Published in final edited form as:
Physiol Behav. 2012 December 5; 107(5): 623–640. doi:10.1016/j.physbeh.2012.05.014.

Have studies of the developmental regulation of behavioral phenotypes revealed the mechanisms of gene-environment interactions?

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Abstract

This review addresses the recent convergence of our long-standing knowledge of the regulation of behavioral phenotypes by developmental experience with recent advances in our understanding of mechanisms regulating gene expression. This review supports a particular perspective on the developmental regulation of behavioral phenotypes: That the role of common developmental experiences (e.g. maternal interactions, peer interactions, exposure to a complex environment, etc.) is to fit individuals to the circumstances of their lives within bounds determined by long-standing (evolutionary) mechanisms that have shaped responses to critical and fundamental types of experience via those aspects of gene structure that regulate gene expression. The phenotype of a given species is not absolute for a given genotype but rather variable within bounds that are determined by mechanisms regulated by experience (e.g. epigenetic mechanisms). This phenotypic variation is not necessarily random, or evenly distributed along a continuum of description or measurement, but often highly disjointed, producing distinct, even opposing, phenotypes. The potentiality for these varying phenotypes is itself the product of evolution, the potential for alternative phenotypes itself conveying evolutionary advantage. Examples of such phenotypic variation, resulting from environmental or experiential influences, have a long history of study in neurobiology, and a number of these will be discussed in this review: neurodevelopmental experiences that produce phenotypic variation in visual perception, cognitive function, and emotional behavior. Although other examples will be discussed, particular emphasis will be made on the role of social behavior on neurodevelopment and phenotypic determination. It will be argued that an important purpose of some aspects of social behavior is regulation of neurobehavioral phenotypes by experience via genetic regulatory mechanisms.

Keywords

Environmental enrichment; social isolation; maternal deprivation; gene-environment interaction; epigenetic mechanisms

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Introduction

Over the last 50 years there has been accumulating evidence that particular experiences, often at particular critical periods during development, produce permanent alterations in behavioral phenotypes – and thus account for a substantial proportion of the variability in these phenotypes. Although all species have variability (the building blocks of evolution), substantial variability was found to be the result of differences in experience of particular types, at particular ages, affecting particular behaviors [1]. This review will begin by summarizing some of the main findings from investigations that have sought to purposefully manipulate aspects of early experience in order to determine the relationship between that experience and variability in later behavioral phenotypes, as well as the underlying biological mechanisms that produce this variation. This is an extensive literature, so this review is intended to be neither exhaustive for any specific experimental manipulation, or to completely summarize the types of altered experiences that produce changes in neurobehavioral phenotypes; rather, the examples taken are intended to illustrate the extent of variation in neurobehavioral phenotypes that can be produced by altered experience, as well as the depth of understanding of the processes involved that can, with the advent of modern genomics and epigenetics, be used to elaborate precise genetic and epigenetic mechanisms controlling what are usually termed “gene-environment” interactions.

Effects of early experience on visual system development

Hubel and Wiesel were awarded the Nobel Prize in 1981 for their work on visual perception. A very important aspect of this work was that visual input to the cerebral cortex is a critical regulator of visual system development and, in particular, cellular survival [2]. Grossly put, their findings have often been described as “use it, or lose it”, a statement that is to the point in some respects, but underestimates the subtleties of their findings, as they identified a number of limitations of the principle: not all brain structures were affected in the same manner and the effects of sensory input on visual system development were highly dependent on when that visual input occurred, thus identifying specific “critical periods” for visual system development. Their classical experiments on monocular deprivation [3] demonstrated that deprivation of input from one eye led to reduced responses in primary visual cortical neurons in response to input from that eye and a shift in the proportion of cells responding only to the non-deprived eye, e.g. a shift in ocular dominance [4]. Importantly, deprivation of input did not lead to reductions in the numbers of cells responsive to the deprived eye in the lateral geniculate nucleus [5], suggesting that only some levels of the visual system were regulated by early life visual experience. The same changes in visual cortex function were observed whether light input was completely occluded or only partially occluded by a translucent device that eliminated form vision with far less impact on total light input [4]. Importantly, this indicates that it is not deprivation of all visual input that is important to the development of the ocular dominance columns in striate cortex, but specifically visual input of aspects of form, to which these cells were responsive.

Thus, exposure to visual stimuli during development determines overall sensitivity to particular types of visual stimuli in the mature animal, i.e. the visual behavioral phenotype. Importantly, deprivation of visual input only produced these changes in ocular dominance if they occurred during a certain *critical developmental periods* [5], between 1 and 3 months of age in cats, and were not observed when similar experiments were done in adult animals. Studies in very young animals, done just as the eyes opened, indicated that the effects of deprivation influenced the survival of cells or cellular connections [2]. The discovery at about the same time of neurotrophic factors which were necessary for neuronal cell survival [6] provided a potential explanation for such phenomena. The release of neurotrophins

consequent to cellular activity may provide an explanation for certain classes of experience-dependent neurodevelopmental processes in which the release of trophic factors occurs in the same synapses that are activated by the experience, subsequently affecting the function of those synapses and the survival of those cells. However, other types of experience-dependent neurodevelopmental processes involve more distributed regulation, across many aspects of behavioral function, involving diverse brain regions. Although it is certainly likely that trophic factors are involved in these processes as well, such mechanisms alone cannot account for them, and other signaling mechanisms are likely to be involved, including endocrine signals.

Environmental Enrichment

One way to think of the studies on visual system development is that experience with specific stimuli can affect the development of those parts of the cerebral cortex that respond to those stimuli. At about the same time that these findings were reported Rosenzwieg and colleagues demonstrated that overall environmental complexity (e.g. enrichment, termed by them “environmental complexity and training” or ECT) has very broad effects on the cerebral cortex and behavior dependent on the cerebral cortex [7]. As was the case for differences in visual experience, environmental enrichment produces changes in brain anatomy and chemistry (summarized initially in [8]). This “enrichment” consisted of housing from weaning of groups of rats in large cages with platforms for food and water and ample room for climbing on the wire sides. A small wooden maze and a set of “toys” (varying in shape and color) were presented on a rotating basis which the rats could manipulate, and interact with; indeed many of the toys were large enough to climb on, including a “swing” and a “ladder” (see Fig. 1 in Krech et al, 1960). Additionally, the rats were exposed to a variety of mazes during this enrichment period as well. Thus, environmental enrichment in these studies consisted of multiple components that separately might affect neurological and behavioral development, including exposure to complex visual and tactile cues, motor learning experiences associated with climbing and manipulating objects, spatial learning and hypothesis testing associated with maze training, exposure to learning under motivated circumstances and exposure to the physical cues and species typical interactions provided by other rats. From the outset it was recognized that each of these aspects of the enrichment experience might have separate effects on behavior and brain function. This was done to maximize the possibility of producing detectable changes in brain chemistry and function. It was recognized from the outset that the effects might be attributable to only some of the components of the ECT procedure; indeed, this was incorporated in the original experimental design with two control groups: an isolated condition (IC), which eliminates all components of the ECT procedure, including social interaction, and a social condition (SC) which eliminates all components of the ECT procedure except social interaction. The SC procedure is often found to produce effects that are intermediate between the ECT and IC groups, but at times the SC and ECT groups are not different, suggesting that the effects are purely the result of deprivation of social interaction.

Early findings with environmental enrichment demonstrated enhancement of learning in ECT rats, although often the comparisons were only to IC rats and limited to specific types of procedures. For instance, although there is no difference between ECT and IC rats in acquisition of a visual discrimination, IC rats are substantially impaired in acquisition of subsequent reversals of that discrimination [7]. These changes in learning are accompanied by dramatic changes in brain function. Gross brain weight, particularly of the cerebral cortex, is greater in ECT rats [9–11], as well as cortical thickness [12–14], numbers of glia [13], size of neuronal perikarya [14], length of postsynaptic thickenings [15] and the density of dendritic spines in occipital cortical pyramidal neurons [16]. The large increase in glial

numbers (but not neurons) accounts for the increased cortical volume but actually leads to reduced synaptic counts per unit area under some conditions [15]. Diamond et al. (1975) also had a social condition, and the SC rats were similar to the ECT rats indicating that the main effects were due to impoverishment (or social isolation) rather than enrichment, in this case. Surprisingly this increase in synaptic size is accompanied by an overall decrease in the number of synapses of about 33%, but a shift in the frequency distribution towards larger synapses (52% on average) in ECT rats compared to IC rats, resulting in an overall increase of total synaptic area of about 40% [17]. A series of detailed anatomical studies by Greenough and colleagues [18–22] on occipital cortex morphology in EC, SC and IC rats specified these differences in more detail. Reduced neuronal density is found in EC rats, but along with a greater number of synapses per neuron [21], increased length of synaptic contact zones [18], increased dendritic length and branching [22], and increased glial, capillary and mitochondrial measures indicative of metabolic adjustments [19, 23]. As for the more gross anatomical changes mentioned above, SC rats are intermediate to EC and IC rats for some measures [18, 21], but not others [19, 23], for which EC rats are different from both SC and IC rats. Gross anatomical changes are also accompanied neurochemical changes including increases in acetylcholinesterase activity [9, 24]. Subsequent studies have also identified differences in serotonin, dopamine, glutamate, and other neurotransmitters systems [25–30], which is not surprising given the widespread morphological changes to neuronal structure and distribution produced by environmental enrichment identified in these and subsequent studies (see [31]) for a complete review of this literature). Indeed, environmental enrichment reduces apoptosis and increases neurogenesis [32].

