

Review article

Behavioral consequences of abnormal cortical development: insights into developmental disabilities

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Abstract

Cerebral cortical development occurs in precisely-timed stages that can be divided into neurogenesis, neuronal migration and neuronal differentiation. These events occur during discrete time windows that span the late prenatal and early postnatal periods in both rodents and primates, including humans. Insults at particular developmental stages can lead to distinctive cortical abnormalities including cortical hypoplasia (reduced cell number), cortical ectopias (abnormalities in migration) and cortical dysplasias (abnormalities in the shapes or numbers of dendrites). In this review, we examine some of the most extensively-studied animal models of disrupted stages of cortical development and we compare long-term anatomical, neurochemical, and behavior abnormalities in these models. The behavioral abnormalities in these models range from alterations in simple motor behaviors to food hoarding and maternal behaviors as well as cognitive behaviors. Although we examine concisely animal models of cortical hypoplasia and cortical ectopias, we focus here on developmental manipulations that affect cortical differentiation, particularly, those that interrupt the normal ontogeny of the neurotransmitter-defined cortical afferent systems: norepinephrine, serotonin, dopamine and acetylcholine. All of these afferents presumably play a critical role in the maturation of their cortical targets; the timing of the afferents' entry into the cortex and their effects on their cortical targets, however, are different. We, therefore, compare the specific anatomical, neurochemical and behavioral effects of manipulations of the different cortical afferents. Because of the considerable evidence that cortical development proceeds differently in the two sexes, when data are available, we address whether perinatal insults differentially affect the sexes. Finally, we discuss how these developmental studies provide insights into cellular and neurochemical correlates of behavioral functional abnormalities and the relevance of these data to understanding developmental disabilities in humans. © 1997 Elsevier Science B.V.

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1. Introduction

The development of the mammalian cerebral cortex involves a complex series of precisely-timed events which creates an intricate neural circuitry. This circuitry, once developed, will be critical in the integration of sensory information as well as cognitive functions

and many aspects of voluntary movement in the adult animal. As has been expertly reviewed in the past, building normal cortical circuitry requires coordinated generation, migration and differentiation of neurons and glia [42,98,184]. Synchronizing these developmental events is essential so that nerve cells from different parts of the brain assemble at the appropriate times and places to form functional circuits. Considering the complexity of events in the ontogeny of cortical circuitry and the complexity of the functions that will later be

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mediated by this circuitry, it is not surprising that these events are exquisitely vulnerable to disruptions during the developmental period. Furthermore, it is not surprising that when disruptions in the normal cortical development do occur, they can have profound and long-lasting influences on the behavior of the animal.

What happens when an injury interferes with the normal developmental program of the cerebral cortex? In humans, alterations in cortical morphology that result from abnormal cortical development are associated with developmental disabilities ranging from mild dyslexias to severe mental retardation [41,66,94,182]. Clinicians and basic researchers alike have long assumed that structural abnormalities of cerebral cortex are the substrates for the abnormal behaviors seen in developmental disorders. However, the precise relationship between developmental insults and behavioral abnormalities is not fully understood. Do abnormalities in cortical architecture and connectivity, in fact, cause behavioral abnormalities? To best answer this question, it is necessary to explore animal models and experimental manipulations which interfere with normal cortical development.

Animal models of developmental insults which affect adult behavior abound in the literature [148]. Unfortunately, only a modicum of these models include anatomical and neurochemical data as well as assessment of behavioral deficits in adulthood. In this review, we will focus on those animal models for which structural, neurochemical and ample behavioral data exist, albeit not always from the same laboratory. For the most part, we will examine rodent studies (mouse and rat), but where available, we will make reference to other species. In most cases, the rodent experiments explore cortical responses to neonatal lesions or to pharmacological/toxicological manipulations during early development. Some more recent experiments involve neurological mutant and transgenic mice. It is our aim to examine how the timing of the experimental manipulation, the neurotransmitter systems involved, and the sex of the animal affect the extent of pathology in the cortex and the consequent behavioral outcomes. Our review focuses on literature available from 1975 to present and was accumulated through searches of developmental, cortical and neurotransmitter-specific topics.

We review here experimental approaches that do not directly injure the cerebral cortex. The effects of direct neonatal cortical lesions have been reviewed thoroughly recently and hence need not be repeated [111]. It is also not our intention to compare effects of manipulations performed in adult animals with those performed in developing animals. The fact that the effects of developmental manipulations differ from those in the adult animal will come as no surprise. Perinatal manipulations affect a nervous system that is not fully formed

and alter its developmental course. In contrast, adult manipulations remove from, or add to, an intact functional network.

Animal models affecting cortical neurogenesis and migration will be reviewed concisely. However, we will focus on the effects of manipulating the neurotransmitter-defined cortical afferents, norepinephrine, serotonin, dopamine, and acetylcholine. The effects of interrupting neurotransmitter systems, at different developmental stages, on cortical architecture and behavioral measures will be compared. This emphasis on these cortical afferent systems stems from our own work which first demonstrated a developmental role for acetylcholine in cortical morphogenesis and subsequently in adult cognitive behaviors in mouse [7,89].

In the process of reviewing the relevant literature and analyzing our own recent data, it has become clear that developmental regulation of cortical morphogenesis and behavior differs between the sexes, probably due to perinatal steroid hormones. This hormonal influence likely explains why many aspects of cortical structure and function are sexually dimorphic. With this in mind, we will address, when data are available, whether a given perinatal manipulation results in different morphology and/or behavior outcomes for the sexes. As one might guess, these interactions are not always straightforward, nor do they always fall into predictable patterns. Some general principles do emerge from available studies which provide insights into cellular correlates of functional abnormalities.

2. Milestones in cortical development: timing is everything

In order to understand the effects of manipulations that alter cortical development, it is necessary to first understand some of the features of normal cortical development. Cortical development can be simplistically divided into three major phases which occur during discrete developmental time windows: neuronal

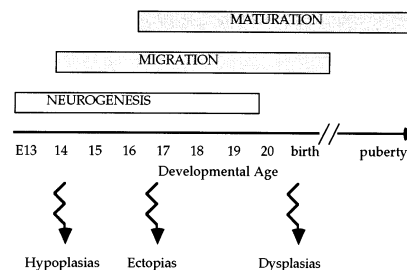


Fig. 1. Cortical developmental time line. Shown is the approximate timing of the beginnings and endings for the different phases of cortical development: neurogenesis, migration, and maturation in rodents (after [112]).

generation, migration and differentiation (see Fig. 1) [10]. Most cortical neurons are generated in the proliferative zone near the cerebral ventricles between embryonic (E) days 14 and 20 in rats [10,226], from E12 to E16 in mice [4,34,68] and during early and middle parts of gestation in primates [186]. The laminar structure of the cerebral cortex is formed by the migration of successively generated neurons along radial glial scaffolding [184]. Neurons generated first settle while newer generated neurons push past older neurons to form an inside-out layered pattern [4,184]. In rodents, migration occurs generally 2–4 days after neuronal generation [10].

Cortical neuronal differentiation includes cell maturation and dendrite formation, synaptogenesis and the development of short and long connections which are the wiring for sensory integration and behavioral outputs. Simultaneously, cortical glial cells and the vascular network are maturing towards adult patterns. In rodents most of the synapses in the neocortex are formed and many intrinsic and extrinsic cortical connections are refined during the first 3–4 weeks postnatal [75,219,242]. A host of factors contribute to cortical differentiation and maturation; some of the best studied maturation effects are those involving the cortical afferent neuromodulatory systems. Before birth, dopaminergic, serotonergic, noradrenergic and finally cholinergic afferent fibers from subcortical regions innervate the cortex [226]. Classic studies in the 1970s and 1980s describe how these afferent systems orchestrate the establishment of cortical circuitry and act as maturation signals to cortical neurons [58,89,106,118,120]. Right around the time of birth, steroid hormone receptors peak in the cerebral cortex [137,206], suggesting that these hormones can also influence cortical development during this phase. Environmental factors, such as enrichment, can influence cortical differentiation and dendritic maturation well into the first month postnatal in rodents [51,69,76]. The multitude of factors that influence cortical differentiation make this the most enigmatic, and debatably, the most intriguing phase of cortical development to study. The frequently cited correlation between cortical synaptogenesis and behavioral development emphasizes the importance of this developmental phase and its relevancy to behavior [47,140,159]. In humans, cortical differentiation extends through the first two decades of life [228], making this phase the most relevant to study in relation to human developmental disabilities and their potential treatment.

