Development and Psychopathology **17** (2005), 735–752

Printed in the United States of America
DOI: 10.1017/S0954579405050352

Early adversity and mechanisms of plasticity: Integrating affective neuroscience with developmental approaches to psychopathology

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Abstract

Interest in the effects of early adversity on children's development reflects contemporary emphases on early experience in the behavioral sciences and plasticity in the neurosciences. Over the past decade, powerful new tools and approaches for understanding the neural circuitry involved in emotion have become increasingly available. Yet, research in developmental psychopathology has not reaped the full benefits of affective neuroscience approaches and methods. Integration of affective neuroscience approaches can excavate developmental mechanisms, thereby advancing knowledge about the etiology, prevention, and treatment of mental health problems in children. Here, we consider two general principles that can guide understanding of plasticity in the neural circuitry of emotion systems and the development of psychopathology.

Children who experience early adversities such as abuse, deprivation, neglect, poverty, and trauma are at increased risk for the development of behavioral, emotional, and social problems later in life (Cicchetti & Manly, 2001). However, little is currently known about the biological mechanisms linking early adversity with the development of these problems. The premise of this paper is that knowledge about the neural mechanisms through which adverse (and positive) experiences exert lasting impact upon an individual's long-term functioning is of central importance for understanding both typical and atypical human development. Here we discuss an affective neuroscience approach to examining the brain–behavior relationships involved in emotional behavior. Emotions are complex sets of processes that individuals use to evaluate their environments and adjust their behaviors. Over the course of development, these processes interact seamlessly and rapidly, affording successful adaptation. A developmental affective neuroscience approach may clarify the factors underlying plasticity in the neural circuitry involved in distinct aspects of emotional behavior. In this case, the heuristic of *plasticity* refers to how experience leads to changes in these affective neural networks, including the efficiency, activation thresholds, and the time course of those activations.

This Special Issue of *Development and Psychopathology* comes at an exciting time in the biobehavioral sciences. It marks the intellectual coming of age of the affective neuroscience approach, and the current zeitgeist of considering how the interactions of affective

The author was generously supported by the National Institutes of Mental Health (MH 61285, MH 68858) and by the University of Wisconsin. Elizabeth Shirtcliff, Alison Wismer Fries, Jessica Shackman, and Julia Kim–Cohen provided thoughtful comments on an early draft of this paper. The author also thanks Dante Cicchetti and Michael Posner for their critical reviews of the manuscript and Erin Henigan for help with preparation of this manuscript.

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and cognitive processes may be conceptualized at a mechanistic level. To date, most research on the developmental effects of early adversity in children has yielded information that provides rich description of children's behaviors. However, the behavioral data generated has been difficult to map on to specific neural systems. Although there has been some movement in developmental psychopathology to invoke affective neuroscience constructs (see, e.g., the Special Issue of *Development and Psychopathology* edited by Cicchetti and Tucker in 1994), developmental psychopathologists tend to rely heavily upon child or parent self-report interviews and questionnaires. These approaches are informative for addressing how children or adults introspect, attend to, or choose to describe their behavior. However, how research subjects say they might feel, respond, or think in different situations cannot uncover biological mechanisms because research subjects do not have awareness of the neural processes involved in the processing of their emotional states. Moreover, traditional methods do not lend themselves to the kinds of experimental manipulations necessary to test precise hypotheses about how children process emotional information. For these reasons, many of the research methods commonly accepted in the fields of psychopathology and emotional development are rarely used in cognitive, language, or perceptual development. We would not expect to understand language development, for example, by asking children how they might parse a sentence with multiple embedded clauses; clearly, the subject has no idea (for further discussion of this issue, see Davidson, 2003).

In recent years, the emerging field of affective neuroscience has offered powerful new perspectives and methods for understanding the processes linking observations of overt social behavior with the circuitry of the developing brain. These advances offer potential for new insights into both typical and atypical development of children. Yet, there is a caveat in encouraging use of the many new neuroscience-based methods that are now available. Discrete observations of single genes, relative levels of isolated hormones, indices of regional brain activation, or gross brain abnormalities are not likely to theoretically integrate systems of interconnectivity and patterns of effects over time. Simply: the use of new methods in the absence of a developmental theory or framework is unlikely to meaningfully inform our understanding of the emergence of psychopathology. This paper is intended to illustrate two general principles to guide the application of affective neuroscience methods to the study of developmental psychopathology. The first principle is that the developmental processes of interest must be specified with as much precision as is supported by extant knowledge. The second principle is that new insights will likely emerge if greater emphasis is placed upon understanding the mechanisms through which changes occur within an individual. These two principles are then applied to the study of emotion regulation, an area of considerable interest with clear application to both typical and atypical development.

Principle 1: Specify Components of Complex Social Processes

It is difficult to link observations of children's socioemotional behavior (the symptoms of psychopathology) to the developing brain. One impediment to uncovering these brain–behavior relationships is a lack of clarity about what particular affective processes are the targets of inquiry. For example, many of the constructs frequently used in the developmental literature such as *attachment*, *attention*, or *emotion regulation* are likely to be constellations of processes that emerge as the output from multiple neural systems. Therefore, it is essential to develop precise, empirically informed, biologically plausible models of the mental processes in question. By dissecting complex social behaviors, we can begin to address questions not only about underlying mechanisms, but also how different neural systems come to function coherently and seamlessly. The importance of a developmental approach to this issue is that domain specific outcomes observed in studies of adults do not confirm domain specific beginnings. In other words, affective systems in mature organisms may

operate so coherently as to appear to be unified, but the coordination of subprocesses may itself be a developmental product of an individual's experience. Therefore, an affective neuroscience perspective can augment traditional research approaches by disambiguating the brain–behavior processes of interest.

