuronal migration (cf. Rakic, 1988a, 1988b) during the second trimester of gestation also is likely to be anomalous, as should the neuronal connectivity and circuitry (Arnold, 1999; Weinberger, 1995). In addition, Lewis, Hashimoto, and Volk (2005) concluded that there are atypicalities in cortical inhibitory neurons (i.e., GABA neurons) in Schizophrenia and that these abnormalities play a role in the impairments of working memory function that are a core feature of clinical Schizophrenia. Moreover, alterations in dopamine and glutamate neurotransmission in the dorso lateral prefrontal cortex (DLPFC) also are involved in the working memory dysfunction in Schizophrenia. Relatedly, Meyer-Lindenberg et al. (2005) have discovered that hippocampal dysfunction may manifest in Schizophrenia because of an inappropriate bidirectional modulatory relation with the DLPFC.

4. A growing body of neuroimaging studies has identified gross structural neuroanatomical changes in young, untreated patients in their first psychotic episode. Further, and in contrast to a Kraepelinian (1919) neurodegenerative viewpoint, these investigations also have failed to discover evidence of deterioration in these neuropathological markers with increasing length of illness (Marenco & Weinberger, 2000).
5. A number of the unaffected first-degree relatives of schizophrenic patients manifest the structural and functional brain abnormalities observed in schizophrenics, implying that such abnormalities may be mediated, in part, by genetic predisposition to the disorder (Cannon et al., 1993; Cannon, Mednick, et al., 1994). Homeobox genes, which serve as transcription factors regulating gene expression, represent potential candidate genes in disorders in which a disruption of cortical neurogenesis has been implicated, such as in Schizophrenia (Ruddle et al., 1994; Steingard & Coyle, 1998).

We wish to underscore that the extant models linking neurodevelopment and Schizophrenia point to a nonlinearity of relations. Specifically, a significant amount of time elapses between the gestational events hypothesized to create a predisposition to Schizophrenia and the onset of the symptoms of the disorder later in life. Longitudinal follow-up of individuals who have experienced traumatic insults to the brain at early stages of development, such as is likely the case in many instances of Schizophrenia, enables investigators to chart and observe the changing expression of these early lesions as development modifies behavior in general.

Alternatively, for some individuals it also is conceivable that the lesion directly affects later developmental processes via cascade, propagation, and expansion (Cicchetti & Tucker, 1994a; Courchesne et al., 1994; Post et al., 1994; Steingard & Coyle, 1998). These options all provide an opportunity to discover how brain and behavior reorganize following the experience of insults at different points in the developmental course.

Because not all persons who experience the gestational disturbances noted in the literature go on to develop clinical Schizophrenia, Gottlieb's (1992) concept of probabilistic epigenesis is evoked. Furthermore, the existing research reveals that there are a number of pathways through which the early neurodevelopmental anomalies may result in Schizophrenia. The identification of these diverse pathways to Schizophrenia provides insight into how specificity and differentiation into a syndrome may result from a commonality of initiating circumstances (i.e., equifinality; see Cicchetti & Rogosch, 1996). These multiple pathways embrace a number of possible contributors that may potentiate or mediate the links between early neurodevelopmental anomalies and Schizophrenia in genetically vulnerable individuals. These include the normal developmental changes that take place during late adolescence and early adulthood, such as: (1) synaptic pruning of the prefrontal cortex (Feinberg, 1982; McGlashan & Hoffman, 2000), (2) pubertal increases in gonadal hormones during adolescence (Spear, 2000; Walker, Sabuwalla, & Huot, 2004), (3) developmental transformations in prefrontal cortex and limbic brain regions (Dahl, 2004; Keshavan & Hogarty, 1999; Marenco & Weinberger, 2000), (4) continued myelination of intracortical connections (Benes, 1989; Gibson, 1991; Yakovlev & LeCours, 1967), (5) alterations in the balance between mesocortical and mesolimbic dopamine systems (Benes, 1989, 1997; Benes, Turtle, Khan, & Farol, 1994), (6) the stress that arises during postnatal social development (Keshavan & Hogarty, 1999; Walker & Diforio, 1997), (7) the transformations that occur in cognitive and social-cognitive development (Keating, 1990; Noam, Chandler, & LaLonde, 1995; Spear, 2000), and (8) the growing importance of the peer group (J. G. Parker, Rubin, Price, & DeRosier, 1995).

Such an integrative, interdisciplinary approach is necessary to capture the full complexity of schizophrenic illness,

including the multiple pathways to, and the diverse outcomes associated with, the disorder. Thus, it appears likely that the processes underlying the normal development and maturation of cortical circuitry and connectivity may have gone awry in Schizophrenia (Arnold, 1999; Benes, 1995; McGlashan & Hoffman, 2000; Weinberger, 1987). Unraveling these misorganizations in brain development should contribute greatly to understanding the genesis and epigenesis of schizophrenic disorders.

As highlighted in the previous sections, advances in neuroscience have begun to inform neurodevelopmental theories of Autism and Schizophrenia. Other lines of research have begun to examine other forms of psychopathology (e.g., Attention Deficit/Hyperactivity Disorder, Conduct Disorder, Bipolar Disorder) in a neurodevelopmental context (see Cicchetti & Cannon, 1999a; Cicchetti & Walker, 2003). In fact, it is clear that developmental psychopathology has made great strides in recent years to incorporate multiple levels of analysis in its conceptual and empirical framework, and the understanding of the development of psychopathology generally has made great advances by employing findings from basic neuroscience and normal brain development. As previously noted, one of the fundamental tenets of developmental psychopathology is that knowledge of normal development can and should inform the study of deviant developmental trajectories eventuating in psychopathology. One logical extension of this approach is the investigation of the mechanisms and developmental pathways that eventuate in positive outcomes despite the experience of significant adversity. Knowledge from neuroscience and its associated subdisciplines has only recently been brought to bear in preliminary theoretical discussions of a biology of resilience (Charney, 2004; Curtis & Cicchetti, 2003), and, to date, no published empirical studies have incorporated this level of analysis in the investigation of resilience. As part of a complete integration of multiple levels of analysis (including biological) into the developmental psychopathology framework, we believe it is critical to begin to examine the biological contributors to resilient functioning.

RESILIENCE

Positive adaptation in the face of adversity has captured the interest and imagination of humanity over the ages. However, systematic empirical study of the phenomenon that is today referred to as resilience began only a little more than 30 years ago (Cicchetti & Garmezy, 1993; Masten, Best, & Garmezy, 1990). In the early 1970s, a few researchers investigating the development of psychopathology began to discuss the importance of examining characteristics of children who did not develop psychopathology, despite being at risk (e.g., Anthony, 1974; Garmezy, 1971, 1974), marking an important shift in theoretical depictions of the causes and consequences of psychopathology. Previously, investigations conducted on high-risk and mentally disordered populations across the life span had portrayed the developmental course as deterministic, inevitably resulting in maladaptive and pathological outcomes (Luthar et al., 2000). As researchers discovered that not all high-risk children manifested the dire consequences that extant theories of psychopathology predicted, understanding the processes through which children at risk did not develop psychopathology became viewed as important for informing theories on the development of maladaptation and pathology. The advent of modern neuroscience along with its many associated subdisciplines represents an unprecedented opportunity to augment current conceptual and methodological approaches to the study of resilience (Cowan et al., 2000).

A large volume of research over the past 3 decades has examined the psychosocial correlates of individual, interpersonal, familial, and broader environmental contributors to resilience (Luthar, 2003; Luthar et al., 2000; Masten, 2001). However, the empirical study of resilience, for various historical reasons, has focused exclusively on behavioral and psychosocial correlates of, and contributors to, the phenomenon, and has not examined biological correlates or contributors (Curtis & Cicchetti, 2003; Luthar et al., 2000). Taken as a whole, the extant empirical literature on resilience has traditionally employed behavioral indices of adversity and positive adaptation.

Although this research has yielded a wealth of knowledge concerning the psychosocial correlates of, and contributors to, resilience, early theorizing and research in resilience (e.g., Anthony, 1974; Garmezy, 1974; Murphy, 1974), as well as several subsequent large-scale longitudinal studies of resilience (e.g., Garmezy, Masten, & Tellegen, 1984; Garmezy & Tellegen, 1984; Masten & Garmezy, 1985; Werner & Smith, 1982), were undertaken prior to the inception of modern techniques for examining the neural and biological correlates of human behavior and development. In addition, the scientific study of resilience had its roots in the psychodynamic and behavioral theoretical traditions, where research was largely guided by the study of risk and symptom treatment (Masten & Reed, 2002). Within these conceptual frameworks, which dominated clinical and developmental psychology through much of the twentieth century, there was little interest in discovering the

biological mechanisms that could potentially contribute to a more integrated understanding of behavioral differences (Nelson et al., 2002). Undoubtedly, the relative neglect of the brain and biology as relevant to developmental theorizing on the unfolding of adaptive and maladaptive behavioral outcomes was due, in part, to the paucity of information that existed about the structural and functional organization of the brain (Johnson, 1998; Segalowitz, 1994). There simply was not enough knowledge about brain development and function to articulate its role in the genesis and epigenesis of normal and deviant mental processes. Several cogent and extensive summaries of resilience theory and research have been published that have explicated the need to examine the processes contributing to resilience from multiple levels of analysis, in particular from the level of brain and neurobiological functioning. An important discussion has begun concerning the incorporation of the biological level of analysis into the theoretical framework of resilience (see, e.g., Curtis & Cicchetti, 2003; Luthar et al., 2000; Masten, 2001; Masten & Reed, 2002; Nelson, 1999), and preliminary proposals concerning the empirical examination of the biological foundations of resilience have recently been made (Charney, 2004; Cicchetti, 2003; Curtis & Cicchetti, 2003; Davidson, 2000). At this point in the empirical investigation of resilience, the next logical step is to include a biological perspective on resilience in order to achieve a truly complete understanding of this phenomenon.

Within the scope of this section, it is not be possible to cover all of the areas of biological functioning that might potentially contribute to resilient functioning. Rather, we focus on several broad areas that directly and/or indirectly reflect the functioning of major human biological systems that have clear links to human behavior. In particular, we consider the possible contributions of genetics, neuroendocrinology, immunology, emotion, cognition, and neural plasticity to resilient functioning. There is evidence to suggest that the environment and experience may exert an impact on these areas, thus, perhaps, playing a role in resilient functioning. Within each of these areas, we evaluate the pertinent evidence supporting the association of that particular system with resilience and suggest possible research methodologies that could be brought to bear to examine general questions and hypotheses concerning the likely relation between resilience and each area reviewed.

Going forward, it is critically important to keep in mind that biological domains do not function independently, but, more often than not, the functioning of one system influences the functional properties of one or more other systems, through a cascade of bidirectionally influenced processes (Cicchetti & Cannon, 1999a; Gottlieb, 1992; Gottlieb et al., 1998; Thelen & Smith, 1998). In addition, based on the reality that biological systems function interdependently as much as possible, the goal of future research on resilience and biology should be to increasingly incorporate multiple biological measures as part of a multiple levels of analysis approach to resilience research (Cicchetti & Curtis, in press). With this as an ideal, admittedly the challenges involved in a true integration are great. To be complete, such synthesis must involve integration at the highest level across disciplines (i.e., neuroscience and psychology), but also must examine multiple biological systems within the organism (e.g., neuroendocrine and emotion) as well as investigate different levels within the same system (e.g., neuroanatomical and neurochemical). Historically, conceptual distinctions among and within systems have been created (e.g., higher and lower order cognition) in order to more conveniently study the functional details of these systems. However, given the increasing recognition of the importance of considering many levels of interdependent processes simultaneously in order to advance the understanding of a multifaceted phenomenon, such as resilience, it is incumbent upon resilience researchers to meet the challenge of simultaneously incorporating multiple levels both across and within systems.

The discussion in this section of the chapter focuses in part on the conceptual basis for the consideration of biological processes that may potentially yield contributions to expanding our knowledge about resilience. In addition, we discuss various types of neuroimaging and other technologies, such as magnetic resonance imaging (MRI), functional MRI (fMRI), electroencephalography (EEG), event-related potentials (ERPs), assay techniques for neuroendocrine and immune functioning, and methods for investigating gene expression as methodological tools that could be employed to help answer questions about the contribution of biology to resilience. However, the discussion of these tools are secondary to what we believe is the more important general discussion of biology and resilience, as well as the research questions that should be developed to further our understanding of the interface of these two areas.

Theoretical Approach

One of the formidable challenges inherent to examining resilience from a biological perspective is the need to extend current theoretical conceptualizations about resilience in order to incorporate the various new levels of analysis potentially involved in this approach. Most investigators in the area of resilience do not have formal training in neuroscience or biology, whereas those investigators who do

have such training generally have not been involved with research in the area of resilience. Given the vast range of expertise that could ultimately be required to investigate the role of biology in resilience, it is imperative that a multidisciplinary approach to both theory building and empirical investigation is brought to bear on this problem. Indeed, given that self-righting, one of the basic mechanisms underlying resilience, has its historical roots embedded in the fields of embryology and genetics (Fishbein, 1976; Waddington, 1957), we think that it is especially unfortunate that behavioral scientists have thus far eschewed the inclusion of biological measures in their research armamentaria on resilience.

In setting forth a conceptual model of biology and resilience, particular attention must be paid to the relation between the dynamic process of resilience and key components of the central nervous system, neuroendocrine, and other neurobiological systems. An explanatory model of resilience and biology will build and expand upon the extant theoretical framework around resilience, in particular, one that views resilience as a dynamic process that is influenced by neural and psychological self-organization, as well as transactions between the ecological context and the developing organism (Cicchetti & Tucker, 1994a; Egeland, Carlson, & Sroufe, 1993). Specifically, the transactional, organizational perspective (Cicchetti & Schneider-Rosen, 1986; Cicchetti & Sroufe, 1978), one of the major theoretical approaches in the field of developmental psychopathology, provides an orientation that inherently takes into account multiple levels of analysis and allows for combining biological and psychological mechanisms within the same explanatory framework (Cicchetti & Tucker, 1994a), thus providing a ready-made structure for the integration of a biological perspective into resilience. In addition, a transactional, organizational perspective is useful in that it does not ascribe ascendancy to any level of analysis over another, and it attempts to break down the traditional restrictive conceptual boundaries between nature and nurture and biology and psychology (Cicchetti & Cannon, 1999a; Gottlieb, 1992).

As we described earlier in this chapter, advocates of a self-organizing systems-theory viewpoint of neurobiological and psychological development contend that individuals actively participate in the creation of meaning by structuring and restructuring experience through self-regulated mental activity (Cicchetti & Tucker, 1994a; Mascolo, Pollack, & Fischer, 1997). Early experience and prior levels of adaptation neither doom the individual to continued maladaptive functioning nor inoculate the individual from future problems in functioning. Change takes place in a system as new needs and environmental challenges destabilize the existing organizations, necessitating the emergence of new organizations that may prove to be more adaptive than the preexisting ones in the current context. The reorganizations that occur both within and between developmental domains (e.g., emotion, cognition) provide critical opportunities for resilient adaptation (Cicchetti & Tucker, 1994a).

Furthermore, despite the important role that genetic information plays in regulating, guiding, and controlling brain development (Rakic, 1988a, 1988b, 1995), as we noted earlier, a not insignificant portion of postnatal brain development is thought to occur through interactions and transactions of the individual with the environment (Black et al., 1998; Cicchetti & Cannon, 1999a; Johnson, 1998; O'Leary, 1989). This potential for structural and functional reorganization of the brain in response to environmental demand and afferent input shapes development in the form of a nonlinear, dynamic feedback system (Elbert, Heim, & Rockstroh, 2001). Such development proceeds hand in hand with structural modifications of the brain that can occur on both a microscopic, cellular scale with, for example, alterations in synaptic efficiency, synapse formation, and changes in properties of dendrites, as well as at a macroscopic level with functional reorganization of entire neural networks (Elbert et al., 2001). Consequently, each individual may traverse a potentially unique and partly self-determined developmental pathway of brain building that we believe may have important consequences for the development of resilient adaptation (Black et al., 1998; Cicchetti & Tucker, 1994a). Much of the underlying empirical work in support of this perspective on neural development has been in the area of sensory, language, and perceptual organization and function (e.g., Cheour et al., 1998; Elbert, Pantev, Wienbruch, Rockstroh, & Taub, 1995; Hubel & Wiesel, 1979). However, it is probable that parallel processes shape the development of higher-order, widely distributed cortical functions involved in emotion and cognition that more directly underlie complex, behaviorally manifested phenomena, including resilience.

Avoiding Reductionism

In attempting to integrate a biological perspective into the study of resilience, it is critical to avoid the potential pitfall of reducing the phenomenon of resilience to one that is exclusively mediated by biology. It is possible that the discussion of the biology of resilience could lead to the mistaken conclusion that, if biological mechanisms were associated with resilient outcomes, then the forces of biol-

ogy would be of primary importance in achieving positive outcomes in the context of adversity. However, nothing could be further from the truth.