We will examine animal models of disrupted neurogenesis, migration and differentiation. Experimental manipulations that disrupt cortical neurogenesis will most likely result in hypoplasia, reduction in cortical cell number (see Fig. 2); manipulations that interrupt cortical cell migration will likely result in ectopias, abnormal locations of neurons (see Fig. 3); manipulations

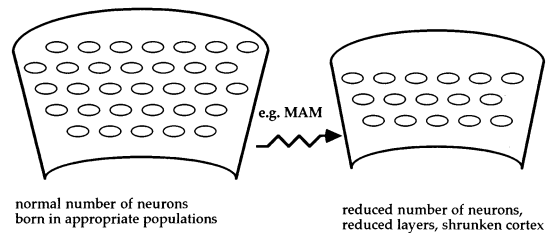


Fig. 2. Cortical hypoplasias. Reduced numbers of cortical neurons can result from developmental insults during a specific time window (after [10]).

tions that interrupt cortical differentiation signals will likely result in dysplasia, abnormalities in the shapes or numbers of dendrites and the dendritic trees (see Fig. 4). Each of these manipulations can lead to alterations in connectivity patterns in the mature cortex and to changes in behavior.

3. A model of interrupted cortical neurogenesis

In experimental animal models, micrencephaly (brain hypoplasia) has been noted following prenatal exposure to alcohol, irradiation, cocaine and a number of other drugs [10,78,101,164,226] (see Fig. 2). In many cases, these drug exposures interrupt more than one phase of cortical development which makes it difficult to isolate the effects of the hypoplasia. The best characterized model of cortical micrencephaly results from treatment of pregnant dams with the antimetabolic agent methylazoxymethanol (MAM) [81]. A single administration of MAM to a pregnant rat dam on E14 or 15, during the peak of cortical neurogenesis, results in a more than 50% decrease in cortical thickness in the offspring [48,155]. Earlier injections, for example on E10 before cortical neurogenesis has begun, result in offspring whose cortices appear histologically and histochemically normal [68]. Neocortex and hippocampus are the most severely affected following E14/15 MAM administration. Decreases in other regions of the brain are also evident, including a 25% decrease in striatal mass and a

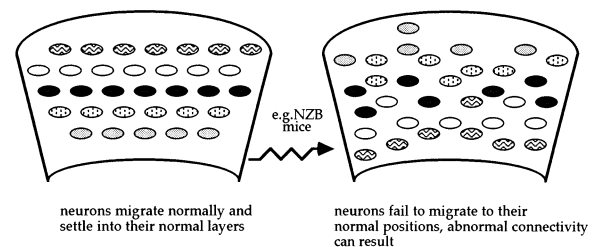


Fig. 3. Cortical ectopias. Cortical neurons fail to migrate to their normal positions because of developmental insults during a specific time window (after [10]).

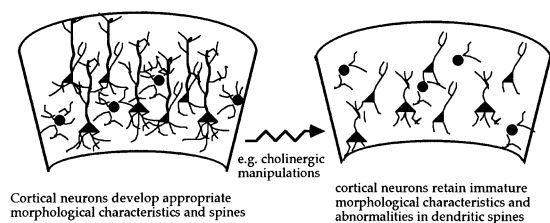


Fig. 4. Cortical dysplasias. Cortical neurons fail to develop mature morphological characteristics because of developmental insults during a specific time window (after [10]).

10% reduction in other non-cortical regions [103]. MAM-treated offspring exhibit a marked loss of neurons which are destined for layers II, III and IV of the neocortex, consistent with the fact that these cortical neurons are generated on E14/15 in rats [100,158]. Similar effects are noted following MAM treatment on E13 in mice [68]. Cortical neuronal loss in MAM-treated offspring is further supported by the marked reduction in GABAergic markers (found normally in stellate interneurons and other non-pyramidal cells) in the cortex [218].

Cytoarchitectural disturbances in the cortex [65], as well as reductions in dendritic branches and spines and abnormalities in commissural connections in hippocampus [211,212] have also been noted following MAM treatment. These hippocampal abnormalities may be secondary effects that result from reduced neocortical inputs. Considering that entire populations of cortical neurons are prohibited from forming in MAM-treated offspring, the cytoarchitectural disruptions are surprisingly moderate. The catecholaminergic innervation of cortical regions appears to be spared in MAM-treated offspring, while the serotonergic and cholinergic innervation of the cortex is somewhat reduced. The relative sparing of these afferents results in a corresponding hyperinnervation of the shrunken cortex [99,103]. This sparing is consistent with the fact that the neuronal cell bodies of these projecting afferents lie in subcortical structures and are generated primarily before E15 in rats.

If a simple relationship between the number of cortical neurons and resulting cortical function did apply, one would expect severe behavioral deficits in tasks requiring the cortex in adult rats exposed to MAM transplacentally. This, however, is not necessarily the case. MAM-treated offspring appear to have normal righting and startle reflexes and normal patterns of maternal behavior [8,59]. Rats that have received MAM lesions are also not impaired in operant training, on visual discrimination tasks or in passive avoidance retention [32]. Open field hyperactivity has been noted in both female and male MAM-treated offspring by some researchers [197,230], but not by others [61]. This

latter study did, however, report hyperactivity on prolonged tests during the dark cycle. Hyperactivity, therefore, is the most consistently noted behavioral abnormality in MAM-treated rats [155] and may, in part, account for altered performances in other cognitive tasks.

Cognitive performance of MAM-treated offspring have been examined on a wide variety of mazes. Performance deficits have been noted using complex mazes such as the eight-arm radial maze, Hebb-Williams maze, T-maze delayed alternation, multiple alternations, but generally not using simpler mazes and discrimination tasks [5,48,70,123,155,209,230]. In reviewing this literature Moran and Coyle [155], therefore, suggested that the complexity of the task is critical in determining whether or not cognitive deficits are exhibited by MAM offspring. These authors also demonstrate that MAM-treated offspring show a developmental delay in behavioral responses to medial forebrain bundle electrical stimulation, perhaps related to an inability of the MAM pups to withhold behavioral responses as compared to controls. However, a recent study contradicts this interpretation and earlier findings by showing no significant differences in running a complex maze in MAM-treated rat offspring of either sex [61]. Ferguson and collaborators suggest that some of the earlier deficits noted both in cognitive and motor tasks in MAM-treated rats may, in fact, be due to light-shyness and hyperreactivity rather than learning or memory deficits. In fact, in dimly lit circumstances, MAM-treated offspring make the same number of errors, and have the same running times on a complex maze as control rats. These researchers also report a response perseverance in operant conditioning and decreased dominance in MAM-treated offspring [59,60].

In total, it appears that a 50% reduction in cortical neurons and alterations in cortical connectivity result in some motor hyperactivity, increased hyperreactivity and cognitive deficits that depend very much on the complexity and type of task examined. It is still unclear, however, to what degree light-shyness and hypoplasia in non-cortical regions contribute to the observed deficits in performance. Sex differences do not seem to be a prevalent feature in this model, as female and male MAM-treated offspring perform behavioral tasks similarly [61,230]. In humans, micrencephaly is frequently associated with mental retardation [141,173]. The hypoplasia noted in these cases, however, is generally accompanied by considerable modifications in neuronal differentiation and connectivity, thus complicating the interpretation of these data. Mental retardation and/or reduced intelligence, however, do not appear to be an inevitable consequence of micrencephaly. In a number of cases, severe micrencephaly was noted only post-mortem or via brain scans in the absence of apparent behavioral abnormalities [126,173].

What seems clear is that a dramatic reduction in cortical gray matter due to an interruption of neurogenesis does not result in a seemingly comparable impairment of behavioral outputs, including cognitive abilities. These data raise questions about the extent to which neuronal populations in the cortex are predetermined to reside in particular cortical layers and become part of specific functional circuits. It certainly appears that early in development the cerebral cortex is sufficiently plastic to compensate for the loss of specific precursor populations, perhaps by altering the fate of neurons that are born later, which can result in the normal appearance of many aspects of behavior.