One of the most fundamental questions about the effects of environmental enrichment (and all other neurodevelopmental manipulations) involves the question of critical periods. One of the earliest such studies [24] found that environmental enrichment of both young and adult rats increases the weight of cortical subregions as well as total acetylcholinesterase activity. Indeed, for some measures the effects in adults actually appear to be more pronounced, but other measures indicate that although enrichment has effects in both young and adult animals, including measures of cortical thickness across diverse brain regions [33], the basis of these enrichment induced changes differs in young and adult rats in a variety of ways. In that study the effects of social housing conditions were most prominent at earlier ages and environmental enrichment at later ages, and affected somewhat different brain regions. Importantly, many of the changes in cortical weight resulting from enrichment can be observed in individually housed/enriched rats [34]. By contrast, differences in the length of postsynaptic thickenings in occipital cortex appear to be largely due to social isolation rather than environmental enrichment per se, e.g. SC rats are similar to ECT rats, and both are different from IC rats [15]. Thus, there appear to be somewhat separable effects of alterations in the physical environment and the social environment in studies of environmental enrichment.

Another way to address the question of critical periods is to determine whether later enrichment can reverse the effects of impoverishment: If the effects of enrichment/impoverishment have a critical period, then they should not be reversed by later enrichment. Some of the first studies found that later enrichment does reverse some of the effects of early impoverishment [35, 36], but these first findings were limited to the most basic measures of gross weight of cortical tissue and total acetylcholinesterase activity. In an experiment examining the persistence of the effects of environmental enrichment after subsequent environmental impoverishment, the persistence of the effects of enrichment were determined by both the duration of the initial ECT experience as well as the duration of the subsequent IC experience [37]. When the initial experience incorporates the entire period of juvenile development, up to 80 days, the effects of ECT on both gross brain measures and

neurochemical measures are highly persistent. Persistence of the effects of enrichment is observed for behavioral consequences as well [38].

These changes in cortical structure and chemistry are associated with improved learning in a variety of tasks [30, 39–43]. However, many of these comparisons have been between EC and IC rats, so at least some of these differences may be attributed to isolation-induced differences, discussed in more detail in a later section. Some learning differences in EC rats are associated with increases in REM sleep [40]. Importantly, this study used both SC and IC comparison groups; the IC group was impaired at initial learning compared to both EC and SC groups, while EC was superior to both groups in memory recall. Since EC groups had substantially more REM sleep than either SC or IC groups this was taken to be the basis of this effect. However, effects on memory alone do not account for enhanced learning in EC rats, as they also adopt more effective learning strategies than IC rats [41]. The extent to which deprivation of social interaction plays a role the differences observed between EC and IC rats is a complex question. Conspecifics no doubt constitute a major component of environmental complexity, contributing in some ways as general environmental stimuli (e.g. as complex visual, olfactory and tactile stimuli) and also in a specific interactive, experiential manner. Thus under some circumstances IC rats perform more poorly in learning paradigms compared to both EC and SC rats, while under other, more demanding circumstances EC rats perform superiorly to both SC and IC rats [44]. One approach to isolating these effects is to examine the effects of environmental complexity under equivalent social conditions; enrichment has been found to affect exploratory behavior [45], and improve learning [46] in isolated rats. Even the mildly enriching procedure of placing a gerbil, otherwise reared in isolation, in a different environment each day for 30 day increases dopamine fiber density in the prefrontal cortex and basolateral amygdala [47].

Studies have suggested that environmental enrichment affects dopaminergic systems based on behavioral, neurochemical and pharmacological data, including both reduced [48–53] and increased responses to psychostimulants [53–55]. Although the data is not entirely consistent, it would appear that self-administration is reduced while acute locomotor effects are increased. As part of this series of studies increased impulsivity was observed in IC rats, and opposite effects of amphetamine in EC and IC rats on impulsive choice [56], and faster extinction in EC rats and greater reinstatement in IC rats [51]. In a test of Pavlovian conditioned approach to examine incentive salience, EC rats were found to be “goal-trackers”, while IC rats were “sign-trackers” [57]. However, these studies have generally compared EC and IC conditions, and therefore cannot separate the consequences of environmental enrichment from isolation rearing, an important consideration given the profound effects that isolation rearing alone has on these behaivors. Some studies have included an SC group. EC rats had increased responses to both the locomotor stimulant and reinforcing effects of amphetamine compared to both IC and SC rats [58], but in a later study IC rats had increased self-administration compared to both EC and SC rats [50]. The protective effects of “enrichment” were also associated with the social component of enrichment, rather than the non-social component, in a study of cocaine escalation [59]. Schrijver *et al*. [43] specifically set out to dissociate the effects of social deprivation and environmental enrichment on cognitive function by examining the enrichment in both isolation-reared and socially reared rats. Those authors examined behavior dependent on hippocampal neocortical pathways (spatial memory formation) and behavior dependent on prefrontal corticostriatal pathways (reversal learning). Isolation rearing impaired reversal learning, but did not impair spatial learning and memory; while environmental enrichment improved spatial learning, but had no effect on reversal learning. However, some of these effects are not neurodevelopmental in their basis, as recent studies have shown that environmental enrichment after initial drug treatments in adults eliminated cocaine conditioned place preference, sensitization and reduced cue or drug induced reinstatement

[60–62] (see also [31]) for a complete discussion of this work). Another factor that may make the social and non-social aspects of enrichment especially hard to separate is that environmental enrichment has been shown to increase social interaction and social play in adolescent rats in comparison to socially housed rats housed in a non-enriched environment [63, 64].

The effects of social deprivation on emotional development in primates

While the first studies of environmental enrichment, which included a social component to enrichment, focused primarily on the effects of enrichment on cognitive function and consequent changes in brain structure, other studies specifically examined the effects of social deprivation on emotional development. The seminal studies of Harlow found that prolonged periods of social deprivation in primates produces profound impairments of emotional and social behavior [65–67]. Quite interestingly given the effects of environmental enrichment on learning in rats discussed above, and despite rather extreme behavioral disruptions in socially deprived monkeys, cognitive deficits are limited in deprived monkeys which are so abnormal in many other respects. Indeed, social deprivation of primates, and rodents as well, leads to such abnormal behavior that social deprivation models have been suggested to model a variety of pathological conditions: the self-clutching and crouching behavior exhibited by socially deprived rhesus monkeys upon their initial release from these conditions has been compared to autistic children [67]; isolation housing of adult animals has been suggested to model phobia and anxiety [68]; isolation-rearing of rats has been suggested to model schizophrenia [1, 69]; repeated maternal deprivation in rodents has been suggested to model depression [70]; while both maternal deprivation and isolation rearing produce phenotypes that predispose individuals to addiction, although perhaps via different mechanisms [71].

One of the most important questions in considering deprivation of social experience as models of these disorders, and the potential underlying mechanisms, is the extent to which deprivation of specific types of social interaction induce specific changes in subsequent behavior. The key to this question is the nature of the deprivation experience itself, and how that is related to the behavioral regulators of the natural development of the organism across the lifespan. Harlow initiated his studies from a developmental perspective by describing the development of multiple affectional systems in rhesus monkeys (*Macaca mulatta*): mother-infant, infant-mother, peer, heterosexual and paternal [72]. Each of these is defined by the nature of the interactors (e.g. mother, infant, peer, etc.) and is related to distinct developmental stages. Furthermore, the development of each of these affectional systems is also subdivided into distinct stages based upon the type of social interactions between the actors. Although most famous for his studies of contact comfort with “cloth mothers”, Harlow described the effects of social deprivation under a variety conditions: differing durations, occurring at different ages, involving different types of social behavior and consequently affecting the development of systems related to these different affectional systems. Infant monkeys raised apart from their mothers would prefer a cuddly cloth surrogate mother without food over a wire surrogate mother that provided food [65, 66]. This is not to say that provision of nutrition was not important. Infant monkeys would prefer a lactating cloth surrogate over a non-lactating cloth surrogate, but contact comfort determined the infant’s preference for physical contact more than nutrition. Indeed, the cloth surrogate was a sufficiently adequate maternal replacement that deprived infant monkeys, in the presence of the surrogate, would exhibit somewhat normal exploration of inanimate and animate objects. This pattern of exploration using the cloth surrogate as a base is similar to that observed in normal infants with their mothers, as was the immediate return and contact clinging to the surrogate mother when frightened. Other sensory aspects of a surrogate mother are also preferred, including movement (e.g. rocking), warmth and texture [73, 74].

