Early experience and depressive disorders: human and non-human primate studies

William S. Gilmer*, William T. McKinney

The Asher Depression Center, Northwestern University, Feinberg School of Medicine, 446 E. Ontario, Suite 7-100, Chicago, IL 60611, USA

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Abstract

This paper reviews evidence from both human and non-human primate studies concerning the role of early adverse experiences in the onset and course of adult depressive disorders. Despite accumulating evidence that stressful life events can play a major role in precipitating the onset of depressive episodes in humans, the mechanisms by which early experiences mediate and moderate the risk for later affective illnesses are not fully understood. Experimental paradigms in primates have documented the important role of undeveloped (social deprivation) or disrupted attachment systems (social separation). Effects of early social deprivation can be seen in many domains. Behavioral effects include repetitive idiosyncratic behaviors, increased self-directed behaviors, inappropriate expression of aggressive behaviors, non-modulated patterns of consumption, and inappropriate sexual and maternal behaviors. Cognitively, such animals require longer habituation time for any task and demonstrate increased perseverance on tasks following non-reward. Physiological effects include an altered hypothalamic–pituitary–adrenal response to stress, changes in diurnal temperature regulation, and alterations in immune function. Neurochemical effects include abnormalities in noradrenergic, serotonergic, and dopaminergic systems. Even neuroanatomical changes following early social deprivation have been reported. Studies with primates have also confirmed that early maternal and peer separations are major behavioral and neurobiological events with both short- and long-term consequences that parallel human depression. Future utilization of experimental paradigms in non-human primates may assist in better understanding the role of early experiences in predisposing to the development of affective illnesses in humans. This review concludes by presenting a model for understanding a developmentally based vulnerability to adult depressions.

Keywords: Depression; Development; Early experience; Life events; Primate

1. Introduction

Although life events play a major role in precipitating the onset of adult depressive episodes (Paykel and Cooper, 1992; Kessler, 1997), questions remain
regarding the nature of this role, especially for early events. Do specific types of early events lend special vulnerability to adult depression? Alternatively, might early stress interact with genetic endowment through nonspecific means to confer increased vulnerability to psychopathology in general? In recent decades, animal studies have supported the premise that adverse early experiences, including prenatal stress, can help shape behavior, neurobiology, neurochemistry and neuroanatomy, as well as response to later challenges. This paper examines human and non-human primate studies in an effort to understand better the contribution of early life experiences to clinical depression.

2. Early life experiences and depression: humans

Childhood loss and separation

Historically, literature regarding the role of adverse early experience as a risk factor for adult clinical depression focused on parental loss. The literature does suggest a possible association of later depression with early maternal loss (Finkelstein, 1988; Patten, 1991; Roberts and Gotlib, 1997). However, the effect of loss on an individual may depend on whether loss occurs through death, divorce or parent–child separation (Tennant, 1991). In comparing loss by death and separation, Tennant noted that little evidence remains for parental death as a significant risk factor for adult depression. While evidence suggests that separations occurring in the context of family or parental discord may contribute to adult depression, interpretation is difficult due to potential confounds, including genetic vulnerability and environmental factors. Brown (1988) and Brown et al. (1990) have suggested that methodological limitations account for many of the inconsistent results in these studies. These limitations include measurement and design problems, such as population dependent differences and intervening history.

Informed by Bowlby’s attachment theory (Bowlby, 1969, 1973), Brown, Harris and Bifulco have attempted to distinguish between vulnerability factors and provoking agents for depression in adult women (Harris et al., 1986, 1987; Brown et al., 1988). Brown (1988) observed that loss is not as critical as the complex chain of experiences that precede and follow loss. In their study of women from Walthamstow (Harris et al., 1986, 1987; Brown, 1988), the investigators found that early maternal loss acted as a vulnerability factor and increased the risk of later depression only in the presence of subsequent provoking agents. Rutter (1971) similarly described the difference between “risk indicators” and “risk mechanisms.” Risk indicators signal an increase in risk but do not necessarily reflect the processes that mediate the increase. Thus, in the Walthamstow study, parental loss was a risk indicator; however, the increased risk was derived from inadequate care subsequent to parental loss and was more common after loss of a mother. In addition, poor parenting without loss increased risk, but loss increased risk only in association with poor parenting (Harris et al., 1986).

Additional vulnerability factors identified in the Walthamstow study included: (1) current absence of a confiding relationship with a partner; (2) maternal loss before age 11 by death or separation of at least 1 year; (3) presence at home of three or more children under age 15; and (4) unemployment. The researchers theorized that these experiences result in a generalization of hopelessness, which Beck (1967) described as the core of depressive experience. Furthermore, the lack of a supportive relationship in childhood or adulthood might lead to a poor self-image that could promote this generalization of hopelessness after a severe loss. Although the quality of caretaking following parental loss is critical, Rodgers (1990) has argued that interactions with non-caretakers, including peers and siblings, must also be considered.