4. Animal models of altered cortical migration and ectopias

Several strains of mutant mice present with disturbances in cortical migration. The best studied of these mutants is the reeler mouse. Reeler mice contain the normal complement of cortical neurons, however, layering develops abnormally resulting in an inversion of the relative positions of the cortical layers; in other words the earliest formed neurons come to lie in the most superficial positions [187]. The ‘inverted’ cortical neurons in the reeler exhibit normal afferent and efferent connections, however, some subtle changes in cortical connectivity and topography, electrophysiology and nerve growth factor synthesis have been noted [96,142,187]. It would at first appear that the reeler is an ideal model in which to examine the behavioral consequences of altered cortical migration. Several factors, however, limit the usefulness of this model. There are abnormalities in several non-neocortical regions including the hippocampal region, olfactory bulb, dorsal thalamus, tectum, brainstem, and cerebellum [185]. Abnormalities in this latter structure likely lead to the ‘reeling’ disturbance of gait in these animals. These profound movement disturbances have limited the exploration of cognitive deficits in these mutants probably because many assessments of cognitive function are based on an animal’s ability to move and exhibit a particular learned behavior.

Several other strains of mutant mice do present with disturbances in cortical migration that do not appear to be accompanied by other serious brain malformations or motor deficits. A recent series of studies have examined both anatomical and behavioral consequences in BXSB and NZB strains of mice [45,46,193,201]. Approximately 30–50% of BXSB and NZB mice exhibit one or more ectopic collections of neurons and glia in the molecular layer (layer I) of the cortex, neuron-free spaces in other cortical layers, and ‘focal microgyri’. Generally, the ectopic nests are seen unilaterally. In the NZB strain the ectopias are present primarily in senso-

rimotor and somatosensory cortex while in the BXSB strain these ectopias are present primarily in frontal/motor cortex. These ectopias, though generally found in the molecular layer of the cortex, cause alteration in the dendrites and axons in the adjacent regions and underlying layers of the cortex, leading most likely to disruptions in both short and long cortical circuits [207,208]. There are no sex differences in the incidence of ectopias in either strain of mice [45,46,193,201]. Although the exact cause of the ectopias is not known, it is likely that these abnormalities are caused by disruption of the radial glial guidance during the late stages of neuronal migration [207]. Similar types of cortical abnormalities have also been noted in female and male dreher mutant mice; however, these mice have not been tested extensively on behavioral paradigms [202].

Because the types of cortical abnormalities seen in the mutant NZB and BXSB mice are similar to those found in individuals with dyslexia [66], these mice are being used as animal models for developmental learning disorders [46,192]. One serious drawback to these models is that the mutant mice exhibit autoimmune deficiencies. Teasing apart the contributions associated with cortical abnormalities from those associated with immune deficiencies has proven a difficult task. NZB and BXSB mice have been tested on a battery of behavioral paradigms, including cognitive tasks. Performance of these mutants have been examined in a spatial water escape task, Morris swim maze, a black/white discrimination, a complex Lashley maze, and shuttlebox avoidance [46,201]. Correlations have not been found between ectopia number, size, or site with behavioral measures, such as water escape latency, discrimination choice accuracy or Lashley maze learning scores. Ectopias do, however, seem to be associated with poorer performance on discrimination learning tasks, as well as, several parameters of the Morris water maze task. It is important to recognize that some of the reported differences may be due to a hypoactivity exhibited in the ectopic mice. Somewhat surprisingly, environmental enrichment, a relatively late intervention strategy that begins at the time of weaning, can counter some behavioral deficits in ectopic mice [201]. Also surprising is the fact that consistent sex differences in behavior have not been seen in these ectopic models, considering that sex differences in the incidence of dyslexias in humans are quite pronounced [66].

In total, mutant mice with cortical ectopias show alterations in motor activity and slight impairments in discrimination and spatial learning that appear to be independent of the autoimmune deficits [193,201]. As with models of micrencephaly, the apparent normality of measures of cognitive function is a striking feature of these ectopic mice. The relatively mild cognitive deficits seen in the NZB and BXSB mutants are, in fact,

consistent with findings in humans. Dyslexias are difficulties in how to read and write and are not associated with abnormal intelligence or mental retardation [66]. Another noticeable feature in these ectopic mice is that their behavior is consistently more extreme, sometimes better and sometimes worse, than that of their non-ectopic littermates. We [16] and others [241] have noted that behaviour in mice with a specific genetic mutation can be quite variable; mutant mice can be severely impaired on a given task, perform normally, or can perform better than controls. All of these studies suggest that the plasticity that occurs in response to a developmental insult (genetic or physical) could lead to reorganization of cortical circuits that could improve the performance of some activities while impairing the performance of others. Because of the variability and unpredictability of behavioral alterations seen following these early physical and genetic manipulations, it appears that behaviors are not genetically hardwired within particular cortical circuits before birth.

5. Perinatal manipulations of cortical afferents: dysplasias and behavioral consequences

Early evidence suggested that cortical differentiation was influenced by the long projection noradrenergic (NE) fibers that innervated cortex before birth [37,109,120]. This evidence stimulated a wealth of studies examining the effects of both NE and other cortically projecting fiber systems on cortical morphology and function. The serotonergic, dopaminergic, and cholinergic afferent projections to the cortex were obvious candidates, along with NE, to play a critical role in cortical differentiation and maturation, and as such were also the subject of intense investigations. These afferent systems all have in common the fact that they innervate the developing cortex early on [119] and they can modulate cortical synapses in adulthood [82]. Each afferent, however, arrives at the cortex at a slightly different time in development and reaches full maturity at different times (see Fig. 5). Because all of these

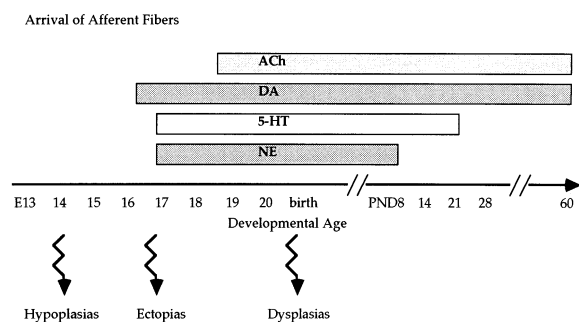


Fig. 5. Time line of arrival and maturity of major cortical afferent systems.

afferent systems innervate the neocortex after neurogenesis and migration have begun, their manipulation will affect most likely cortical differentiation and synaptogenesis and lead to cortical dysplasias. By and large, the functions of these various neuromodulator systems has been investigated by depleting or lesioning the system of interest or manipulating it pharmacologically around the time of birth to assess how cortical structure and behavioral ontogeny proceed in its absence.

5.1. Norepinephrine

In rodent, the cerebral cortex receives all of its noradrenergic innervation from the locus coeruleus (LC). The peak generation of LC neurons is E12 and their fibers can be seen entering developing neocortex about E17 [37,120,125]. The widespread distribution and density of NE fibers achieve their adult-like pattern by postnatal day (PND) 7.

Numerous studies have examined cortical development and behavior in the absence of the noradrenergic system. The older studies relied on mechanical lesions, while some later studies relied on neurotoxins. How then do cortical ontogeny and behavior develop in the absence of norepinephrine? The data are not completely consistent, however, it does appear that norepinephrine plays an essential role in the differentiation of the cerebral cortex and in the performance of complex behavioral tasks, particularly those requiring attention.

Maeda et al. [138] reported abnormalities of pyramidal neurons in cortical layer VI in adult rats who received electrolytic lesions to LC on PND1: dendrite lengths were increased, while arborizations were decreased. Wendlandt et al. [233] were not able to confirm alterations in layer VI neurons following mechanical lesions at birth. These authors did find small but significant increases in the number of dendritic branches in pyramidal neurons in layers III and IV. We can find no technical differences in these studies that account for the differences in observed results. The mechanical lesions used in both the Maeda et al. [138] and the Wendlandt et al. [233] studies were evidently difficult to perform accurately. In each case 300 rats were lesioned and four or five, respectively, were used in analyses. Because of this difficulty, most subsequent studies concerning the effects of NE depletion on cortical structure employed the catecholaminergic neurotoxin 6-hydroxydopamine (6-OHDA). This agent is taken up primarily by NE neurons when injected systemically; it is also taken up by peripheral sympathetic neurons. The i.c.v. injections appear to affect both NE and dopamine levels in the cortex. Additionally, the time of the injection influences its relative selectivity; injections within the first 24 h of birth reportedly destroy the NE system selectively [129,196,223].