Infant monkeys respond quite similarly to removal of actual mothers and cloth-surrogate mothers at 6 months of age [75]. Presence of the attachment object in a novel circumstance, or in the presence of a stranger, evokes contact cling, while absence of the attachment object evokes agitation, vocalization and fearful responses. However, one should not conclude from these findings that the surrogate mother was a complete replacement for the real thing. Indeed, in considering the degree of normalcy engendered by the surrogate mother Harlow pointed out that one of the main roles of mothers is to shape the developing behavior of the infant monkey [76] – an essential point when considering the critical aspects of experience that might mediate the effects of maternal deprivation. The maternal role includes the security and protection roles previously described that are so necessary for initial interactions with the physical and social environment that lead to the transition away from infant behaviors like excess clinging and non-nutritive sucking. This process is more often initiated by the mother than the infant and leads the infant towards age-appropriate social behaviors with peers and adults. One immediate role of the mother as infants begin to interact with peers is to regulate play behavior, particularly levels of aggression. These functions of maternal experience cannot be replaced by an inanimate surrogate and indicate how these experiences regulate subsequent behavioral competency. Importantly, one can also infer interactions between the consequences of maternal behavior directed towards the infant at this stage and later social development. Another important role of the mother is to train her infant to comprehend gestural and vocal communication. Infant monkeys deprived of the experiences necessary to regulate emotional reactions and communicate with other monkeys are asocial and subject over time to increasing ostracism and violence from other young monkeys. Finally, it should also be noted that different maternal attributes, some captured by the inanimate maternal surrogate and some not, affect the development of different behavioral and psychological attributes in infants. This diversity of neuro-regulatory factors increases as other types of social interactions are considered.

Studies of responses of infant rhesus monkeys to separation from their mothers [77–79] described a sequence of reactions beginning with agitation (characterized by frantic activity, climbing, screeching and crying), followed by a period of despair (characterized by greatly reduced activity) and finally proceeding to a period of “grief and mourning”. Confirming the central role of the mother as an emotional base from which subsequent exploration of the world originates, when infant monkeys were allowed a period of access to other infant monkeys during a period of maternal separation peer-peer interactions were decreased [77–79]. In those same studies, when maternally deprived monkeys were reunited with their mothers aspects of infant-mother/mother-infant interaction increased for a short time (e.g. cradling, embracing, clinging, and ventral contact). During this period peer-peer contact was also increased, over pre-separation levels, but was also of a somewhat different quality, more aggressive than prior to the separation. Nonetheless, surrogate-reared rhesus monkeys, when subsequently allowed access to peers, initially exhibited abnormal behavior, but their behavior gradually normalized to a large extent over the first year of life [80]. Play was an important part of this process of normalization subsequent to maternal deprivation. This did not happen when monkeys were subsequently isolated from their peers [81]. These experiments emphasize the interacting and complex nature of life events occurring during different developmental stages.

Extended periods of early deprivation that deprived young monkeys of both maternal and peer social interactions, termed “total social isolation” [82, 83], has been consistently associated with a variety of types of aberrant behavior. These include compulsive oral behavior, repetitive stereotypical behavior, decreased exploration of non-social stimuli, aggression, self-injurious behavior and an inability to form normal social and sexual attachments later in life. The severity of these symptoms increases with the duration of the deprivation and total social isolates were described as “depressed” [84], the longer the

period of deprivation the greater the deficits. Monkeys isolated for 6 months show profound changes in behavior in a novel playroom when placed with control monkeys, with almost no behavior directed at other monkeys (contact play or threat), and minimal activity play (parallel play). In this circumstance the effects of long term deprivation are very consistent over long periods of subsequent testing, manifested by asociality of the isolated monkeys. Over time, in that experiment, control monkeys exhibited more and more aggression towards the isolates, to the point where testing had to be terminated.

Although extremely illuminating as to the degree of behavioral disturbance that can be engendered by social deprivation, the combination of altered experience in these experimental designs makes it difficult to isolate causal factors. Although maternal deprivation has very profound effects by itself, Harlow noted of the role of early social experience that “play is the variable of primary importance in the development of normal social, sexual and maternal functions” [74]. Furthermore, play itself is by no means a unitary construct, there being a number of distinct types of play in primates that appear to have quite different developmental roles [85, 86]. The consequences of deprivation of these experiences early in life are highly persistent; later in life (10 yrs), rhesus monkeys isolated for the first 9 months of life exhibited self-injurious behavior (e.g. self-biting, slapping, or head-banging) in response to a stressor or conditioned aversive stimulus [87].

When deprived rhesus monkeys later became mothers themselves (note that this was accomplished with some difficulty as they were highly incompetent sexually) they were extremely abusive and neglectful to their infants [88–90]. These studies of what were termed “motherless mothers” raise the very interesting possibility that deviant behavior patterns may be passed from generation to generation because maternal deprivation leads to aberrant maternal behavior that leads to abnormal, impaired or insufficient maternal behavior in the next generation. Indeed, when offspring of motherless mothers were studied they were found to be deficient in social play and sexual behavior, but more aggressive [89], the same attributes that characterized their mothers. Indeed, this might be considered to be a “purer” experiment of the consequences of decreased maternal interactions because it was not imposed by the experimenters, but rather a natural consequence of the behavioral tendencies of the mothers. Furthermore, common allelic variants may also produce variation in maternal behavior [91] that might be similarly expected to affect behavioral development.

Two fundamentally important issues regarding these effects involve the persistence and reversibility of the consequences of these early experiences. Although effects of total social isolation are observed after 3 months, they are largely reversible, but this is not the case for longer periods of deprivation [82]. However, even in more severe cases resulting from extended isolation for 6 or 12 months, aberrant social behavior could be rehabilitated, to a certain extent, by subsequent exposure to peers, but only younger peers [83, 92]. Most of the outcomes explored in these primate models involved emotional and social behaviors. Another important issue is the degree of specificity resulting from deprivation of specific social experiences. Importantly, although producing substantial disturbances in emotional and social function, the 3 month isolation paradigm produces no differences in learning [93–95], in stark contrast with environmental enrichment paradigms. Social deprivation in primates may produce some of same changes as isolation rearing in rodents. Thus, it appears that maternal deprivation in monkeys reduces self-administration of psychostimulants [96], although self-administration of drugs in primates appears to be affected by a variety of manipulations affecting interacting factors, including social dominance, which seem to be mediated, at least in part, by changes in D2 receptor function [97].

The behavioral consequences of social deprivation in rhesus monkeys indicate the potential involvement of several brain systems, but particularly those involved in regulation of

responses to aversive stimuli, stress and other aspects of emotional behavior. The mechanisms underlying these changes have been better elaborated in studies of maternal deprivation in rodents, particularly as they contrast with the effects of post-weaning peer deprivation in rodents.

Maternal deprivation in rodents

Although the consequences of maternal deprivation are often discussed in terms of "stress" or "adversity", and certainly do affect stress responsiveness, the effects of maternal deprivation are highly dependent upon the developmental state of the pup. The effects of maternal deprivation differ over the first three weeks of life prior to weaning depending in part upon the age of the pup when the deprivation occurs [1, 98]. Indeed, different intervening factors mediate the consequences of deprivation at different ages. At earlier ages these are largely passive (e.g. warmth, nutrition, physical contact) while at later ages these become much more active (e.g. active contact, non-nutritive suckling, maternal licking). Hofer has described these factors as "hidden regulators" [98], a concept which could certainly be applied to other types of environmental and experiential effects. These include changes in gross physiological parameters such as changes in heart rate and respiration during separation from the dam between 7 and 16 days postnatal [99–103], as well as behavioral changes, including the levels of locomotion, rearing, digging, self-grooming and ultrasonic vocalizations (USV) during this period [103]. The behavioral effects depend in part on whether the isolation occurs in the nest or a novel environment [103], indicating that different sensory aspects of the experience may mediate different physiological and behavioral consequences of separation. For instance, although cardiovascular effects could be reversed by feeding, the behavioral activation that was observed during this period could not [104], while the presence of a non-lactating foster mother during deprivation would reverse the behavioral activation but not the cardiac changes [105, 106]. Thus, a different and distinct component of pup-dam interaction appears to regulate each consequence of maternal deprivation. Supporting this conclusion, another consequence of maternal deprivation, sleep disturbance, was regulated by a completely different factor – milk composition and rhythmicity of milk delivery [107].