Brown (1988) proposed two main lines of influence or strands that may link early maternal loss with depression in adulthood. The first strand, characterized as a “conveyor belt of adversity”, involves external influences varying according to time and place. The second strand involves intrapsychic factors such as enduring cognitive sets and coping styles shaped by early events, which may influence responses to subsequent stressors. In the Walthamstow study, the first strand factors included institutionalization or educational deprivation. The second strand factors included self-esteem and the tendency to be
mistrustful or resentful. Notably, these strands may occur in parallel and cross-interact.

Citing the work of others including Brown and Harris, Rodgers (1990) offered three mechanisms by which early experiences may influence mental well-being in adulthood: (1) development of increased emotional susceptibility to a disorder that may be seen, even in the absence of significant stressors; (2) increased likelihood of adverse life experiences in adulthood; and (3) differential ability to cope with later adversities.

Kivela et al. (1998) suggested that early parental loss may create a lasting vulnerability detectable even in old age. In their longitudinal study of elderly Finns, they found that early loss of an opposite-sex parent was an independent predictor of developing depression. The investigators proposed that such losses lead to personality characteristics that make the individuals more vulnerable to later stressors, including other losses later in life. They also reported that the loss of an opposite-sex parent prior to age 20 predicted depression in older age.

Several investigators have considered the consequences of parental divorce, though loss by divorce and parental death are often combined (Tennant, 1991; Roberts and Gotlib, 1997). Hetherington et al. (1989) point out that divorced families are no longer atypical and are not necessarily pathogenic. Accordingly, the National Comorbidity Survey (Kessler et al., 1997) highlighted the uncertain relationship between parental divorce and later depression. Factors contributing to the complexity of the question include quality of family relationships, extrafamilial resources, visitation arrangements and personal characteristics of the child including age, temperament and possibly gender (Hetherington, 1989; Palosaari and Aro, 1994, 1995; Palosaari et al., 1996; O’Connor et al., 1999).

3. Childhood maltreatment

Childhood maltreatment generally can be separated into childhood sexual abuse (CSA), physical abuse, emotional abuse and neglect. While it is desirable to consider each form of maltreatment separately, their frequent co-occurrence confounds their separation. Other limitations of the childhood maltreatment literature include the frequent lack of control groups, possible recall bias, substantial psychiatric comorbidity and broad variances in case ascertainment, definitions of abuse and the assessment and definition of psychiatric sequelae, e.g., symptoms vs. disorders.

Studies of childhood maltreatment have frequently combined subjects who have sexual and/or physical abuse histories. Sample size and frequent coexistence of these conditions have limited the assessment of effect for one type of abuse without the other (Mullen et al., 1996; McCauley et al., 1997; MacMillan et al., 2001). While the number of studies specifically addressing the role of childhood physical abuse (CPA) is limited, most have found an association with later depression and other psychiatric morbidity (Holmes and Robins, 1987; Duncan et al., 1996; Kessler et al., 1997).

Significant gender differences in rates of physical and sexual abuse further complicate assessment of abuse literature, with the prevalence of physical abuse being higher in men and sexual abuse higher in women (Finkelhor et al., 1990; Brown and Anderson, 1991; Windle et al., 1995; MacMillan et al., 1997). Whether there are actual gender differences in the association of CPA with later depression is less clear. The US National Comorbidity Survey (Kessler et al., 1997) and the St. Louis Epidemiological Catchment Area Study (Holmes and Robins, 1987) found little support for such gender differences. However, in a large community sample study of physical and sexual abuse by MacMillan et al. (2001), childhood physical abuse was associated with depression and other psychopathology in women but not men.

There have been numerous investigations of CSA and its relationship to later psychopathology including depression, anxiety disorders, posttraumatic stress disorder (PTSD), borderline personality disorder, sexual disorders, suicidality, substance abuse and alcoholism (Brown and Anderson, 1991; Boudewyn and Liem, 1995; Fergusson et al., 1996; Kessler et al., 1997; Bulik et al., 2001). Commenting on their meta-analysis of 37 published CSA studies finding a significant correlation with depression, PTSD, suicide, sexual promiscuity, sexual perpetration and academic performance, Paolucci et al. (2001) argued that their results “support the multifa-
ceted model of traumatization rather than a specific sexual abuse syndrome of CSA.’’

A study of working class mothers by Bifulco et al. (1994) reflected the complexity of studying the consequences of CSA. Although they found that female victims of CSA were more likely to suffer clinical depression as adults compared to those without a CSA history, the authors noted the importance of considering other adverse experiences in the study population. Specifically, there was a significant association between CSA and parental indifference, parental violence towards the child and childhood institutional stay. When the timing of such events was considered, these other early negative experiences were most often found to be present before the first episode of CSA, indicating that sexual abuse occurred in the context of pre-existing familial dysfunction. In a related finding by Stern et al. (1995), greater degrees of family dysfunction (e.g., maternal mental health problems, marital problems, unemployment and communication problems) were present in families of children who had been sexually abused than in control families. As in studies of parental loss, the question arises regarding the extent to which familial dysfunction serves to mediate or moderate the development of later depression.