In the early 1980s, several laboratories reported the effects, or lack thereof, of 6-OHDA on cortical morphogenesis. In one of the earliest reports, Onténiente et al. [169] saw a 16% reduction in the thickness of layers II and III in the temporal cortex in juvenile rats that were treated intracisternally with 6-OHDA on PND1. These injections resulted in a 95% reduction in NE uptake in brain, and a 60% reduction in DA content, while serotonin (5HT) content was unchanged following i.c.v. injections. Ebersole et al. [54], however, could not confirm alterations in cortical cell density, size or distribution following large subcutaneous doses of 6-OHDA in PND1 rat pups. In another study, Parnavelas and Blue [174] observed toxin-induced changes in cortical synaptogenesis following systemic 6-OHDA injections which should selectively deplete NE. Felten et al. [58] reported a small but significant reduction in dendritic length and loss of dendritic spines in pyramidal neurons of layer III and V after massive 6-OHDA lesions given on PNDs 1–7. The alterations were seen primarily in the frontal and cingulate cortex; the extent and severity of alterations in the cortex correlated with reductions in NE, but not DA in the cortex. Lidov and Molliver [127] injected rat dams intrauterine with 6-OHDA on E17 and failed to find alterations in cortical cytoarchitecture and morphology. These investigators did note occasional (about 33% of the time) migratory defects in the cortices of the treated rats. Brenner et al. [27] reported reduction in cortical weight following neonatal subcutaneous injections of the toxin which could be partially reversed with enriched housing [28]. In mouse, Loeb et al. [130] did not find quantitative dendritic changes or cytoarchitectural changes in the barrel field areas of the somatosensory cortex after intraperitoneal 6-OHDA injections which resulted in 96–98% NE depletions in the parietal cortex. These authors, however, did note changes in dendritic orientation of some layer IV neurons. These widely divergent results from different laboratories may, in part, be explained by differences in time and manner of toxin administration, strain or species used and, to some degree, to the region of the cortex examined. In total, these studies suggest that depleting the noradrenergic system right around the time of birth does lead to subtle permanent cortical dendritic changes, suggesting alterations in cortical differentiation. The specific cortical layer that is altered varies widely in the different reports and may be related to the precise timing and dose of the toxin used. Significant changes in cortical neuronal number or gross changes in cortical cytoarchitecture, however, have not been convincingly demonstrated in the studies reviewed here. This may be because the 6-OHDA toxin treatments occurred postnatally, well after cortical neurogenesis, and after NE afferents have begun to innervate the cortex. Unfortunately, the sex of the animal is not mentioned in any of

these anatomical studies, making it impossible to assess whether or not sex differences existed.

For the most part, investigators interested in behavioral responses to perinatal 6-OHDA differed from those studying cortical morphogenesis in the 1970s and 1980s. As such, virtually no structure/function correlations within the same experimental paradigm were attempted at that time. In most reported studies using 6-OHDA neonatal lesions, both NE and DA were affected throughout the brain. In a few cases, however, NE was selectively depleted by administering the 6-OHDA systemically within the first 24 h after birth; we will focus on these more selective depletion studies. Raskin et al. [188] report impairments in learning on a T-maze and in shuttle box avoidance learning in juvenile male and female rats who were neonatally treated with 6-OHDA. This group also reported that spatial and place learning was not impaired in the neonatally-lesioned rats, but there did appear to be deficits in attention paradigms. Several reports suggest that by adulthood, many aspects of behavior in neonatally-treated pups are normal including locomotor activity, runway acquisition and two-way avoidance acquisition [18,196]. Two more recent studies suggest that adult rats with neonatal NE depletion do not show impaired spatial learning [112] and do show improved performance on a Hebb-Williams maze as compared to controls [172]. In total, these studies suggest that growing up without noradrenergic cortical innervation results in mild, and perhaps only transient, alterations in learning that may be related to attention.

An excellent series of recent studies, many from Kolb, Sutherland and collaborators have maintained interest in the role of NE in the developing cortex and behavioral functions in the 1990s. In contrast to earlier studies, Kolb, Sutherland and collaborators have investigated behavioral functions and cortical morphology in the same rat, creating the potential for structure/function correlations. These researchers use an interesting paradigm in which they remove sections of the frontal cortex on PND7 and then allow the rats to grow to adulthood. Generally, following these PND7 frontal lesions, there was remarkable sparing of adult behavioral functions. NE depletion in neonatal rats, however, prevents this sparing of function in the frontally-lesioned rats [220]. Neonatal NE depletion on PND1 also reduced dendritic branching which led to thinner cortices and smaller brain sizes in rats with frontal cortical damage and in controls [112], suggesting that the NE ordinarily plays a critical role in the sparing of function following frontal lesions. Numerous other studies suggest that neonatal NE depletions are effective in altering morphological and behavioral responses to physically enriched environments [153,168]. In contrast, Murtha et al. [162] tested the effects of neonatal NE depletion on the behavioral and morphological re-

sponse to enriched environmental rearing conditions and was unable to find any effect. The most significant difference between the study by Murtha et al. [162] and the other experiments appears to be the toxin route of administration. Murtha et al. [162] made i.c.v. injections and pretreated with bupropion to create a specific NE lesion, whereas in other studies, the toxin was applied subcutaneously, thus leaving open the possibility that some of the previously observed effects were due to peripheral NE depletion.

Making sense of the behavioral and anatomical effects of neonatal NE depletion is a arduous task. This task is made even more complex by the difficulty in judging whether the morphological and behavioral alterations are the result of direct NE depletion of the cortex, indirect effects on other NE projections (e.g. hippocampal projections), or effects on other neurotransmitter systems. For example, in cat, 6-OHDA may interact with muscarinic cholinergic receptors [210]. Additionally, depletion of one neurotransmitter system may lead to compensatory sprouting of another system [20]. In the one study in which cortical morphology and spatial learning were tested in the same group of animals, 6-OHDA reduced brain size and cortical dendritic branching without affecting spatial localization behavior [112]. Do these data suggest that NE depletion at birth alters cortical morphogenesis, but not sufficiently to affect behavior? Probably not. It is likely that the spatial localization task used by Kolb and collaborators was not sufficiently difficult to pick up subtle cognitive deficits in the neonatally-lesioned animals. As previously noted, deficits are apparent in several behavioral paradigms, particularly related to attention, following neonatal NE depletion. After several days of training, spatial localization probably does not require intensely focused attention.

In total, it does appear that neonatal depletions of NE affect cortical dendritic structure, to varying degrees depending on the method and timing of administration and the species used. Decreases in dendritic branching and spine density have been reported more consistently than increases. It also seems clear that neonatal depletions of NE affect some, though not all, cognitive behaviors; attention appears to be the most compromised. NE also seems to be involved in recovery of behavioral functions following cortical lesions and is disputably involved in cortical responses to enriched environments. In short, the subtle cortical dysplasia that results from neonatal NE depletions leads to small, but significant, alterations in adult behavior. Interestingly, the behavioral effects of NE depletion in adulthood are also subtle and related to attentional processes [199]. In humans, NE deficits have been noted in some children with attention deficit disorders [194,205]. The human and rodent data appear consistent in the sense that attentional disorders are noted

and they are not necessarily accompanied by other serious cognitive deficits.

5.2. Serotonin

The serotonergic innervation of the neocortex comes almost exclusively from the dorsal and median raphe nuclei [128,154]. Raphe neurons are generated from about E11 to E15, making them some of the earliest developing neurons in the rat CNS [120,122]. The serotonergic innervation parallels the noradrenergic innervation and arrives at the cortical anlage at about E17 [128,231]. At birth, these fibers penetrate all cortical layers and show a transient exuberant distribution pattern, then decline markedly to the mature pattern at about 3 weeks postnatal, thus later than the NE system [43,52,189]. In adulthood, the serotonergic distribution mirrors that of the NE system.

There is little direct evidence that cortical morphogenesis is altered or that significant cortical dysplasia results from perinatal 5HT depletion. Relatively few studies have examined the course of cortical development in the absence of serotonin; two detailed and well-designed studies, however, do exist which suggest cortical somatotopic connections are altered following neonatal 5HT depletion. Blue et al. [19] have reported a delay in the emergence of the thalamocortical innervation pattern in rats who were treated neonatally with *p*-chloroamphetamine, a selective 5HT neurotoxin. Using another serotonergic toxin 5,7-DHT, Bennett-Clarke et al. [12] depleted cortical 5HT in PND0 rat pups and found long lasting reductions in the mystacial cortical whisker representation. This reduction did not alter the overall somatotopic organization of thalamocortical afferents or overall cortical weight, in other words, no gross alterations in cortical maturation were noted. In addition to this direct evidence that 5HT depletion at birth affects subtle changes in somatotopic cortical representations, there is considerable indirect evidence that 5HT plays a role in cortical differentiation and maturation: (1) *in vivo* and *in vitro*, 5HT acts as a morphological and biochemical differentiation signal for serotonergic targets in the developing brain [118,119,121,122], (2) the timing of serotonergic innervation of the cortex coincides with pronounced growth and synaptogenesis in rat cerebral cortex [21] and (3) perinatal manipulation of 5HT affects cortical serotonin receptors [26,135]. We could not, however, find any reports of changes in dendritic number, branching patterns or alterations in cortical thickness (either overall or in a specific layer) following neonatal serotonin depletion. Similar to the anatomical studies following NE depletion, the laboratories that have carefully examined anatomical changes in response to neonatal 5HT depletion did not examine its behavioral effects.