In fact, reducing psychological phenomena to components of neuroanatomical, neurochemical, neurophysiological, and genetic factors dismisses the great impact that the environment has on these processes, and demotes psychology to the realm of ephemeral behavioral marker of biological processes (see Miller & Keller, 2000). This reductionism is of particular concern in the study of psychopathology, where over the past decade there has been an increasing emphasis on the neurobiology of mental disorders, often attributing (reducing) the etiology of psychopathology to purely innate characteristics of the individual, such as genes, neuroanatomy, or brain function (Charney, Nestler, & Bunney, 1999; Torrey, 1997). More broadly, the artificial distinction between biology and behavior within the human organism contradicts years of research indicating co-actions between all levels of analysis, from the environment broadly construed to the molecular (e.g., Cicchetti & Tucker, 1994a; Gottlieb & Halpern, 2002), and it also highlights the importance of avoiding the perpetuation of the outmoded dichotomy in developmental science between nature and nurture (e.g., Hinde, 1992; Johnston, 1987). Thus, in the context of the current discussion of resilience and biology, we do not wish to convey or encourage the reduction of resilience to biological process. Rather, consistent with a transactional, organizational, general systems theory framework, we believe that biology is but one part of what should be an all-encompassing systems approach to understanding resilience, which needs to take into account all levels of analysis, from molecular to cultural.

Equifinality and Multifinality

Diversity in process and outcome are hallmarks of the developmental psychopathology perspective (Cicchetti, 1990; Cicchetti & Rogosch, 1996; Sroufe, 1989). The existence of equifinality, the recognition that a diversity of paths may eventuate in the same outcome, and multifinality, the acknowledgment that different outcomes are likely to evolve from any original starting point, challenges theorists and researchers to entertain more complex and varied approaches to how they conceptualize and investigate normal development, psychopathology, and resilience (Richters, 1997).

The application of equifinality to a biology of resilience requires that researchers be aware that a variety of developmental progressions may eventuate in disorder or resilience (Luthar et al., 2000). Clearly, biological and psychological factors both can play a role in the pathways to these diverse outcomes. Furthermore, the relative contributions of biological and psychological contributors to disorder and resilience will vary among individuals.

Likewise, the concept of multifinality alerts resilience researchers to the fact that individuals may begin on the same major developmental trajectory and, as a function of their subsequent "choices," exhibit very different patterns of maladaptation or adaptation (Sroufe, 1989; Sroufe, Egeland, & Kreutzer, 1990). The pathway to either psychopathology or resilience is influenced, in part, by a complex matrix of the individual's level of biological and psychological organization, experience, social context, timing of the adverse event(s) and experiences, and the developmental history of the individual.

Technology, Methodology, and Resilience

There is a vast array of rapidly evolving technologies in the biological sciences that can be applied to the study of development and psychopathology, many of which can now potentially play an important role in the study of the interface between biology and resilience. However, an important caveat with respect to these new tools is that the utilization of technology, without an underlying model or theoretical framework, does not serve the advancement of science (see also Peterson, 2003). In the absence of any specific, empirically based knowledge concerning the relation between biological systems and a particular behaviorally manifested psychological phenomenon (e.g., resilience), the initial challenge during the early stages of such research is to, at the very least, generate a priori, testable hypotheses that have a reasonable degree of fidelity with a clearly specified conceptual model. Although the construction of an elaborate, formal theory that specifically describes the relation between biology and resilience is overly ambitious at this juncture, it is nonetheless critical to ground empirical endeavors in some framework that is based either on a viable model or some type of functional theory.

In addition, with the continuing advances in and increasing utilization of new technologies in neuroscience and psychology, particularly neuroimaging, it is of paramount importance to avoid having the construction of theory and subsequent generation of hypotheses driven or constrained by the nature of the data that is attainable by a particular measurement technology. Thus, it is important not to exclusively conceptualize a psychological phenomenon, such as resilience, through the lens of a particular methodology. For example, fMRI is an excellent tool for localizing the functional aspects of brain regions and

networks. Thus, application of this method would be ideal for answering questions about where in the brain a particular cognitive or emotional operation is taking place. However, the types of tasks that can be administered to individuals during the fMRI scanning procedure are, by necessity, often limited to those that can be physically adapted to the MRI scanner environment. Thus, the questions that can be answered by functional imaging are to a great degree dependent upon the nature and demands of the task administered, which may often be quite narrow in scope.

Furthermore, although fMRI affords excellent spatial resolution (on the order of a few millimeters), it does not provide good temporal resolution of neural activity (continuing advances in technology have somewhat improved this aspect of the technology, however). Alternatively, ERPs are an example of an ideal brain-imaging technology for detecting the temporal sequence of brain processing (resolution on the order of milliseconds), but unfortunately, the spatial resolution of ERPs is relatively poor (again, this aspect of ERP technology is also improving due to high density electrode arrays and improved source localization algorithms). Thus, the particular characteristics of these two measurement techniques in large part determine what type of data can be derived and, more fundamentally, what types of questions can be asked in research utilizing them. Of course, combining these two methods is an ideal solution for overcoming their individual limitations (e.g., de Haan & Thomas, 2002).

Moreover, as technology in biologically based areas of inquiry becomes increasingly complex and more specialized skills are required to carry out research employing these tools, researchers will naturally become more knowledgeable in the use of one particular methodology and measurement technique (e.g., fMRI). This increasing specialization may have the unintended consequence of narrowing the focus of model building and hypothesis generation. Clearly, no one individual can master all available techniques, thus pointing to the importance of collaboration across disciplines in research examining multiple levels of analysis. Ideally, a comprehensive research program would employ several measures at various levels of analysis, such as molecular genetic, neuroendocrine, functional brain imaging, neuropsychological assessment, and observational ratings of behavior.

EXPERIENCE AND THE BRAIN: A BRIEF HISTORY

From the perspective of modern neuroscience and associated disciplines, it is a given that certain types of experience result in enduring physiological changes in the brain, by way of a process referred to as neural plasticity. These changes can occur and are observed on one or more levels of analysis, including molecular, cellular, neurochemical, and anatomical brain systems, and are manifested at the highest order by changes in behavior. However, in fairly recent scientific history the fundamental question of whether experience resulted in changes in the physiological characteristics of the brain did not have a clear answer, and was a subject of active empirical inquiry.

In a comprehensive historical review of research on the relationship between experience and the brain, Rosenzweig, Bennett, and Diamond (1972) reported that the earliest recorded scientific account of physical changes in the brain as a result of experience was written in the 1780s by Michele Gaetano Malacarne, an Italian anatomist. He experimented with two dogs from the same litter, as well as pairs of parrots, goldfinches, and blackbirds, each pair from the same clutch of eggs. He trained one member of each pair to perform various tasks (in the case of the dogs) and to make specific vocalizations (the birds). He did not train the other member of the pair. After the experiment ended, he examined the animals' brains, and found that there were more folds in the cerebellum of the animals that had gone through the training procedure. Given that the cerebellum is involved in motor functioning, finding increased complexity in this part of the brain was consistent with the intensive training.

In 1791, the physiologist Samuel Thomas von Soemmering wrote that anatomical measurements might demonstrate the effects of experience on the brain, most likely in reference to the work by Malacarne (Renner & Rosenzweig, 1987). Beyond this single reference to Malacarne's work, there is no indication that any other scientists during this era attempted to follow up on this line of research (Rosenzweig et al., 1972).

In the late nineteenth century, scientists became interested in the relation between intellectual ability and training and brain anatomy in humans. Darwin (1874) wrote:

> I have shown that the brains of domestic rabbits are considerably reduced in bulk, in comparison with those of the wild rabbit or hare; and this may be attributed to their having been closely confined during many generations, so that they have exerted their intellect, instincts, senses and voluntary movements but little. (p. 53)

In this passage, Darwin is pointing out not only the hereditary nature of brain size, but also attributes it to the rela-

tive experiential deprivation of domestic rabbits compared to wild rabbits.

In the early part of the twentieth century, a scientist and inventor named Elmer Gates claimed that the results of research he conducted, similar to that of Malacarne, demonstrated support for his hypothesis of "brain building" (Renner & Rosenzweig, 1987). Gates theorized "that every conscious mental operation or experience creates in some part of the brain or nervous system new structural changes of cell and fiber . . . producing the embodiment of more mind" (1909, as cited in Renner & Rosenzweig, 1987). Gates apparently did not publish his research findings in any scientific journals; however, some of his work appeared as a series of articles in a publication called *The Metaphysical Magazine* (Renner & Rosenzweig, 1987).

In addition, Gates did not hesitate to extrapolate his work to humans. He is further quoted as saying: "The applications of these principals to human education is obvious. . . . Under usual circumstances and education, children develop less than ten percent of the cells in their brain areas. By processes of brain building, however, more cells can be put in these otherwise fallow areas, the child thus acquiring a better brain and more power of mind. . . ." (pp. 9–10, as cited in Renner & Rosenzweig, 1987). Although Gates did not quite have the details of the impact of experience on brain development correct, his bold (at the time) statements may yet prove prophetic.

In more mainstream scientific and academic circles, researchers in the last quarter of the nineteenth century failed to show that training resulted in changes in the gross anatomy of the brain. In 1895, Cajal speculated, based on the assumption that the brain does not produce new neurons, that cerebral exercise might lead to the establishment of "new and more extended intercortical connections." This notion was not to be confirmed until many years later. However, at the end of the nineteenth century, the hypothesis of an intrinsic relationship between brain size and use of the brain or intellectual ability was generally abandoned. In addition, a consensus in the scientific community developed that such anatomical changes could not be detected (if indeed there were any). Hence, scientists of this era generally gave up looking for experientially induced changes in brain anatomy.

In 1949, Donald Hebb published his seminal book, *The Organization of Behavior,* in which he outlined a comprehensive theory of behavior that attempted to integrate the physiology of the nervous system and behavioral psychology (Hebb, 1949). A central tenet of his theory was that experience modifies the brain. A few years before this book was published, Hebb (1947) reported on the first experiment that systematically compared the problem-solving ability of rats reared in different conditions. He reared two litters of rats in his home as pets. They were frequently out of their cages and had free run of Hebb's house (Hebb, 1949). At maturity, these home-raised rats scored better than laboratory-reared rats on the Hebb-Williams maze (Hebb & Williams, 1946). Hebb concluded that "*the richer experience of the pet group during development made them better able to profit by new experiences at maturity*—one of the characteristics of the 'intelligent' human being" (Hebb, 1949, p. 299, italics in the original). Subsequent replications of Hebb's research under more controlled experimental conditions resulted in similar findings (e.g., Hymovitch, 1952).

However, none of the investigators in this subsequent set of experiments discussed any role that differential brain development may have played in the behavioral results obtained. However, the thinking of these scientists was no doubt influenced by the prevailing dogma of the first half of the twentieth century concerning brain development, which held that the anatomy and physiology of the brain was fixed by a genetic blueprint. It was believed that development proceeded according to this fixed plan until adulthood, after which change in the brain was not possible, except in the case of injury and/or decay from the aging process (Renner & Rosenzweig, 1987). However, during the 1950s, some neuroscientists began to speculate that subtle aspects of the brain may be impacted by experience, such as connections between neurons and neurochemistry (Bennett, Diamond, Krech, & Rosenzweig, 1964). Unfortunately, at this time, scientific methods did not exist that would reliably allow detection of these types of brain processes, and the question reverted to a more speculative realm.

During the early 1960s, a group of scientists at the University of California, Berkeley, began to examine the relation between neurochemical changes in the brain and learning in rats. The results of a series of their early experiments confirmed their specific hypothesis of a linkage between increased cortical activity of the neurotransmitter acetylcholine (ACh), greater efficiency of synaptic transmission, and successful problem solving in rats (e.g., Krech, Rosenzweig, & Bennett, 1960). Indeed, rats who were good at learning mazes had higher ACh activity than those who were not, and it was later found that stimulation and training did, in fact, increase levels of ACh (e.g., Bennett et al., 1964). This early work lead to a now classic line of research comparing the brains of rats reared in complex environments to those reared in standard laboratory conditions.

NEURAL PLASTICITY

A recent search of literature databases in medicine and psychology by the authors yielded nearly 10,000 citations that used the term "neural plasticity" as a key word or phrase, with a seemingly exponential increase in the number of publications over the past 5 to 10 years. It would be a daunting task to synthesize the knowledge that has accumulated about neural plasticity generally, and in particular to attempt to apply this knowledge systematically in order to gain a clearer understanding of a behavioral phenomenon, such as resilience. Nearly all of the work on neural plasticity is highly technical, conveyed within specialized reports concerning the mechanisms of neural plasticity at nearly all levels of analysis, including neurochemical, molecular, genetic, and neuroanatomical, intended for a highly trained audience of neuroscientists and biologists (among others). Being able to glean something about the relevance of neural plasticity for resilience (or for that matter, any behavioral phenomenon) from such a highly technical literature is a formidable undertaking.

The study of neural plasticity in modern neuroscience and associated disciplines has brought to bear a wide range of empirical methodologies to describe all aspects of the observed dynamic processes at the synaptic and cellular levels that appear to underly neural plasticity. Neural plasticity is increasingly viewed as a dynamic nervous system process that orchestrates nearly constant neurochemical, functional, and structural CNS alterations in response to experience. It is possible that advances in the study of neural plasticity could be fruitfully employed as a model to begin to hypothesize about the biological underpinnings of resilience. Several authors recently have alluded to the possible relation between the principles of neural plasticity and resilience (e.g., Cicchetti, 2003; Curtis & Cicchetti, 2003; Davidson, 2000; Masten, 2001; Nelson, 1999), and at the conceptual level, there are several intriguing parallels between processes involved with neural plasticity and resilience. Thus, it is important to examine resilience in the context of this vast body of knowledge on neural plasticity, and to evaluate whether neural plasticity may have relevance for the study of a biology of resilience. The following sections attempt to provide a broad conceptual overview of neural plasticity, and briefly examine some of the fundamental mechanisms underlying this inherent characteristic of the brain and how it may potentially inform the study of resilience.

Plasticity: General Definition

Webster's dictionary (1979) defines plasticity as "the capacity for being molded or altered." The term plasticity is employed in a variety of fields in modern science, and until fairly recently has primarily been applied in engineering and physics to index the ability of material to change characteristics depending on environmental and thermodynamic conditions. In its purest semantic sense, plasticity simply connotes the capacity of something (e.g., a material, an organism) to change, and does not take into account the context (i.e., precipitating event[s]) in which this change may come about. In practical usage, however, it is assumed that such change takes place as a result or consequence of an event or context in the environment (e.g., expansion of a material due to increased temperature).

Plasticity can also be used to describe change in the sense of "recovery," in that the degree to which a material or system is plastic modulates the degree to which that material or system can return to its "original" condition prior to some event that leads to its modification (e.g., brain injury). However, the processes described by plasticity would imply that, regardless of the degree of recovery back to an original structural or functional state, no material (or organism) can ever return to an exact copy or duplicate of a previous condition once that initial condition has been altered. For example, a steel beam expands and contracts without structural disruption within a specified range of temperature. However, if the temperature goes beyond this range (e.g., if it becomes too hot) then the beam changes (melts), but is not able to return to its original shape after the temperature returns to normal. Analogously, the human brain is able to recover from some injuries through self-repairing mechanisms in the central nervous system. However, if the structural integrity of the physical substrate is disrupted to a great degree (e.g., a significant part of the frontal cortex is destroyed via head injury), then the organism may survive but is permanently changed, as the brain's restorative mechanisms are not able to cope with the degree of change. However, unlike the steel beam whose molecular structure may remain unchanged in the context of the expected range of expansion and contraction due to thermal changes in the environment, an organism may exhibit some degree of functional and/or behavioral recovery from brain injury, but there inevitably are differences in underlying cellular and neuroanatomical structure.

Neural Plasticity: Fundamental Concepts from Neuroscience

Plasticity is of particular interest in the field of neuroscience, and is considered to be one of the fundamental functional mechanisms of the central nervous system. In modern neuroscience, the term neural plasticity generally refers to modification of the component neural substrate of

the brain and other central nervous system structures as a result of some change in conditions (generically referred to as experience), with the assumption that such modification is adaptive for the continued survival and optimal functioning of the organism. Several decades of empirical investigation have revealed that plasticity is an inherent property of the central nervous system, and that the manifestation of plasticity is part of a normative process in the mammalian central nervous system (e.g., Kempermann, van Praag, & Gage, 2000). Indeed, it has been suggested that the plasticity of the human brain, which is broadly reflected behaviorally by learning and adaptation, is one of the central defining mechanisms of the evolutionary success of the human species (Hyman & Nestler, 1993).

There is evidence that all levels of the central nervous system exhibit some form of plasticity, typically in a "bottom-up" fashion, with changes at lower levels supporting (and precipitating) changes at higher levels of the central nervous system. Many, if not all, of the lower-level changes in neural functioning are believed to underlie changes in higher-level neural processes as well as neuroanatomical structure that, in turn, are reflected in changes at higher levels of analysis (e.g., neural networks, learning, memory), producing both short-term and long-term changes. The manifestation of such changes in the neural substrate takes place at varying timescales, from milliseconds to years (Destexhe & Marder, 2004). Within neuroscience, it is clear that the term neural plasticity is used to refer to a multiplicity of processes occurring at many levels of analysis. In addition, the study of neural plasticity must include identifying not only what changes are to be classified as neural plasticity (i.e., what constitutes neural plasticity), but also the mechanisms by which these changes take place (i.e., how does neural plasticity occur), as well as the adaptive, functional, and behavioral outcomes of these changes (what are the consequences of neural plasticity) across multiple levels of analysis. Of course, in many instances the changes that constitute plasticity and the mechanisms by which these changes take place must be described in tandem in order to characterize the broad process referred to as neural plasticity.