The value of specifying affective behaviors into more specific components can be illustrated by analogy. In the field of cognitive neuroscience a major emphasis has been dividing tasks into constituent operations. For example, early studies of attention began with assessments of overt behavioral responses (such as reaction times) thought to reflect mental chronometry. These studies were then supplemented with data from very different levels of analysis, single-cell recordings in monkeys and lesions in humans, to better understand the cognitive operations involved. These studies uncovered knowledge about how the mechanisms of selective attention relate to different kinds of behavioral problems (see Rafal, 1996, for a review). As a result, we know about the roles of neurotransmitter systems (Marrocco, Witte, & Davidson, 1994), the distinction between the orienting reflex and later attentional processes (Motter, 1998), how various sensory and motor systems are influenced by attention (Roland, 1993), and how attentional mechanisms work in conjunction with sensory-processing areas to gate information at cortical levels (LaBerge, 1995). Neuropsychological and neuroimaging data were used to decompose operations such as attention, selecting/filtering, and response processes, to distinguish between automatic and controlled processes, and understand networks involved in engaging, disengaging, and shifting of attention (Posner & Petersen, 1990). Based upon these advances in our understanding of how attention operates, an integrated view of affect regulation and brain function, even if rudimentary and incomplete, has enormous potential for understanding issues of emotional development and psychopathology.

Example: Attachment system(s)

This point may be illustrated by the study of social attachment. Attachment is typically assessed through patterns of responses to a behavioral paradigm wherein the infant is separated and reunited with his or her parent. The ingenuity of this approach is the focus on how the infant organizes a broad range of complex behaviors (e.g., affect expression, social interaction, exploration, attributions, comfort, wariness) in response to changing circumstances. Because this approach relies exclusively on the measurement and categorization of overt behaviors, little attention has been directed toward isolating the constituent developmental processes underling the behaviors. For example, security and distress behaviors might reflect distinct neural systems (cf., Bischof, 1975). There are other examples of psychological constructs that, like security and distress, appeared to be opposite poles of the same system, but turned out to have distinct neural circuitries. For example, hunger–satiety and positive–negative affect (Critchley & Rolls, 1996) first seemed to be opposite poles of the same continua, but are based on distinct neural systems.

What might such constituent attachment systems look like? Ancillary evidence suggests that infants may have a system of neural circuitry that becomes activated in response to fear (of being left alone, of separation; Caldji et al., 2004; Kalynchuk & Meaney, 2003). Such a *fear system* might protect the infant from the environment, motivate proximity to caregivers to deal with stress, or generate cries that alert the caregiver to perceived threat over the course of development (LeBar & LeDoux, 2003). Such a fear system might become coordinated with a distinct *affiliation system* that motivates social contact including shared affect between infant and caregiver, elicitation of joint attention, and social responsivity.

A number of studies have implicated neurohypophyseal peptides, such as the oxytocin (OT) system, as a neurobiological mechanism responsible for the regulation of complex social behaviors such as affiliation and parental care (Carter, Braver, Barch, Botvinick, & Noll, 1998; Insel, 1992, 1997). OT is a peptide hormone that is produced in the hypothalamus and released centrally and peripherally into the blood stream via axon terminals in the posterior pituitary (Kendrick, Keverne, Bald-

win, & Sharman, 1986). Quite distinct from hormonal markers of the fear system, OT receptors appear to be part of the neural system of reward circuitry that includes the nucleus accumbens (NAC; Lovic & Fleming, 2004). In the prairie vole, a monogamous rodent, higher levels of OT are associated with decreases in stress hormones and increases in positive social interactions and attachment behaviors (Witt, Carter, & Walton, 1990). In additional, OT appears to facilitate the consolidation of social memories, a key component of selective social attachments (Popik, Vetulani, & Van Ree, 1992). In contrast, hormonal markers of fear response systems appear to impair memory functions (Erickson, Drevets, & Schulkin, 2003).

Most research on the functions of the OT system has been conducted with nonhuman animals, and evidence for a neurobiological marker of attachment-related behavior in humans remains compelling, but inconclusive (Wismer Fries, Ziegler, Kurian, Jacoris, & Pollak, in press). However, these animal studies suggest that the neurobiological circuitry involving affiliative behaviors may be one subcomponent of social attachment in humans. Moreover, a central question is how reward circuitry becomes linked with the circuitry of the fear system. Multiple systems (including OT, dopamine [DA], estradiol, arginine vasopressin, serotonin [5-HT], and progesterone) are implicated in feedback loops involving reward circuitry and the regulation of social behaviors in the brain (Insel & Fernald, 2004). Thus, the interesting question is not which neuropeptides are activated during attachment behaviors, but how a social bond develops and becomes tied to a response system (Insel, 2003). One possibility is that because social attachment requires that stimuli become linked to major information streams, early adversity might affect attachment-related behaviors through corticolimbic pathways.

Both DA and 5-HT pathways within the mesolimbic system and prefrontal cortex (PFC) are particularly sensitive to adversity (e.g., Braun, Lange, Metzger, & Poeggel, 1999; Ziabreva, Schnabel, Poeggel, & Braun, 2003). It has been demonstrated that alterations of monoaminergic receptor densities in the medial PFC, amygdala, hippocampus, and NAC may induce lasting effects on behavioral flexibility and regulation (Jinks & McGregor, 1997; Ragozzino, Detrick, & Kesner, 1999). However, there are multiple ways in which breakdowns within corticolimbic circuitry could affect an individual's ability to use contextual cues to guide behavior (Dawson, Hessl, & Frey, 1994; Heidbreder, Weiss, Domeney, Pryce, Homberg, Hedou, Feldon, Moran, & Nelson, 2000). For example, the ventromedial cortex (including the orbitofrontal cortex [OFC]) is critical for associating incoming stimuli with existing response–reinforcement contingencies (Adolphs, 2002; Bechara, Damasio, & Damasio, 2000). The medial PFC provides goal-directed motor plans selected within the NAC on the basis of contextual and emotional associations from both the hippocampus and amygdala (Grace, 2000). Therefore, a focus only on one particular brain region or only on the complex behavioral output of the attachment system is unlikely to reveal how various aspects of information become integrated into a coordinated response system or the means by which such a system may be changed by experience.