Investigation of the interaction between vulnerability for depression and childhood maltreatment has yielded inconsistent findings. Brown et al. (1990) determined that depression was associated with childhood abuse or neglect only in the presence of psychological or environmental vulnerabilities, which included “negative elements in core relationships”. The authors proposed that female CSA leads to premarital pregnancy and marriage to an undependable man, which lead to greater marital stressors. Depression is the ultimate result of this process. Alternatively, they also described the development of depression through a cognitive pathway related to a “helpless cognitive set which interferes with development of successful supportive relationships, which in turn increases risk once a stressor arises.”

Bifulco et al. (1991), Fergusson et al. (1996) and others reviewed in Weiss et al. (1999) have demonstrated that the severity, frequency and duration of CSA are associated with the development of depression. A twin study by Bulik et al. (2001) found that increased risk of depression was associated with attempted or completed intercourse, abuse by a relative and the use of force or threats. Cessation of abuse upon reporting it and less distress at the time of the abuse were significant protective factors. Conversely, Lister (1982) suggested that forced silence regarding abuse serves to increase the risk of depression.

Although there are a limited number of studies comparing male and female victims of CSA, a critical review of CSA studies by Weiss et al. (1999) suggested that male victims might not experience an increased rate of depression when compared to male nonvictims. This is in contrast to the nearly consistent findings in the literature of increased depression in female CSA victims over female nonvictims. If true, one might speculate whether there are other developmental or psychosocial factors that mitigate the development of depression in males, or possibly even a gender differential in the neurobiological response to early stress. However, the meta-analysis by Paolucci et al. (2001) found that gender did not modify the CSA effect. They also found no influence on CSA effect by socioeconomic status, age when abused, type of abuse, number of incidents of abuse or relationship of the perpetrator to the victim. In summary, the key findings in the association of childhood sexual or physical abuse with depression are as follows: (1) the effect of physical and/or sexual abuse is nonspecific for psychopathology; (2) factors such as age, gender and type of abuse are not consistent in their effects; and (3) the response of others to the child may shape the child’s ultimate response to the abuse.

4. Factors impacted by early experiences and shaping their effect

Early experiences do not occur in a vacuum. Clearly, there are numerous other factors including gender, age at time of occurrence, context, and severity or “dosing” of experience that may influence the impact of early experiences; yet there are limited data regarding these variables (Rutter et al., 1997). Other personal factors that are influenced by early experiences, such as affective regulation, cognitive styles, social support and various biological processes, may also shape the effect of those experiences.
To add to the complexity, the concept of resiliency may combine elements of multiple factors. Numerous authors have discussed the concept of resiliency (Rutter, 1985; Garmezy, 1991; Schissel, 1993; Cicchetti and Rogosch, 1997). There is a paucity of research, however, on the actual processes that allow maltreated children to function competently. Cicchetti and Rogosch (1997) defined resiliency as “the individual’s capacity for adapting successfully and functioning competently despite experiencing chronic stress or adversity, or following exposure to prolonged or severe trauma.” They appropriately cautioned against considering resiliency to be a static condition or trait. Additionally, they noted that children who have been maltreated are not affected uniformly by those experiences.

Regulation of affect is one of several primary developmental tasks that children face (Cicchetti and Toth, 1995). Various authors have discussed the potential for affective dysregulation to occur in children who have been maltreated (Thompson, 1994; Eisenberg et al., 1997). Affective dysregulation may lead to a variety of childhood behavioral problems and relationship difficulties (Cicchetti and Toth, 1995). While the effect is not specific for mood disorders, the possible association of childhood affective dysregulation with the development of adult affective instability and/or mood disorders requires further consideration.

The contribution of early life events in shaping an individual’s perception of themselves, their world and subsequent life events is of particular interest. Building upon adult cognitive theories (Beck et al., 1963; Seligman, 1975; Abramson et al., 1978, 1989), the literature provides some support for the role of cognitive styles in the development of depression (Reinecke, 2002). Perhaps because of the heterogeneity of cognitive styles among depressives, the literature contains arguments both for and against the applicability and specificity of current models (Rose and Abramson, 1992; Abela, 2001; Lewinsohn et al., 2001).