It also is important to consider neural plasticity broadly in terms of a nonlinear dynamic feedback system, one that constantly reshapes and reorganizes the organism. Previous neuroplastic changes inevitably influence the form of, and processes underlying, changes that might take place in the future (e.g., Elbert et al., 2001; Johnson, 1999). Neural plasticity takes place as a result of some event (or experience) impinging upon the organism that precipitates a change in the central nervous system. After the change in the system has taken place, the organism is essentially "different," and the manifestations of this change are represented at multiple levels (although at varying time scales), including behavior (e.g., memory or learning). Finally, such changes can potentially bring about further instances of neural plasticity.

Neural plasticity is not only a property of the developing brain but of the adult brain as well, although the central nervous system is more likely to undergo changes during early development and within certain sensitive periods of development. Moreover, neural plasticity must be thought of in the context of the overall developmental time course of an organism, with neural plasticity being more or less likely to occur at different time points along an organism's developmental trajectory (e.g., during sensitive periods—see Cicchetti & Tucker, 1994a, 1994b).

In sum, neural plasticity is a multidimensional, highly dynamic process that is strongly consistent with the principles of self-organization of the brain. The primary dimensions of neural plasticity that need to be considered are temporal (i.e., potential developmental constraints as well as time course of neural change), level of action (i.e., cellular, genetic, neural network), precursors (i.e., precipitating event, such as enriched experience, injury), and finally, the resultant change in terms of modified neural structure function and/or observable behavior (see Figure 1.1).

Such a broad systems approach to the understanding of neural plasticity points to the necessity of a multidisciplinary approach to the potential translation of a vast body of information concerning the biochemistry of neural plasticity to the level of observable behavior. The following sections provide a brief overview of some of the types of neural plasticity, and some of the mechanisms underlying them, and begin to identify potential candidate processes that might inform the study of a biology of resilience.

Forms of Neural Plasticity: What Changes

Generally, neural plasticity has predominantly been thought of as reorganization within systems or subsystems of the central nervous system, evidenced by changes in anatomy, neurochemistry, or metabolism, and is most typically studied in the context of several types of events impinging on the central nervous system. Such measures may include physical damage to neural structures, sensory deprivation, normal development of the organism, and a variety of environmental inputs generally referred to as experience (Bavelier & Neville, 2002; Nelson, 2000b). The neuroplastic changes that take place are often dramatic, and can include observable changes in the neural substrate that are translated into changes observable at the behavioral level. Such changes that are the hallmarks of

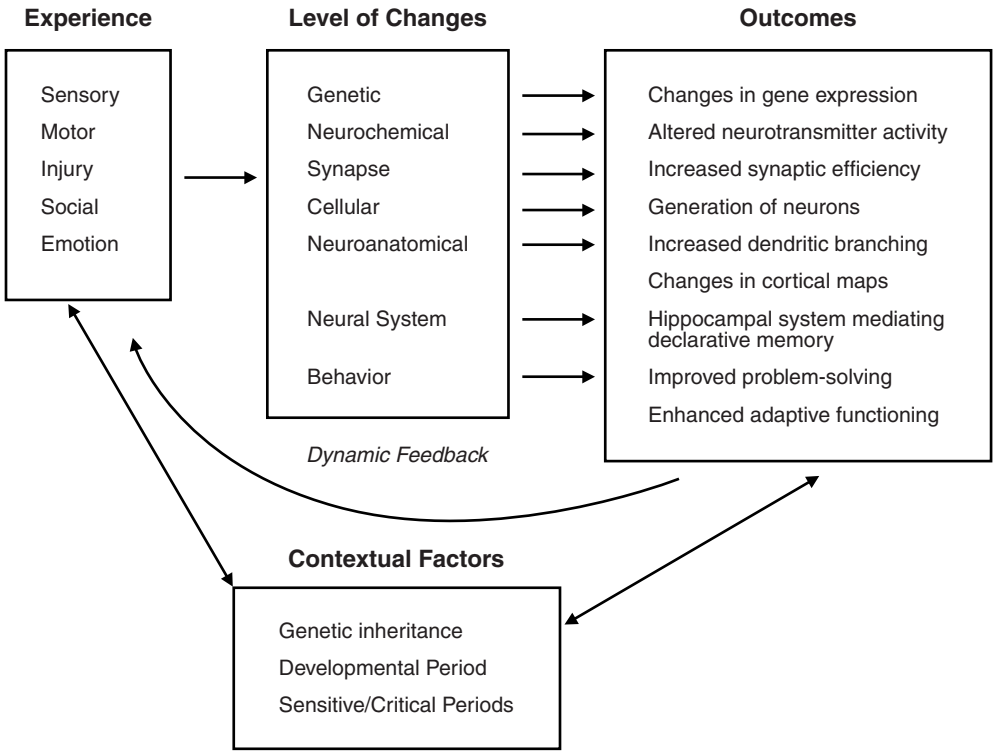

Figure 1.1 A general schematic of neural plastiticy.

plasticity can occur on one or more levels of analysis, including molecular, cellular, neurochemical, neuroanatomical, and at the level of brain systems (Nelson, 1999).

Neuroplastic changes can be manifested in a number of ways, including: the characteristic behavior of single ion channels; the generation of new neural circuitry; dendritic outgrowth and the formation of synapses; the strengthening and weakening of some neural circuits through the processes of synaptogenesis and synaptic removal, respectively; and the sprouting of new axons, or elaborating their dendritic surfaces (Kolb & Gibb, 2001). Advances in the development of sophisticated molecular technologies and sensitive brain-imaging methods have enabled scientists to enhance their comprehension of the functional importance of dendritic spine heterogeneity (Segal, 2005). Empirical evidence suggests that dendritic spines may undergo complex alterations in both shape and number over time following exposure to novel experiences (Segal, 2005), thereby relating these spines to neuronal plasticity and long-term memory formation. Finally, these changes often are exhibited through observable behavioral changes. The following sections briefly summarize a sampling of different types of neural plasticity across several levels of analysis.

Short-term synaptic plasticity involves changes in synaptic activity that occur depending upon the frequency of stimulation and the history of prior activity (Schwarz, 2003). This type of plasticity allows synaptic strength to be modulated as a function of previous activity and can result in large changes in responses during physiologically relevant patterns of stimulation. Hebb (1949) originally suggested that synaptic contacts are modified as a consequence of simultaneous activation of the pre- and post-synaptic neuron (hence, the oft-cited phrase from Hebb, "cells that fire together wire together"). Long-term potentiation (LTP) and long-term depression (LTD) are forms of use-dependent plasticity at the synaptic level that have been the focus of a great deal of inquiry because of their likely correlation with some forms of learning and memory.

Synapses may show declines in transmission or increases in synaptic efficiency over time courses ranging from seconds to minutes to hours (in the case of LTP). These short- and long-term modulatory effects that neurotransmitters exert on their target neurons by way of changes in synaptic activity can be viewed as the fundamental basis of neural plasticity (Nestler & Duman, 2002), and serve as the foundation of higher levels of change within the central nervous system. For example, it is cur-

rently believed that LTP may be a key metabolic mechanism for memory formation (e.g., Chen & Tonegawa, 1997; Malenka & Nicoll, 1999), and it has been further suggested that LTP and LTD are fundamental in the process of behavior change based on experience (Post & Weiss, 1997). Other forms of synaptic plasticity also have been examined as well. For example, synaptic scaling has been examined as a general form of use-dependent regulation of synaptic transmission (e.g., Turrigiano, Leslie, Desai, Rutherford, & Nelson, 1998).

Further elaboration on neural plasticity at the cellular level is beyond the scope of this chapter. Although far removed from behavior, it is important to recognize that these molecular and cellular processes are the very building blocks that form the scaffold for neural plasticity that eventuates in changes in neuroanatomy and neural networks that are then manifested at the level of observable behavior.

Recent work has demonstrated neural plasticity in a wide range of neuroanatomical structures in the cortex. One example of this is reorganization that occurs in the motor cortex, with changes in the motor homunculus (the nonlinear map of the body across the motor cortex) observed as a consequence of the acquisition of motor skills (Steven & Blakemore, 2004). In addition, extensive training of specific limb movements in mammals leads to observable reorganization of the neural substrate of the motor cortex (e.g., Karni et al., 1995; Pascual-Leone et al., 1995).

The somatosensory cortex also has shown evidence of reorganization of representational zones as a result of somatic stimulation. In a well-established line of inquiry with musicians, Elbert and colleagues (e.g., Elbert et al., 1995; Pantev, Engelien, Candia, & Elbert, 2001) have shown enlargement in those areas of the somatosensory cortex of musicians devoted to the particular fingers used to play their instrument. Similarly, the cortical representation of the reading finger in blind Braille readers is increased compared to that of their nonreading fingers and compared to the fingers of sighted and blind non-Braille readers (Pascual-Leone & Torres, 1993). Also, there is evidence that extensive perceptual learning (experience) contributed to the correction of vision deficits in children who previously experienced visual deprivation (Grigorieva, 1996).

Other research has demonstrated neural plasticity in the form of local remapping in the primary visual cortex (V1) in animals in response to discrete retinal lesions. Most knowledge concerning alterations of the visual cortex in humans as a result of experience comes from studies of individuals deprived of sight. There is a large body of evidence indicating that the visual cortex in persons without sight is responsive to tactile and perhaps auditory stimulation (e.g., Sadato et al., 1996). Neuroimaging studies have enabled the direct observation of neural plasticity in humans, and new findings continue to be published at an increasing rate demonstrating structural and functional neural plasticity of many areas of the human brain. For example, a recent structural MRI study showed that learning a second language increased the density of grey matter in the left inferior parietal cortex, with the degree of increase modulated by not only the degree of proficiency attained in the language, but also the age of acquisition (Mechelli et al., 2004).

Neural Plasticity Associated with Environmental Enrichment

Nearly all of the classic and ongoing studies of neural plasticity in animals and humans involve neuroplastic changes that impact the structure and function of primary sensory processes. Much less is known about the influence of experience on cognitive abilities, intellectual functioning, or affective and social development. A vast body of studies from the animal literature point to the direct impact of enriched rearing (relative to standard laboratory cages) on the brain and behavior of several animal species, most typically in rats. The enriched conditions (EC) for rats typically involve being housed in larger-than-standard cages, with a small maze and an assortment of toys inside, whereas control rats are reared in cages by themselves and do not have any contact with other rats. This extensive literature has indicated that being reared in enriched conditions is associated with changes in laboratory animals in neurochemical, physiological, neuroanatomical, and behavioral systems, and has revealed not only changes in the neural substrate of rats but also in their behavior.

Early studies examined changes in neurotransmitter systems in rats in response to rearing in enriched conditions, and these studies consistently demonstrated that the total activity of ACh and ChE was significantly greater in the cortex of the EC raised rats than in control rats reared in isolation, with the greatest increase in the visual cortex (e.g., Bennett et al., 1964; Krech, Rosenzweig, & Bennett, 1962). In addition, rats reared in enriched conditions were shown to have a 6% greater RNA to DNA ratio, suggesting an overall higher metabolic activity in the brains of rats reared in enriched conditions (Bennett, 1976), and there is evidence to suggest that rearing in complex environments enhances the efficiency of molecular transport through axons (Grouse, Schrier, Bennett, Rosenzweig, & Nelson, 1978). In addition, electrophysiological studies have demonstrated that rats reared in enriched conditions

modify their behavior more quickly in response to environmental feedback (e.g., Leah, Allardyce, & Cummins, 1985), and other evidence points to decreased nervous system excitability in EC rats (Juraska, Greenough, & Conlee, 1983).

Numerous studies have demonstrated that the most obvious gross anatomical difference between EC reared rats and those raised in isolation is in total weight of the cortex. Replicated over 16 successive experiments, Rosenzweig et al. (1972) reported that the total cortical weight of EC rats was on average 5% greater than that of control rats, with an average 7.6% increase in the occipital (visual) cortex, 4% in the ventral cortex (which includes the hippocampus), and a 3% increase in the somatosensory cortex. These changes also were found in rats blinded before being placed in the enriched condition, or even when the differential rearing took place in total darkness (Rosenzweig et al., 1969). It thus appears that the brain effects seen in enriched rats are due to multisensory stimulation from the enriched environment, and is not restricted to the visual modality. The observed increase in cortical weight has generally been attributed to, among other factors, a 20% to 30% increase in the number of glial cells in the brains of EC rats (Diamond et al., 1966). EC rats also exhibit thicker cortical regions, with an average increase in thickness of 5% overall (Diamond, Krech, & Rosenzweig, 1964), as well as consistently larger neuronal cell bodies and nuclei than control rats (Diamond, Linder, & Raymond, 1967).

Although a 5% increase in the weight of the cortex may not seem particularly large in an absolute sense, changes of this magnitude in such a central component of the central nervous system can, and do, result in large behavioral changes. For example, destruction of less than 5% of the tissue in the rat occipital cortex can result in a functionally blind animal (Renner & Rosenzweig, 1987), and small lesions in the cortex caused by stroke or injury in humans can result in behavioral changes of great magnitude, such as aphasia or other disorders.

Over the past 30 years, Greenough and his colleagues have addressed how environmental complexity exerts an impact on the actual organization of the brain. Initial work from this laboratory demonstrated that rats reared in complex environments consistently had more high order dendritic branches and more dendritic synapses per neuron in several occipital cortical cell types and the temporal cortex, but not in the frontal cortex (e.g., Greenough, Volkmar, & Juraska, 1973). Environmental enrichment also appears to actively induce synapse formation (Greenough, Hwang, & Gorman, 1985). In addition, rats reared in enriched environments have increased relative density of dendritic spines, more synapses per neuron, and more multiple synaptic boutons (Jones, Klintsova, Kilman, Sirevaag, & Greenough, 1997; Turner & Greenough, 1985). Other features indicative of greater synaptic efficiency, such as larger synaptic contacts, also have been found in EC rats (e.g., Turner & Greenough, 1985).

Neuroanatomical changes as a result of enriched rearing conditions also have been found in brain regions outside the cortex. For example, Floeter and Greenough (1979) have demonstrated structural plasticity of Purkinje cell bodies, critical in coordination of movement, in the cerebellum of the Japanese macaque as a function of rearing in differential environments. Somewhat more recently, EC rats have been shown to undergo broad structural modifications of the cerebellar cortex as a result of complex motor skill learning (e.g., Kleim et al., 1998).

Given the importance of the role the hippocampus plays in memory, the influence of differential rearing experiences on this brain structure would be of particular interest. Rats reared in enriched environments have been reported to have more granule cells in the dentate gyrus, a structure adjacent to the hippocampus and a key component of the hippocampal memory circuit, as well as increases in dendritic branching and overall size of the dendritic field (e.g., Susser & Wallace, 1982). Mice reared in enriched conditions showed an overall 15% increase in the depth and number of neurons in the hippocampus (Kempermann, Kuhn, & Gage, 1997).

Behavioral Effects of Enrichment

The most consistent finding across studies is that of superior performance of EC animals in complex problem solving. For example, rats reared in enriched environments show advantages on tasks involving reversal of previously learned visual discrimination (Krech et al., 1962) and other tasks requiring response flexibility (M. J. Morgan, 1973), and are superior at response inhibition in a bar pressing task (Ough, Beatty, & Khalili, 1972) and passive avoidance tasks (e.g., Lore, 1969).

Many studies of learning in rats reared in differential environments have involved spatial problem-solving tasks with various types of mazes, demonstrating improved learning in EC rats (e.g., Brown, 1968) and mice (Kempermann et al., 1997). This superior maze performance appears to be long lasting, even with a 300 day delay period between being taken out of the complex environment and the beginning of the testing period (Denenberg, Woodcock, & Rosenberg, 1968). Others have demonstrated that pregnant rats housed in enriched conditions had offspring who performed better on a Hebb-Williams maze than offspring

of mothers housed in isolated and control environments while pregnant (Kiyono, Seo, Shibagaki, & Inouye, 1985). EC rats also demonstrate more organized and complex bouts of interactions with objects than control rats, perhaps reflecting a higher level of exploratory behavior (Smith, 1972). In addition, mice reared in enriched conditions were less fearful, and exhibited lower levels of both state and trait anxiety (Chapillon, Manneche, Belzung, & Caston, 1999).

Although there are no direct human analogs to animal studies of rearing in enriched versus impoverished conditions (of course, such studies would be unethical), some nearly analogous nonexperimental paradigms involving human enrichment do exist. Programs, such as Head Start, and more recently the Abecedarian Project, have attempted to improve cognitive development and social competence in high-risk young children (e.g., Ramey & Ramey, 1998; Zigler & Valentine, 1979). The Abecedarian Project was designed as a research and intervention study, in order to test whether mental retardation correlated with inadequate environments could be prevented by providing intensive, high-quality preschool programs beginning shortly after birth and continuing at least until children entered kindergarten (Ramey & Ramey, 1992).