Influences of "associated" processes

In addition to issues of fear and affiliation, other affective, perceptual, cognitive, and motor processes are activated in situations in which attachment-related behaviors are observed and measured. A focus on the development of these brain–behavior processes can clarify which systems are coordinated with attachment behaviors.

One example of associated processes is the communication, signaling, and decoding of emotional signals that occurs in situations in which attachment is observed. Selective impairments following brain damage suggest that different neural systems may support how individuals communicate what they are feeling to others, generate their emotional states, and recognize and encode emotional signals from others (Heilman, 1994). An early stage in the processing of social information involves the child's perception of salient signals from the environment, including facial expressions, tone

of voice, and body language. Most research on emotion perception has been directed at the network of cortical circuitry involved in face perception (De Renzi, 1997).

Elegant work by Kanwisher and colleagues (e.g., Kanwisher, McDermott, & Chun, 1997) has demonstrated that regions in the fusiform gyrus respond more to faces than other animate regions such as human hands. Similar brain regions emerge when subjects view dynamic (as opposed to static) facial images (Sato, Kochiyama, Yoshikawa, Naito, & Matsumura, 2004). This research raises two compelling issues that bear upon the development of psychopathology. The first issue is that studies of mature subjects do not address the developmental origins of neural architecture. Thus, the fusiform gyri might be prepared to processes faces specifically; or this brain region may not begin as face specific but instead may be particularly sensitive to experience and expertise with salient stimuli such as facial expressions (Tarr & Gauthier, 2000). A second question concerns specificity of the systems used to recognize faces (face vs. hands), emotions (angry vs. sad), and identities (mother vs. stranger). Rather than difficulty processing faces per se, children who have experienced early adversity show atypical patterns in decoding specific emotional signals (e.g., anger vs. sadness, or mild vs. intense anger) in the human face (Pollak, 2004).

Less frequently studied, but also central to aspects of emotion communication, is children's understanding of tactile, gestural, olfactory (e.g., pheromones), and auditory affective cues. The human voice contains in its acoustic structure a wealth of information on the speaker's identity and emotional state, yet little is known about the neural basis of vocal emotion communication. A recent study with adult subjects found that voice-selective regions along the upper bank of the superior temporal sulcus showed greater neuronal activity in response to vocal sounds, whether speech or nonspeech, than to nonvocal environmental sounds. These regions selectivity responded more to human voices than to matched control stimuli (Belin, Zatorre, Lafaille, Ahad, & Pike, 2000). These voice-selective areas in the superior temporal sulcus may represent the counterpart of the face-selective areas in human visual cortex and may be critical for understanding children's perception of auditory emotional signals. Indeed, recent electrophysiological studies of severely abused children revealed that auditory anger cues from their own mothers engaged more attentional resources in these children relative to controls (Shackman & Pollak, 2005). Thus, questions remain about whether and how the type and amount of emotional experience children receive affect the neural systems that subserve emotion processing.

A second example of processes that are inextricably tied to social attachment is attention. Within a social encounter there are countless cues that the developing child must attend to including interoceptive information (e.g., subjective feeling states: distress, pain, comfort, anxiety, pleasure), contextual features (familiar vs. unfamiliar settings or people), and the social signals being expressed by others. To successfully select and utilize these cues, the child will rely upon attentional processes that include orienting to relevant stimuli, filtering of irrelevant stimuli, shifting attention between key features in the environment, and sustaining attention over time. Through processes of selective attention, some sensory inputs will become more readily available to influence memory and behavior (Egeth & Yantis, 1997; Posner, 1994).

Regions of the parietal and frontal lobes appear to be involved in mediating various aspects of attentional control (for review, see Goldberg, Bisley, Powell, Gottlieb, & Kusunoki, 2002). For instance, the parietal cortex may represent a general-purpose mechanism for directing visual attention (Wojciulik & Kanwisher, 1999) including the abilities to orient attention toward sensory stimuli while ignoring other stimuli (Mirsky, 1996). Areas of the PFC also play a role in selective attention and filtering of irrelevant information. For example, patients with lesions of the lateral PFC have difficulty focusing attention while filtering out irrelevant information (Gehring & Knight, 2002). Dopaminergic systems linking the frontal lobes with midbrain regions appear to play a role in how attentional responses are related to behavioral regulation (King, Tenney, Rossi, Colamussi, &

Burdick, 2003; Pruessner, Champagne, Meaney, & Dagher, 2004), but little is known about the development of these systems in humans.

Less is currently known about how attentional networks become differentially activated in response to emotion-related information. Using Stroop-type tasks, Compton, Banich, Mohanty, Milham, Herrington, Miller, Scalf, Webb, and Heller (2003), found that the left dorsolateral PFC and medial PFC are involved in maintaining attentional set for both neutral and emotional stimuli, suggesting a common selective attention system. However, this same study demonstrated that areas of the right occipitotemporal region are recruited when emotional (compared with neutral) stimuli were to be ignored, suggesting a specialized emotion filtering system. In addition, anterior regions of the anterior cingulate cortex (ACC) appear more active in response to attended emotional stimuli (Fichtenholtz, Dean, Dillon, Yamasaki, McCarthy, & LaBar, 2004) and when subjects attend to their own internal emotional responses (Lane, Fink, Chau, & Dolan, 1997). The roles of these processes in forms of affective regulation, such as attachment, require further examination.