Many of the changes that occur in rodents that are maternally deprived very early in life involve short-term responses to loss of the sole source of nutrition. Thus mechanisms controlling metabolism and growth are down-regulated immediately after an extended period of maternal deprivation, including ornithine decarboxylase [108], growth hormone [109] and heart rate [110], although the brain may be partially protected from some of these changes [108]. Suppression of growth hormone release can be reversed by administration of growth hormone-releasing factor [111]; interestingly, these effects are dependent on 5-$HT_{2A/2C}$ signaling. Some long-term effects of maternal deprivation are observed, including reductions in weight and feeding and changes in food preferences [112].

Many of the neurodevelopmental regulators of neonatal development involve active interaction between the dam and pup, which become more important as the pup develops increased behavioral capability and complexity. An important response to separation from the dam is USV, which elicits attention from the dam in the nest or pup retrieval if the pup is outside of the nest. When the mother forages away from the nest, her extended absence elicits USV from the pups after a period of time [113]; thus, the duration of USV is normally regulated by the time required for her foraging, and thus variably dependent upon environmental conditions, such as the density of food resources. The production of USV in pups is determined by a number of specific sensory aspects of isolation, including temperature. USV is minimal at thermoneutrality, but increases with slight deviations with temperature [114]. Although the suppressive effect of littermates during isolation is at least

partially due to effects on thermoregulation, the ability of littermates alone to suppress USV increases with age, while the effects of temperature wane, indicating that other factors are present. In pups less than a week old maintenance of temperature alone is sufficient to suppress USV [115], while in 5 to13 day old pups tactile and olfactory cues are necessary to reduce USV [116], and in pups over 14 days of age the presence of a sibling or dam is necessary to suppress USV [113]. At this age passive tactile, olfactory and thermal cues are sufficient to suppress USV, e.g. an anesthetized pup or an anesthetized dam [117, 118].

Hypothalamic-pituitary-adrenal (HPA) axis activity, and changes in HPA axis sensitivity, are important in these effects, but are certainly not the only mechanisms involved. For instance, there is evidence of endogenous opioid release during maternal deprivation [119], the greatest opioid release being observed in the presence of nest bedding, which partially suppresses USV. This may indicate that stimuli associated with the dam come to produce opioid release – the comparison here to contact comfort is perhaps not unwarranted. This reduction in USV could be reversed by naltrexone, which has no effect in the absence of nest bedding, and may indicate that the involvement of endogenous opioids is an adaptive response to familiar or dam-associated stimuli. Under unfamiliar conditions other behavioral changes are observed, including locomotor activity, USV and hyperalgesia [120–123]. These could also be considered to be adaptive responses, the behavior which is most adaptive varying with the duration and chronicity of deprivation. Importantly, vocal interactions may be reciprocal, as recent studies in *octodon degus* have demonstrated effects of maternal vocalizations on the behavior of maternally deprived pups [124, 125].

Much work on maternal deprivation has examined the role of maternal interactions in the development of HPA axis reactivity. USV is emitted during the first hour after separation, but then subsides, followed by increased signs of stress including plasma corticosterone increases [126]. Although adrenocortical responses to some stimuli are reduced or absent during the first two weeks of life [127], the so-called “stress hyporesponsive period”, extended periods (2 hr or more) of maternal deprivation can increase corticosterone levels from postnatal day 5 onward [126], responses becoming more robust thereafter [128, 129]. Maternally deprived pups exhibit HPA responses to stressors at ages which non-deprived pups are not yet responsive [130, 131]. In contrast to some of the other effects of maternal deprivation, the corticosterone response to maternal deprivation could not be reduced by milk [132] or the presence of siblings [133], but was reduced by the presence of the dam [132]. Returning a pup to the dam after a stressor reduces stress responses [134], but importantly the ability of a dam to inhibit pup stress responses is quickly lost after 20 days of age [133, 135].

There is a critical period for the effects of maternal deprivation on the HPA axis reactivity of about 6 to 15 days postnatal, with reduced effected observed earlier (4–6 days postnatal), and later (20 days postnatal) [112, 129–131, 136–141]. Enhanced responses to stressors are associated with reduced glucocorticoid negative feedback [129, 139, 142] and enhanced sensitivity to adrenocorticotropic hormone (ACTH) [128, 134]. Maternal deprivation accelerates HPA axis development [143], but it also appears that different aspects of pup-dam interactions regulate different aspects of these neuroendocrine changes [144], which also include changes in corticotrophin releasing factor (CRF) [137, 138, 145], and norepinephrine [146] function.

Either a single long episode or repeated shorter episodes of maternal deprivation induce permanent changes neural and neuroendocrine function; the duration, age of the pups and chronicity of the experience influence these permanent outcomes. As for more acute effects of maternal deprivation many, though not all, of the effects described above are reversed by anogenital stroking during deprivation [138, 147]. Interestingly, although dexamethasone

treatment blocked the effects of maternal deprivation on ACTH and corticosterone, many of the central consequences (e.g. reduced hippocampal glucocorticoid receptor (GR) mRNA, elevated paraventricular nucleus (PVN) cFos mRNA and reduced PVN CRF mRNA) were unaffected, but could be reversed by stroking or stroking plus feeding [147]. This indicates that the aspects of the deprivation experience that affect these functions are more than just elevations in HPA axis activity, so, not surprisingly, the nature of the deprivation environment is a critical aspect of any maternal deprivation procedure [148].

Deeper understanding of the underlying mechanisms of maternal deprivation has come from comparisons to mice that received very short periods of deprivation (5–15 minutes), termed "handling", in addition to unhandled controls. Many of the long-term effects of handling have been observed to be in direct opposition to the effects of extended periods of maternal deprivation: although handling accelerates the development of stress response early in life [149], it produces permanent reductions in HPA axis responsivity. The critical factor here has been determined to be increases maternal attention when the pup is returned to the dam [150, 151]. Thus, when assessed as adults, handled pups have decreased basal corticosterone, ACTH and CRF levels [152, 153], reduced stress-activated CRF, ACTH and corticosterone responses [154–156], and reduced behavioral indices of emotional responses to stressors [157]. These changes occur in part because of increases in glucocorticoid negative feedback in the hippocampus [155, 158, 159]. Indeed, differences in stress responses may account for some apparent effects of neonatal handling on learning, such as impaired aversive conditioning [160], particularly since some other types of learning unaffected [161] are enhanced [160].

In contrast to the effects of handling, extended maternal deprivation enhances activity of the HPA axis and this enhancement persists into adulthood. Increased stress responsivity [162–167] in maternally deprived animals is mediated in large part by decreased negative feedback mediated by hippocampal glucocorticoid receptors [163, 168, 169], but is also associated with increased activity at other levels of the HPA axis [112, 153, 163, 165, 167, 170, 171]. Changes in hippocampal feedback to the HPA axis are part of broader constellation of changes in hippocampal circuitry and function which may involve brain derived neurotrophic factor (BDNF) and glutamate function [172]. However, although maternally deprived rats exhibit some learning deficits in adulthood, these seem to be associated with stress hyper-responsiveness and can be reversed by glucocorticoid receptor or adrenergic receptor antagonism [167].

Maternally deprived rodents are anxious in adulthood [112, 162–164, 166, 173–175], exhibit increased depressive-like behavior [167, 175, 176] and increased ethanol consumption [162, 177, 178], which correlates with stressor evoked corticosterone release [162]. Consistent with hypotheses that these types of experience relate to the etiology of depression both increased anxiety and increased ethanol consumption can reversed by antidepressant treatments [162, 177]. Perhaps also consistent this possibility are reductions in responses to drug rewards and other responses associated with mesolimbic dopamine function [179–181], consistent with reduced dopamine turnover in the striatum [182]. However, not all responses to reinforcers or stimulants are reduced [181, 183–186], and dopamine responses to amphetamine are actually increased in the nucleus accumbens [187]. Levels of dopamine D_1 and D_2 receptors are unaltered in most brain regions in maternally deprived or handled rats compared to unhandled controls, including the cortex and striatum [178]. Thus, although some maternal deprivation procedures seem to produce consistent effects on responses to drugs of abuse, the responses across paradigms are variable suggesting that procedural factors, particularly those that alter the nature of the deprivation experience, may account for what appear to be conflicting results, as suggested previously [98], and as discussed recently [188]. Indeed, those authors have found that lengthy maternal deprivation produces a

leftward shift in the dose response curve for cocaine self-administration, while brief maternal separation substantially reduces self-administration, compared to non-handled controls [189]. In many of the experiments described above pups were separated from the dam in groups, and repeatedly throughout the neonatal period. By contrast, a procedure that involves isolation from both the dam and littermates at early postnatal ages, and consequently may be more stressful, increases cocaine self-administration [190, 191]. However, this procedure does not affect other behavioral responses to cocaine [190], and increases ventral striatal dopamine release in response to cocaine [192]. Artificial rearing, which also combines maternal and sibling isolation increases incentive salience in a conditioned approach task, increases sucrose consumption and the conditioned place preference produced by morphine [193, 194]. Other authors have suggested that maternal deprivation produces differences in responses to cocaine that are observable in adolescence, but not adulthood [195].