Generally, outcome studies of Head Start and other similar programs have shown initial IQ gains followed by subsequent declines, but with positive impact on general school and social competence (Lazar, Darlington, Murray, Royce, & Snipper, 1982). Those who participated in the Abecedarian Project, aside from a small overall advantage in IQ (approximately 5 points overall compared to children not enrolled in the Abecedarian Project), at age 12 and at age 15 also scored significantly higher on a variety of achievement tests, with the intervention group exhibiting a 50% reduction in the rate of failing a grade during elementary school (Campbell & Ramey, 1995). This project in particular has provided evidence that those children who began the program with greater risk benefited the most (Martin, Ramey, & Ramey, 1990). For example, children whose mothers had IQs less than 70 had IQs, on average, 21 points higher than the control children at 4½ years of age. This is in contrast to the mean gain of approximately 8 IQ points for the intervention sample as a whole.

In addition to the measured behavioral and intellectual advantages found in those children who participate in early enrichment interventions, one study has reported the impact of an early human enrichment program on the island of Mauritius on psychophysiological measure of arousal and orienting (Raine et al., 2001). At age 11 years, children who were randomly assigned to an enriched nursery school intervention at ages 3 to 5 years showed greater skin conductance amplitude, faster rise times and recovery, both at rest and during a continuous performance task, compared to children who received a normal preschool educational experience. In addition, children who had experienced the enriched preschool program showed less slow-wave EEG activity both at rest and during a continuous performance task. These findings suggest both better information processing as well as a greater degree of cortical maturation in the children who participated in the early enrichment intervention (Raine et al., 2001). The results of this study are striking in that they demonstrate a strong association between early enriched preschool experience in humans and later direct measures of brain and psychophysiological functioning.

In a longitudinal follow-up of this sample, the children who participated in the environmental enrichment program at ages 3 to 5 years had lower scores on self-report measures of schizotypal personality and antisocial behavior at age 17 years, as well as showed lower rates of self-reported criminal offenses at age 23 years, compared to those who did not participate in the enrichment program (Raine, Mellingen, Liu, Venables, & Mednick, 2003). These effects were most pronounced in those children who showed signs of malnutrition at age 3 years.

Mechanisms of Neural Plasticity: How Does This Change Take Place?

The mechanism of experience-based neural plasticity begins with the organism interfacing with its environment. Experience "enters" the brain by way of afferent inputs through the sensory modalities. These signals are then relayed via established neural networks to higher cortical areas where a myriad of processes ensure proper disposition of these inputs. There are many hypothesized mechanisms to account for neural plasticity at all levels of analysis, with discrete regulatory mechanisms that occur at each level of neuroplastic change. It also appears that mechanisms governing higher levels of neural plasticity (e.g., changes in representational maps in somatosensory cortex) build upon fundamental processes at the cellular and molecular levels.

The fundamental processes underlying neural plasticity at all levels are believed to be two mechanisms underlying the modulatory effects of neurotransmitters. One of these is protein phosphorylation and the other is the regulation of gene expression (Hyman & Nestler, 1993). It would appear that protein phosphorylation is the major molecular mechanism of neural plasticity, and is generally the mechanism by which the modulation of

neuronal function is achieved, through alterations in the functional state of many different types of neuronal proteins, such as ion channels, neurotransmitter receptors, and processes by which neurotransmitter storage and release is regulated (Hyman & Nestler, 1993). Protein phosphorylation regulates both presynaptic and postsynaptic neurotransmitter receptors, with corroborative evidence suggesting that phosphorylation alters the functional activity of receptors (Hyman & Nestler, 1993). In addition, protein phosphorylation plays a central role in cell growth, differentiation, and movement.

The second primary mechanism by which neurotransmitters can effect long-term changes on the function of target neurons is by regulating gene expression within those neurons. Such changes in gene expression appear to produce quantitative as well as qualitative changes in the protein components of neurons, including, for example, alterations in the numbers and types of ion channels and receptors present on the cell membrane as well as levels of proteins that regulate the morphology of neurons and the numbers of synaptic connections they form (Hyman & Nestler, 1993). Further, neurotransmitters continually regulate neuronal gene expression as a way to fine-tune the functional state of neurons in response to many varied synaptic inputs (Hyman & Nestler, 1993). Regulation of neural gene expression by neurotransmitters can, in some cases, produce quite long-lasting changes in virtually all aspects of neuronal functioning.

Within the brain, gene expression can be activated by both normative and nonnormative (i.e., drugs) physiological processes and experience. Such endogenous or exogenous processes initiate a cascade of events, beginning with incoming afferent sensory information, activate increasingly higher-level neural networks in the brain, eventually resulting in activation of neurons and networks involved with higher-order processing (e.g., language, cognition). In turn, within each of the cells involved in this process, the generation of action potentials as well as the activation of second messenger systems alters the rate of expression of specific genes and, as a result, the expression of multiple types of neuronal proteins (Hyman & Nestler, 1993). The altered levels of these proteins produce changes in processing of subsequent synaptic information by these neurons, thus leading to further changes in the processing of sensory input. It is believed that such mechanisms account for many of the longer-term consequences of experience on brain functioning. Such a regulatory process, whereby activity in one neuron regulates gene expression in another neuron, is referred to as transsynaptic regulation of gene expression, and a class of proteins termed transcription factors (e.g., c-Fos, Zif268) plays a central role in the regulation of neural gene expression (Hyman & Nestler, 1993).

Generally, changes to the central nervous system mediated by protein phosphorylation do not involve changes in protein synthesis and, therefore, are likely to have a rapid onset, be more readily reversible, and have a shorter duration compared to neural plasticity mediated by gene expression. However, both of these processes serve to mediate the long-term effects of experience on the brain. The biochemical and molecular changes brought about through these two processes, through a cascade of intermediate neural processes, lead to changes in the function and efficacy of synapses, changes in the processing of information by individual neurons, and ultimately to changes in the way multicellular neural networks within the brain communicate with each other (Hyman & Nestler, 1993). Protein phosphorylation and gene expression are in some ways considered to represent a form of molecular memory within individual neurons. Likewise, learning and memory at the level of the whole brain are mediated by accumulations of complex combinations of the fundamental types of changes in the function and efficacy of synapses brought about by these two basic processes.

The challenge of future research attempting to relate neural plasticity to particular behavioral phenomenona is to find associations between specific alterations in neural processes, brought about by phosphorylation and gene expression and behavior. This challenge is great, given the probable high degree of complexity of linkages between such distal processes, separated by multiple levels of analysis. Greenough, Black, Klintsova, Bates, and Weiler (1999) have proposed an integrative perspective on neural plasticity that may be a starting point for building a framework that enables the large gap between molecular and genetic processes involved with neural plasticity and the expression of behavior to be bridged. They advocate moving beyond a focus on synapses to a consideration of the process of neural plasticity occurring in surrounding tissue elements, cooperative regional neural networks, and diffuse endocrine modulatory effects. As increased understanding of the cellular mechanisms of neural plasticity accumulates, this new knowledge may prove to be fruitful for comprehending some of the molecular processes contributing to resilient functioning. To fully reap these potential benefits of such understanding, it is important that multidisciplinary collaborations take place between neuroscientists and developmental psychopathologists.

Connecting Neural Plasticity and Behavior

Greenough et al. (1993) have stressed that a necessary condition for the behavioral and brain effects of enrichment to be manifested in rats is direct physical interaction with the environment. Animals reared inside an enriched environment but kept in cages to prevent them from physically in-

teracting with the environment do not show the brain or behavioral effects of their littermates who are allowed to physically interact with the enriched environment (Ferchmin, Bennett, & Rosenzweig, 1975). There is also evidence that direct physical interaction with the environment may be important for human development, as exemplified by the work of Bertenthal, Campos, and Barrett (1984), suggesting that interaction with the environment produced by self-locomotion may be an important component of cognitive and emotional development in early childhood.

Together, these motor and sensory processes facilitate learning. How learning-related neuronal activity becomes translated into changes in the structure of neurons, and the mechanisms by which environmental experience becomes translated into structural modifications of neuronal connections, is not yet completely understood (Torasdotter, Metsis, Henriksson, Winblad, & Mohammed, 1998). It appears that the general mechanism responsible for this phenomenon is gene expression, which is one of the fundamental ways that cells adjust to changes and demands placed upon them (Greenough et al., 1993). This process involves the activation of genes in the nucleus of the cell, whereby messenger RNA (mRNA) is transcribed from the genes and codes for the proteins necessary for the formation of new synapses and dendrites. Several studies have begun to show a direct link between gene expression processes and the structural changes resulting from learning (e.g., Alcantra, Saks, & Greenough, 1991).

The second stage in the process of the impact of experience on the brain is in the output, or how these neuronal changes are translated into observed changes in behavior. If neurons have more synapses, then there is more opportunity for these synapses to form or participate in networks, leading to quicker and more efficient processing. This would in turn manifest itself in observable behavior. For example, the behavioral attributes that would correlate with greater levels of neuronal connectivity are most likely the hallmark characteristics of increased flexibility in problem solving seen in rats exposed to complex environments. Finally, it is important to note that the cycle of modification of an organism in an enriched environment builds upon itself in the form of a feedback loop from the second phase to the first, with subsequent change building upon change resulting from previous experiences with the environment.

Applications of Neural Plasticity to Resilience

Although the processes and mechanisms underlying neural plasticity are beginning to be fairly well understood, the difficult challenge faced by theorists and researchers in resilience is to devise a model whereby mechanisms of plasticity at the neural level could be linked to the behavioral manifestation of resilience in humans. However, it is important to explicitly examine whether the principles or processes of neural plasticity can contribute to our understanding of resilience. Although understanding the process and manifestation of neural plasticity may serve as a useful heuristic in the investigation of the biological correlates of, and contributors to, resilience, neural plasticity, per se, may not serve as the ultimate explanatory biological mechanism underlying resilience. Therefore, the primary question to be addressed in the following sections is how principles of neural plasticity might inform theory and research on resilience.

Neural Plasticity and Resilience: Some Potential Linkages

A multitude of studies have consistently demonstrated the brain's ability to recover varying degrees of functioning after lesions and other injuries to its physical structure (for review, see Kolb & Gibb, 2001). Kolb and Gibb outline three ways in which the brain could manifest neuroplastic changes in response to injury. In one scenario, there could be reorganization of the remaining, intact neural substrate, most likely involving the generation of new synapses in preexisting neural pathways. Alternatively, there could be development of entirely new neural circuitry. Finally, new neurons and supporting glia might be generated to replace some of these structures lost in the injury. It is important to consider that all of these regenerative processes most likely occur in tandem with one another, although the exact combination of processes utilized by the brain may vary depending on the developmental age of the organism at the time of injury (Kolb & Gibb, 2001). Finally, each of these neuroplastic processes may also be influenced by other factors, such as experience (i.e., training), neuromodulators, and hormones (Kolb & Gibb, 2001).

Analogous to neural plasticity that takes place in response to brain injury, resilience can be viewed as the ability of an individual to recover after exposure to trauma or adversity (Cicchetti & Rogosch, 1997; Masten et al., 1990). In this view, adversity is thought to exert a damaging effect on one or more neural substrates, and mechanisms of neural plasticity bring about recovery in an individual. This might lead to the conclusion that certain individuals, classified as resilient, may have some increased innate capacity (plasticity), above and beyond normative levels, to recover from environmental insults that impact the brain. This view of resilience conceives of adversity in the environment as "bad" for the brain, with recovery as an innate property of the brain itself. This perspective, however, does not

consider the impact of a positive environment, or of the individual's active attempts at coping, on such recovery (Cicchetti, 2002; Cicchetti & Rogosch, 1997).

Another conceptualization of resilience would be one of greater than normative resistance to the impact of environmental adversity on the brain, such that resilient individuals may not succumb to the potentially damaging effects that adversity may have on the brain and other biological systems. This view of brain-adversity interaction would not strictly be classified as involving neural plasticity. Thus, for these individuals, the term recovery of function may not apply, in that they did not "lose" function at all. Despite the fact that this distinction may seem trivial, it may lead to important theoretical implications when considering the contribution of biology, and, in particular, processes described as neural plasticity, to resilience. Although quite general, the distinction between these two formulations of resilience also can generate important research questions concerning the relation of neural plasticity to resilience. Such questions underscore the importance of utilizing longitudinal research designs that can begin to examine the bidirectional relation between the brain's capacity to either resist damage from adversity versus its restorative capabilities.

Investigating Neural Plasticity and Resilience

The rapid growth in sophisticated techniques that permit imaging of the brain directly has resulted in the availability of a variety of methodologies to developmental psychopathology researchers, many of which could be utilized to examine neural plasticity, as well as brain structure and function, in detail. These new tools make it possible to now undertake empirical investigations of the relation between neural plasticity and resilience, perhaps enabling an examination of the direct linkage of these two processes. Questions about how neural plasticity may play a role in the development and maintenance of resilient functioning could be addressed, as well as whether the mechanisms of neural plasticity may operate differently in individuals classified as resilient.

Included among these new tools are: ERPs, magnetoencephalography (MEG), MRI, fMRI, positron emission tomography (PET), single-photon emission-computed tomography (SPECT), and magnetic resonance spectroscopy (MRS). Diverse information about the brain that is correlated with neural structure and functioning can be obtained by these various imaging techniques, including: (1) brain metabolic processes, such as cerebral blood flow and blood volume, and glucose metabolic rate; (2) biochemical changes within brain cells, such as changes in neurotransmitter receptors; and (3) a sharp temporal resolution of brain functioning.

Among the compelling questions about resilient adaptation that could potentially be addressed utilizing brain imaging methodologies are: (1) Is brain structure and function different in resilient and nonresilient children matched on experiences of adversity? (2) Is the brain structure and function of resilient individuals who have experienced adversity different from normal children reared in nonadverse environments? (3) Are particular areas of the brain more likely to be activated in resilient than in nonresilient functioning during challenging or stressful tasks? (4) What aspects of brain structure and function differentiate individuals who function resiliently, despite experiencing early adversity, from those who function in a nonresilient fashion and who encounter adversity early in life (i.e., what is the role of early experience?) (5) Are there sensitive periods beyond which the achievement of resilience is improbable or is resilience possible to achieve across the life span? and (6) Are there changes over time in brain structure and/or functioning in individuals classified as resilient that may reflect processes of neural plasticity? The inclusion of neuroimaging techniques to the existing predominantly psychological approaches to charting the pathways to resilience, along with the biological and molecular genetic methods discussed next, results in many exciting discoveries about the complex processes that eventuate in competent outcomes despite the experience of significant adversity.

Aside from investigating the proximal relation between resilience and neural plasticity, there are several neurobiologically mediated processes (e.g., cognition, neuroendocrine functioning) that may have a direct relation to resilient outcome, some of which is described in the following sections. Although such processes may have a clear impact on resilient functioning, neural plasticity may, to some degree, be the common, underlying mechanism that mediates the relation between such processes and resilience. The behavioral manifestations of two of these realms, emotion and cognition, have been extensively investigated and their relation to resilience documented. In the sections that follow, possible links between the biological aspects of these phenomena and resilience is described.

Emotion and Resilience

Emotion encompasses a wide range of behavioral expressions and associated biological processes that play a vital role in many aspects of human development and adaptation. There are at least three primary, interrelated functional

realms of emotion in humans, including perception, expression, and regulation of emotion. The first part of this section focuses on emotion regulation as a key factor in resilient outcome, while the second part reviews and examines the relation between cortical EEG asymmetry, emotion, and resilient functioning.

One important contributor to resilience at the level of individual characteristics, and often cited as a potential protective factor against adversity in studies of resilience, is the ability to regulate emotion. Emotion regulation is conceived as the intra- and extra-organismic processes by which emotional arousal is redirected, controlled, modulated, and modified to enable an individual to function adaptively in emotionally arousing situations (Cicchetti, Ackerman, & Izard, 1995; Cicchetti, Ganiban, & Barnett, 1991; Gross, 1998; Thompson, 1990). Factors, such as organizational changes in central nervous system functioning, the ontogenesis of neurological inhibition systems in the prefrontal cortex, cerebral hemisphere lateralization, the development of neurotransmitter systems, children's growing cognitive and representational skills, and the development of a coherent sense of self, are some of the important intrinsic factors that shape the development of emotion regulatory abilities (Cicchetti et al., 1991; Cole, Martin, & Dennis, 2004; Eisenberg, 2002; Fox, 1994; Fox & Davidson, 1984; Gross, 1998; Kelley & Stinus, 1984; Schore, 1994; Tucker, 1981). Extraorganismic factors that exert an influence on the ability to regulate emotion include increased parental response and tolerance of affect and the parents' socialization of affective displays during interactions (Cicchetti et al., 1991). A number of characteristics are often referred to in the context of emotion regulation, including emotional reactivity, stress reactivity, temperament, or positive and negative emotionality (e.g., Davidson, 2000; Masten et al., 1999; Masten, 2001; Watson & Clark, 1984). Generally, these constructs represent the function of a diverse set of associated brain and neuroendocrine systems, which act in concert to produce and modulate the behavioral manifestations of an individual's response to emotional challenges and stressors.