Breese et al. [25,26] were among the first to report the effects on behavior of perinatal administration of 5,7 DHT, a serotonergic neurotoxin. These and other authors have described the serotonergic behavioral syndrome, induced by serotonergic agonists, that consists of rigidity, head weaving, splayed feet, tremor, salivation and forepaw treading [225]. Adult rats who have received intraventricular 5,7 DHT on PND3 exhibited a potentiated behavioral syndrome, as compared to controls, suggesting permanent alterations in serotonergic receptors and behavior. Significant non-drug induced behavioral alterations, however, were not reported in the absence of a drug challenge. It is impossible to determine if this potentiated behavioral syndrome resulted from cortical serotonergic changes following these i.c.v. injections. Several recent studies do suggest that maternal stress may affect the 5HT behavioral syndrome in pups and that this effect may be related to serotonin in the cortex. Peters [177,179] reports that maternally-stressed offspring have altered 5HT receptor binding, increased 5HT levels in the cortices, and decreased 5HT behavioral syndrome when compared to non-stressed offspring. Additionally, the offspring of maternally-stressed females display increased open field motor activity [177]. Further support that stress, possibly via the serotonergic system, may influence cortical differentiation comes from the fact the aforementioned effects are only noted in the offspring of females stressed from E15 to E20, but not from E3 to E14 [178]. This former period clearly coincides with the time window in which cortical neuronal maturation has begun (see Fig. 1). It is interesting to note that prenatal stress reportedly feminizes male cortices such that a characteristic female laterality pattern is displayed [2,62,216].

Other indirect evidence further supports a role for serotonin in cortical development and behavior. Treating developing rat pups with monoamine oxidase (MAO) inhibitors significantly reduces cortical serotonergic innervation and severely impairs passive avoidance performance in the juvenile rats [237]. Additionally, prenatal hypoxia, induced by sodium nitrite from E13 to birth, delays both serotonergic and cholinergic fiber ingrowth into the parietal cortex [167]. Mice with prenatal hypoxia exhibit hyperactivity, and impairments in attention and spatial memory in adulthood [31,166]. In total, these behavioral studies suggest a subtle role for 5HT in these behavioral deficits which is potentiated when other neurotransmitter systems are affected; MAO inhibitors affect serotonin as well as other monoamines, prenatal hypoxia affects cholinergic as well as serotonergic fiber ingrowth, and stress very likely affects several neurotransmitters.

In total, though considerable evidence exists that 5HT acts as a morphological differentiation signal in vitro, we could find little direct evidence that postnatal

serotonin depletions alter cortical morphogenesis dramatically in vivo. It is important to point out that relatively few in vivo studies examine the effects of specific serotonergic depletions and in those relatively few studies, the effects have been subtle. Two interpretations are possible: (1) serotonin plays a very minor role in cortical morphogenesis, or (2) serotonin's influence on cortical morphogenesis is largely prenatal and 5HT depletion postnatally (characteristic of the studies that we have found) miss the appropriate developmental time window. It is currently impossible to select between these alternatives. Not surprisingly, many of the reported behavioral effects of neonatal 5HT depletion are subtle, sometimes apparent only in a pharmacological challenge. It seems something of a paradox that autism, a debilitating developmental disorder in humans, has been related most consistently with hyper-serotonism [3]. Perhaps, animal models of serotonin hyperinnervation, rather than the depletion models discussed here, will provide a better model for changes in autism. Alternately, autism likely involves a series of developmental aberrations of which serotonin imbalance may be only a small part.

5.3. Dopamine

Dopamine (DA) innervation of the cortex comes primarily from the ventral tegmental area; these neurons are generated from E10 to E15 in rodents [229]. The first dopaminergic fibers arrive at the developing cortical anlage about E16, thus slightly earlier than NE or 5HT fibers in the rat [226]. Cortical dopaminergic fibers become restricted to the prefrontal and entorhinal cortex and reveal their adult pattern of innervation in the second month postnatal, hence later than many of the other long projecting fiber inputs [106]. DA innervation of the cortex develops earlier in females than in males [217]. Neonatal gonadal hormones appear responsible for this difference.

The effects of early DA depletion on adult behavior in rats was studied by a number of laboratories in the 1970s and 1980s. The most commonly used technique for depleting DA was 6-OHDA administered intraventricularly following a dose of desmethylimipramine (DMI), a NE uptake inhibitor. Depending on the time of drug administration and the dose, 6-OHDA can result in motor hyperactivity that is either permanently [56,86,171,204] or only transiently expressed [85,150]. Sex differences are not seen in the development or magnitude of this effect [55]. Rats with neonatal 6-OHDA also exhibit significantly impaired performance on T-mazes and shuttle box avoidance [188,204,213], and impaired learning ability in an operant task [85]. In this latter study, male rats displayed greater acquisition deficits than did female rats. On spatially-oriented cognitive tasks, the results are somewhat less consistent.

Place learning is impaired on a spatial navigation task [171,235], however, radial arm maze performance is not [176]. In more ethologically-based behaviors, neonatal dopamine depletions impair ingestive behavior [24,30,36,213], however, orienting to tactile stimuli [236] and sucking and weaning are relatively normal [29]. Additionally, rats treated intracisternally with 6-OHDA neonatally are supersensitive to dopaminergic agonists and exhibit self-mutilating behaviors in response to dopaminergic challenges later in life [23,40]. In a recent study, transgenic mice that are unable to synthesize DA exhibit severe hypoactivity, adipsia and aphagia which can be reversed by administration of a DA agonist [244]. While all of these studies suggest a critical role for DA in the development of these behaviors, it is essential to keep in mind that intraventricular 6-OHDA and the transgenic mice exhibit decreased DA levels in the striatum as well as the cerebral cortex. As such many of the aforementioned effects likely result from combined striatal and cortical DA reductions.

In a recent series of studies, Kalsbeek et al., using a thermal lesion technique, have examined the developmental role of dopaminergic fibers projecting to the prefrontal cortex [105–108]. In these studies, cortical DA is depleted (approximately 60%) by thermal lesions to the ventral tegmental area in PND1 rats; cortical serotonin is also significantly decreased. Cortical anatomical, neurochemical, as well as behavioral changes result from this early dopaminergic/serotonergic depletion. Anatomically, these neonatal lesions result in a 30% decrease in the length and branching frequency of pyramidal layer V basal dendrites. A small decrease in cortical thickness in response to the neonatal lesion was reported in one study [105] but not in another [108]. Following a neonatal i.c.v. 6-OHDA lesion with DMI injections, Pappas et al. [171] reported a 40% reduction in cortical DA, but failed to see any decrease in cortical thickness. In this study, the 6-OHDA injections did result in significant impairments in the performance of two spatial navigation tasks in juvenile rats and these effects were reversed by raising the rats in an enriched physical environment.

Neonatal thermal mesolimbic lesions (used by Kalsbeek and collaborators) impair food hoarding in males, but not in females [106]. Spatial alternation is impaired in adulthood, as is the response to stress in these rats following neonatal lesions [57]. This latter effect appears to be due to compensatory lesion-induced alterations in all of the monoaminergic systems. Locomotor activity is altered in the juvenile, but not in the adult rat following these neonatal lesions [107], reminiscent of the effects of neonatal 6-OHDA treatments. In this study, both DA and 5HT are reduced in the prefrontal cortex by 50%. However, the aforementioned behavioral deficits are not seen when only serotonin is depleted; additionally, several of the behavioral measures corre-

late with DA content in the prefrontal cortex. Both of these findings lead Kalsbeek and collaborators to suggest that the anatomical and behavioral changes noted result from the cortical DA depletion. However, a combined DA/5HT effect cannot be eliminated.