Summary

A challenge in attempting to understand the neural processes underlying children's socioemotional behaviors is that we often lack clarity or specificity about the particular affective processes in question. Most research methods lack the specificity necessary to determine links to discrete neural systems. This point is illustrated by the construct of social attachment. This complex phenomenon is likely to emerge from multiple processes including (but not limited to) biobehavioral systems involved in affiliation and fear regulation, affective processes such as the expression and perception of multimodal emotion cues, and attentional processes. To advance understanding of the developmental basis of attachment problems in children, it is necessary to discern how these various systems come to function in synchrony. Through which mechanisms do various emotional processes become relatively activated with reference to each other? An affective neuroscience approach may be useful in excavating the neural foci of activation, the network of functional connectivity, and the interactions of various networks associated with both separation distress and attachment/security. Rather than viewing such an approach as *biological reductionism* of complex psychological processes, such a perspective, in tandem with traditional approaches, allows us to address a new generation of compelling developmental questions.

Principle 2: Specify Mechanisms Underlying Change

Although the developmental sequelae of early adversity have been well documented, little is currently understood about how and why certain kinds of early experiences lead to behavioral disorders. Similarly, research on normative emotional development has also failed to address the mechanisms underlying changes in emotional processes. As a result, the neurodevelopmental processes involved in the organization of affective systems remain largely unknown. Fortunately, a next generation of research can focus on the discovery of causal mechanisms in the ontogenesis of emotion and explain the long-term effects of early experiences on individual functioning. The development of such causal models will require, first, a precise parameterization of the rich, complicated, "booming, buzzing, confusion" of sensory experiences to which humans are exposed within moments of birth. Second, such models will need to account for the ways in which those sensory experiences influence the neural architecture underlying complex social behaviors. Whatever core cognitive and affective processes the infant possesses upon entering the world, it is clear that the kinds and capacities of emotional behaviors the individual can engage in change drastically over time. Therefore, a central question is how to explain these changes. The effects of experience on the developing individual have both basic science and applied importance in that change may be critical for experience-independent maturational processes or dependent upon environmental input. Understanding both of these kinds of

mechanisms may help account for individual differences in responses to early experience and also intervention-induced changes in the form of psychological treatments.

Although the present paper focuses on biological mechanisms of emotional development, theories accounting for mechanisms of change need not be based on neural systems. For example, mechanisms may be addressed at computational, cognitive, or other levels of analysis. Central to a mechanistic account, however, is specifying a causal relationship between input and output: how it is, for example, that some kind of early emotional experience results in an affective style or behavior. Such explanations need to account for the process through which sensory input initially affects the individual and specify which processes maintain those changes over time.

Linking biology with experience

Two kinds of information appear critical for understanding processes of change: the constraints of the developing nervous system and the sources of plasticity within that same system. Even the most powerful young learners are not blank slates. Ultimately, affective plasticity or learning must be explained by a combination of biological predisposition and experiential input.

To begin to unpack how affective systems can change in response to different kinds of experiences, measurement of the effects of early adversity on child development must now become more nuanced. In the past, it was sufficient to select study populations based on whether children did or did not experience some form of adversity, such as child maltreatment. However, now it is necessary to parse the effects of variations in adverse experiences on developmental outcomes. For example, factors such as the intensity/severity, chronicity/duration, and developmental timing of experience may be critically related to the development of different forms of psychopathology (cf., Manly, Kim, Rogosch, & Cicchetti, 2001). It is not trivial to measure a child's experience, nor is it clear that there are currently solid standards for evaluating how adverse an experience was for a given child or precisely how long the experience lasted. However, with the exception of some work done on rats, little is presently known about sensitive periods for the impact of experience on the stress and emotion–regulatory systems. Moreover, even in the existing rodent models, there is little specificity about what constitutes the underlying mechanisms.

The value of an affective neuroscience approach is the possibility of linking a child's experience, physiology, behavior, and genes. Indeed, the kinds of questions that need to be answered to address public health questions are unlikely to be addressed from only one level of analysis. For example, more precise models are necessary to determine what kind of events lead to long-term alternations in neural systems and how to define individual differences in the thresholds after which environmental influences begin to dysregulate affective systems. To advance research in these areas, we need not only to identify gene polymorphisms in clinical populations but also to address what the gene is doing: how it causes or maintains disorders, how it directs or constrains an organism's interaction with the environment, whether it has the same function early in development as in adulthood, and whether the gene functions similarly across species. However, genetic analyses in isolation are unlikely to advance our understanding of psychopathology. Whatever the sequential particulars of the three billion DNA subunits that make up a child's genotype, they are meaningful only in the context of phenotype, of a child's life history and experiences. Developmental approaches will need to consider how experiences turn on and off certain genes and through which mechanisms genetic polymorphisms act in combination with "stressful" experiences to produce psychopathological syndromes (see, e.g., Caspi et al., 2003).

Candidate mechanisms of plasticity

Social stimuli are diverse and complex. Therefore, the developing child's behavioral responses need to be guided by some representations based upon past experiences. Networks involving the ventromedial cortex and OFC are critical for processes such as associating incoming stimuli with existing response contingencies, linking

stimuli with motivational significance, and for holding these representations in working memory as behavioral responses are selected (Adolphs, 2002; Gottfried, O'Doherty, & Dolan, 2003; O'Doherty, Kringelbach, Rolls, Hornak, & Andrews, 2001). Animals with lesions to these systems demonstrate impaired object–reward association memory (Gaffan & Parker, 2000) and impaired contextual fear conditioning (Li, Inoue, Nakagawa, & Koyama, 2004). Which systems might explain the associations between early adversity and the emergence of socioemotional behaviors?