There is an unfortunate paucity of empirical studies or conceptual work directly addressing if and how emotion and the regulation of emotion may serve as a protective factor in resilience. One of the primary questions involves whether individuals classified as resilient are to a large degree impervious to the typically insidious effects of stress, a view of resilient individuals as "invulnerable" (cf. Luthar et al., 2000); alternatively, it may be more accurate to characterize resilience in this context as the unique ability to react to stress in an adaptive way. Also important is the question of how resilient individuals manifest adaptation in the face of stress and adversity at the level of biology.

Resilience, Emotional Reactivity, and Startle

Davidson (2000) has suggested that the capacity for rapid recovery from negative affective events, one specific aspect of emotion regulation, may constitute a critical component of resilient functioning. Davidson (1998a) outlines what he terms an affective chronometry, which is used to describe the time course of affective responding during experimental paradigms investigating emotion-modulated startle. In particular, Davidson (2000) has hypothesized that for resilient individuals, who tend to maintain high levels of positive affect and well-being in the context of adversity, negative affect does not persist. Thus, in this view, resilience does not entail never experiencing negative affect, but rather involves the ability to recover more quickly and to more easily return to a positive affective state, and also a heightened ability to learn from the experience of negative affect (Davidson, 2000). The specific biological underpinnings of the ability to recover quickly from negative affect are more than likely mediated by a fairly complex neural network, which has been shown to include (but is not limited to) the amygdala, several regions of the prefrontal cortex, brain stem structures, the hippocampus, and aspects of the cingulate cortex (Davidson, 2000; LeDoux, 1996, 2002).

The startle reflex is a methodological tool that has historically been utilized to examine individual differences in reaction to emotional stimuli, and is widely held to be a measure sensitive to individual differences in emotional reactivity. Generally, startle is an involuntary response to a sudden and intense tactile, visual, or acoustic stimulus that occurs across many species (Koch, 1999; Landis & Hunt, 1939). The response pattern consists of a fast twitch of facial and body muscles, which includes eye lid closure along with contraction of facial, neck, and other muscles. It is generally believed that this pattern of responding is a primitive reflex intended as a defensive response to protect against injury and as a preparation of a fight/flight response (Koch, 1999). The startle response can be easily measured in humans by recording the timing and intensity of the eye blink, which is the typical manifestation of the startle reflex.

The neuronal circuitry underlying the acoustic startle reflex is well understood in rodents and is relatively straightforward. It consists of an afferent pathway from the cochlear root neurons in the inner ear to the neurons in the nucleus reticularis pontis caudalis, and then to the motoneurons in the facial motor nucleus or the spinal cord (in

the case of the whole body startle; Davis, Walker, & Lee, 1999). However, other investigators have attributed the startle reflex to a slightly more complex pathway, which may include other brain stem structures, such as the dorsal and ventral cohlear nucleus, the lateral superior olive, and the ventrolateral tegmental nucleus (see Koch, 1999, for a review). Although the neural pathway mediating the startle reflex in humans may be somewhat more complex, it is nonetheless analogous in function to the rodent model.

A vast body of research has consistently and reliably demonstrated that the startle reflex can be modulated with presentation of emotional stimuli in conjunction with the startle stimulus (e.g., Bradley, Cuthbert, & Lang, 1993; Cuthbert, Bradley, & Lang, 1996; Lang, 1995; Vanman, Boehmelt, Dawson, & Schell, 1996). Consistent findings in both animal and human research have shown that the startle reflex is amplified when accompanied by negative emotional stimuli and, conversely, the magnitude of the startle reflex is attenuated when the startle-inducing stimuli are accompanied by positive emotional stimuli.

Modulation of the startle reflex due to emotional context implies that a secondary circuit modulates the primary reflex pathway described. It appears that the central nucleus of the amygdala is critically involved in some forms of fear-potentiated startle, via a descending pathway from this structure to the nucleus pontine reticularis in the brain stem (Davis, 1992). Lesions of the central nucleus of the amygdala have been shown to block the fear-potentiated portion of the startle response, but not the baseline (e.g., Campeau & Davis, 1995; Vrana, Spence, & Lang, 1988). In addition, based on anatomical and lesion data, other structures have been implicated in the potentiation of the startle response, including the central gray and the bed nucleus of the stria terminalis, depending on the type of startle-enhancing stimuli employed (Davis et al., 1999). There has been less work directly examining the mechanism for the attenuated startle response seen with presentation of positive emotional stimuli, but it would appear likely that the amygdala also plays a central role in this phenomenon.

Investigators have examined individual differences in the human startle reflex in a variety of populations suffering from the sequelae of trauma or who are at risk for anxiety, including individuals with posttraumatic stress disorder (PTSD; e.g., Grillon, Morgan, Southwick, Davis, & Charney, 1996; C. A. Morgan, Grillon, Southwick, Davis, & Charney, 1996). In the context of threat, male combat veterans diagnosed with PTSD exhibited an exaggerated startle response. However, there are conflicting results in studies of baseline startle response (i.e., startle reflex, induced without a threat of aversive stimulus) in those with PTSD, with some investigations showing exaggerated baseline startle (e.g., Orr, Lasko, Shalev, & Pitman, 1995), and others revealing normal baseline startle (e.g., Orr, Solomon, Peri, Pitman, & Shalev, 1997). Women with PTSD resulting from sexual assault were found to have an exaggerated baseline startle response (C. A. Morgan, Grillon, Lubin, & Southwick, 1997). However, women with PTSD associated with childhood sexual abuse had a normal startle response (Metzger et al., 1999). These conflicting results have been attributed to differences in the aversive, threatening, or stressful context of the experiment (Grillon, Morgan, Davis, & Southwick, 1998).

In addition to the fairly extensive literature on startle and adults with PTSD, a few studies have examined the startle response in children with this disorder. One such investigation examined the startle response in a small sample of children with PTSD, aged 8 to 13 years (Ornitz & Pynoos, 1989). These investigators found a reduced baseline startle amplitude in both boys and girls compared to a group of control children. These findings, which are not consistent with findings of exaggerated startle in adults with PTSD, suggest that the age at which the PTSD-inducing trauma is experienced may have an impact on the type of effect seen in subsequent baseline and modification of startle responsiveness. In a startle study of adolescents, male offspring of parents with anxiety disorders were shown to have an increased fear-potentiated startle response (in a contextual threat condition) compared to low-risk control subjects (Grillon, Dierker, & Merikangas, 1998). The baseline startle magnitude was not different for the high-risk males. However, in this study, a sex difference emerged where female offspring of parents with anxiety disorders did not show elevated startle magnitude in the threat condition but exhibited elevated baseline startle magnitude. This is in contrast to an earlier study by Grillon, Dierker, and Merikangas (1997) where both male and female offspring of parents with anxiety disorders showed exaggerated baseline startle magnitude compared to a group of low-risk control children. However, the subjects in the latter study were several years younger than those in the Grillon, Dierker, et al. (1998) study. These authors suggest that the sex difference either may be a result of differences in brain structures that underlie affective responses to threat, or that development of those vulnerable to anxiety may proceed differently for males and females. Despite the discrepant findings obtained in these studies, which may be attributable to methodological differences, in general, the results of investigations with individuals diagnosed with PTSD or at risk for anxiety disorders have implied that startle reactivity may reflect the impact of en-

vironmental stressors on the brain systems mediating startle, and may in fact serve as a vulnerability marker for the development of anxiety disorders (Grillon et al., 1996).

In a recent investigation, the first of its kind, Klorman, Cicchetti, Thatcher, and Ison (2003) examined the baseline startle response in a large sample of children maltreated by their caregivers and a group of nonmaltreated comparison children. In this study, physically abused boys demonstrated a smaller startle-reflex amplitude and slower onset latency than did demographically matched nonmaltreated comparison children, consistent with findings in Ornitz and Pynoos (1989). In contrast, the younger maltreated girls in this sample demonstrated smaller startle amplitudes than younger comparison girls, whereas the older maltreated girls showed larger startle response magnitudes than did the nonmaltreated comparison girls of similar ages. The findings for the boys in this study are suggestive of a generalized defensive reaction that may lead to reduced responsiveness to noxious stimulation and subsequent down-regulation of the startle response that may be linked to reduced cortisol levels (Klorman et al., 2003). However, the findings for the girls in this sample are more difficult to interpret, given the relative dearth of studies investigating startle in traumatized women with PTSD, as well as the differences in the trauma experienced by men (e.g., combat) and women (e.g., sexual abuse/assault) with PTSD enrolled in most studies of startle.

Although there are some inconsistencies in the literature concerning the impact of adversity on the startle reflex, there is evidence to indicate that exogenous environmental influences do reliably effect this reflex and the underlying brain stem network that modulates this response. In particular, investigation of emotion-modulated startle is yet another tool that could be employed to further our understanding of the role of emotional regulation and reactivity in the promotion of resilience. Basic investigations of emotion-modulated acoustic startle could examine individual differences in the modulation of startle reactivity in the context of positive and negative foreground stimuli, such as emotionally toned pictures from the International Affective Picture System (IAPS; Lang, Bradley, & Cuthbert, 1995). Given that there is some Q-sort personality data indicating that individuals classified as resilient are more successful with emotion regulation (e.g., Cicchetti & Rogosch, 1997; Cicchetti, Rogosch, Lynch, & Holt, 1993; Flores, Cicchetti, & Rogosch, 2005), one prediction that could be tested would be that individuals manifesting resilient functioning would display less overall increase in magnitude of the blink response when presented with unpleasant pictures than would individuals not classified as resilient but with equivalent levels of exposure to adversity.

Davidson (2000) has employed emotion-modulated startle to examine the role of the time course in affective responding and has indicated that this detailed analysis may contribute to our understanding of resilience. Davidson (2000) has suggested that by placing the acoustic-startle probes at various points before, during, and after the presentation of the emotional stimulus, then, in addition to the measurement of the response itself, the anticipatory and the recovery phases can be measured. Davidson (2000) has hypothesized that a rapid recovery phase after negative emotional stimuli is important in the development of resilience. Such a scenario suggests that negative affect, although experienced by resilient individuals, does not persist, and may be part of a ubiquitous predisposition for rapid recovery in multiple biological systems after exposure to negative and/or stressful experiences (Davidson, 2000).

Hemispheric EEG Asymmetry

Another area of emotion research directly involving the brain that may hold promise for the study of resilience is examining hemispheric asymmetries in cortical EEG activity, where a growing body of evidence has indicated differential roles for the left and right prefrontal cortex in emotion (Hugdahl & Davidson, 2003). In general, it appears that the left hemisphere participates more heavily in positive affect, whereas the right hemisphere mediates negative emotion (see reviews by Davidson, Ekman, Saron, Senulis, & Friesen, 1990; and Fox, 1991). Several investigators have found that induced positive and negative affective states can reliably shift hemispheric asymmetry (e.g., Ahern & Schwartz, 1985; Davidson et al., 1990; Jones & Fox, 1992). Negative affect induced by showing negatively toned stimuli (often in the form of film clips) increases relative right prefrontal activation as measured by EEG, while positive affect resulting from viewing positive stimuli is associated with increased activation in left prefrontal. This effect also has been demonstrated using PET to measure regional glucose metabolism, a by-product of increased neuronal activity (Sutton, Davidson, Donzella, Irwin, & Dottl, 1997; see also Pizzagalli, Shackman, & Davidson, 2003, for a selective review of PET and fMRI investigations on human emotion that have discovered lateralized activations).

In addition, many investigations have found an association between dispositional affective style and baseline levels of asymmetric activation in the prefrontal cortex (e.g., Sutton & Davidson, 1997; Tomarken, Davidson, Wheeler, & Doss, 1992). Generally, individuals with greater left

frontal activation report more positive affect than those with greater right frontal activation. Other work has shown that individuals who vary in resting prefrontal EEG activation asymmetry respond differently to positive and negative emotional stimuli (e.g., Tomarken, Davidson, & Henriques, 1990; Wheeler, Davidson, & Tomarken, 1993). Specifically, Wheeler et al. (1993) found that subjects with greater relative left hemisphere activation reported more positive affect when viewing positively toned film clips and less negative affect after viewing negatively toned film clips. Thus, fairly strong experimental evidence has suggested that not only do negative and positive emotion exert an impact on relative left-right activation of prefrontal regions, but also that baseline anterior activation asymmetry is associated with differences in emotional response.

Similar results concerning frontal EEG asymmetry have been demonstrated in infants and children. For example, studies of infants have generally reported increased right frontal EEG activity during the expression of negative emotions, such as crying and sadness, and increased left frontal activation during the expression of what are termed approach emotions, such as happiness (e.g., Bell & Fox, 1994; Dawson, Panagiotides, Klinger, & Hill, 1992). Hemispheric asymmetry in EEG activity also has been observed in children of depressed mothers, with infants and toddlers of mothers experiencing depressive symptomatology showing reduced left frontal EEG activation during baseline (e.g., Dawson, Grofer Klinger, Panagiotides, Hill, & Spieker, 1992; Dawson, Frey, Panagiotides, Osterling, & Hessl, 1997; Dawson et al., 1999; Field, Fox, Pickens, & Nawrocki, 1995; Jones, Field, Fox, Lundy, & Davalos, 1997). These findings appear to be analogous with Davidson's evidence of frontal EEG asymmetry in normal adults suggesting that the left hemisphere is generally involved with positive affect. It is conceivable that the inability of mothers with depressive disorder to provide their children with adequate positive emotion and to facilitate their children's self-regulation of emotion not only affects their children's behavioral regulation capacities but also exerts an impact on the neurobiological systems that underlie these abilities (Cicchetti et al., 1991; Cicchetti & Toth, 1998; Dawson, 1994).

Finally, hemispheric EEG asymmetry has been observed in adults with depression (e.g., Allen, Iacono, Depue, & Arbisi, 1993; Henriques & Davidson, 1991). Generally, individuals diagnosed with depression have been shown to exhibit decreased left prefrontal EEG activation, although some studies have failed to replicate this finding (e.g., Reid, Duke, & Allen, 1998). However, utilizing PET to assess regional glucose metabolism, Baxter et al. (1989) reported that individuals diagnosed with depression demonstrated reduced left frontal activity; similar findings have been reported by Drevets et al. (1997).

Resilience and Hemispheric Asymmetry

Davidson and colleagues view individual differences in hemispheric asymmetry in prefrontal activation as a contributing factor to the development of affective style (Davidson, 1998a, 1998b). Further, Davidson (1998a, 1998b) characterizes such individual differences in hemispheric asymmetry in the context of depression as diatheses that might bias the affective style of an individual. In turn, this affective style bias may act as a risk factor for, or exacerbate a person's vulnerability to, depression.

Analogously, an important consideration is that any relation between hemispheric asymmetry and resilience is more than likely a distal one, with many intervening processes between asymmetry and the process of resilience. In addition, discussing a phenomenon, such as hemispheric asymmetry in the context of resilience, provides an opportunity to state that there is certainly no one single biological characteristic or phenomenon that is ascendant in the process of resilience over the course of development. Across time, the relative importance of various biological systems for promoting resilience may vary within an individual.

Given these caveats, one immediately obvious application of findings concerning emotion and hemispheric asymmetry for the study of resilience would be to examine individual differences in prefrontal hemispheric EEG activation in individuals who have experienced significant adversity to discern whether or not those classified as resilient based on their psychological profiles demonstrated a different pattern of EEG asymmetry than those not characterized as resilient. An often-cited group of individual characteristics predictive of good adaptation in the context of risk includes positive self-perception, a positive outlook on life, and a good sense of humor (Masten & Reed, 2002). Given the importance of these individual characteristics as protective factors, it would be reasonable to hypothesize that resilient individuals might show greater left frontal baseline EEG activity. Moreover, evidence of good emotion regulation skills and lower emotional reactivity in individuals classified as resilient could lead to the hypothesis that individuals labeled as resilient may display less reactivity to emotionally toned stimuli, as measured by changes in frontal EEG asymmetry.

Neuroendocrinology, Immunology, and Resilience

A significant amount of research with a variety of species, including rodents, nonhuman primates, and humans, has

been devoted to examining the effects that stress and adversity exert on the brain and neuroendocrine and immunological systems (for reviews, see Granger, Dreschel, & Shirtcliff, 2003; Gunnar, 1998; Kaufman, Plotsky, Nemeroff, & Charney, 2000; Kiecolt-Glaser, McGuire, Robles, & Glaser, 2002; Ladd et al., 2000; McEwen, 2000; Meaney et al., 1996; Sanchez et al., 2001; Sapolsky, 1992, 1996), as well as on cognitive performance (Heffelfinger & Newcomer, 2001). However, and more relevant to resilience, the important task that lies ahead is discerning the protective processes that serve to moderate the impact of adversity on neurobiological systems, and discovering the mechanisms by which these palliative forces come into play (e.g., Charney, 2004).

To date, research that has been conducted with rodents and nonhuman primates has demonstrated that traumatic events experienced early in life can modify typical behavioral, neuroendocrine, and immunological responsiveness; brain morphology' gene expression; and neurochemistry (Meaney, 2001; Meaney et al., 1996; Sanchez et al., 2001). Work conducted with humans experiencing adversity, including children reared in orphanages, children who reside in lower-socioeconomic environments, and children who have been abused or neglected, reveals similar negative consequences on stress and brain systems, as well as gene expression (Caspi et al., 2002; Cicchetti & Rogosch, 2001a, 2001b; Cicchetti & Walker, 2001; DeBellis, 2001; DeBellis, Baum, et al., 1999a; DeBellis, Keshavan, et al., 1999b; Foley et al., 2004; Gallo & Matthews, 2003; Gunnar et al., 2001; Lupien, King, Meaney, & McEwen, 2001).