Further support for the role of DA in cortical development can be gleaned from the literature on perinatal exposure to cocaine, a DA uptake inhibitor. Prenatal exposure to cocaine in the mid- and late-gestational period results in alterations in cortical morphology somewhat reminiscent of, but more severe than, the effects seen in the Kalsbeek model discussed above. Mid- and late-gestational cocaine exposure results in a 16% reduction in cortical thickness and alterations in cortical lamination particularly in cortical layers IV–V [78], thus reminiscent of some of the cortical alterations reported by Kalsbeek et al. [105]. The cocaine picture, however, is complicated by the fact that midgestational exposure to cocaine also results in altered generation and migration of cortical neurons. The behavioral effects of prenatal cocaine exposure range from simple motor effects, similar to those seen following 6-OHDA lesions, to deficits in cognition and attention. These effects have been noted in both animal models and humans exposed prenatally to cocaine [53,63,115,124,238]. In the rodent models, these effects also appear to be sex-dependent; on some tasks (e.g. radial arm maze) females are more severely impaired than males [63,124] while on other tasks (e.g. spontaneous alternation and water maze) males are more affected [215]. While cocaine can certainly not be considered a specific dopaminergic drug, because both serotonergic and cholinergic neurotransmitter systems are affected [1,78], it does appear that some of the effects following this drug treatment resemble those following more specific neonatal dopaminergic lesions. Thus, it is reasonable to conclude that at least some of the permanent anatomical and behavioral effects of prenatal cocaine exposure are due to neonatal loss of the DA system.

In total, the data are convincing that neonatal DA depletion affects cortical morphogenesis; both dendritic length and branching patterns in pyramidal layer V neurons reportedly decrease [105,108]. Neonatal cortical DA depletion does not, however, consistently alter cortical thickness or lamination patterns. These studies, therefore, suggest that DA axons provide an important growth stimulus and differentiation signal for the dendrites of cortical pyramidal cells. Neonatal DA depletion also permanently alters a variety of experimental and ethologically-based behaviors, adding further support that cortical circuitry is permanently altered. Sex differences in cortical innervation and behavioral responses to DA depletion have been noted. The effects of DA depletion appear greater in magnitude and more consistent than those reported following neonatal NE

or 5HT depletion. However, this conclusion is tenuous because of the lack of neurotransmitter specificity in many of the treatments that we have reviewed. This seemingly larger effect of DA depletion could be due to a number of factors. One, it is possible that DA has a greater influence on prefrontal cortical morphology than the other two transmitters. It is just as likely that neonatal DA depletion influences cortical morphogenesis over a longer period of time than 5HT or NE depletion. DA fiber projections reach their adult pattern at about 2 months, in other words, much later than either NE or 5HT. This slower ingrowth could provide a larger time window in which the effects of DA depletion can be noted. Additionally, because neonatal ventral tegmental lesions also deplete serotonin, it is not possible to exclude a combined dopaminergic/serotonergic effect in both the anatomical and behavioral deficits noted.

5.4. Acetylcholine

The cholinergic fibers innervating the cortex are the last of the major modulators to arrive in the developing rat cortex [226]. In mouse, neurons of the basal forebrain (BF), which will provide the primary innervation to the cortex, are generated E11 through E16, and cholinergic fibers arrive in the cortex on about E19 [221]. In both mice and rats, these afferents develop largely postnatally and reach mature levels towards the end of the second postnatal month [39,90,117,227].

Experiments by Hohmann et al. [87] examined cortical morphogenesis following an 85% reduction in the cholinergic innervation to the mouse cortex. This interruption of cortical cholinergic innervation was accomplished by an electrical current lesion aimed at the BF. Light microscopic studies revealed a delay in the appearance of normal cortical cytodifferentiation in layers II through V. Golgi studies of layer V pyramidal cells confirmed a long-lasting alteration in dendritic branching patterns, immature spine morphology and reduced pyramidal cell soma in the sensory-motor cortex [91]. Alterations in cortical afferents and efferents were also noted in adult mice who had received BF lesions as neonates [93]. It should be pointed out that electrolytic lesions to the BF result in a transient decrease in norepinephrine and serotonin levels; however, 5,7-DHT lesions affecting NA or 5HT afferents did not produce comparable changes in cortical cytoarchitecture [87]. Sengstock et al. [203] reported alterations in pyramidal cell branching and dendritic volume in the cortex following a neonatal BF ibotenic acid lesion in rat, hence essentially replicating the findings of Hohmann and collaborators. A cholinergic role in cortical morphogenesis is also supported by a recent study involving systemic application of nicotine during gestation [195]. These authors report alterations in neuronal density,

decreased dendritic branching and increased spine density in layer V pyramidal neurons in the cortices of the gestationally-exposed rat offspring. Our most recent studies confirm decreases in layer V thickness, as compared to controls, in both female and male adult mice who received BF lesions as neonates [92]. Preliminary data, however, do reveal sex differences in other cortical layers; layers II + III are decreased in females but increased in males; while layer IV is decreased in males but not in females in adult mice that have received BF lesions as neonates [92].

These studies and many others [88] support a critical role for the cholinergic afferents to the cortex in the maturation and differentiation of their targets. Derailed cholinergic afferent innervation and/or selective abnormalities in cholinergic neurotransmission have been documented in a variety of developmental disorders in humans including Down syndrome [38,44], Rett syndrome [102,163,234], lead toxicity [180], ethanol toxicity [13,200], hypothyroidism [72,83,95,175] and anoxia [31,165,167]. Furthermore, cortical dysplasias in animal models of lead [180] and ethanol [151,152] toxicity and in individuals with Down syndrome [182,222] bear striking similarities to those in our neonatal BF lesion model.

Direct structure/function correlations between altered cortical morphology and cognitive behaviors have been attempted following neonatal cortical cholinergic depletion. Sengstock et al. [203] showed impaired passive avoidance retention, active avoidance and radial arm maze performance in adult rats that had received BF lesions as neonates. We have also examined behavior and morphology in adult mice following neonatal BF lesions. As adults, the neonatally-lesioned pups exhibit dark cycle hyperactivity, impaired retention on a passive avoidance task and a severe deficit on a Morris swim maze task [7]. Furthermore, correlation analyses revealed a significant correlation between water maze performance and abnormal cytoarchitecture and passive avoidance retention and abnormal cytoarchitecture. Altered activity levels, on the other hand, were not correlated with cytoarchitectural changes. These initial assessments of cortical structure/behavioral function correlates were based on qualitative (albeit blind to the behavioral data) ratings of cortical morphology and restricted to a sample of only nine animals. Recent data support these previous findings and further reveal that neonatally-lesioned males are more severely impaired, than neonatally-lesioned females, on a swim maze task, but not in passive avoidance retention [17]. At this point, it is not possible to determine if this sex difference is due to the fact that male control mice outperform female control mice on this spatial task and the lesion causes a more pronounced and noticeable effect in males. Alternatively, cholinergic efferents to the cortex may follow a different developmental time course in

the two sexes such that at the time of lesioning, PND1, afferents in males are more disturbed by the lesion than those in females. This latter interpretation is compatible with other data showing timing differences in female and male neocortical ontogeny and behavior [35,77,161,243] and by the reported sex differences in the development of the cholinergic septo-hippocampal pathway [131]. Finally, it is possible that the sex differences in performance result because females and males differentially engage cortical regions in performing this spatial learning task. If males are more dependent on cortical regions to successfully solve this spatial task, then it follows that they would be more affected by the resulting cortical dysplasia. Other studies have shown that females and males may use different strategies in solving spatial mazes [14,239]. At the moment, it is not possible to distinguish among these alternatives.

Further support for a critical role of cholinergic afferents in cortically-related behaviors comes from a number of studies involving pharmacological manipulation of the cholinergic system around the time of birth. Ricceri et al. [190] report impairment of passive avoidance learning in mice following early postnatal administration of an anti-NGF antibody, a treatment that is thought to specifically impair the function of cholinergic BF neurons. Behavioral deficits have also been noted following perinatal injections of AF64A, a cholinergic neurotoxin whose specificity is the subject of considerable debate [143]. Nevertheless, early postnatal injections result in hyperactivity and severely impaired spatial learning in adult rats, as well as permanent alterations in hippocampal cholinergic receptors [6,67,133]. These deficits are blocked when rats are pretreated with hemicholinium-3, a specific inhibitor of high affinity choline uptake, adding support that these deficits result directly from the cholinergic losses [22]. In attempts to augment cholinergic markers perinatally using an acetylcholinesterase (AChE) inhibitor, Castro et al. [33] showed an improvement in short term memory capacity. Similarly, Smith et al. [214] report dose-dependent improvement in single-trial passive avoidance learning in young rats following injections of cholinomimetic drugs, but not following injections of a series of non-cholinergic drugs. In contrast, Gupta et al. [80] report impaired operant behavior following administration of an organophosphate AChE inhibitor. This latter effect could be due to the toxicity of the organophosphate or be related to the particular dose used in the study. In an elegant series of studies, Meck, Williams and collaborators have explored the effects of perinatal choline supplementation on cognitive function, neuronal morphology and chemistry [132,146,147]. Choline supplementation, which increases cholinergic markers in the BF, cortex and hippocampus, also increases pyramidal cell branching and size in the hippocampus (personal communication).