Given a cognitive stress–diathesis, individuals might develop a clinical depression based upon their interpretation of life events. In a meta-analytic review of 28 studies involving over 7500 children and adolescents, Gladstone and Kaslow (1995) found that maladaptive attributional patterns for both positive and negative events correlated with depressive symptoms. Kuiper et al. (1986) reported that global perceived stress level influenced the impact of negative life events upon depression, supporting the relevancy of cognitive appraisals of life events. Similarly, a study of adolescents by Deal and Williams (1988) found that cognitive distortions were a stronger predictor of depressive tendencies than actual measures of life stress. Finally, the age at which early adverse events occur may influence the type of cognitive style that makes one more vulnerable to depression. Moran and Eckenrode (1992) studied adolescent females and found that child maltreatment before the age of 11, along with low self-esteem and external locus of control for good events, increased risk for depression. They suggested that having an internal locus of control for good, but not bad, events might have buffered the girls from deleterious effects of the maltreatment. Of note, the girls who first experienced maltreatment before age 11 years were less likely to have that adaptive characteristic than those who first experienced maltreatment at 11 years of age or older.

In recent years, there has been significant investigation into the neurochemical, neurophysiological and neuroanatomical correlates of early stress with the development of depression and/or anxiety or stress disorders. The reader is referred to Bremner and Vermetten (2001), Heim and Nemeroff (2001) and Kaufman and Charney (2001) for more detailed reviews. Considerable attention has been given to effects upon the hypothalamic–pituitary–adrenal (HPA) axis by early developmental experiences, including parental loss (Breier et al., 1988; Weller et al., 1990; Luecken, 1998), parental socioeconomic status (Lupien et al., 2000), and physical and sexual abuse (Heim et al., 2000; De Bellis et al., 1994a). Kaufman et al. (1997) reported that depressed children with a history of maltreatment had a greater post-CRH ACTH response than non-abused depressed and normal control children; however, the effect was eliminated if the child was currently living in a stable environment. In their study of adolescents, Goodyer et al. (1998, 2000) reported that elevated midnight cortisol/DHEA ratios were associated with an increased number of subsequent personal disappointments and chronicity of depression at follow-up. The direct contribution of stress mechanisms to
central nervous system pathology (Sapolsky, 1996) may offer an intriguing explanation for interference of cognitive processes, resulting in behaviors that lead to undesirable experiences and further increased risk for depression.

Investigations into the effects of early adverse experiences upon other biological systems associated with depression are more limited. De Bellis et al. (1994b) reported increased catecholamine activity in sexually abused girls, aged 8 to 15 years, and Kaufman et al. (1998) reported greater serotonergic system dysregulation in depressed children who had been abused. However, there has been little investigation of early stressors on the activity of other neurotransmitter systems in clinical populations (Heim and Nemeroff, 2002) and the existing literature focuses primarily on early abuse experiences in patients with PTSD as opposed to depression.

While chronobiology and circadian neuroscience are also integral to a complete understanding of mood disorder physiology (Wirz-Justice, 1995), early life experiences and their effect upon biological rhythms remain largely unexplored. An exception is the work by Glod et al. (1997) who found that abused children had significantly greater nocturnal activity levels than normal control or nonabused depressed children. Attenuated circadian activity levels and sleep phase delay were seen only in abused children without PTSD symptoms and depressed children (Glod and Teicher, 1996).

Finally, imaging studies to date are inconclusive. In contrast to the hippocampal atrophy seen in MRI studies of adult depressives (Sheline et al., 1996; Bremner et al., 2000) and adult victims of childhood abuse (Stein et al., 1997), evidence of hippocampal changes in children and adolescents with depression and histories of maltreatment is lacking. A study of abused children with PTSD (De Bellis et al., 1999) did find reductions in intracranial and cerebral volume, but no hippocampal reduction. Thus, it appears that the neuroanatomical findings observed in abused individuals with PTSD cannot be generalized to abused individuals with depression who do not have PTSD (Bremner and Vermetten, 2001).

5. Implications for depression

Although there is empirical support for the influence of multiple factors in the expression of depressive vulnerability, the degree to which mediating and moderating factors differ across the broad range of mood disorder presentations is unknown. Various groups have found that recall of recent stressful life events prior to onset of first episode of affective illness is higher than for subsequent episodes (Dunner et al., 1979; Johnson et al., 2000; Kohn et al., 2001). However, this association has not been found consistently for all mood disorders. Nor is it clear as to which mood disorders require earlier stress inoculation. Does the effect of early life experience upon depressive vulnerability differ among mood disorders? Can early adverse experiences lead to phenotypic variations in age of onset, course, comorbidity or even treatment response? A review of the current literature in this area indicates that these questions warrant further consideration for all mood disorder presentations.

Glassner and Haldipur (1983) reported that patients with early onset bipolar disorder have fewer life events prior to the first and subsequent mood episodes. Similarly, Johnson et al. (2000) found that patients with bipolar illness who had a family history of affective disorders experienced an earlier age of onset and fewer stressors prior to their first episode than those without a family history of affective illness. Unipolar patients experienced the same level of recent stressors prior to onset, regardless of family history. These findings suggest that some patients, such as those with early onset bipolar disorders, have a genetic vulnerability that makes them less dependent upon life stressors to develop their first mood episode. However, Post et al. (2001) reported that early sexual or physical abuse was associated with an earlier onset of bipolar illness. One might hypothesize that early adverse life experiences interact with genetic vulnerability to bipolar illness in ways that later stressors do not.