The activation of the HPA axis in response to physical and psychological perturbations is adaptive and critical for the survival of challenges to the organism's homeostasis. In this sense, the stress response can be said to serve a protective function (McEwen, 1998). However, the chronic mobilization of the stress response (i.e., hypercortisolism) also can exert damaging, even pathogenic, effects on neurons (e.g., neuronal atrophy, neurotoxicity, and neuroendangerment; Bremner, 1999; McEwen & Sapolsky, 1995; Sapolsky, 1996, 2000a, 2000b). Moreover, the elimination of glucocorticoids (i.e., hypocortisolism) also can cause damage to neurons (Gunnar & Vazquez, 2001; Heim, Ehlert, & Hellhammer, 2000).

One primary means through which hormones affect behavior is via their impact on gene expression (McEwen, 1994; Watson & Gametchu, 1999). Stress hormones have been shown to exert direct effects on the genes that control brain structure and function, including neuronal growth, neurotransmitter synthesis, receptor density and sensitivity, and neurotransmitter reuptake (McEwen, 1994; Watson & Gametchu, 1999). The glucocorticoid receptors that reside in a cell's nucleus are responsible for the influence that stress hormones exert on the expression of genes that govern brain function (Watson & Gametchu, 1999). As noted earlier in this chapter, it has been demonstrated that chronic stress eventuates in a persistent inhibition of granule cell production and changes in the structure of the dentate gyrus, suggesting a mechanism whereby stress may alter hippocampal function (Gould & Tanapat, 1999).

Moreover, close, interpersonal relationships that are discordant also can be associated with the dysregulation of the immune system (Kiecolt-Glaser et al., 2002). Social stressors can cause neurotransmitters (e.g., the catecholamines) and stress hormones to elevate substantially; furthermore, these hormones and neuromodulators exert multiple immunomodulatory effects on the functioning of the immune system (Granger et al., 2003; Segerstrom, 2000). In addition, the experience of negative emotions, such as anxiety and depression, can exert a direct impact on the cells of the immune system by either up or down regulating the secretion of proinflammatory cytokines (Granger et al., 2003; Kiecolt-Glaser et al., 2002).

Importantly, research conducted with rodents demonstrates that early social experiences do not exert immutable negative consequences for the developing nervous system. For example, the results of investigations carried out by Francis et al. (1996; see also Meaney, 2001) have revealed that interventions, such as providing opportunities for maternal handling, licking, and grooming to rat pups who had experienced prolonged periods of maternal separation early in life, alter the central circuitry of emotion that results in these rat pups having a decreased responsivity to stress in later life (Meaney, 2001). Thus, these early interventions underscore the plasticity of emotion circuitry in rat pups. It remains to be discovered whether this circuitry is capable of being modified if interventions with rat pups who have experienced pronounced periods of early maternal separation are not provided until childhood or in adulthood.

In research with humans, Nachmias, Gunnar, Mangelsdorf, Parritz, and Buss (1996) found that a secure mother-child attachment relationship buffered the functioning of the HPA axis. Specifically, securely attached toddlers who were behaviorally inhibited did not exhibit significant elevations in cortisol, whereas insecurely attached toddlers who were behaviorally inhibited displayed significant elevations in cortisol. In addition, Gunnar, Brodersen, Nachmias, Buss, and Rigatuso (1996) discovered that attachment security moderated the cortisol response to the distress of inoculation. In particular, Gunnar et al. (1996) found that the combination of behavioral inhibition and

insecure attachment resulted in these toddlers exhibiting elevated cortisol levels post inoculation. Taken together, these findings suggest that the sensitive caretaking that is characteristic of the mothers of securely attached youngsters may play an important role in the modulation of the HPA axis, especially if the child possesses a behaviorally inhibited temperament.

Gunnar and colleagues (2001) found that six and a half years postadoption, children who had been reared in Romanian orphanages for greater than 8 months in their 1st year of life had higher morning (AM) basal cortisol levels than did Romanian orphans who were adopted within the first 4 months of their lives. Moreover, the longer that the Romanian orphan children were institutionalized beyond 8 months, the higher were their AM basal cortisol levels. Intervention studies would help to ascertain whether the cortisol levels of the orphans who had been institutionalized greater than 8 months were modifiable, or whether such prolonged institutionalization exerted indelible effects on the HPA axis. Likewise, longitudinal follow-up of these children who were reared in Romanian orphanages could reveal whether the functioning of the HPA axis is stable and whether those children adopted before 4 months exhibit resilient functioning, whereas those who were adopted after 8 months of institutionalization display nonresilient functioning in middle childhood. Furthermore, assessments of the quality of the parent-child relationship and of family stress could enable the detection of some of the mediators linking early experience and later outcome.

Despite the fact that the experience of persistent stress is usually associated with deleterious biological and psychological outcomes, not all organisms are affected in the same fashion (Sapolsky, 1994). It is important to note, in keeping with the general systems theory concept of multifinality, that similar stressful experiences may not exert the same impact on biological and psychological functioning in different organisms. Furthermore, the same outcomes, be they positive or negative, that were the result of stressful experiences may have eventuated from different developmental pathways (i.e., equifinality).

The confluence of a number of factors, including physical status, genetic makeup, prior experience, and developmental history, determine the differential ways in which organisms may react to a stressful event (McEwen, 1994; Sapolsky, 1994). In particular, the combination of genetic makeup, previous experience, and developmental history could either sensitize or protect the organism from subsequent stressful challenges. Additionally, more long-term stress responsiveness is characterized by interindividual variability and is related, in part, to experiential influences on gene expression (Meaney, 2001; Meaney et al., 1996). Thus, there are multiple converging pathways—including not only the neural networks that are activated by physical, psychological, and immunological stressors, but also the influence of genetics, early experience, and ongoing life events that determine the neural response to different stressors (McEwen, 1994; Sapolsky, 1994).

The ability to measure the functioning of the HPA axis through a variety of techniques enables researchers to more precisely quantify the "stress" component of diathesis-stress models of psychopathology and to examine the relation between stress and mental disorder. Moreover, the utilization of salivary biomarkers as relatively noninvasive measures of neuroendocrine and immune functioning makes it feasible for a larger number of researchers, including those investigating the pathways to, and correlates of, resilience, to implement neuroendocrinological and immunological assays into their work.

Among the most widely employed existing measures of neuroendocrine regulation are stress-reactivity paradigms that may increase HPA axis activity. There are several such procedures that are commonly utilized in the literature on HPA axis regulation. These include the Cold Pressor Test (CPT; Bullinger et al., 1984; Edelson & Robertson, 1986), the Trier Social Stress Test (TSST; Kirschbaum, Pirke, & Hellhammer, 1993), and maternal separation paradigms (Nachmias et al., 1996). For such paradigms, saliva for subsequent cortisol assaying is typically collected three times—once at baseline, 25 to 30 minutes poststressor, and once more 25 to 30 minutes after the second collection. A number of procedures also are used to index other aspects of HPA functioning, including assessments of the diurnal regulation of cortisol, 24-hour circadian rhythm collections, and biochemical challenge tests (Vazquez, 1998). Recently, salivary alpha-amylase, a surrogate marker of the sympathetic nervous system component of the stress response, has been employed to test biosocial models of stress vulnerability (Granger et al., in press). It has been discovered that patterns of salivary alpha-amylase stress reactivity differ from those obtained utilizing salivary cortisol measurements. These findings suggest that it is important to integrate measurement of the adrenergic component of the sympathetic nervous system, as indexed by alpha amylase, into investigations of normal development and psychopathology (Granger et al., in press). Furthermore, scientists have begun to examine multiple salivary biomarkers of neuroendocrine (e.g., cortisol and dehydroepiandrosterone [DHEA]) and immune functioning (e.g., IgA, Neopterin, and possibly cytokines), as well as neuroendocrine-immune system interactions (e.g., Granger

et al., 2003; Granger, Hood, Dreschel, Sergeant, & Likos, 2001; Schwartz, Granger, Susman, Gunnar, & Laird, 1998).

The incorporation of these readily obtainable salivary biomarkers in prospective longitudinal studies that also collect psychological indicators of resilient functioning may serve to enhance the understanding of the pathways to competent adaptation in the face of adverse circumstance. For example, are individuals who function resiliently more likely to return to baseline levels of neuroendocrine functioning more quickly in stress-reactivity paradigms than are individuals who are not functioning in a resilient manner? Are individuals who function in a resilient fashion less likely to develop negative neurobiological sequelae despite experiencing extreme stress? When individuals who function resiliently do evidence harmful biological sequelae, do these individuals recover their function more readily than do nonresilient individuals (i.e., do individuals who function in a resilient manner manifest greater neural plasticity)? Finally, are individuals who function resiliently better able to regulate their allostatic load—the cumulative long-term effects of physiological responses to stress (McEwen, 1998; McEwen & Stellar, 1993)?

Because they play critical roles in numerous adaptive and harmful physiological outcomes, the neuroendocrine system and the sympathetic nervous system are considered among the major mediators of allostatic processes. Repetitive social challenges in a child's environment, such as being reared in an institution and being abused or neglected, can cause disruptions in basic homeostatic and regulatory processes that are central to the maintenance of optimal physical and mental health (Repetti, Taylor, & Seeman, 2002). It is conceivable (and indeed there is some evidence at the psychological level; see Cicchetti & Rogosch, 1997) that individuals who function resiliently are more adroit at coping with stress. Relatedly, might the ability of resilient individuals to cope successfully with stress be associated with healthy, well-regulated immune functioning? For example, can the activation of the cytokines, effector molecules that are hypothesized to mediate our classic sensory functions, affect developmental plasticity via their effect on emotional, cognitive, and behavioral processes (Granger et al., 2003)? Measures of neuroendocrine regulation and reactivity and of immune function must increasingly become a part of the measurement batteries used in studies on resilient adaptation.

Cognitive Processing and Resilience

A consistent finding across several studies of resilience is that better intellectual skills are associated with more positive outcomes in individuals reared in adverse environments (e.g., Cicchetti & Rogosch, 1997; Garmezy et al., 1984; Luthar & Zigler, 1992; Masten et al., 1999; White, Moffitt, & Silva, 1989). In these studies of resilience, intellectual functioning is primarily measured with traditional measures of intellectual ability (e.g., the Peabody Picture Vocabulary Test-Revised [PPVT-R]; Dunn & Dunn, 1981), that are assumed to reflect a heterogeneous set of underlying cognitive processes that are manifested behaviorally as intelligence and adaptive functioning. These processes may include, but are not limited to, memory, attention, reasoning, and behavioral inhibition. Unfortunately, the global nature of most of these indices has, for the most part, prohibited a direct examination of which (or if) individual components of cognition may be associated with resilience.

However, some preliminary work has examined the contribution of specific facets of cognitive functioning to resilient outcomes (Curtis, 2000). This investigation was, in part, based on previous findings indicating an association between cognitive functioning and academic and social competence (Pellegrini, Masten, Garmezy, & Ferrarese, 1987). Curtis (2000) examined the relation between resilience and a set of empirically derived components of cognition, including some aspects of attention, problem solving, inhibition, creative thinking, and humor in the Project Competence cohort, a longitudinal investigation of the correlates and pathways of adaptive functioning in the face of adversity (e.g., Masten et al., 1999). These components were drawn from several measures of cognitive functioning that were administered to a subset of 90 participants in the initial assessment of this cohort in the early 1980s, when they were approximately 8 years of age.

Three composite scales of cognitive functioning were derived from these measures through a process of correlation, factor analysis, and reliability analyses: verbal ability, problem solving, and attentional functioning. Performance on these composite scales was compared across individuals classified during adolescence into one of three groups based on their level of competence across salient developmental domains and adversity. This work demonstrated that individuals classified as resilient (high adversity, high competence) during adolescence had better problem-solving ability in middle childhood, and also performed better on some aspects of attentional functioning than individuals in the same cohort classified as maladaptive (high adversity, low competence). Superior performance on the measures making up this composite may reflect good executive functioning, which would include planning ability, logic,

and general problem-solving skills in the context of interpersonal relationships.

These findings suggest that good functioning on certain cognitive processes is associated with resilience in this cohort, and also begin to provide a more detailed picture of what aspects of intelligence and superior intellectual functioning serve to promote resilience. However, considering the extreme complexity of the specific operations referred to as cognition, the problem-solving composite scale from this study is very nonspecific. A variety of interdependent cognitive skills involving the coordinated action of multiple neural networks are required to solve the problems associated with this scale and other traditional assessments of higher-order cognitive processes. In general, it is difficult to extrapolate from findings from paper and pencil measures of intellectual functioning to particular cognitive processes and brain structures that may be involved in such functioning; moreover, traditional tests of intellectual and cognitive functioning have not been tied to specific functional brain regions (other than the obvious linkage between the frontal cortex and higher-cognitive functioning). Neurocognitive measures that are able to differentiate performance on specific, circumscribed cognitive processes need to be employed in order to determine in more detail the cognitive abilities that may be associated with resilience, or that might serve as protective factors for good functioning in the context of adversity. In addition, without the application of brain-imaging techniques to determine the structural and functional attributes of specific neural substrates of cognitive abilities that may be associated with resilience, or at the very least data from neuropsychological measures that include tasks that have been tied to particular brain regions, it is impossible to determine with any degree of certainty which specific cognitive abilities might be associated with resilient functioning.

Assessment of Links between Cognition and Resilience

One assessment instrument in particular, the Cambridge Neuropsychological Testing Automated Battery (CANTAB), a computer-based neuropsychological test of nonverbal memory and executive functioning, would be well suited to examining the relation between cognitive functioning and resilience (Fray, Robbins, & Sahakian, 1996). Linkages between specific CANTAB tasks and neuroanatomical systems have been established in neuroimaging studies of adults (Owen, Evans, & Petrides, 1996). This assessment was originally developed to measure cognitive functioning in geriatric populations, although normative data on children's performance on the CANTAB has recently been published (Luciana & Nelson, 2002). This assessment instrument, while providing only an indirect assessment of brain functioning, would nonetheless be a relatively inexpensive and highly accessible option for examining linkages between specific aspects of cognition and resilience. Not only is CANTAB a highly sensitive and well-validated measure of a wide range of cognitive processes, but also it potentially would allow for the investigation of the differential contribution of a number of different types of cognitive processes to resilient functioning. For example, the CANTAB could be employed to examine whether superior ability in a particular type of memory process (e.g., spatial memory span, spatial working memory, recognition memory) contributed to resilient functioning, or, alternatively, whether those who exhibit resilient functioning may exhibit high functioning in multiple realms of memory. Also, one could examine the possible differential contribution of various types of executive functioning (e.g., inhibition, logical planning, and memory) to resilient functioning.

Brain Imaging, Cognition, and Resilience

Given the consistent association between greater intelligence and resilient functioning (e.g., Cicchetti & Rogosch, 1997; Garmezy et al., 1984; Luthar & Zigler, 1992; Masten et al., 1999), previous studies examining brain functioning in those of superior intellectual ability may have some relevance for the study of resilience. A fairly well-established body of research has directly examined brain functioning in individuals with superior intellectual ability, and to date most investigations directly examining brain activity and intelligence have suggested that the brains of individuals with superior intellectual abilities are less active during problem solving than those of individuals with average intellectual abilities (e.g., Haier, Siegel, Tang, Abel, & Buschbaum, 1992; Jausovec, 2000; Jausovec & Jausovec, 2001; O'Boyle, Benbow, & Alexander, 1995). In particular, PET studies have shown that brain metabolic activity is lower during problem-solving tasks for individuals of higher intelligence (e.g., Haier et al., 1988), whereas studies of EEG activity have shown that individuals with greater intellectual ability have less complex and more coherent EEG waveforms (Anokhin, Lutzenbeger, & Birbaumer, 1999; Jausovec, 2000). In addition, more intelligent individuals show a decrease in the volume of activated gray matter during an oddball task (a simple discrimination task where the participant is instructed to respond to a

low frequency event, such as the infrequent presentation, e.g., 20% probability, of the letter x in the context of the frequent presentation, e.g., 80% probability, of another letter), as shown using a method of low-resolution brain electromagnetic tomography (LORETA; Jausovec & Jausovec, 2001; Pascual-Marqui, Michel, & Lehmann, 1994).

These findings are generally interpreted as reflecting greater brain efficiency in those of superior intellectual ability, whereby brain areas not needed for good performance on a particular task are not utilized, while those areas specifically relevant to the task are used in a more concentrated fashion (Haier et al., 1992; Jausovec & Jausovec, 2000, 2001). In effect, fewer and more specific brain networks are activated during problem-solving tasks.