Similar to our BF lesion model, sex differences in response to choline supplementation are apparent. Male rats respond to both pre- and early postnatal application of choline, while females respond only to the prenatal applications.

In contrast to the studies supporting a role for the developing cholinergic system in adult behavior, a recent comprehensive study by Pappas et al. [170] shows that specific cholinergic lesions in PND7 rat pups do not lead to significant deficits in spatial navigation or delayed spatial alternation performance in the adult rats. In this study, the authors use a cholinergic immunotoxin 192 IgG saporin that has previously been shown to specifically eliminate cholinergic basal forebrain projections to hippocampus and cortex in adult rat [84] and produce spatial navigation deficits in adult rats [15]. Neurochemically, the PND7 192 IgG saporin lesion reduced cortical ChAT by 42% and increased NE by 59% in adult rats. Additionally, alterations in cortical morphology of layers III–V are not apparent in the adult rats that received the immunotoxin on PND7, in contrast to reports following an electrolytic nBM lesion on PND1 in mice [7,89]. These data initially point towards a limited role of the cholinergic system in the development of the cerebral cortex and cognitive behaviors, however, another explanation is possible. The immunotoxin lesions were performed on PND7, in contrast to the numerous studies with earlier cholinergic manipulations, such as neonatal electrolytic nBM lesions performed on PND1 [7,89], ibotenic acid-induced lesions made on PND2–3 [203], or cholinergic supplementation studies [146,147] where manipulations occur within the first week of life. It is therefore possible that lesions on PND7 miss a critical earlier time window in which cholinergic afferents most heavily influence cortical morphogenesis. Further clarification of this issue awaits a specific cholinergic immunotoxin that can be used in mice and lesion specific lesion protocols at earlier neonatal periods.

In total, the data are strong and consistent that perinatal manipulations of acetylcholine lead to persistent alterations in cortical morphology and behavior. Furthermore, abnormal cortical morphology is correlated directly with cognitive, but not with motor behavioral abnormalities [7]. These data, however, must be viewed in light of the fact that neonatal electrolytic or ibotenic acid BF lesions affect more than just the cholinergic system. The one study using a specific cholinergic toxin [170] showed conflicting results, though this may be a function of the timing of the lesion. Sex differences have been noted in response to neonatal BF lesions and in response to neonatal choline augmentation [146,147]. Taken together the data strongly suggest that the cholinergic system influences cortical development and behaviors differently in the two sexes.

6. Conclusions: the search for general principles

The types of perinatal manipulations and genetic models, reviewed here are varied—they interrupt different phases of cortical development and affect different receptor and neurotransmitter populations. Considering the diversity of manipulations, is it possible to determine any general principles? We believe that it is.

6.1. Do earlier perinatal insults result in more behavioral recovery than later insults?

We believe that the answer to this question is a qualified yes. Even though behavioral deficits can be seen following insults at every stage of cortical development—neurogenesis [48,155], migration [201] and maturation [7,108], it appears that the behavioral deficits seen following insults to cortical neuronal differentiation are more pronounced and extensive than those following insults during neurogenesis or migration. Rats with a 50% reduction in cortical neuronal number can run several simple and complex mazes successfully and their movement patterns appear normal [61,155]. Similarly, mice with abnormalities in cortical neuronal migration can perform successfully complex spatial mazes and discrimination tasks with normal movement patterns [46,201]. By contrast, rodents with neonatal lesions of the cholinergic and dopaminergic systems at birth exhibit severe deficits in performing spatial navigation tasks [7,106] as well as the simpler passive (inhibitory) avoidance task [7]; even basic ingestive behaviors [106] are disturbed. It is important to point out that in our cholinergic neonatal lesion model, cortical cholinergic markers have returned to normal levels in adulthood [92]. This finding strongly suggests that the behavioral deficits noted are not related to an acute cholinergic deficit at the time of behavioral testing, but rather from altered cortical differentiation.

We hypothesize that following the earliest injuries (during cortical neurogenesis or migration), there is the potential for reorganization of cortical circuitry which leads to remarkable sparing of functions. If neurogenesis is interrupted, for example, the fate of neurons born later can potentially be altered. Perhaps, cortical neurons originally destined to serve in one type of ‘behavioral circuit’ can be taken over by another circuit, somewhat reminiscent of ocular dominance column plasticity, where the territory in the cortex normally devoted to a deprived eye can be ‘taken over’ by axonal inputs from the other eye [116]. It is feasible then that reorganization of cortical circuits are possible because the neurotransmitter specific afferents to the cortex develop normally despite interrupted cortical neurogenesis and migration. For example, an interesting feature of the MAM model is that the cortical afferents appear to grow relatively normally into the cortex despite the

reduction in the number of cortical neurons that they will innervate. If these cortical afferents provide critical maturation signals to the cortical neurons, we may expect cortical maturation to proceed relatively normally in this model. In fact, we have not found evidence that cortical dendritic density or pattern is altered after MAM treatment. Also, dendritic density and pattern do not appear to be altered following the migrational aberrations in BXSB or NZB mice. In total, the ‘normal’ maturational signals from the cortical afferent systems may provide the substrate for the plasticity that leads to reorganization and the subsequent sparing of behavioral function noted following insults to neurogenesis or migration.

Interrupting the cortical afferents, by contrast, appears to have a fundamentally different effect on cortical development than interrupting neurogenesis or neuronal migration. When the afferents arrive in the cortex, neurogenesis and migration of cortical neurons are largely complete; hence modifications in overall cortical number, lamination patterns, and migration are not generally reported when these afferents are manipulated at birth. Noradrenergic, serotonergic, dopaminergic, and cholinergic afferents all appear to provide critical signals to the developing cortical neurons which affect dendritic length [58,138,233], dendritic arborization [91,105,108], spine density, morphology, and orientation [27,58,91,138,195,203,233], as well as the manner in which sensory inputs interact with cortical neurons [12,19]. Not surprisingly, loss of these critical afferents at birth lead to a wide array of persistent behavioral deficits that affect cognitive behaviors [57,85,145,156,188,213], motor behaviors [108,235], as well as more ethologically-based behaviors such as ingestion and food hoarding [24,105,244]. Perhaps, this wide array of severe behavioral deficits are noted because these injuries that interrupt cortical differentiation after some behavioral circuits have already been formed. For instance, the animal is born with the ability to make deliberate movements; this suggests that certain cortical circuits are, at that time, designated for controlling movements. It appears that once a behavioral circuit has been established, altering the maturation of the neurons in that circuit can have a devastating impact on the behavior. Perhaps what is critically affected with the insults to the cortical afferent systems is plasticity, the ability to compensate for injury and adjust to the variety of experiences taking place during normal development. It is also possible that during cortical maturation the potential for reorganization of circuitry is more limited than that present during neurogenesis and migration because the fate of particular neurons has already been assigned.

If we believe earlier lesions tend to be ‘better’ in the sense that they allow for more cortical reorganization and potentially ‘less’ impact on behavioral perfor-

mance, how can we explain the data of Kolb et al. [113]? These authors report that rats with cortical lesions on PND10 show increased compensatory cortical dendritic branching in response to the lesion as compared to rats with lesions on PND1. In other words, these authors report that later lesions are better (result in more plasticity and recovery) in this lesion model. We believe that there is a major difference between the findings of Kolb et al. and what we are proposing. Kolb et al. are comparing two types of injury which affect cortical differentiation, in other words a cortical lesion on PND1 is compared with a cortical lesion on PND10. On the other hand, in this review, we are making a comparison among injuries to neurogenesis, migration, and differentiation, in other words across a much larger spectrum of time. We contend that the earlier lesions to neurogenesis and migration result in more behavioral recovery (and plasticity) than later insults to the differentiation stage. The lesions that Kolb et al. perform in the PND10 rats, may be more akin to an adult lesion when behavioral patterns and functional circuits are more fixed and may be more immune to perturbation. By PND10, the noradrenergic projection to cortex has achieved its adult-like pattern [226], hence the effects seen at this stage in development are fundamentally different from those highlighted throughout the present article, injuries that occur right around the time of birth.