Maternal deprivation can also produce impairments in prepulse inhibition of acoustic startle (PPI) [196], but does not always do so, depending on strain and other factors [197–199], e.g. genetic background, and subsequent experience. Maternal deprivation can even reverse PPI deficits induced by subsequent isolation rearing [200]. Notably, the effects of maternal deprivation are affected by subsequent stress, perhaps due to the sensitized stress mechanisms in these animals [201], effects that include altered expression of serotonin transporter and tryptophan hydroxylase 2 mRNA in the dorsal raphe [202, 203]. Although the effects of maternal deprivation on PPI are equivocal, it facilitates latent inhibition (LI) [204], while, by contrast, post-weaning social isolation and prenatal stress do not affect LI but do impair PPI [204, 205]. Furthermore, Lehmann et al. (2000) found that maternal deprivation normalizes the impairments of PPI produced by prenatal stress, while prenatal stress normalizes the effects of maternal deprivation on LI. Obviously, equating the consequences of these experiences solely to stress is a gross oversimplification.

It might be supposed that long-term changes in HPA axis function are simply a response to elevated HPA activity produced by the deprivation experience; however, the changes in glucocorticoid receptor feedback that occur in the hippocampus are dependent upon both thyroid hormones and serotonin [206–208]. Serotonin has been implicated in the effects of maternal deprivation in rodents [209] and primates [210]. When assessed in adults maternal deprivation decreases hippocampal serotonin levels [182], elevates hippocampal 5-HT_{1A} and 5-HT_{1B} receptor mRNA levels [211], elevates 5-HT_{1A} and serotonin transporter levels in several brain regions [212] and produces other alterations in serotonergic function [211, 213]. Although, neonatal handling induces serotonin release, this only occurs in regions that later demonstrate decreases in both glucocorticoid and serotonin 5-HT_2 receptor binding [209]. Supporting the contention that maternal deprivation may constitute an animal model of depression, chronic desipramine reverses some of the physiological consequences of maternal deprivation, as well as increased in hippocampal 5-HT_{1B} levels, but interestingly, not the changes in hippocampal glucocorticoid receptors [211].

Many of the effects of maternal deprivation are thought to be the result of altered maternal interactions, although some authors have argued that the effects of maternal deprivation on maternal care and changes HPA function can be dissociated [214]. Those authors have proposed that two aspects of maternal deprivation paradigms, alterations in maternal care and stress, determine stress phenotypes in these paradigms [215]. Nonetheless, rat strains that exhibit differences in maternal behavior exhibit effects similar to enforced maternal deprivation, as cross-fostering experiments have demonstrated in Fisher and Lewis rats [216]. Pups of either strain raised by Fisher dams were more active in a novel environment and more responsive to the locomotor stimulant effects of d-amphetamine, and this was related to increased levels of arched-back nursing in Fisher dams. Similarly, maternal care is

negatively correlated with ethanol and cocaine preference in adulthood [217], although interestingly in this study both maternal deprivation groups actually had greater maternal care than controls, consistent with Macri et al. (2004), who showed temporal changes in the pattern of maternal care. Natural variation in maternal care produces identical phenotypes to those observed after maternal deprivation and maternal handling [218], and paradigms that alter foraging requirements produce alterations in maternal care [219]. Furthermore, as was previously demonstrated for primates, rats that had experienced maternal deprivation as pups show deficits in maternal behavior in adulthood [220, 221]. Not surprisingly, complete maternal and sibling deprivation (artificial rearing; AR) produces profound impairments in social learning that require olfactory cues about conspecifics [161]. Artificial rearing also impairs maternal behavior when AR rats have offspring, an effect that can be reversed by simulating “licking” during the AR experience [222], as can some of the other sequelae of AR [223]. Other aspects of the deprivation experience also contribute to these behavioral changes, including exposure to maternal odors and social stimulation from littermates [224], auditory stimulation from the mother [124] and prolactin in milk [225].

Deprivation of social play in rodents

Many studies of environmental enrichment in rodents confound the sequelae of social deprivation and reduced environmental complexity, although some studies have shown separate contributions of each to the sequelae of environmental enrichment paradigms. Although social isolation paradigms can also be confounded with non-social environmental effects (see [226]), such paradigms more specifically assess the consequences of deprivation of social contact in rodents under standard (e.g. non-enriched) housing conditions. The most common procedure involves permanent isolation from weaning (isolation-rearing). Prior to weaning, at about 21 days of age, rodent behavior is directly largely towards the dam, while after weaning rodent behavior is directed primarily at same-sex conspecifics [227]. The most characteristic type of social interaction at this age is rough-and-tumble play which is replaced by adult types of social interactions by about 50 days of age. Adolescent animals are highly motivated to engage in this type of play. When otherwise deprived of contact with other adolescent animals, subjects allowed a period of time to interact with another adolescent animal will engage largely in this behavior [228], which is highly motivated [229]. Indeed, socially isolated weanling rats will even choose social interaction over food when food-deprived. Short play experiences can mitigate the effects of isolation [230]. Isolated animals will exhibit preferences for places paired with social interactions, effects that are greater in adolescents than adults [231]. The fact that play itself is rewarding has substantial importance for understanding the neurodevelopmental sequelae of play and conversely, deprivation of play. In this regard, it is interesting to note that males, which exhibit more pronounced play behavior, may be more susceptible to the effects of isolation-rearing [232]. However, it must be noted that aspects of non-physical contact also contribute to the effects of isolation rearing [233].

Since many consequences of isolation rearing are thought to be due to deprivation of play experience, it is interesting to note that the consequences of some other procedures that produce similar effects may also be associated with changes in social play. For instance, the effects of prenatal stress and environmental enrichment on HPA axis function may be related to their effects on social play in adolescent rats [63], and rhesus monkeys raised with a surrogate played less with age-mates than mother-raised monkeys [67], raising the possibility that some of the effects observed in those experiments are the result of deprivation of social play. These examples illustrate the difficulty of separating causality in neurodevelopment.

Play likely sub-serves multiple purposes, including the development of dominance hierarchies, which develop in early adolescence when rough-and-tumble play dominates their social interactions. Rough-and-tumble play involves mock-fighting, or wrestling, among similarly aged young mice, with winners that chase or pin the losers, that run away or get pinned. One of the interesting aspects of this process is that the winners and losers become more consistent over time until they assume distinct phenotypes, distinct enough that we categorize them with those names, dominant and subordinate. Serotonin plays a role in this developmental process. Serotonin lesions enhance both dominant and subordinate responses [234], perhaps accelerating this process towards more adult type behavior, while fluoxetine treatment does the opposite [235].

When adolescent animals are isolated at weaning they do not go through this process; thus, the immediate question would be, in the absence of this normal process of socialization, what phenotype results? One hallmark of isolation rearing is increased weight gain [236], which might be associated with dominance, as dominant rats typically weigh more than subordinate animals. Another prototypical effect of isolation rearing that could be associated with a dominant phenotype is enhanced aggression [237], although it must be noted that isolation in adulthood (isolation housing) increases aggression as well (e.g. [238]). However, the behavior of isolation-reared rats is different from normal dominant individuals and distinctly aberrant in several respects from animals reared under social conditions, even if isolated as adults [239]. One of the first findings in isolation-reared rats was muricide [240], which is rarely seen in non-isolated rats. Aggression is also observed in isolated mice [237, 241] under conditions that do not normally evoke aggression in socially housed mice. One of the results of the development of dominant and subordinate traits is reduction of intraspecies aggression, indeed this is one of the reasons for the development of these traits. Isolation rearing impairs the development of these behaviors and the ability to recognize social signals, although this is certainly a process that begins with imprinting and social interaction, including maternal interaction and imprinting, at an early period (see discussion by [242]).