Other investigations have recently examined the location of the neural substrate mediating intellectual functioning. In a PET study by Duncan et al. (2000), these investigators found that a diverse set of tasks designed to tap general intelligence (Spearman's *g*), compared to a set of control tasks, were associated with selective neural activation in the lateral frontal cortex. This result suggests that general intelligence, rather than requiring the use of multiple brain areas, may derive from a specific neural system located in the frontal cortex that mediates many different types of cognitive demands. Gray, Chabris, and Braver (2003) employed an event-related fMRI design to examine the hypothesis that general fluid intelligence is mediated by brain regions that support attentional functioning. Utilizing a relatively large number of subjects ($n = 48$) for an fMRI study, Gray et al. (2003) were able to apply a multiple regression analysis to localize brain functioning to primarily the lateral prefrontal cortex during a demanding working memory task designed to be a test of general fluid intelligence. However, contradictory to many studies showing less brain activity in those with superior intellectual ability during problem solving, Gray et al. (2003) found that higher fluid intelligence, indexed by performance on Raven's Advanced Progressive Matrices (APM; Raven, Raven, & Court, 1998), was associated with greater activity in the lateral prefrontal cortex during a fairly difficult working memory task. It is possible that this finding is a result of the relatively highly challenging nature of the task administered, in comparison to more simple tasks employed in other studies of brain function and superior intelligence.

The ERP is an index of central nervous system functioning thought to reflect the underlying neurological processing of discrete stimuli (Hillyard & Picton, 1987). ERPs represent scalp-derived changes in brain electrical activity, believed to be generated by changes in membrane potentials of nerve cells, thus reflecting activity associated with neuronal connections (Hugdahl, 1995; Nelson & Bloom, 1997). ERP data is collected across a discrete temporal window (typically a few seconds), obtained by averaging time-locked segments of the EEG that follow or precede the presentation of a stimulus. In this manner, ERPs allow for monitoring of neural activity associated with cognitive processing in real time (Donchin, Karis, Bashore, Coles, & Gratton, 1986). Their particular strength lies in the high temporal resolution they provide, allowing for a finely detailed examination of the timing of cognitive operations in the brain at the level of milliseconds.

Studies utilizing ERPs to examine brain electrophysiology and intelligence have consistently demonstrated that the amount of time for ERP wave forms to reach their peak amplitude is negatively correlated with IQ, indicating that cognitive operations may be occurring more rapidly in the brains of individuals with greater intellectual ability (e.g., Barrett & Eysenck, 1994; Bazana & Stelmack, 2002; Burns, Nettelbeck, & Cooper, 2000; Jausovec & Jausovec, 2001). In particular, it appears that this difference occurs in the P300 ERP component, and not in earlier occurring components associated with lower-level sensory processes (Jausovec & Jausovec, 2001). The P300 is generally viewed as reflecting cognitive processing related to learning as well as the transfer of sensory information about a stimulus into working memory, referred to as context updating (Donchin & Coles, 1988). Latency of the P300 is associated with the amount of time it takes for an individual to evaluate the novelty or significance of a stimulus, and is typically prolonged in individuals with neurodegenerative disorders (Donchin & Coles, 1988; Hugdahl, 1995).

Other investigations have measured the relation between resting brain activity and intellectual ability. Findings from these studies have been less conclusive, but, generally, greater EEG coherence has been shown to be associated with increased intellectual ability. It is assumed that increased coherence again reflects more efficient utilization of neural networks.

Unfortunately, most studies examining the relation between intelligence and brain functioning have not been designed to delineate the relation between brain functioning and particular aspects of intelligence. Hence, the tasks employed during these studies have not been specific to any particular cognitive process, but rather have been chosen to reflect intellectual ability in general. In addition, creativity has been controlled for in many of these studies, given that persons high on measures of creativity differ from those high only on intelligence with respect to

brain activity during problem-solving tasks (e.g., Carlsson, Wendt, & Risberg, 2000; Jausovec, 2000).

A major difficulty in examining the role of intelligence in promoting resilience is the vastly complex constellation of cognitive and executive functioning skills possibly associated with performance on psychometric measures of intelligence. The association between performance on some executive function tasks and IQ is moderate at best; whereas some aspects of executive functioning appear not to have a relation with IQ (e.g., Luciana & Nelson, 2002), other studies have suggested that executive functioning, subserved by the frontal cortex, is one of the underlying essential functions of creativity (Carlsson et al., 2000). Finally, many basic cognitive processes, such as attention and memory, are clearly associated with psychometric indices of intellectual functioning, but exactly how is unclear.

Thus, the first step in examining the nature of the strong association of intellectual ability with resilience would be to determine which aspects of intellectual functioning were more or less important in their contribution to resilient functioning. For example, in the Curtis (2000) study, the verbal and performance scales of an intelligence assessment loaded on two different composites of cognitive functioning, with the performance scale differentiating resilient and nonresilient groups, whereas the verbal scale did not. More comprehensive neuropsychological assessment of resilient and nonresilient individuals, such as administration of entire IQ batteries rather than abbreviated versions, would be useful in determining which aspects of traditional psychometric intelligence were important in promoting resilience. Also, it is essential that many different components of cognition and executive functioning be assessed in order to determine what particular grouping of skills may be associated with resilience. It seems unlikely that any one aspect of cognition and executive functioning alone is the critical defining feature of resilience. Rather, it seems reasonable to hypothesize that strengths on a variety of cognitive and executive functions, such as memory, attention, flexible problem solving, and inhibition, contribute to resilient functioning. However, it is of critical importance to ascertain which of these processes does or does not contribute to resilience in order to inform prevention and intervention. Utilizing instruments, such as CANTAB, a measure of more subtle and specific aspects of neuropsychological functioning, is essential in the study of cognition, executive functioning, and resilience.

Going beyond traditional neuropsychological assessment, brain-imaging studies are an important methodology to apply to investigating the role of cognition and executive functioning in resilience. Although neuropsychological assessments measure aspects of cognitive functioning and allow inferences to be drawn about the neural substrate(s) involved, it is essential to employ brain imaging in order to directly determine the temporal, structural, and functional aspects of cognition and the brain (Toga & Thompson, 2003). Brain imaging allows for the direct examination of the neural substrate involved with cognition and executive functioning in individuals classified as exhibiting resilient functioning. Neuroimaging methods, such as fMRI, also can be utilized to determine if aspects of brain functioning in such individuals are unique in some way compared to competent individuals not exposed to adversity.

In addition, ERPs also can be utilized to elucidate the possible relation between cognitive efficiency and resilience. In particular, two questions can be addressed. First, it would be useful to determine whether or not individuals classified as resilient demonstrate greater cognitive efficiency in general compared to individuals not demonstrating resilience. This could be accomplished by comparing peak latencies of the P300 during cognitive tasks, such as the oddball paradigm or a recognition memory task.

Secondly, it would be informative to compare cognitive efficiency on a variety of tasks to ascertain whether there is a specific type of cognitive function that resilient individuals are able to accomplish more efficiently, or if the efficiency is an overall strength, independent of the type of cognitive operation. In this regard, it also would be informative to compare resilient individuals with those exhibiting competent functioning but not exposed to adversity. It is possible that competent functioning, despite exposure to significant adversity, may be associated with cognitive efficiency in a different way than it is for individuals not exposed to adversity. This approach can help to elucidate, at the level of brain functioning, whether speed of processing is an underlying factor in resilience, and, if so, for which type of cognitive processes is this increased efficiency important in the context of resilient functioning.

Although ERPs are particularly advantageous in determining the chronology of neural processes, this methodology does not lend itself to the precise localization of these processes. FMRI, however, does enable the localization of brain functioning with relatively great precision (see Casey, Davidson, & Rosen, 2002 and de Haan & Thomas, 2002 for relevant reviews of this methodology). FMRI is a rapidly evolving technology that has exciting, but as of yet unexplored, potential in the study of resilience. In particular, application of this methodology would be extremely useful in examining questions about the role of cognition and executive functioning in promoting resilience. For example, it would enable the examination of whether cogni-

tive operations of those classified as resilient took place in the same or perhaps different brain systems than those experiencing adversity but not classified as resilient.

Additionally, fMRI would allow direct examination of the impact of adversity on brain structures, such as the hippocampus, which has been shown to have decreased volume in patients diagnosed with PTSD related to war combat exposure or childhood sexual and/or physical abuse (e.g., Bremner et al., 1995, 1997; Gurvits et al., 1996; Stein, Koverola, Hanna, Torchia, & McClarty, 1997; Villarreal et al., 2002). Although the cause of this volumetric reduction has not been definitively established (in fact, it is possible that reduced hippocampal volume precedes, and is a risk factor for, PTSD), the predominant view, proposed by Bremner (1999), is that reduced hippocampal volume is a result of neurotoxic effects linked to traumatic events. This neurotoxic process appears to be due to an interaction between elevated levels of glucocorticioids and excitatory neurotransmitters (e.g., glutamate), with the specific, targeted effect on the hippocampus due to its high concentration of glucocorticoid receptors (for review of this process, see McEwen & Magarinos, 1997).

In the case of individuals classified as resilient who, by definition, have been exposed to significant adversity or trauma, it would be reasonable to formulate two hypotheses: (1) As a result of this exposure to adversity over time, such individuals may have reduced hippocampal volume compared to controls but do not show expected behavioral deficits in memory. Memory functioning in these individuals may be mediated by other neuroanatomical structures and networks, thus compensating for possible diminished functional capacity of the hippocampus, or (2) Resilient individuals, despite exposure to adversity or trauma, do not have reduced hippocampal volume. In either case, volumetric MRI studies to ascertain the degree to which, if any, the hippocampus has reduced volume could be employed. In addition, functional brain imaging studies utilizing fMRI would be useful to ascertain what compensatory mechanisms are being employed (if reduced hippocampal volume were confirmed).

MRI diffusion tensor imaging (DTI), a relatively new technique that allows imaging of white matter tracts that connect neural tissue across brain areas, also holds great promise in studying cognition and resilience. DTI has provided evidence of differences in intercortical connectivity in individuals with neuropsychiatric disorders (e.g., Kubicki et al., 2002; Lim et al., 1999). Application of this technique to the study of resilience could potentially demonstrate differences between resilient individuals, nonresilient individuals exposed to adversity, and competent individuals not exposed to adversity in connectivity between regions of the cerebral cortex, possibly offering evidence of neural plasticity as one of the underlying mechanisms of resilient outcome.

Genetics and Resilience

From a genetic perspective, resilience can be conceptualized as the extent to which individuals at genetic risk for maladaptation and psychopathology are not affected (Garmezy & Streitman, 1974; Luthar et al., 2000; Rende & Plomin, 1993). Additionally, there may be genetic contributors to resilient adaptation that protect some individuals in families where there is a high genetic loading for developing maladaptation and mental disorder from succumbing to these deleterious outcomes. Moreover, genes are equally likely to serve a protective function against environmental insults for some individuals. Thus, it is apparent that genetic influences on maladaptation and psychopathology operate in a probabilistic and not a deterministic manner.

To date, there has been a paucity of investigations that have examined genetic contributors to resilient functioning. Rende and Plomin (1993) have explicated the ways in which the designs and methods of quantitative behavior genetics may be utilized to uncover the genetic and environmental contributions to resilience. Herein, we provide several examples of how molecular genetic techniques may be utilized to proffer insights into the pathways to resilient adaptation.

Buccal swab sampling procedures provide a relatively easy and painless method for collecting DNA from research participants (Freeman et al., 1997; Plomin & Rutter, 1998). The buccal swabs can be easily stored in the laboratory; subsequently, the DNA is purified, ideally as soon as possible, utilizing a DNA Extraction Kit. In the particular kit used in our laboratory, the extraction solution is alloquated in 0.5 ml amounts into sterilized DNAse and RNAse free 1.5 ml microcentrifuge tubes, which are labeled and stored in a freezer at—80°C until usage. The equipment needed to extract and purify DNA is relatively inexpensive, and the methodology is not difficult to learn. Hence, it is quite feasible for researchers without expertise in molecular genetics to carry out DNA extraction in their own laboratory. Alternatively, collaborations with geneticists in universities or medical school settings could facilitate the application of these techniques.

Polymerase Chain Reaction (PCR) is a quick, fairly cost-efficient technique for producing an unlimited number of copies of any gene. The powerful duplication ability of PCR enables researchers to utilize tiny amounts of cells or

tissues (such as those obtained with the buccal swabbing technique) to amplify or copy DNA and to subsequently undertake molecular genetic analysis. Although PCR itself is not very expensive, the equipment necessary to conduct subsequent molecular genetic analyses, such as a gene sequencer, is substantially more costly. The relative ease with which DNA can be collected enables even developmental psychopathologists who are not well versed in molecular genetics to obtain DNA from participants and to examine the relation of this genetic material to normal, maladaptive, and resilient behavioral outcomes.

Recently, great progress has been made in the mechanisms involved in the study of gene expression. These advances provide exciting new opportunities for enhancing knowledge not only on the genesis and epigenesis of maladaptive development and mental disorders, but also of resilience. Molecular genetic methods now exist that enable researchers to investigate the expression of particular genes or of large numbers of genes simultaneously (so called "gene profiles"). Through the utilization of complementary DNA (or cDNA) microarrays, researchers can discover the type and quantity of messenger RNA (mRNA) being produced by a given cell, thereby indicating which genes are "turned on" (i.e., activated; Hacia & Collins, 1999; Mirnics, Middleton, Lewis, & Levitt, 2001; Raychaudhuri, Sutphin, Chang, & Altman, 2001). DNA microarrays can be utilized to index changes in the expression of genes that are essential for brain function (Greenberg, 2001; Walker & Walder, 2003). By examining the concurrent and longitudinal relations among environmental, gene expression, neurobiological, hormonal, and psychological processes in individuals who have experienced significant adversity, researchers may be in a stronger position to elucidate the development of resilient adaptation. Such multiple level of analysis investigations may reveal the mechanisms responsible for activating and inhibiting the expression of genes that are probabilistically associated with maladaptive developmental outcomes and psychopathology. Likewise, these multidisciplinary approaches may proffer insights into the mechanisms that "turn on" genes that may serve a protective function for individuals experiencing significant adversity.

Utilizing animal models of learning and gene expression, several studies have begun to show a direct link between the gene expression process and structural changes in the brain that result from learning. For example, Post et al. (1998) found higher levels of mRNA and nerve growth factor (NGF) in the visual cortex and hippocampus of rats exposed to an enriched environment for 30 days, evidence that a gene transcription process was occurring. Training on a passive avoidance task resulted in significant elevation of c-*fos* mRNA levels in the chick forebrain. A gene expression transcription factor (Anokhin, Mileusnic, Shamakina, & Rose, 1991) and C-*fos* induction also has been found in the rat brain after shuttle-box training (Maleeva, Ivolgina, Anokhin, & Limborskaya, 1989), as well as in Purkinje cells in the cerebellar paramedian lobule following training of rats in a reaching task (Alcantra et al., 1991). Also, the transcription factor zif-268 has been found in the visual cortex of rats only 4 days after being placed in an enriched environment (Wallace, Withers, Weiler, & Greenough, 1991).

Thus, at the level of learning and cognition, gene expression and the subsequent cascade of processes that eventuate in structural changes in neural substrate may be one process that could be examined as a correlate of resilience. Gene expression in learning, which comes about as a result of transactions with the environment, is perhaps the foundation upon which positive adaptation to adversity is built. In addition, this multilevel perspective, showing linkages among gene expression, neurochemistry, neuroanatomy, and experiences in the environment, again points to the importance of a multiple-levels-of-analysis approach to the study of resilience.

Other work in the area of gene expression has demonstrated the relation of this process to the development of psychopathology in humans. For example, changes in gene expression due to environmental adversities have been implicated in the development of affective disorders (e.g., Post et al., 1994; Post et al., 2003). Similar to the evocation of gene expression through interaction with the environment in animal models of learning, Post et al. (1994) hypothesized that acute events in the environment can have a permanent impact on gene expression, thus accounting for long-lasting changes in subsequent behavioral responses to stressors in the environment. Thus, the interplay of early experience and gene expression processes can potentially lead to vulnerability, depression, posttraumatic stress disorder, and other disorders possibly rooted in changes in gene expression (e.g., Schizophrenia; Post et al., 1994). This formulation, a model based on electrophysiological kindling and behavioral sensitization to psychomotor stimulants and stress, emphasizes an active and dynamic process of transactions between genetic vulnerabilities and experientially mediated effects on gene expression over the entire life span. Also, Post et al. (2003) have theorized that, in addition to pathological changes in gene expression that eventuate in affective disorders, there may in fact be

changes in gene expression that are adaptive and possibly serve as endogenous antidepressant mechanisms. Post et al. (2003) suggest that the proportion of pathological and adaptive changes in gene expression may be a key determining factor in an individual's propensity to have recurring episodes of affective disorder. Likewise, individuals classified as resilient may be found to have a higher proportion of adaptive gene expression processes, allowing them to maintain positive behavioral adaptation in spite of adversity (see also Cicchetti, 2003).

Very recently, molecular genetic methods have been utilized to examine the role that genetic factors, in interaction with social experience, might play in the epigenesis of maladaptive behavior. In a large, longitudinal birth cohort of male children who were studied from birth to adulthood, the investigators sought to determine why some maltreated children grow up to develop antisocial behavior where other maltreated children do not (Caspi et al., 2002). It was discovered that a functional polymorphism in the gene-encoding the neurotransmitter-metabolizing enzyme monoamine oxidase A (MAOA) moderated the effect of maltreatment. Polymorphisms are common variations that occur in the sequence of DNA among individuals. Specifically, a polymorphism is a gene that exists in more than one version (or allele), and where the rare form of the allele occurs in greater than 2% of the population. Caspi and colleagues (2002) found that the effect of child maltreatment on antisocial behavior was far less among males with high MAOA activity than among those with low MAOA activity. The investigators interpreted their findings as providing evidence that a functional polymorphism in the MAOA gene moderates the impact of early child abuse and neglect on the development of male antisocial behavior (Caspi et al., 2002).