One candidate is the network involving the medial PFC. In particular, the ACC has extensive reciprocal connections with the limbic system via the hippocampal formation, the shell region of the NAC and the amygdala. Part of this network is likely to involve dopaminergic and serotonergic modulation of cortical activities related to socioemotional behavior (Ziabreva et al., 2003). These cognitive–affective interactions are best understood through work with nonhuman primates. The amygdala is implicated in the processing of social information (Adolphs, Tranel, Hamann, Young, Calder, Anderson, Phelps, Lee, & Damasio, 1999; see Aggleton & Young, 2000, for review). In primates, the amygdala projects directly to the medial thalamic nucleus, which in turn projects to the ventromedial PFC. This circuit appears to participate in learning and memory-related processes (Mishkin, Malamut, & Bachevalier, 1984). Early reports of amygdala lesions in monkeys described profound social and emotional changes, including problems appreciating the emotional significance of stimuli (Kluver & Bucy, 1939). Similarly, it has been reported that human patients who have suffered bilateral amygdala damage display deficits in the recognition of facial expressions of emotion (Adolphs et al., 1999; Broks et al., 1998; Calder, Young, & Rowland, 1996). These subjects show normal performance on tests of visuoperceptual processing of facial features, suggesting that the impairment is specific to the reading of emotional information (Adolphs, Baron–Cohen, & Tranel, 2002).

One brain region is unlikely to be responsible for the range of complex emotional behaviors. Yet, there are possible mechanisms through which the amygdala contributes to deficits in social behavior. One hypothesis is that the amygdala plays a critical role in stimulus–reinforcement conditioning, whereby neutral cues acquire positive and negative incentive status and emotional meaning (Aggleton & Young, 2000; Bechara, Tranel, Damasio, Adolphs, Rockland, & Damasio, 1995; Emery & Amaral, 2000; Gottfried et al., 2003; LeDoux, 1996). Consistent with such a view, individuals with lesions to the amygdala show poor performance on associative learning tasks involving emotional expressions (Boucsein, Weniger, Mursch, Steinhoff, & Irle, 2001). In addition, monkeys with lesions of the amygdala do not show the usual pattern of initial wariness and situation evaluation in dyadic interactions (Emery, Capitanio, Mason, Machado, Mendoza, & Amaral, 2001).

It is likely that this circuitry also informs issues of learning and development. As a case in point, a failure to perceive potential threat in the environment was found in infant monkeys who had received amygdala lesions as neonates (Bauman, Lavenex, Mason, Capitanio, & Amaral, 2004). In contrast to control and hippocampus-lesioned monkeys, amygdala-lesioned monkeys did not maintain proximity to their mothers. Interestingly, the mother–infant interactions appeared normal for the first few months of the infants' lives. A compelling aspect of these data is that the amygdala deficits were not apparent until the infant had opportunities for situational and contingency learning to occur. Thus, the amygdala may allow for proper evaluation of the situation through utilization of current sensory information about the partner, current contextual information, and information about past experiences.

Repeated stressful experiences appear to alter the balance of both excitatory and inhibitory inputs in the limbic system (Poeggel, Helmeke, Abraham, Schwabe, Friedrich, & Braun, 2003). Corticolimbic afferents from areas such as the amygdala, hippocampus, and PFC carry contextual information that may cause release of DA and facilitate approach to rewarding objects. However, the basolateral amygdala system may also receive stress signals from the ventral tegmental area (VTA),

facilitating learning through DA neurons within VTA, NAC, and other limbic and cortical areas (Datla, Ahier, Young, Gray, & Joseph, 2002; Stevenson & Gratton, 2003). Another possibility is that DA in the medial PFC allows animals to attend to behaviorally relevant stimuli (Passetti, Dalley, & Robbins, 2003). Impairments of DA within the basolateral amygdala would offset an organism's ability to appraise situations, thereby leading to inappropriate behavioral responses in situations of uncertainty or risk. Such a view is consistent with data suggesting that dopaminergic mechanisms may impair PFC functioning during stress, resulting in behavioral responses that are mediated more by subcortical than by prefrontal systems (Arnsten & Goldman–Rakic, 1998). On this view, the medial PFC would provide goal-directed motor plans generated from both the hippocampus (context) and amygdala (affective state). Dysfunction within this circuit might render the individual unable to combine environmental cues efficiently, leading to inappropriate behavioral responses. If correct, this theory would link chronic stress to problems such as attention deficit and hyperactivity (Heidbreder et al., 2000) and account for how DA may trigger autonomic and neuroendocrine responses to stress (Abercrombie, Keefe, DiFrischia, & Zigmond, 1989).

Although the DA system acts as a learning signal for behavioral reinforcement (Schultz, 1998), the numerous reports of DA release in response to aversive stimuli in animals are difficult to fit into theories of reward. These seemingly contradictory findings have lead to the suggestion that DA is involved in motivation and attention underlying behavioral responses to important events (whether aversive or appetitive; Berridge & Robinson, 1998; Redgrave, Prescott, & Gurney, 1999; Salamone, Cousins, & Snyder, 1997). A recent study suggested that repeated social stress affected DA binding in the NAC (which projects to the VTA) and also affected animals hypothalamic–pituitary–adrenocortical (HPA) responses (Lucas, Celen, Tamashiro, Blanchard, Blanchard, Markham, Sakai, & Mcewen, 2004). Indeed, the effects of early stress appear to be specific to the ascending DA systems (e.g., DA transporter) and nonspecific in terms of alterations in CRF expression in the PVN of the hypothalamus, differences in pituitary ACTH, and release of glucocorticoids (Meaney, Brake, & Gratton, 2002). Early adversity appears to alter the development of the HPA axis and extrahypothalamic corticotropin-releasing hormone (CRH; Shea, Walsh, MacMillan, & Steiner, 2004). Behaviorally, such changes are reflected as an individual's diminished capacity to maintain homeostasis if challenged by adverse events. However, critical unanswered questions remain such as whether such atypical responsivity increases the risk of psychopathology, whether such disorganization following adversity occurs in genetically vulnerable individuals, whether hypo- versus hyperresponsivity may change over development (DeKloet & Oitzl, 2003), and the effects of different kinds of adversity on these processes.