There have been some findings that challenge earlier assumptions. For example, a study by Harkness and Monroe (2002) found that severe physical abuse, sexual abuse, and poor parental care had a greater association with RDC-defined endogenous depressions than nonendogenous depressions. High levels of stressful life events have also been associated with late onset affective illness, suggesting a higher stress requirement for the mood disorder to manifest (Johnson et al., 2000; Glassner and Haldipur, 1983). In a study of unipolar depressives,
Kohn et al. (2001) found that mild to moderate, nonmelancholic depressives reported more negative life events than severe, melancholic depressives. Might this reflect a genetic vulnerability in the melancholic patients that is less influenced by the moderation of later life events? One could speculate that the increased number of life events seen in nonmelancholic patients and in patients with early separation reflect a propensity for these individuals to experience more adverse life events, as opposed to reflecting the degree of adverse life events “necessary” to precipitate a first episode. Alternatively, the inconsistent findings in unipolar patients may simply reflect the heterogeneity of unipolar depression as well as less genetic vulnerability for some subtypes.

Information regarding the influence of early experiences upon other phenomenological presentations of mood disorders is limited. A history of childhood abuse has been associated with increased depressive symptoms during pregnancy (Benedict et al., 1999) and during the postpartum period (Buist, 1998). However, the influence of early experience in psychotic depressions, seasonal affective disorder, and recurrent brief depressions is unknown. A number of experiential factors have been associated with severity of mood disorders. In the study by Post et al. (2001), physical or sexual abuse in childhood or adolescence was associated with a more malignant course of bipolar disorder, characterized by increased cycle frequency, suicidality, and greater psychiatric comorbidity. Similarly, Garnefski et al. (1990) found childhood or adolescent maltreatment to predict greater severity of depressive symptoms later in life. Hammen et al. (1992) noted that early onset of unipolar depression was associated with increased severity over time. They proposed that the interaction of adverse family history and early age of depressive onset leads to a stress generating process that serves to perpetuate the disorder.

In summary, early life experience and subsequent life events, through partial mediation and/or moderation of heredity factors, influence the onset and course of mood disorders in ways that are inadequately understood. Future investigation in this area may benefit by focusing on the development of specific phenomena (e.g., anhedonia, sleep-phase shift, anergia, cycling, cognitive disorganization, etc.), rather than solely relying upon our current nomenclature for heterogeneous syndromes.

6. Early life experiences: experimental studies in primates

6.1. Background

Evidence from animal studies consistently document the important role of early experiences in shaping neurobiology and behavior, thereby enhancing vulnerability and predisposition to differential reactions to stressors later in development (Plotsky and Meaney, 1993; Newport et al., 2002a,b; Hofer, 1983, 1984, 1987, 1996; Kuhn and Schanberg, 1998). Early adverse events, e.g., social separations, social deprivation, and maternal neglect and abuse, can alter both behavior and a variety of neurobiological parameters, including neuroanatomy, that are relevant for the understanding of depression and other psychiatric disorders. To put in context the early adverse experiences in humans and animals, a basic understanding of the psychobiology of early social attachment in primates is important. Kraemer (1997) reviewed the changing perspectives on the causes and effects of affiliation that are crucial to our understanding of developmental psychopathology, with special emphasis on the mother-infant relationship in primates. The organization of cognitive and emotional systems that regulate social behavior in rhesus monkeys depends on early infant-caregiver attachment; disruption of this attachment leads to abnormal behavior and changes in the activity of various brain neurochemical systems. These effects might serve as a model for the etiology of some forms of human psychopathology. Caregiver privation alters basic cognitive processes and the development of usual relationships in neurochemical and neuroendocrine system activity. Kraemer has argued that “the long standing effects of caregiver depriva-
tion on behavior and on emotionality are probably attributable to changes in multiple regulatory systems and cognitive-emotional integration rather than restricted effects on the activity of any specific set of neurochemical systems.”

Animal models incorporate experimental paradigms developed in one species for the purpose of studying specific phenomena occurring in another species. Willner (1991a,b,c) has described animal models as representing an important interface between clinical psychiatry and basic research in the behavioral neurosciences. It has been argued that non-human primates are not suitable for genetic studies; however, two recent reports demonstrate how primates may, indeed, provide an avenue for investigating gene–environment interactions using candidate genes for physiological and behavioral traits. In a pioneering report, Clarke et al. (1995) provided the first evidence of heritability of levels of the biogenic amines norepinephrine (NE), serotonin (5-HT) and dopamine (DA) in the cerebrospinal fluid of rhesus monkeys. In a subsequent paper, Bennett et al. (2002) reported that a length variation of the serotonin transporter gene-linked polymorphic region that results in allelic variation in 5-HT expression is associated with decreased serotonergic function and 5-HT-mediated psychopathology. They found an analogous variation of the gene’s regulatory region in monkeys, which interacts with early experience to affect central 5-HT function. In the context of this paper, animal models have made it possible to precisely control the conditions of early experience and study the behavioral, cognitive and neurobiological effects on both a short-term and long-term basis.