Of relevance to research on resilience, it is conceivable that the gene for high MAOA activity may serve a protective function against the development of antisocial behavior in maltreated children (Cicchetti & Blender, 2004). Maltreated children grow up in highly stressful environments. The results of the Caspi et al. (2002) investigation suggest that some maltreated children, but not others, develop antisocial behavior via the effect that neurotransmitter system development exerts on stressful experiences. Specifically, the probability that child maltreatment will eventuate in adult violence is greatly increased among children whose MAOA is not sufficient to render maltreatment-induced changes in neurotransmitter systems inactive (Caspi et al., 2002). Thus, a gene x environment interaction appears to determine which maltreated children will, and will not, develop antisocial behavior. These findings are compelling and this investigation is one of the first studies to document a genetic contribution to resilience in humans. We urge researchers to conduct additional molecular genetic studies with other samples of humans who experience similar and different types of significant adversity in order to ascertain the mechanisms underlying resilient adaptation.

CONCLUSION AND FUTURE DIRECTIONS

Although many questions remain unanswered, a great deal of progress has been made in our understanding of the construct of resilience (Luthar, 2003; Luthar et al., 2000; Masten, 2001). Much of the research focused on elucidating the correlates of, and contributors to, resilient functioning has utilized child, family, and contextual assessments (Luthar, 2003; Luthar et al., 2000). We have emphasized that the time has come to incorporate biological measures into research programs examining the determinants of resilient adaptation. We also assert that the inclusion of biological measures into the psychological research armamentaria currently employed in resilience research, as well as in resilience-promoting interventions, results in a more precise understanding of the mediators and moderators underlying resilience.

Now that the theories and neuroscience techniques are available, and since our understanding of brain development and functioning in both normality and psychopathology has grown, it seems necessary to inquire as to why there has been no research to date conducted on the biological correlates of, and contributors to, resilient adaptation. One impediment to the incorporation of biology into the field of resilience research is that most investigators who examine pathways to resilient functioning have not been trained in the various neuroscience approaches (e.g., molecular genetics, neuroimaging, psychophysiology, neuroendocrinology, immunology). Regardless, this state of affairs can be modified through a number of avenues, including: (1) changing existing training programs and philosophies for graduate and medical students; (2) fostering interdisciplinary and multidisciplinary collaborations; and (3) providing incentives and opportunities for faculty to acquire knowledge and expertise in one or more new scientific areas.

Perhaps an even larger reason for the absence of biological variables in research on resilient functioning is that evidence for the role of biology in resilience could be interpreted as representing a personal attribute of the individual

and that if only the individual had this biological characteristic, then he or she could have withstood the adversities to which the individual was exposed. In essence, the individual could be blamed for not possessing the needed characteristics to function resiliently.

However, as the theoretical underpinnings of research in developmental psychopathology, dynamic developmental systems theory, and developmental neuroscience illustrate, the belief that the identification of a biological factor would inevitably result in resilience (or maladaptation for that matter) is fallacious. Our viewpoint does not reduce resilience to biology, let alone to a unitary biological variable. A multiple-levels-of-analysis perspective to resilience should not be misinterpreted as equating resilience with biology. Moreover, the inclusion of a biological perspective in resilience research should not hearken scientists back to the time when some espoused the view that there were "invulnerable" children.

To the contrary, existing theories in developmental neuroscience are very compatible with organizational and systems theories in the fields of developmental psychology and psychopathology (see Cicchetti & Cannon, 1999a, 1999b; Cicchetti & Walker, 2001, 2003). The incorporation of a biological perspective into research on resilience still requires adherence to a dynamic, transactional view that respects the importance of context. Omitting biology from the resilience equation is tantamount to omitting psychology. Biological and psychological domains are both essential to include in basic research on resilience and in resilience-promoting interventions. If we are to grasp the true complexity of the concept of resilience, then we must investigate it with a commensurate level of complexity.

Regardless of whether it may be a normal or abnormal neural system, building a brain is a dynamic, self-organizing, genetic and epigenetic, multilevel process that unfolds from the prenatal period throughout adulthood. We think that it has become essential for investigators in the disciplines of developmental neuroscience and developmental psychopathology to carry out prospective longitudinal studies that examine the same individuals over developmental time utilizing a multiple-levels-of-analysis perspective. Research also must be conducted to elucidate the similarities and differences in the fundamental neural mechanisms involved in the development of various mental disorders. Furthermore, additional molecular biological investigations on the structure and function of genes and protein involved in neural proliferation, migration, and differentiations must be implemented (Nowakowski & Hayes, 1999).

Moreover, it is important that investigations with human participants be undertaken to ascertain whether, and if so, how, specific environmental occurrences, such as the presence of serious psychopathology in caregivers, child maltreatment, repeated fostercare placement, residing in an orphanage, and/or having a mental disorder, selectively exert a deleterious impact on the development of children's various neurobiological systems as a function of the timing and duration of exposure to these adverse experiences (Cicchetti, 2002; Dawson, Ashman, & Carver, 2000; Gunnar et al., 2001; Parker & Nelson, 2005a). In a related vein, investigations must be conducted to discover what, if any, particular aspects of parenting foster optimal brain development and function in children (Bruer, 1999; Nelson, 2000b).

Now that it is evident that experience can impact the microstructure and biochemistry of the brain, a vital role for very early and continuing neural plasticity throughout epigenesis in contributing to the development of, and recovery from, various forms of maladaption and psychopathology is suggested. Research has revealed that some early lesions may not be easily reversible, despite the historically prevalent belief that brain insults occurring near the beginning of development were most amenable to reorganization and repair. Conversely, contemporary neurobiological research suggests that in some domains (e.g., sensory, motor, cognitive, memory, and linguistic) and in some areas of the brain, plasticity is possible, including new neuron generation, well into adulthood (Cicchetti & Tucker, 1994a, 1994b; Nelson, 2000a). Moreover, future research must be conducted to examine the limits of plasticity in the social and emotional domains (see Davidson, 2000; Davidson, Jackson, & Kalin, 2000, for evidence of neural plasticity in the central circuitry of emotion). It also is essential to discover the mechanisms whereby latent progenitor cells are controlled and glial cell activation is modulated, in order to elucidate the bases of the brain's self-repair processes across various neurobiological systems (Lowenstein & Parent, 1999). If scientists can discover the mechanisms underlying the neural plasticity of the circuits of specific domains in individuals with various high-risk conditions and mental disorders, then such information should provide crucial insights for prevention and intervention efforts.

In this regard, prevention research can be conceptualized as true experiments in altering the course of development, thereby providing insight into the etiology and pathogenesis of disordered outcomes (Cicchetti & Hinshaw, 2002). Relatedly, the time has come increasingly to conduct interventions that not only assess behavioral

changes, but also ascertain whether abnormal neurobiological structures, functions, and organizations are modifiable or are refractory to intervention (Cicchetti, 1996). There is growing evidence that successful intervention modifies not only maladaptive behavior but also the cellular and physiological correlates of behavior (Kandel, 1979, 1998, 1999).

Unlike the belief espoused by Huttenlocher (1984) that "intervention programs, to be effective, would have to be implemented during [the] early prenatal period, and certainly prior to school age, by which time synaptic and neuronal plasticity appears to be greatly diminished, if not totally lost" (p. 495), recent demonstrations of plasticity across an array of developmental systems suggest that interventions have promise to exert ameliorative effects long beyond the early years of life (Bruer, 1999; Nelson, 2000b). A major implication of a dynamic developmental systems approach is that the implementation of intervention closely following the experience of trauma or an episode of mental illness should ameliorate the intensity and severity of the response to the illness, as well as the illness course (Toth & Cicchetti, 1999). Such interventions that are closely timed to trauma and disorder onset also should decrease the probability of developing, in a use-dependent fashion, sensitized neural systems that may cascade across development (Post et al., 1998).

As Nelson (2000b) has articulated, "the efficacy of any given intervention will depend on the capacity of the nervous system (at the cellular, metabolic, or anatomic levels) to be modified by experience" (p. 204). Likewise, Nowakowski (1987) asserted that "in order to understand how a modification in a developmental process exerts its influences, it is essential to know where the developmental process is being modified, how the structure of the mature brain will be changed, and how the structural changes that are produced will change the ability of the brain to process the information it confronts during a complex behavioral task" (pp. 568–569). Successful psychotherapy, behavioral therapy, or pharmacotherapy should change behavior and physiology by producing alterations in gene expression (transcription) that produce new structural changes in the brain (Kandel, 1979, 1999). For example, as discussed earlier, stress has been demonstrated to suppress the birth of new neurons in adulthood (see also Sapolsky, 2000a, 2000b), and serotonin has been shown to enhance the rate of neurogenesis in the dentate gyrus. Extrapolating from these findings, Jacobs and colleagues (2000) hypothesized that stress-induced decreases in dentate gyrus neurogenesis play an important causal role in precipitating episodes of major depressive disorder. Reciprocally, pharmacotherapeutic interventions for depression that increase the neurotransmission of serotonin work at least partly through their role in augmenting the birth of new neurons in the dentate gyrus, thereby contributing to the recovery from episodes of clinical depression.

A number of antidepressants have been shown to increase adult neurogenesis in the hippocampus. Santarelli and colleagues (2003) conducted a study to ascertain the functional significance of this phenomenon. These investigators demonstrated that the disruption of antidepressant-induced neurogenesis in serotonin 1A receptor null mice also blocked their behavioral responses to fluoxetine, a selective serotonin reuptake inhibitor. The results of the Santarelli et al. (2003) investigation provide suggestive evidence that the behavioral effects of antidepressant drugs may be mediated by the stimulation of neurogenesis in the hippocampus.

A substantial amount of research literature suggests that not all individuals who have similar vulnerabilities and who have been exposed to similar adverse experiences develop in a similar fashion (Luthar, 2003; Luthar et al., 2000; Masten, 2001). For example, although child maltreatment can exert a negative impact on the structure, functioning, and organization of the developing brain, it does not appear that the brains of all maltreated children are affected in the same manner. Moreover, because some maltreated children function resiliently despite having been exposed to significant adversity (Cicchetti & Rogosch, 1997; Cicchetti et al., 1993), it is likely that the experience of child abuse and neglect may exert different effects on the neurobiological structure, function, and organization in well-functioning maltreated children than it does in the typical maltreated child. Accordingly, there may be an enhanced neural plasticity in resilient individuals.

Thus, it appears that the impact of life experiences, such as child maltreatment and mental disorder, on brain microstructure and biochemistry may be either pathological or adaptive. In the future, neuroimaging investigations should be conducted in order to discern whether the brain structure, functioning, and organization of individuals who are functioning extremely well despite being exposed to significant adversity and/or having vulnerabilities to mental disorder differ from those individuals with similar experience and/or vulnerabilities who are functioning less adaptively.

Presently, we do not know if the neurobiological difficulties displayed by some persons with mental disorders or individuals who have experienced significant life adversity are irreversible or whether there are particular sensitive periods when it is more likely that neural plasticity will occur.

Moreover, it is not known whether some neural systems may be more plastic than other neural systems or whether there are particular sensitive periods when it is more likely that neural plasticity will occur. Furthermore, it is not known whether particular neural systems may be more refractory to change or have a more time-limited window when neural plasticity can occur. Consequently, it is critical that research investigations on the correlates and determinants of resilient adaptation begin to incorporate neurobiological and molecular genetic methods into their predominantly psychological measurement armamentaria (Curtis & Cicchetti, 2003).

Luthar and Cicchetti (2000) concluded that research on resilience "should target protective and vulnerability forces at multiple levels of influence" (p. 878). The incorporation of a neurobiological framework and the utilization of genetically sensitive designs into interventions seeking to promote resilient functioning or to repair positive adaptation gone awry may contribute to the ability to design individualized interventions that are based on knowledge gleaned from multiple biological and psychological levels of analysis. For example, if an individual has the polymorphism for a gene that is probabilistically associated with a particular negative behavioral outcome and if it is known how this polymorphism affects a specific neurotransmitter system, then psychopharmacological treatment can be initiated (Cicchetti & Blender, 2004). Similarly, because stressful experiences can harm the brain (e.g., Bremner, 1999; McEwen & Magarinos, 1997), biological and psychological intervention techniques can be provided to help an individual to better understand and cope with stressful situations. The identification of stress-sensitive neural processes may ultimately provide a basis for the formation of pharmacological and behavioral interventions to ameliorate the deleterious effects of early traumatic experiences (Kaufman et al., 2000; see also Post et al., 2003). Moreover, the inclusion of neurobiological assessments in evaluations of interventions designed to foster resilience enables scientists to discover whether the various components of multifaceted interventions each exert a differential impact on separate brain systems. We think that is it possible to conceptualize successful resilience-promoting interventions as examples of experience-dependent neural plasticity. If assessments of biological systems are routinely incorporated into the measurement batteries employed in resilience-facilitating interventions, then we will be in a position to discover whether the nervous systems have been modified by experience.

Despite the fact that we separately described the biological assessments that we believed would augment our knowledge base in resilience, we advocate that researchers investigating basic processes contributing to resilience and those conducting and evaluating interventions that strive to promote resilience and return function to positive levels of adaptation incorporate a multiple-levels-of-analysis approach (see Cicchetti & Dawson, 2002). Adopting such an approach is essential because, in actuality, biological and psychological systems interact and transact with one another throughout the course of development (Cicchetti & Tucker, 1994a; Gottlieb, 1992).

Furthermore, many of the biological processes that have been discussed in this chapter as possibly being related to resilience are in fact normative processes. For example, neural plasticity is one such process that has clearly been shown to be an inherent property of the central nervous system. This highlights an interesting parallel to a suggestion put forth by Masten (2001), who discusses resilience as an ordinary phenomenon that may mostly come about through the operation of "basic human adaptational systems." This perspective stresses that, although resilience is a valid, identifiable phenomenon, extraordinary individual qualities may not be necessary in order to overcome adversity. Likewise, at the biological level of analysis, normative processes may mediate resilient outcomes, as long as these systems are functioning within normal parameters. This viewpoint serves to underscore the importance of the interaction of normative systems at all levels of analysis in the promotion of resilience.

Several scholars have contended that the construct of resilience adds nothing to the more general term "positive adjustment" (see review in Luthar, Cicchetti, & Becher, 2000). Because empirical evidence has demonstrated that there are different patterns of positive adjustment that occur with and without adversity and given that there are several studies indicating that the pathways to resilience and positive adaptation may differ, it is indeed likely that positive adaptation and resilience reflect distinct constructs (Luthar et al., 2000). Moreover, the incorporation of biological and genetic measures and methods into research that strives to differentiate between individuals who function well in adversity and those who function well without (or with minimal) adversity may reveal differential neurobiological and genetic correlates of, and contributors to, resilience and positive adaptation, respectively. If distinctions between those two constructs can be made at the neurobiological, molecular genetic, and behavioral levels, then there would be strong evidence for the distinctiveness of positive adaptation and resilience.

In the beginning of the twenty-first century, it is imperative that the field of developmental psychopathology adopts

a multiple-levels-of-analysis approach to the study of both deviant and adaptive functioning. New programs of research must take into account both normal and abnormal developmental processes in examining psychopathology, and intervention studies must be undertaken in order to more fully establish the characteristics of and processes underlying brain-behaviors relations. Most importantly, beyond the calls for research programs incorporating multiple levels of analysis seen in recent overviews of the field (e.g., Cicchetti & Blender, 2004; Cicchetti & Dawson, 2002), such research must actually be supported by funding agencies, many of which still view multiple-levels-of-analysis approaches to research questions as too broad and risky to merit financial support. In addition, journal editors also need to encourage such research by increasing their willingness to publish papers that investigate a phenomenon across multiple levels of analysis, some of which might fall somewhat outside the purview of the particular journal. Furthermore, research in developmental psychopathology that is driven by broadly based theory incorporating multiple levels of analysis must be increasingly encouraged by faculty in the context of graduate training.

In order to ensure that future generations of scholars in developmental psychopathology are exposed to a broad, dynamic, systems-based, multiple-levels-of-analysis perspective, graduate and undergraduate programs in clinical and developmental psychology should encourage students to take courses in a broad spectrum of areas (Cicchetti & Toth, 1991; Pellmar & Eisenberg, 2000). These might include courses on basic neurobiology, neuroendocrinology, and developmental processes, as well as courses that incorporate information on brain-imaging technology, molecular genetic methods, neuroendocrine assay techniques, and other tools involved in assessing neurobiological and genetic processes. Likewise, students in basic science areas, such as neuroscience or molecular genetics, should be encouraged to gain exposure to the fundamentals of basic normative and atypical developmental processes. Further, specific interdisciplinary programs, for both students and faculty, spanning interest areas from clinical intervention to basic neuroscience, would help to foster communication and collaborative research endeavors between the fields of developmental neuroscience and development psychopathology (see, e.g., Cicchetti & Posner, 2005).

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