One possibility is that early stress exaggerates a typical developmental process such that chronically elevated glucocorticoids speed the overall reduction of neuron densities in core regions of the limbic system (Poeggel, Lange, Hase, Metzger, Gulyaeva, & Braun, 1999). However, the direction of causality in these findings is not clear. Stress-induced DA release is partly influenced by circulating cortisol levels (Marinelli & Piazza, 2002), which also increase during stress. Pruessner et al. (2004) have demonstrated that psychological stress causes DA release in humans. A lab-induced psychological stressor caused a significant release of DA in the ventral striatum as measured by positron emission tomography in adults who reported that they received poor parental care in childhood (Pruessner et al., 2004). This model may be particularly helpful in understanding long-term behavioral responses to stress such as depression and posttraumatic stress disorder.

Summary

The neurophysiological models presented here are certainly underspecified and overly simplistic. However, these recent findings are useful in thinking about the mechanisms through which experience may influence individual developmental organization. Such models will become substantially more complex and so-

phisticated as further studies on mechanisms are completed. *The key is that in defining a mechanism of development, whatever the level of analysis, the focus must be on processes or mechanisms that are responsible for or driving developmental change.* Those developmental changes may be experience-independent maturational processes or may be dependent upon experience/environmental input. Understanding the ways in which the environment affects developmental organization is central to a developmental approach to addressing etiological and treatment issues in psychopathology.

Application of the "Specificity" and "Mechanisms of Change" Principles: Regulatory Control

The construct of regulation has achieved extremely broad popularity in the biobehavioral sciences and promises to account for how and why some psychological processes can facilitate and organize behavior (Cole, Martin, & Dennis, 2004). This construct has appeal in that it can integrate understanding of both normal and abnormal developmental processes. The explanatory power of *regulation* is diminished, however, because the concept refers to such a broad range of diverse phenomena that it may becloud rather than clarify underlying developmental mechanisms. Consider, for example, the variety of terms used to interpret behavior in regulatory terms: self-regulation, neuroticism, behavioral regulation, emotional regulation, emotion, emotional control, attentional regulation, reactivity, monitoring, response modulation, arousal, and inhibitory control, all of which are used frequently in the developmental literature. Defining what is meant by regulation is a classic Wittgenstinian problem. An individual is "well regulated" compared to whom; a process is "dysregulated" compared to what? Employing an affective neuroscience framework may aid in addressing the two principles discussed above: specifying the process(es) of interest and the relationships between and circuitry of regulatory systems as well as accounting for the mechanisms of change in these processes.

The primary conceptual and methodological problem in this area is the difficulty in parsing *what is being regulated from what is doing the regulating*. In other words, how can we separate an individual's affect from their affect regulation? When a child is acting aggressively most of our current methodological tools cannot differentiate whether the child has a poor regulatory capacity or whether that child has more affect (or arousal, or relevant thoughts) that need to be regulated in the first place. The conundrum of disentangling the elicitation of a subject's initial emotion response from the activation of emotion regulatory mechanisms is that these processes overlap in time. Indeed, verification that a particular emotional state has been elicited in an individual is a vexing issue in affective science. This is because exploration of what a subject is feeling includes the challenges both of measuring (a) individual differences in the intensity with which emotions are felt and (b) the timing of how long the emotional states persist. Another challenge in resolving the mechanisms underlying the regulation of emotion is that most tasks used in studies of "emotion regulation" themselves load on multiple processes. Indeed, there appear to be many varieties of emotion regulation suggesting that different constellations of regulatory processes may be evoked in different contexts. Some processes may be voluntary and others automatic; others are modulated by context (situational, personal), and still others may work on different time scales (short term as in milliseconds or seconds, long term as in hours, days, or months).

Our understanding the origins of these processes, and their relation to the development of psychopathology, will be aided by theoretical clarification on the type of mechanism being examined, and by additional research on both proximal factors (such as children's voluntary effortful control, reappraisals, perceived control, attentional deployment) and distal factors (such as early learning history, genetic factors, and individual differences in baseline affect) influencing their regulatory control. One approach to understanding the developmental processes involved in emotion regulation is to begin to look at neural cir-

cuitry (with techniques such as functional magnetic resonance imaging) rather than discrete regions of activation. Mayberg (2002) has convincingly made the point that while individual regions of brain activation may be interesting, an understanding of pathological processes will require understanding the interactive loops of brain activity. How is it that motor, cognitive, and affective systems become coordinated? The goal in such research endeavors must be to define networks of connectivity linked to complex affective behaviors.

However, where might we begin to look for windows into such systems? Possibilities include the networks discussed above: ventromedial sections of the PFC, middle frontal gyrus, circuitry involving the subcortical regions that send significant projections to the PFC, and areas involved in cognitive processes (such as attention, memory, action) that can be used to regulate emotion (Bechara, Damasio, Damasio, & Anderson, 1994; Eslinger, Flaherty–Craig, & Benton, 2004). Because patients with damage to the PFC show disinhibited and inappropriate social behaviors despite intact cognitive abilities (Berlin, Rolls, & Kischka, 2004; Damasio, 1994; Rolls, Hornak, Wade, & McGrath, 1994), most studies of emotion regulation address top-down regulatory processes. Similarly, top-down mechanisms, such as attention, may serve as models of how neural activity may be increased or decreased in networks to establish processing priorities (Posner & Rothbart, 2000). This approach could be used to explore how children can use voluntary cognitive or metacognitive strategies to regulate their emotions and behavior. Yet, little is known about the development of such processes.