Isolation rearing has been suggested to alter the trajectory of the development of adult-like behavioral flexibility and exploratory behavior [243]. Thus, most behavioral consequences of isolation rearing are not simply interpretable in terms of a dominant-like phenotype - but appear to involve increased responsiveness to a variety of environmental stimuli. The most consistently replicated consequence of isolation rearing that has been observed is locomotor hyperactivity in a novel environment [48, 244–247]. Novelty is an essential component, and isolation-reared rats have increased exploratory tendencies [248], or perhaps reduced habituation as their locomotor behavior is characterized by a shift towards more repetitive, straight, distance-covering movements characteristic of initial exploratory responses [249]. Based on a simple comparison between isolation rearing induced hyperactivity and stimulant-induced locomotion, isolation rearing was hypothesized to produce a hyperdopaminergic state, which has been confirmed by a variety of findings. Pharmacological studies have consistently found increased responses to both direct and indirect dopamine agonists in a variety of circumstances [48, 50, 237, 250–260]. In some cases isolation rearing has been shown to alter responses to amphetamine while maternal deprivation does not [204]. Isolation-reared rats exhibit a variety of behavioral characteristics associated with enhanced dopaminergic function [244, 250, 261, 262]. Based on this evidence for dopaminergic hyperactivity, the effect of isolation rearing on PPI was examined [246, 263]. Isolation-reared rats have impaired PPI, similar to that observed in schizophrenia or after the administration of dopaminergic agonists. Enhanced dopamine function in the nucleus accumbens is the critical mediator of these effects as 6-OHDA lesions of the nucleus accumbens ameliorate PPI deficits in isolation reared rats [264]. Furthermore, these deficits in PPI can be reversed by drugs with established or suspected

antipsychotic efficacy [263, 265–268]. Although latent inhibition was not found to be affected by isolation rearing from weaning [246], isolation rearing beginning at postnatal day 28 may do so [269]. Behavioral findings indicative of enhanced dopamine function are supported by *in vivo* microdialysis studies demonstrating increased reactivity of ventral and dorsal striatal dopamine systems to indirect dopamine agonists [246, 257, 270, 271] and conditioned stimuli [272]. There are strain differences in these effects [271], notably Sprague-Dawley rats are less sensitive to the effects of isolation rearing, that are also observed for differences in tissue dopamine levels [273]. Importantly, the effects of isolation rearing on PPI are permanent, and not reversed by later social housing [274] nor are they observed in animals isolated as adults [246].

One way to consider some of the changes discussed above are that they represent a generally enhanced responsiveness to certain environmental stimuli, perhaps over others, which would make sense from an evolutionary sense since such animals, more than those in social groups, would have to respond to all threats and identify all resources necessary to survive. In this light, it is not surprising that isolation-reared animals show enhanced responses to other classes of stimuli. Isolation-reared rats exhibit enhanced anxiety-like responses in most standard rodent anxiety models [275–282] and are more emotionally reactive [283]. Similarly, although isolation-reared rats exhibit a preference for a novel environment, this is dependent on the aversiveness of the environment [284], and similar effects are observed in anxiety tests [285, 286], and account for *apparent* learning deficits in Stone's Maze [287]. Although there is evidence that long-term isolation is stressful [275, 288], unlike maternal deprivation, examination of basal HPA axis function in isolation-reared animals has produced inconsistent results [275, 289, 290] and HPA axis activation does not appear to be different in most studies ([291–293] but see [294]). Although less well characterized than changes in serotonergic and dopaminergic systems, there may also be changes in gabaergic mechanisms and neuroactive steroids (for review see [295]) as well as cannabinoid systems, which may be relevant to these effects [296]. Isolation-rearing may affect responses to other chronic stressors however [297, 298]. At least some effects of isolation-rearing on anxiety, and perhaps associated impairments in learning, may be more related to acute housing state, as these effects are at least partially reversible by later social/enriched housing, and isolation of social/enriched reared animals have the opposite effects [299]. Isolation-rearing is also associated with depressive-like behavior [282], while environmental enrichment has opposite effects [300–303], and some of these effects are reversed by antidepressant treatments. The effects of isolation on anxiety and depressive phenotypes may be more related to acute housing state as both the behavioral effects and associated reductions in hypothalamic α-melanocyte stimulating hormone were reversed by resocialization [282].

Just as the consequences of isolation-rearing contrast sharply with those of maternal deprivation, they also contrast sharply with those of environmental enrichment. Although in some circumstances isolation-rearing has been found to produce impairments in learning [7, 41, 287, 304–308], many of these effects appear to be the result of other consequences of isolation-rearing that indirectly affect learning, such as increased anxiety, and indeed increased learning is observed in some paradigms [309, 310]. Some of these learning impairments may reflect more specific changes in cognition that result from isolation-rearing rather than the apparently broad cognitive enhancing effects produced by environmental enrichment. For instance, isolation-reared rats are not impaired on acquisition of either a spatial or a non-spatial visual discrimination, nor reversal learning using an intra-dimensional shift, but are substantially impaired at switching selective attention from previously relevant perceptual dimensions to previously irrelevant perceptual dimensions, that is between spatial and non-spatial visual cues [311]. Selective impairments of extra-dimensional set shifting are produced by 6-OHDA lesions of prefrontal cortex [312], which produce elevations in striatal dopamine similar to those observed in isolation-rearing.

Reversal learning is impaired by isolation rearing, and these deficits are ameliorated by clozapine [313]. Several aspects of behavioral choice appear to be affected by isolation rearing. Isolation-reared rats also do not inhibit responding during extinction, or when sated prior to testing, like socially reared rats [308, 314–316]. Motor impulsivity in a go/no-go task is not affected by isolation rearing, but cognitive impulsivity in a delayed reinforcement task is reduced [317]. Similarly, Dalley and colleagues (2002) found increased perseverative behavior in the 5-choice serial reaction time task in isolation-reared rats; there were no differences in impulsive behavior, except after amphetamine administration which increased impulsive behavior in socially reared rats, but not in isolation-reared rats.

As mentioned above, the effects of isolation rearing on prefrontal cortex function may be quite different from other dopamine terminal areas. Tissue levels of dopamine metabolites are reduced in the prefrontal cortex [318, 319] as are dopamine fiber densities in isolation-reared gerbils (*meriones unguiculatus*) [320] consistent with the original suggestion by Blanc et al. (1980) that reductions in prefrontal cortex dopamine function is associated with increases in striatal dopaminergic function. Jones et al., (1992) also found changes in dopamine laterality in the prefrontal cortex of isolation-reared rats, which suggests alterations in mesocorticolimbic inputs which seems to be confirmed by electrophysiological results [321]. An *in vivo* microdialysis study in mice found that basal prefrontal DA levels are higher in isolation-reared subjects, but DA release stimulated by K^+ or a 5-HT_{1A} agonist is reduced [237]. Another study failed to find basal differences in the prefrontal cortex, but isolation-reared increased the ability of atypical antipsychotics to increase prefrontal dopamine release [322], effects suggested to be mediated by 5-HT_{1A} receptors. There is also a reduction in calbindin-D28k expression and dendritic atrophy in prefronto-cortical pyramidal cells [323] indicative of broader changes in prefrontal function. Antipsychotics, including clozapine and olanzapine, can increase dopamine release in the prefrontal cortex and this effect is enhanced in isolation-reared rats [324]. However, this may involve their affinity for serotonin receptors, which have also been implicated in the effects of isolation rearing.

By contrast to studies demonstrating increased presynaptic dopamine function in isolation-reared rats, postsynaptic function, particularly dopamine D_2 receptor function, has often been found to be reduced. Pharmacological responses to directly acting postsynaptic agonists and antagonists are reduced [252, 270, 325, 326], as are D_2 mRNA levels in throughout the striatum [327], D_2 binding in the striatum [328] and cAMP responses to D_2 stimulation in the nucleus accumbens [271], despite an increased proportion of high-affinity D_2 receptors [329]. These postsynaptic changes are thought to be compensatory changes produces by elevated dopamine release. Hyperdopaminergic function in isolation-reared rats has been suggested to constitute and animal model of schizophrenia [1], and likely involves altered interactions with the prefrontal cortex, amygdala and hippocampus. Indeed basal c-fos levels are increased in the hippocampus, but decreased in the amygdala [330], an effect that parallels a shift in sensitivity aversive conditioning to contextual and discrete stimuli in trace conditioning [331]. Levels of the presynaptic protein CDCrel-1, which has been associated with schizophrenia [332], are reduced in the striatum of isolation-reared rats, but increased in the hippocampus [333], as are synaptophysin levels and the high correlation between synaptophysin and CDCrel-1 levels observed in socially reared rats is reduced in isolation-reared rats. Levels of n-acetylaspartate, reductions of which are also observed in schizophrenia [334], are also reduced in the temporal cortex of isolated rats [335].