6.2. Do the different cortical afferents affect cortical development in a similar fashion?

We believe that the answer to this question is a qualified no. Strong evidence suggests that each of the cortical afferent system (norepinephrine, serotonin, dopamine and acetylcholine) provides critical morphogenic signals to the developing cortex. Each of these afferent systems arrives at the developing cortex on different days (Fig. 5) and reaches its adult-like distributions at slightly different stages in cortical development. This difference in timing, in and of itself, would argue that the effects of the modulators are likely sequential and not uniform. Generally, norepinephrine and serotonin afferents arrive to cortex early (approximately E17); both reach their adult-like distributions by 3 weeks postnatal. This relatively early arrival in cortex suggest that these two efferent modulators could be directing 'early' cortical morphogenesis. The early arrival of these afferents in the somatosensory cortex is coincident with the emergence of thalamocortical sensory fibers to the cortex which leave the thalamus on E16 and form an adult pattern in cortical layer IV around PND7 [110]. It seems likely that NE and 5HT could provide critical growth permissive signals and stop signals for these sensory inputs to the cortex. It also follows that depleting these two afferents right

around the time of birth would interrupt the normal pattern of sensory input to the cortex. These ideas are supported by the fact that alterations in dendritic morphology in cortical layer IV results from early NE depletion [130,233] and that thalamocortical ingrowth to the cortex is delayed following early 5HT depletions [19]. These ideas are also supported by the fact that early treatments that affect NE and 5HT result in attentional deficits [31,188], but unimpaired performance on cognitive tasks related to spatial learning [112,188].

By contrast, dopamine and cholinergic fibers arrive 1 day earlier and 2 days later, respectively, than norepinephrine and serotonin, and reach their adult-like distributions at about 2 months postnatal, hence considerably later than NE and 5HT. The later development of DA and ACh cortical afferents suggest they probably have less of a direct effect on the ingrowth of thalamocortical sensory afferents to the cortex, but perhaps more of an effect on cortical plasticity as it relates to the development of cognitive functions. DA and ACh are likely having their most significant influence on cortical development later than NE and 5HT, in other words, during the activity-dependent formation of the cortical-cortical networks which support cognitive behaviors. It has been shown that DA and ACh can interact with NMDA receptors during critical periods of cortical plasticity [64,79,160]. NMDA receptors have been extensively related to cortical plasticity both in the developing and adult brain, in particular as it relates to cognitive functions such as learning and memory [11,71,97,157]. An intricate interplay of interactions can be envisioned in which the directed growth and retraction of specific cortical-cortical connections occurs under the orchestration of glutamate receptors [219] in coordination with DA (in the prefrontal cortex) and ACh (throughout the somatosensory cortex). In support of this idea, neonatal DA and ACh depletions are more likely to result in severe impairment of cognitive tasks related to spatial learning, retention and operant behaviors [7,80,203] as compared to NA and 5HT depletions. In total, the evidence strongly suggests that these afferents all work in concert to orchestrate cortical development. The early afferents may serve as the background page upon which thalamocortical afferents make connections with the sensory system while the latter afferents influence the cortico-cortico circuitry that develops the outputs for sophisticated behaviors.

6.3. Does cortical structure relate to behavioral function?

We believe that the answer to this question is both yes and no depending on the aspect of cortical structure one assesses. The studies reviewed here generally sup-

port the idea that abnormalities in neuronal maturity and dendritic structure lead to abnormalities in behavior. The extent of cortical abnormalities following neonatal disruption of cholinergic inputs to the cortex, correlate with spatial navigation and passive avoidance performance, but not motor behaviors [7]. In other words, cortical morphology in this study is correlated specifically with cognitively based behaviors. In another study, Kalsbeek et al. [106] showed that decreased dopamine content (which was associated with altered dendritic morphology in pyramidal layer V neurons) in the prefrontal cortex is correlated with altered food hoarding behavior. Further support for this hypothesis is added by numerous studies in which no direct structure/function correlations were attempted, but a general trend can be noted. For example, the extent of cortical dendritic abnormalities that result from noradrenergic depletion at birth are more pronounced than those noted after neonatal serotonergic depletion; concomitantly, the behavioral deficits that result from neonatal noradrenergic depletion are, in general, more striking than those that result from serotonergic depletion. Cortical structure/cognitive function relationships are also supported by early data related to human developmental disorders. Takashima et al. [222] reported alterations in dendritic length and numbers of spines in cortical cells in newborns and infants with Down's syndrome, a developmental disability almost invariably associated with cognitive deficits. This study by Takashima et al. [222] confirmed initial findings of peculiar dendritic morphology in Down's syndrome individuals reported by Marin-Padilla [139] and Purpura [181] in smaller samples. While these types of correlative studies can never prove that the altered structure caused the disturbed function, they consistently and strongly support the hypothesis that abnormal cortical morphology is the substrate of some of the abnormal cognitive behaviors seen in developmental disabilities. The current prevailing hypothesis is that learning and memory (information storage) is a synaptic phenomenon, in other words, activity-dependent changes occur at the synaptic junctures between neurons [242]. Several lines of evidence point quite directly towards the relationship between dendritic changes and experience, in general, and learning, more specifically [47,51,69,74,140,159,232,242]. For example, dendritic changes have been noted following visual learning and also appear to occur in response to long-term potentiation, LTP, a proposed underlying mechanism in learning and memory [9,191]. It would, therefore, seem to follow that the injuries that profoundly affect dendritic organization will be associated with noticeable changes in memory storage capacity, and by extrapolation to other cognitive deficits.

As it is clear that cortical dendritic structure is correlated with cognitive functions, it is just as clear that

cortical neuronal number is not correlated with behavioral functions. In fact, Stephen Jay Gould [73] went to great lengths to demonstrate that there is little evidence to support Paul Broca's claim that women are less intelligent than men because women's brains are smaller. Gould points out that few correlations exist between cortical number and intelligence or cognitive skills. This apparent lack of a correlation between brain size and intelligence is also noted by Lewin [126] and prompts him to ask 'is your brain really necessary?' because of the number of patients who function normally (both cognitive and social functions) with severe reductions to the cerebral mantle. In other words, neither the human literature nor the animal literature reviewed here indicate that fewer cortical neurons invariably leads to reduced cognitive functions. We have not found any strong correlations between cortical neuronal number and cognitive functions. These studies, therefore, suggest considerable redundancy in cortical circuitry.

6.4. *Where do we go from here?*

It seems clear to us that more studies examining the anatomical, neurochemical and behavioral responses to neonatal brain injury are warranted. Furthermore, the studies that examine anatomical and behavioral measures within a group of animals provide the strongest support for structure/function relationships. Additionally, it is imperative that both sexes be examined. Data are increasing that show that cortical maturation occurs at different rates between the sexes [50,77,149,161,240]. This is not surprising considering that estrogen receptors, which are differentially expressed by the sexes during development [198], are present on cortical neurons [136,137,206,224] and that some of the growth-associated proteins, for example GAP-43, are under estrogen receptor regulation [134]. Yet our understanding of these potential sex differences is shamefully meager and surprisingly few models that we have reviewed here have examined both sexes. Understanding these sex differences will surely shed light on those developmental disabilities that follow different time courses and have different incidences in the two sexes, for example Rett syndrome which appears to selectively affect females, dyslexia which primarily affects males [66], and Down's syndrome in which senile plaques are noted earlier in females than males [183]. Understanding sexual dimorphism of cortical development and how cortical morphogenesis can be disrupted in a sex specific manner will likely shed light on the reason why many forms of mental retardation are more prevalent in males [144].

Finally, the effects of enrichment of the home cage environment following perinatal insult should be examined in more of the developmental models reviewed

here. Numerous studies show that environmental enrichment can compensate for and possibly even reverse some of the adverse effects of developmental insults. For example, environmental enrichment can facilitate cortical dendritic branching [49,51,104] and attenuate behavioral deficits following early direct cortical injury [114] and 6-OHDA lesions [171]. Even more surprisingly, enriched environments for juveniles can attenuate deficits in mice with early cortical migrational deficits [201] and enhance cortical growth in rats after neonatal 6-OHDA depletion [28]. These results taken together suggest a tremendous potential for structural and functional recovery following perinatal cortical injury stimulated by physically-enriched environments; this potential for recovery persists throughout the cortical maturation period. It is encouraging to think that this could also be true in humans. Because it is clear that behavioral circuits are not hardwired, full attention must be given to the environmental factors that can assist in undoing some of the abnormal consequences of neonatal cortical injury.

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