The development of secure attachments in most primate species is as necessary for normal development as it is in humans. The effects of disrupted or never established bonds are devastating. Primate studies utilizing variations in the physical and social complexity of the rearing environment have produced effects remarkably similar to those seen in children with mental, behavioral, and emotional disorders. Thus, it is possible to study the role of adverse early experiences.

One type of early experience recently studied in primates involves variation in the foraging demands placed on mothers rearing their infants (Rosenblum and Paully, 1984). In the control or low foraging condition, mothers of infants were given ad libitum access to food; in the high foraging condition, they had to forage for food. In an in-between condition (variable foraging condition), they sometimes had to forage and at other times did not. Animals exposed to the variable foraging condition, the most stressful condition, had long-standing behavioral changes throughout life including depressive episodes, diminished autonomic functioning, increased timidity and decreased exploratory behavior.

Two of the most studied and dramatic strategies to alter early development, resulting in long-lasting behavioral, cognitive and neurobiological consequences, are social deprivation and social separation. In the social deprivation paradigm, lack of maternal and/or peer experience prevents attachments from ever forming. The social separation paradigm involves the disruption of existing attachment bonds after previous socialization with the mother and/or peers. Fig. 1 illustrates the difference between these two major approaches to altering early experience in non-human primates.

6.2. Social deprivation

Social deprivation of rhesus monkeys results in long-term effects in multiple domains. Behavioral effects include the development of repetitive idiosyncratic behavior, self-injurious behaviors, increased amount of time spent huddling and self-mouthing, inappropriate expression of aggressive behaviors, slow motion and cataleptic-like behaviors,
non-modulated patterns of consumption, and inappropriate sexual and parenting behavior (McKinney, 1974). In the cognitive domain, longer habituation to apparatus is required for any task. Socially deprived monkeys experience increased errors on odd object discrimination, extinction deficits which include increased perseverence on tasks following non-reward and inability to ignore redundant or irrelevant stimuli (Beauchamp et al., 1991; Beauchamp and Gluck, 1988; Gluck et al., 1973; Gluck and Pearce, 1977). Among the physiological effects seen are inappropriate HPA axis responses to stress, characterized by significantly lower basal ACTH levels over the first 6 months of life. Attenuated ACTH or cortisol responses to stressful cage and social transitions are seen in contrast to the notable increases seen in maternally reared monkeys (Clarke, 1993). Other physiological responses include reduced nocturnal body temperature and differences in diurnal temperature regulation (Lubach et al., 1992), long lasting effects on immune responses (Coe et al., 1989, 1992), higher baseline cortisol levels, lower basal growth hormone levels, increased heart rate response and less habituation to novel stimuli (Champoux et al., 1989). Neurochemical effects include reduced cisternal cerebrospinal fluid (CSF) norepinephrine levels (Kraemer et al., 1989), behavioral and neurochemical hypersensitivity to D-amphetamine (Kraemer et al., 1984), differential behavioral response to yohimbine (Coplan et al., 1992) and dopamine receptor supersensitivity (Lewis et al., 1990). Floeter and Greenough (1979), along with Struble and Riesen (1978) and Bryan and Riesen (1989), provided the initial reports of neuroanatomical changes resulting from developmental influences in early social and physical environment. Subsequently, two major primate studies documented neuroanatomical changes in different brain regions, namely the basal ganglia (Martin et al., 1991) and the dentate gyrus granule layer of the hippocampus (Siegel et al., 1993) documenting for the first time that early adverse events can alter either the gross morphology and/or the functional microstructure of the brain.

In summary, findings indicate that subtle changes resulting from environmental manipulations, such as adverse early experiences, may permanently affect cellular process and the structural integrity of particular neurons. Although seemingly “subtle”, these changes may assume greater importance in the context of developmental demands. Additional research is needed to further understand how the anatomical effects relate to the behavioral, cognitive and physiological alterations in individual animals or subgroups of animals.

There are two broad uses of pharmacological agents in primate developmental psychopharmacology: (1) drug challenges where agents with specific mechanisms of action are used to alter neurobiologic function of a particular system and the behavioral effects studied; and (2) the therapeutic use of agents with clinically documented effectiveness to reverse or block behaviors induced by altered rearing conditions. Most studies of therapeutic agents utilize social separation paradigms rather than social isolation paradigm, but several studies of therapeutic agents used primates reared in social deprivation.

The first pharmacological treatment study of socially deprived monkeys found that chlorpromazine reversed many of the abnormal behaviors shown by isolate monkeys, only to have them return when the chlorpromazine was discontinued (McKinney et al., 1973). Diazepam did not have comparable effects (Noble et al., 1976). In a study of isolated rhesus monkeys, Slikker et al. (1976) found that chlorpromazine decreased stereotypic behavior, whereas diazepam, at levels that did not produce ataxia, had no behavioral effect. Lithium also had no behavioral effect.