While certain behavioral differences in isolation-reared rats are consistent with elevated mesolimbic dopamine function, others are more consistent with reduced serotonin function. Post-mortem studies have found evidence for reduced serotonin turnover in isolation-reared rats [270, 336, 337], reductions in serotonin synthesis [338, 339], and reduced tissue levels

of serotonin [303, 340]. Jaffe et al. (1993) also found reduced hippocampal serotonin release *ex vivo in* hippocampal tissue slices. *In vivo* microdialysis experiments have also demonstrated reduced serotonin release in the hippocampus and prefrontal cortex [341–343]. These results are consistent with reduced immunohistochemical staining for serotonergic terminals in the hippocampus [344], although other brain regions may have increased serotonin levels [345], at least in gerbils. Changes in presynaptic serotonin function, like other neurochemical changes in isolation-reared rats, may be highly regionally dependent however. Aversive stimuli and exposure to conditioned stimuli produce increases in serotonin release in the nucleus accumbens that are not observed in socially reared rats [346]. This would seem to indicate that changes in serotonin function are not simply a matter of globally reduced serotonin function, but reflect a shift in the types of responses affected by serotonin in different brain areas, perhaps also mediated by different serotonin receptor subtypes. Consistent with this interpretation, changes in postsynaptic serotonin receptor function are also observed in isolation-reared rats, including increased density of the 5-HT_{2A} receptor, reductions in the 5-HT_{1A} receptor [337, 347] and 5-HT_{1A} mediated dopamine release in the prefrontal cortex [348] and increased sensitivity to some postsynaptic serotonin agonists [349, 350]. Dorsal raphe 5-HT_{1A} receptor function is enhanced [351].

An important consideration for the effects of isolation rearing, as for other neurodevelopmental experiences, is the extent to which these effects are linked to specific developmental periods in which the isolation occurs, which has been demonstrated for a number of the behavioral consequences discussed above [243, 352]. There may be differential effects of isolation on prepubertal and postpubertal adolescent development on some of these behavioral effects [353]. With regard to the specificity of the effects of isolation rearing, it is interesting to note that some other early manipulations, such as stress during the post-weaning period [354], reduce social play and social investigation, which may actually underlie some of the effects of “stress” during this period. By contrast daily handling reverses some of the effects of isolation-rearing [355], but not others [271].

The best approach to specifying the neurodevelopmental window for isolation-rearing effects would be to isolate the subjects for different periods of time during adolescence and then rehouse them socially to determine if the effects are permanent. Although this has not been done very extensively, there are some illuminating examples. An early study of this type failed to find a “developmental window” for the effects of isolation-rearing on PPI, with only complete post-weaning isolation being effective [356]. However, isolating adolescent rats from postnatal days 30 to 35, the peak period of social play, produced immediate sex-dependent behavioral changes at postnatal day 36, associated with reductions in synaptic markers in the prefrontal cortex [357]. Assessment in adulthood found that this experience produces long-lasted reductions in synaptic markers in the infralimbic prefrontal cortex and cingulate gyrus [358]. In a procedure in which rats were isolated for 3 weeks at weaning, and then rehoused socially for 2 weeks, persistent effects of isolation on anxiety and fear-like behavior were observed [359], effects that were associated with CRF receptor alterations in the dorsal raphe that prolonged CRF induced serotonin release in the nucleus accumbens [360, 361]. A 2 week period of isolation produced increases in the number of vasoactive intestinal peptide immunoreactive neurons in the medial prefrontal cortex, along with reductions in the arborizations of pyramidal neurons, which were not reversed by resocialization [362].

The mechanisms of gene-environment interactions

The previous sections have briefly summarized the long history of accumulating evidence that several specific types of experience, and in particular social interactions and learning

experiences that have circumscribed developmental windows, resulting in critical periods for neurobehavioral developmental. As suggested by Hofer [98] these experiences act as neurodevelopmental regulators that produce alternative behavioral and psychological phenotypes. It would appear that the range of these possibilities is *genetically predetermined,* based on the interaction of experience with mechanisms controlling gene expression; that is, for all of these experiences, activation of sets of genes by transcription factors presumably produce permanent epigenetic reprogramming of the organism. As discussed below, the genes that are affected and the epigenetic mechanisms involved are just starting to be elucidated. Furthermore, although some of these experiences are of the more mundane "use it or lose it" type, many of these experiences influence neurobehavioral development much more broadly. Indeed, this may in fact be a *raison d'être* for the existence of many of these behaviors, to act as neurodevelopmental regulators, as it is just this flexibility of phenotype, from generation to generation, in the face of changing environmental demands, that explains the evolutionary benefit that they convey. Furthermore, such mechanisms may be of critical importance for understanding those mechanisms that explain the evolution of certain characteristics of species that produce only a few offspring in each generation (e.g. mammals, and in particular primates), relative to those mechanisms that explain the evolution of characteristics of species that produce large numbers of offspring in each generation (e.g. insects); given this major difference in rate of population increase the solutions to problems that exert evolutionary pressures may be quite different. With current advancements in genomics and epigenetics it should be possible to identify the set of epigenetic programs that control each of these neurodevelopmental processes. This final section discusses the first small steps in that direction.

Epigenetic Mechanisms

The original definition of "epigenetic" mechanisms involved inherited differences in DNA structure (from one organism to its offspring or within a cell lineage) that did not involve changes in DNA sequence; such changes include alterations in CpG methylation, chromatin structure and transcriptional activity (among others, see [363]), as well as the recent recognition of the effects of microRNA on gene expression [364]. In part because of the understanding of some of the mechanisms involved the term "epigenetics" has come to have a broader meaning, of "the combination of mechanisms that confers long-term programming to genes leading to a change in gene function without a change in gene sequence" [365]. An important aspect of the machinery that produces changes in methylation and chromatin restructuring is that many of the proteins involved are relatively non-specific in their actions, but are recruited to particular gene locations by transcription factors [366]. Because DNA methylation alters the covalent structure of the DNA [367], this makes this mechanism particularly interesting as regards long-term changes in gene regulation resulting from differential experience early in life. Thus, it has recently been suggested that "programmed changes in DNA methylation have evolved to serve as an interface between the dynamic environment and the static genome" [368], that much of the inter-individual variation in many phenotypes that is not accounted for by sequence variation may be the result of these epigenetic mechanisms [369], but that under certain circumstances this can be maladaptive [370, 371]. Nonetheless, in many cases authors continue to emphasize stress as the primary mediator of these effects (e.g [372, 373], even when substantial data suggests that many of these effects may be mediated by other aspects of the situations involved – it is not the absence of the experience that does the regulation, but rather the experience. In any case for many experiences, such as maternal deprivation, it remains to be seen what portion of the permanent consequences of deprivation are due to stress, and what are due to alterations in other types of social and non-social interactions with the dam. However, the description of regulation of epigenetic markers during development by Szyf and colleagues, particularly in response to social stimuli, as a "system-wide adaptation of the DNA methylation pattern to

an anticipated environment" should apply to many types of "neurodevelopmental regulators" as was described by Hofer [98].

Environmental Enrichment

Superficially it might be supposed that the mechanisms of environmental enrichment result solely from a simple perspective of "use it or lose it". That is, simply as a matter of conservation of resources that each animal preserves systems that are active and eliminates systems that are inactive in order to maximize efficiency of energy use. Indeed, at about the time the effects of environmental enrichment were being first described, a mechanism that preserves active neuronal connections was discovered: neurotrophic factors [374]. Such a mechanism explains the survival of active cells and differences in synaptic contacts. However, such mechanisms do not necessarily explain the broader consequences of environmental enrichment. One of the areas of the cerebral cortex that is most consistently affected, and which has the greatest magnitude of response to environmental enrichment, is the visual cortical area of the occipital cortex. However, environmental enrichment induces increases in the weight of the occipital cortex even in blinded rats [375]. Thus, visual input alone does not mediate the changes observed in this region.

Surprisingly few studies have addressed changes in gene expression resulting from environmental enrichment. Consistent with the role of neurotrophins in shaping cell survival environmental enrichment induces earlier expression of brain derived neurotrophic factor (BDNF) and glutamic acid decarboxylase (GAD) 65/67, which has been associated with accelerated visual system development [376]. Environmental enrichment also induces the transcription factor NGFI-A [377], which is a transcription factor induced by NGF [378], as well as the transcription factors Arc, c-fos, and zif-268 in the cerebral cortex and hippocampus [379, 380], and ΔFosB in the striatum [381]. A study using a transgenic strain that coupled activation of fos to a reporter gene found that a single exposure to enrichment induced fos in diverse brain regions [382], although this is no doubt a transient signal and only the first in a series of events leading to permanent epigenetic changes. In the nucleus accumbens the phosphorylated (transcriptionally active) form of the transcription factor cyclic adenosine monophosphate response element binding protein (pCREB) is reduced in EC rats compared to IC rats, which was linked to reduced cocaine self-administration and other behavioral effects of enrichment [53]. Those authors also showed that some of the apparent effects of enrichment could be reproduced by administration of a short hairpin RNA via a viral vector that down-regulated pCREB. This, like many other studies of environmental enrichment did not dissociate the effects of enrichment and social deprivation, so it is uncertain which neurodevelopmental regulator mediates these effects. However, it seems likely that a large proportion of the effects are due to social isolation, particularly given the similarity of the effects on cocaine administration to those of Howes et al. [257] in isolation-reared rats.