Nonhuman animal studies provide data that can guide human brain–behavior research in this area (although caution must be used in translating basic findings across species). Many theories of emotion regulation focus on the circuitry involving the connectivity between the PFC and the limbic system (as described above). From a developmental perspective, it is significant that the frontal pole of the brain develops over a protracted period, well into adolescence (Huttenlocker, 1990; Sowell, Thompson, Holmes, Jernigan, & Toga, 1999). For example, the neuronal organization in the dorsolateral PFC (Brodmann areas 9 and 10) changes dramatically until 5–7 years of age (Blinkov & Glezer, 1968), and slows thereafter. This region eventually develops extensive connections with the OFC and ACC, has numerous reciprocal connections to the amygdala and other limbic regions, and appears to be central for understanding emotion regulation (Damasio, 1994; Davidson, Putnam, & Larson, 2000). Other forms of autonomic regulatory processing (arousal, vegetative, circadian, or mood state) may also be controlled by ACC (Brodmann area 25), which links activity in the PFC with activity in brainstem and hypothalamic areas. Most research on the ACC has focused on how this region subserves cognition, particularly its role in a distributed attention network that supports executive functions (Bush, Luu, & Posner, 2000). The ACC surrounds the frontal pole of the corpus callosum, and the top and bottom portions of this region appear to have different functions. Although the upper portion of the ACC tends to show activation in cognitive tasks (such as working memory and response conflict), lesions to the subgenual portion of the structure impair regulation of sympathetic–adrenomedullary (SAM) and HPA responsivity (e.g., Diorio, Viau, & Meaney, 1993; Liu, Diorio, Day, Francis, & Meaney, 2000; Price, 1999).

A similar protracted period of development is suggested by animal studies of the neurotransmitter systems mediating prefrontal activity. Glutamate (Johnston, 1988; Schliebs, Kullman, & Bigl, 1986), GABA (Vincent, Khan, & Benes, 1995), acetylcholine (Kostovic, Skavic, & Strinovic, 1988), norepinephrine (Levitt & Rakic, 1982), 5-HT (D'Amato, Blue, Largent, Lynch, Leobetter, & Molliver, 1987), and DA (Benes, Taylor, & Cunningham, 2000; Berger & Verney, 1984) systems continue to develop past the weaning period when changes in emotional maturity are occurring (Benes et al., 2000). Bourgeois (1993) has plotted the overproduction and pruning of synapses in the Rhesus monkey against that of the human, taking into consideration differences in age compression (i.e., the rate at which each species develops), and has reported remarkable similarity across species.

Although the initial impetus for isolate rearing in Rhesus monkeys was the desire to study aspects of cognition, such as learning, unfettered by differences in mother–infant interaction, these emotionally neglected animals proved difficult to test in the laboratory because they displayed heightened emotional reactivity (Harlow, Harlow, & Suomi, 1971). This led researchers to focus on emotional behaviors such as fear, anxiety, and aggression that followed experiences of early adversity. Sanchez et al. (1998) studied Rhesus monkeys that were reared in isolation for the first year of postnatal life and then returned to normal social groups. When tested at 18 months of age, the monkeys who were deprived of social interactions early in life exhibited "executive function" deficits, such as poor performance on object reversal and delayed nonmatch to sample tasks. Such behavioral problems appear very similar to those noted in earlier social deprivation studies (e.g., Harlow et al., 1971). However, Sanchez et al. were also able to analyze anatomical data that revealed white matter deficits in the parietal and prefrontal cortices of these neglected monkeys. These deficits were associated with the animal's performance on executive function types of tasks. These data point to the importance of communication and networking between brain regions in understanding the effects of early experience.

A critical area for understanding the link between early adversity and the development of psychopathology is the mammalian stress system comprising the HPA and SAM systems (Axelrod & Reisine, 1984). These systems, interrelated at many levels, are believed to be coordinated in the central nervous system, in part, by the action of CRH in extrahypothalamic nuclei, principally the central nucleus of the amygdala and bed nucleus of the stria terminalis (Rosen & Schulkin, 1998). These systems are functional prior to birth but undergo reorganization in the transition to extrauterine life. By the second half of children's first postnatal year, social relationships can buffer stress reactions of these systems (Gunnar, 2000). Specifically, when young children are interacting with sensitive caregivers, it becomes difficult to provoke elevations in cortisol to situations that nonetheless elicit wariness and/or behavioral distress. However, we currently know little about which neural systems allow social attachments to regulate HPA and SAM responses.

In monkeys, early stress does not appear to affect the neuroanatomy or neurophysiology of the HPA axis, perhaps because it is relatively mature at birth (Sanchez et al., 2001). Nonetheless, limbic and frontal areas important in regulation of the HPA and SAM systems do appear to be affected by early adversity. Thus, early deprived monkeys exhibit features such as increased intensity of neurofilament protein immunoreactivity in the dentate gyrus granule cell layer (Siegel, Ginsberg, Hof, Foote, Young, & Draemer, 1993). In primates, early deprivation appears to affect development of the limbic–cortical pathways involved in regulating neuroendocrine and behavioral responses to threat/challenge. For example, Sanchez, Hearn, Do, Rilling, and Herndon (1998) noted increased density of CRH1 receptors within the dentate gyrus and PFC, which may mediate the neural substrates of fear or anxiety.