As previously discussed, early social deprivation of primates has severe behavioral, cognitive, neurobiological and neuroanatomical effects; however, the linkage with specific clinical syndromes is unclear and controversial. The real clinical significance is at a more fundamental level in providing a paradigm that illustrates the profound effect of undeveloped attachment systems. In this regard, it can be likened to neglect in humans, albeit without the nutritional deprivation and other physical consequences that can accompany human neglect. Prior social deprivation paradigms involved more extreme methodologies of deprivation and thus were criticized for not having any applicability to humans; however, subsequent generations of studies used more moderate forms of social deprivation with similar results. Another important clinical point derived from such studies is the
long-term vulnerability that can be induced. Even with therapy that can lead to socially normative behaviors at baseline, such animals remain differentially vulnerable to challenges years later.

6.3. Social separation

Humans, as well as many animal species, are in their most stable condition when they have developed secure social attachment systems. The disruption of these attachment systems is stressful, almost invariably leading to a grief reaction. In some vulnerable individuals, the disruption can serve as a risk factor for the development of clinical depression. Genetic, developmental, social and neurobiological variables all interact to determine the final shape of the reaction to separations. Animal models provide the opportunity to study the relative influence and interaction of these variables.

The earliest work on maternal separation in non-human primates goes back to the 1960s (Jensen and Tolman, 1962; Seay et al., 1962; Hinde et al., 1966; Kaufman and Rosenblum, 1967). Classically, the behaviors of the infant following maternal separation have been described as occurring in two stages: (1) protest or agitation; and (2) despair or depression. During the protest stage, generally characterized by hyperactivity, there are marked increases in locomotion and vocalizations. This typically lasts 24 to 48 h and is followed by a despair stage characterized by significant decreases in activity levels and increases in a variety of self-directed behaviors such as huddling. There is decreased food and water intake; but even with maintained food and water intake, the animals may die during this stage. These stages in primates have been likened to Robertson and Bowlby’s (1952) description of human infants’ reactions to separation from their mothers.

Of special relevance to this paper is the report by Hinde et al. (1966) that short-term maternal separation of rhesus monkeys early in their development has long-term effects two to three years later even without any intervening separations. This study compared control infants with no history of maternal separation with infants that had one or two 6-day separations at 30 to 32 weeks of age. Years later, the two groups did not differ at baseline, but in response to experimental challenge, the animals with an early separation history were significantly less likely to approach strange objects and to explore than control subjects. In a study with rhesus monkeys, Young et al. (1973) found that early life separations led to a more severe response to separations later in development, in contrast to control animals that had not experienced the early separations. Thus, separation in early life seemed to leave “scars” that indicate increased sensitivity to separations later in development.

Work with primates in many laboratories has confirmed the maternal separation reaction as a major behavioral and neurobiological event with long-term developmental implications (McKinney, 1985). The reaction to early maternal separation is accompanied by changes in heart rate, body temperature, neurochemistry, and hormonal and immune systems. The experimental paradigm has helped clarify some of the mechanisms that may underlie the effects of analogous developmental events in humans.

An additional approach utilized in separation studies has been the peer–peer separation model (Suomi et al., 1970; Bowden and McKinney, 1972; McKinney et al., 1972; Mineka and Suomi, 1978). As a rule, the reaction to peer separation is quite similar to that of maternal separation in terms of the classic protest–despair response. Peer groups can be reformed, however, and repetitive separations done in a way that is more problematic than in maternal separation paradigms. A number of variables can influence this response including age, rearing conditions, housing conditions before, during, and after each separation, neurobiological status and treatment with pharmacological agents (Mineka and Suomi, 1978; Kraemer, 1985).

Some of the individual variability in response to separation have been shown to be associated with neurobiological variables. CSF NE in particular appears to be a trait-related marker predicting a more severe response to separation. Animals with lower CSF NE levels respond to separation with more huddling and self-directed behaviors than animals with higher levels (McKinney, 1989). CSF NE levels have also been shown to be highly heritable (Clarke et al., 1995).

Pharmacological agents have also been shown to influence the response to both maternal and peer
separation in primates. In one of the first studies, Hrdina et al. (1979) gave desipramine to *Macaca fasicularis* and reported that it suppressed vocalizations and body play, increased social activities, and lessened the behavioral responses to maternal separation. Other agents studied in primate separation paradigms include diazepam (Kalin et al., 1987), morphine (Kalin et al., 1988), clonidine (Harris and Newman, 1987) and imipramine (Porsolt et al., 1984).

The first pharmacological treatment study in the peer separation paradigm was reported by Suomi et al. (1978). In this study, imipramine was given to rhesus monkeys undergoing peer separations. After a latency period similar to that in humans, imipramine was found to reverse the reaction to peer separation and prevent reaction to future separations as long as the drug was administered. When it was withdrawn, they returned to a more typical separation response.