Even with the limited data currently available it would appear that the affects of environmental enrichment involve diverse transcription factors that activate diverse classes of genes. So far, the genes and transcription factors that have been analyzed were based on *a priori* assumptions about their importance, so it remains to be seen what a more comprehensive and unbiased genome-wide approach would find. Potential epigenetic mechanisms involved in the effects of environmental enrichment are just starting to be considered. Environmental enrichment has been shown to increase histone acetylation and methylation in the hippocampus and cerebral cortex, which was associated with improved learning and memory in a neurodegenerative model [383]. Early, but not later environmental enrichment also ameliorated the effects of a transgenic Rett Syndrome model involving MeCP2, a gene involved in epigenetic modifications [384, 385].

Isolation-rearing

The permanent behavioral changes that results from isolation-rearing have been linked to particular neurotransmitter systems and particular brain regions. Although no comprehensive analysis of transcription factors has been performed, some of these neurochemical and neuroanatomical changes have been linked to particular transcription factors such as c-fos. Thus, cocaine-induced FOS immunoreactivity in the amygdala, nucleus accumbens and striatum is greatly enhanced by isolation rearing [257], while stress-induced reactivity is enhanced in specific subregions of the frontal cortex, dorsal hippocampus, periaqueductal gray and amygdala [343]. No comprehensive examination of gene expression changes after isolation rearing has been conducted but one recent study found reduced expression of numerous serotonin receptor subtypes in the prefrontal cortex of isolation reared mice, including 5-HT_{1A}, 5-HT_{1B}, 5-HT_{2A}, 5-HT_{2C}, 5-HT_{3A}, 5-HT_6 and 5-HT_7, while more restricted reductions were observed in the hypothalamus and midbrain, and no differences except for up-regulation of 5-HT_6 gene expression were found in the hippocampus [386]. The full meaning of these changes remain to be seen, but they are exceptionally striking, as well as consistent with the results of a variety of other approaches that have examined serotonin function in isolation reared rodents. In isolated prairie voles (*microtus ochrogaster*) isolation-rearing induces anxiety, as it does in other rodents species, which is associated with increased mRNA expression for vasopressin, oxytocin, corticotrophin releasing factor and tyrosine hydroxylase in the paraventricular nucleus of the hypothalamus [387].

Neither more comprehensive gene expression analyses nor examination of epigenetic mechanisms have been applied to isolation rearing models.

Maternal Deprivation

The epigenetic mechanisms underlying experiential regulation of behavioral phenotypes has been most examined with regards to maternal deprivation. As discussed earlier, the hippocampal feedback to the HPA axis is regulated during development by maternal behavior, leading to alterations in the duration of HPA axis activity in response to stressors. Although some of these developmental consequences of maternal deprivation may be related directly to glucocorticoid receptor activity, broader changes are also suggested by the involvement of neurotrophic factors, such as the transient increase in hippocampal expression of nerve growth factor (NGF) mRNA after 45 minutes of deprivation [388], and transcription factors cFOS and NGFI-B in the in PVN [137]. Some gene expression changes are only observed after longer or repeated periods of deprivation, including changes in CRF mRNA in the periventricular nucleus [137, 138], CRF_2 receptor mRNA in the ventromedial nucleus [389] and arginine vasopressin in the PVN [373]. In adult rats that were maternally deprived long-lasting changes in BDNF are observed in the hippocampus, striatum and prefrontal cortex [390], and both BDNF and glial derived neurotrophic factor (GDNF) levels are reduced in adult mice that were maternally deprived [391]. Longer-term changes may go in the opposite direction from acute changes as increases in hypothalamic CRF mRNA levels are observed long term [153, 163, 165, 171]. Many of these gene expression changes are relatively permanent, including reduced glucocorticoid receptor mRNA, reduced hippocampal BDNF and NMDA receptor subunit mRNA, and increased arginine vasopressin mRNA [163, 172, 373]. These broader changes in gene expression may also be driven by changes in endocrine function. Repeated early (postnatal day 1 to 10) maternal deprivation increases pre-opiomelanocortin mRNA in the pituitary [373], which appeared to be independent of changes in glucocorticoid receptor expression.

Thus, maternal deprivation, like other experiences, produces a sequence of gene expression changes. The initial changes are short-lasting, but if they are sufficiently strong, prolonged

or repeated, they induce induction of other genes that are permanently affected. It would then appear that the key to understanding the consequences of maternal deprivation would be the mechanisms by which such experiences activate transcription factors that produce long-term changes in gene expression, and the subsequent consequences on cell function and morphology. Indeed, a series of studies has shown that levels of maternal behavior (specifically related to the amount of maternal licking and grooming) mediate the pattern of behavioral effects associated with maternal deprivation by altering DNA methylation patterns, histone acetylation and binding of NGFI-A to the glucocorticoid receptor gene promotor [392, 393], and presumably other genes as well. Maternal deprivation produces a number of behavioral changes, so it is not surprising that epigenetic changes associated with maternal care affect the transcription of several hundred genes [394], including others that may be affected by other transcription factors, such as estrogen receptor alpha [395, 396], and clusters of protocadherin genes involved in synaptogenesis [397]. Changes in glucocorticoid receptor expression in the hippocampus have been specifically linked to a sequence of cell signaling events that include thyroid-hormone dependent increases in serotonin 5-HT_7 receptors, increased activation of cAMP-dependent protein kinase A, induction NGFI-A and binding of both NGFI-A and CBP to the glucocorticoid receptor promotor [207, 398–400]. Differences in arginine vasopressin gene expression after repeated maternal deprivation have been specifically associated with reduced methylation of a promoter region of the AVP gene involved in the binding of methyl CpG binding protein 2 (MeCP2), in part mediated by CAMKII activity dependent phosphorylation of MeCP2 [373]. Interestingly, MeCP2 also affects the transcription of BDNF [401]. Importantly these methylation patterns, consequent changes in glucocorticoid receptor expression and behavior could be reversed pharmacologically by treatment with histone deacetylase inhibitors or methionine in adulthood [392, 394, 402], raising the possibility that even relatively permanent consequences of epigenetic modifications of gene expression may be open to pharmacological intervention. Finally, some allelic variation association with neurodevelopmental phenotypes may act by modifying epigenetic modifications. For instance, serotonin gene polymorphisms may exert their effects by altering neurodevelopmental regulation of gene expression by early life experience, as has been suggested by recent studies in rats [403], primates [404], and humans [405].

Summary and Conclusions

This review has reviewed several, but certainly not all, circumstances in which specific types of experience, in particular social experience, during defined critical periods in life, produce permanent changes in behavior associated with alterations in brain chemistry, anatomy and function. This is far from a complete list of such experiences, but includes some of the most well characterized ones, although certainly each of these could be further divided into component aspects that may have independent mechanisms. The seminal studies of Harlow and colleagues in primates, and the studies of Meaney and colleagues that elaborated the effects of maternal behavior on HPA axis function in rodents, have now lead to an elegant series of studies by Meaney, Szyf and colleagues that have elaborated the precise mechanism underlying the epigenetic mechanism underlying alterations in the HPA axis by maternal interaction. Indeed, Meaney has suggested that these mechanisms are adaptive, and that evolution may have shaped the genome to produce intergenerational transmission of traits via the epigenome to better fit organisms to the circumstances of their lives (the situations of offspring are likely to be similar to that of their parents) [406]. The review here of the effects of alterations in early life experiences certainly supports this view, even without an understanding of the epigenome. These models, and now their underlying epigenetic basis, have been linked to psychiatric outcomes, e.g. early life adversity (child abuse) has been linked to DNA methylation patterns in rRNA [407] and the glucocorticoid receptor gene in the hippocampus [408]. All the same, even if some of the ultimate

consequences are deleterious, the initial neurodevelopmentally determined behavioral outcomes are likely to be highly adaptive. Further elaboration of the epigenetic basis of neurodevelopmental mechanisms will lead toward an understanding of this fundamental issue surrounding the effects of early life experience and the importance of gene-environment interactions in determining behavioral and psychological characteristics.

Acknowledgments

This work was supported by funding from the Intramural Research Program of the National Institute on Drug Abuse (USA).

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Highlights for Review

- Early experience, including visual experience, environmental enrichment, maternal and adolescent peer interactions produce permanent changes in behavior
- The effects of early experience a mediated by particular regulators (e.g. maternal licking and grooming or play)
- The effects of different types of experience are distinct, but interactive
- Changes in brain function, chemistry and anatomy accompany this distinct behavioral changes
- These changes in brain function are mediated by epigenetic programs