Summary

At present, there is little empirical data upon which to define commonly used regulatory terms or to disambiguate between various regulatory processes. Undoubtedly, multiple physiological systems are involved in mediating the developmental impact of early adversity on the individual's ability to regulate their emotional behavior. Although the CRH/HPA system has been studied the most, other systems such as thyroid, 5-HT, growth hormone, and the neurobiological processes regulating sleep and diurnal rhythms have received less attention from developmental psychopathologists and will need to be integrated into models of risk (cf., Dahl, 1996). Thus, an affective neuroscience perspective may aid in specifying the processes that are most central for understanding the risks associated with early adversity. An affective neuroscience approach is likely to clarify the processes through which early adverse experiences result in developmental changes in emotion regulatory abilities. Nonhuman animal data indicate that many brain

systems undergo protracted periods of postnatal development. These periods of time in which neural systems are undergoing organization may allow windows of vulnerability or experience-dependent fine-tuning of key regulatory systems including attention, learning, emotion, and memory (e.g., Black, Jones, Nelson, & Greenough, 1998). Experience-dependent changes in regulatory signaling between brain regions, through dopaminergic and serotonergic systems (Goldman–Rakic, Bourgeois, & Rakic, 1997), appears important for understanding plasticity of the neural circuitry involved in emotion regulatory processes.

Conclusions and Future Directions

Despite the many methodological advances related to brain and physiological development available to developmental psychopathologists, it is striking that there is yet to be a commonly agreed upon understanding of what constitutes the basic "risk" to children from early adversity. An affective neuroscience approach presents developmental psychopathologists with both a remonstration and new opportunities. As a field, we have become uncritical of our traditional methods, accepting that by attending to the psychometric properties of a scale, by refining and pilot testing the wordings of our questions, by applying sophisticated statistical techniques to our questionnaire-based data, or by fastidiously coding children's overt behaviors, we have developed instruments that can inform us about the mechanisms underlying psychopathology or resilience. The problem is that behavioral measures represent only the output of neural systems, and because most behavioral outcomes can be reached through multiple pathways, such data, in isolation, cannot speak to developmental origins. To trace back the ontogenesis of complex social behavior requires a focus on developmental mechanisms, not static lesions or deficits.

The approach outlined here suggests that the search for gross behavioral abnormalities in clinical groups is unlikely to be successful in accounting for the psychological sequelae associated with early adversity. A truly developmental approach to psychopathology must focus on the processes and mechanisms through which individuals respond to the affordances and challenges in their environments. An understanding of the neural circuitry involved in emotions, and the plasticity of this circuitry, can tell us much about threats to children's optimal development. Two general principles are presented here that hold promise for guiding future research. The first principle is that new methods should be used to parse, or unpack, complex developmental processes so that we can see more clearly the ways in which experience affects development. The second principle is that developmental explanations will not be complete unless they can address questions about how individuals change by either maturation or experience.

To remain at the forefront of the biobehavioral sciences, developmental psychopathologists must be poised to embrace new methodologies in the service of innovative questions about the processes and mechanisms underlying behavioral change. We now have the ability to assess changes over development in brain–behavior relationships using noninvasive modern human neuroscience methods that are safe for use with children such as EEG, event-related potentials, magnetic encephalography, diffusion tensor imaging, and functional magnetic resonance imaging. A complementary, ethically sound, approach to assessing brain–behavior relationships involves the sophisticated use of noninvasive measurement of hormones and immunological products. The challenge for using these new technologies, however, is to relate these measurement approaches to the contextual demands facing children. Relating contemporary neuroscience data to children's daily environments is difficult, and even laboratory settings have special ecological demands (e.g., remaining still during a magnetic resonance scan can be frightening, require inhibitory processes, and influence the processes being measured).

A second area reaching scientific maturity is an understanding of how gene–environment relations affect emotional processing. A previous generation of research attempted to determine heritability estimates or highlight

particular genetic abnormalities in clinical groups. However, these approaches cannot address issues of temporal precedence or inform understanding of how genetic vulnerabilities interact with the developing child's experiences (or lack thereof). At the same time, techniques allowing assessment of gene–environment–behavior relationships, assessed by genetic and epigenetic technologies, are becoming essential for parsing individual differences in behavior and are crucial for understanding resilience to adversity. For example, developmental models may be developed through new molecular biological methods that now allow manipulation of gene–environment interactions on behavior at critical stages in development through transgenic and knock out animals and through coactivators.

There are clear limitations of applying research with nonhuman animals to children. Yet, sophisticated animal models, in which experiences can be experimentally manipulated, are now essential for guiding research into the neurodevelopmental processes affected by early experience. This is especially true given the impossibility of conducting true experimental manipulations in studies of psychopathological populations and the ethical limitations of employing some neuroscience methods with human research participants. The key to using nonhuman animal models successfully is to (a) focus on ancillary questions that simply cannot be addressed by research with humans, and (b) select species that express behavior of direct relevance to human affairs.

This problem is not trivial: although nonhuman animal studies do allow us to control, measure, and time experience, it may be quite difficult to conceptually link affective experiences between human and nonhuman animals. Unlike human parenting, maternal care in the rat involves licking and abuse in the monkey is operationalized as biting and dragging. A next phase of research will need to consider the formidable question of how can we best model in nonhuman animals phenomena such as being threatened, criticized, or undermined, and other emotional experiences encountered by maltreated children. Therefore, developmental psychopathologists with expertise in human development must form collaborative relationships with scholars in primate development. Indeed, many key findings that are accepted as commonplace factors in child rearing today emerged from research done on nonhuman primates. To address ancillary questions when nonhuman primate models are not feasible or ethical, mathematical and computational models might support more detailed conceptualization about the importance of developmental timing, foci of lesions to networks, and the specific roles of certain types of input on development.

Although it is difficult to study the processes of developmental change, we are optimistic that new perspectives offered by affective neuroscience approaches will forge deeper insights into the processes that put children at risk. Such knowledge can foster the discovery of interventions tailored to remediate those processes. Such a perspective must take into account anatomical/maturational constraints on the developing brain as well as an understanding of what situations the organism's brain has had to respond. This will require that we understand the developing brain's give and take with the wide welter of signals, sensory inputs, and experiences received from the outside world during both fetal and postnatal development.

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