Alpha-methyl-para-tyrosine, which lowers both norepinephrine and serotonin levels, exaggerates peer separation and can do so at doses that have no effect in the group housing situation or in chronically single-caged animals that are not undergoing the stress of separation (Kraemer and McKinney, 1979). para-Chlorophenylalanine, which blocks serotonin synthesis, has no effect. Low doses of alcohol alleviate the peer separation response, whereas high doses make it worse (Kraemer et al., 1981).

A recent study by Clarke et al. (1999) examined the effects of differential early rearing experience on later responses to the stress of repeated separations and antidepressant pharmacologic manipulation in rhesus monkeys. During subsequent separations, maternally deprived monkeys with a history of peer rearing exhibited significantly more disturbance behavior than mother-reared monkeys. There was no overall difference in disturbance behavior between mother and peer rearing in groups that were not separated (i.e., constant social housing). Differences were only apparent during the stress of separations. Thus, rearing condition predisposes the monkeys to differential response to later stress, in this case, separations. Drug treatment with either fluoxetine or desipramine was equally effective in blocking the increase in disturbance behaviors of peer-reared animals during separations. Moreover, the full drug effect was not significant until 5 weeks after administration, or 3 weeks after separation challenge. Thus, antidepressant drug treatment, whether acting on NE or 5-HT reuptake mechanisms, prevented the increase in disturbance behavior shown by monkeys most at risk, i.e., peer-reared monkeys when separated. This approach illustrates how primate studies can serve as a promising vehicle to study the effects of pharmacologic agents that are used to treat behaviors associated with the adverse response to environmental challenges during development. The approach also provides a template for evaluating the clinical effectiveness and developmental consequences of drug intervention.

### 7. Conclusions

Complex psychiatric illnesses such as depression are heterogeneous in their etiology and course. Animal and human studies suggest that exposure to early stress may interact with genetic predisposition to increase an individual’s risk of developing depression. Depression itself may alter the course of development by interfering with cognitive, psychosocial, and physiological functioning and by increasing other morbidities.

Many variables are involved in understanding the differential impact of exposure to early adverse life events and, in particular, their potential role in depression. Over the years, a variety of integrative proposals have been made for understanding depression (Akiskal and McKinney, 1973; Whybrow et al., 1984; Whybrow, 1997). Building upon these proposals, this paper presents a model for understanding early life events (Fig. 2). No scheme can be completely comprehensive, but data from human and animal literature suggest the following variables are highly relevant: (1) the type of event, e.g., loss of a parent by death, loss due to separation or other events, neglect and abuse; (2) the age at which the event is experienced, with individuals being more sensitive to various events at certain ages; (3) other characteristics of the person/animal experiencing the event, e.g., gender, temperament, genetic endowment and neurobiological makeup; (4) availability of social supports following exposure to the event(s); (5) prior exposure to the same type of event or a similar one; and (6) probable overlap in childhood
adversities with the relative effect of different adversities being more similar than dissimilar (Kessler et al., 1997).

Depending on the interaction of the above factors and others, a differential vulnerability to depression and/or other disorders is conferred. This does not inevitably lead to the development of depression, but does confer an increased vulnerability to future stressors. The closer the challenge is to the original adverse event, the more likely a depressive outcome. Although initial research in developmental neuroscience has yielded some provocative findings, it is premature to focus on only one neurobiological system. Multiple systems are probably affected in complex ways that are just beginning to be understood. It is possible that alterations in circadian biology, resulting in dysregulation of multiple processes, are fundamental to understanding the neurobiological impact of early life events.

Animal models have helped to delineate the mechanisms by which separation and deprivation effects occur. In particular, deprivation studies in non-human primates provide a rough approximation of early and severe neglect in humans, with profound pathology resulting from undeveloped attachment systems in both animals and humans. After such deprivation, the responsiveness to substitute care is tenuous and rehabilitated animals have heightened vulnerability to subsequent stressors. Understanding the mechanisms affected by subsequent substitute care may give insights into systems that are relevant to adequacy of care in humans. Human studies have emphasized the role of subsequent care in mediating or moderating the effect of early adverse effects. Future separation studies in animals may assist in identifying other factors that mediate vulnerability to depression, even in the presence of adequate subsequent care, and may clarify basic mechanisms underlying resiliency and differential responses to adverse events.

Although this paper has focused on the connections between early experience and depression, there is also accumulating evidence that early adverse experiences might increase the risk of other serious diseases (Felitti et al., 1998). This further underscores the need for continued animal research, including primate studies, to delineate the processes arising from these early experiences and to develop effective intervention strategies. Concurrently, preventive strategies should be emphasized so that the tragic chain of events is not set in motion in the first place. In conclusion, data from both human and animal studies are essential to an integrated understanding of the development and course of depressive disorders and other public health concerns.

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