Cognitive disorders affecting infants and children have been classified according to different criteria, most commonly based on the type and severity of deficient skills (Kinsbourne, 1980). Two large groups of deficits can be recognized: those affecting global cognitive development (e.g., mental retardation) and specific disorders, usually less severe, that involve predominantly only one sphere of cognition (e.g., dyslexia), known as learning disabilities.

A second dimension of analysis of developmental cognitive disorders is the temporal one. There are conditions associated with a progressive loss of cognitive skills, which display a wide range of cognitive function, including levels comparable to mental retardation, and are categorized as dementias (Kaufmann, 1992; Rapin, 1989). Typical examples of this group are metabolic disorders affecting either gray or white matter, such as neuronal ceroid lipofuscinosis and leukodystrophies (Dyken & Krawlecki, 1983; Naidu & Moser, 1990; Rapin, 1989).

By contrast, most of the developmental cognitive disorders are more or less stable. This category includes both classic mental retardation and learning disabilities. Moreover, several developmental conditions, such as neurofibromatosis type 1 (NF 1) and tuberous sclerosis, can present the whole spectrum of cognitive impairment from learning disability to severe mental retardation (Berg, 1991; B.H. Cohen, 1991). Finally, underachievement of intellectual functions usually is accompanied by deviant behavior that could be either a constant and primary feature, as in autism, or a secondary adaptive phenomenon (Kinsbourne, 1980). This extremely simplified overview underscores the complexity and importance of understanding the neurobiologic bases of developmental cognitive disorders as a necessary step to improve their diagnosis and treatment. This chapter attempts to characterize and differentiate developmental cognitive disorders from an anatomic perspective, with special emphasis on the neuropathology of mental retardation and learning disabilities.

NEUROANATOMY OF DEVELOPMENTAL COGNITIVE DISORDERS

Neuropathology traditionally has provided key information for a clearer neurobiologic understanding of many neurologic diseases (Hornykiewicz, 1963). However, by reviewing the available neuropathologic literature, it becomes evident that there is no systematic approach to the neuroanatomic bases of disorders affecting the development of intellectual function. Textbooks on neuropathology usually classify brain disorders according to categories that combine etiology, pathogenesis, and morphology (Adams & Duchen, 1992). For example, perinatal brain damage that leads to cognitive impairment usually is classified under perinatal or hypoxic–ischemic categories. This etiologic/pathogenic/morphologic classification

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of mental impairment has some use in clinical management of mental retardation (Jones, 1988; Smith & Simons, 1975); however, there is poor correlation between a particular etiology and its neurobehavioral outcome (Kinsbourne, 1980). Consequently, a mechanistic or pathogenic approach makes it extremely difficult to characterize the neurobiologic or common morphologic features subjacent to developmental cognitive impairment. In spite of this, neuropathologic studies on mental retardation (Huttenlocher, 1991) and dyslexia (Galaburda, Sherman, Rosen, & Kaufmann, 1987) have emphasized the consistent involvement of the cerebral cortex in these disorders. Furthermore, the introduction of advanced neuroimaging, more specifically magnetic resonance imaging (MRI) morphometry, has expanded our neuroanatomic knowledge of mental retardation (Gabrielli et al., 1990; Reiss et al., 1993); dyslexia (Rumsey et al., 1986); and other related cognitive disorders such as developmental dysphasias (Jernigan, Hesselink, Sowell, & Tallal, 1991), attention-deficit/hyperactivity disorder (ADHD) (Hynd, Semrud-Clikeman, Lorys, Novey, & Eliopoulos, 1990), and Tourette syndrome (Singer et al., 1993). These radiologic investigations again have confirmed the critical role of developmental cortical anomalies in developmental cognitive disorders.

NEUROPATHOLOGY OF MENTAL RETARDATION

Of all the developmental cognitive syndromes affecting the pediatric age group, mental retardation is unquestionably the most comprehensively studied, although still not fully understood. Currently, few unifying hypotheses that can explain the mental and behavioral abnormalities in the majority of cases of mental retardation are available. I begin my exposition by presenting data pertinent to mental retardation, emphasizing the general principles that also can be applied to other developmental cognitive disabilities.

From both clinical and anatomic viewpoints, mental retardation is a heterogeneous condition (Smith & Simons, 1975). There are individuals with mild cognitive impairment who show a sustained developmental profile slightly below standards. These cases mainly relate to socioenvironmental factors (Drillien, 1968; Drillien, Jameson, & Wilkinson, 1966; Dobbing & Smart, 1974; Riessman, 1962), and milder forms of chromosomopathies and metabolic disorders (Jones, 1988), and sometimes are associated with minor brain malformations (Blomquist, Gustavson, & Holmgren, 1981). On the other end of the spectrum, one finds individuals with minimal intellectual capabilities who exhibit a developmental delay compatible with psychomotor “stagnation” rather than retardation. In this group, a higher frequency of genetic disorders (mainly chromosomopathies) and major brain malformations is found (Gustavson, Hagberg, Hagberg, & Sars, 1977a, 1977b). The etiologic differentiation between mild and severe mental retardation can be exemplified by the distinct proportion of prenatal (23% and 55%, respectively) and perinatal (18% and 15%–20%, respectively) etiologies (Hagberg & Kyllerman, 1983).

Anatomically, both ends of the spectrum, which can be seen in entities such as Down syndrome, could be characterized by unremarkable and grossly abnormal brains, respectively. Major brain malformations (e.g., agyria/lissencephaly spectrum, pachygyria) (Acardi, 1991; Goertchen, 1975) almost invariably are associated with severe mental disabilities and frequently are accompanied by anomalies in other organs (Jones, 1988). These conditions show greatly deviated macroscopic parameters of the central nervous system (CNS)—for example, brain weight, brain shape, and gray/white matter ratio. Nevertheless, the most severely abnormal structures are the cerebral cortex and subjacent white matter (Barth, 1987; Sarnat, 1987). By contrast, no clearly abnormal brain morphology and a high frequency of cases (40%–50%) without an identified cause are characteristic of mild mental retardation (Blomquist et al., 1981). Yet, the pathologic observations in severe forms of mental retardation have clinical implications if one considers that microcephaly constitutes one of the best predictors of mental retardation (Dolk, 1991). However, the lack of direct evidence of brain pathology, by standard clinical and imaging techniques
(Jones, 1988), has been an obstacle to explaining the significant proportion of severe mental retardation (15%–20%) (Benassi et al., 1990; Gustavson et al., 1977b) without an etiology, to adopting prophylactic measures in many instances, and to determining a prognosis as well.

Standard neuropathology, including microscopic evaluations, was considered an alternative approach to clarify these issues. Nevertheless, pathologic studies are scarce and not particularly informative in terms of disclosing an etiology or pattern of abnormalities in a large proportion of mental retardation cases (Crome & Stern, 1972; Freytag & Lindenberg, 1967). This is especially true of mental retardation that is not associated with particular syndromes, usually termed unclassified (Jellinger, 1972). Negative pathologic findings in mental retardation raise two related questions: What is the cause of most of the mild to moderate cases, and what is the common substrate of the wide spectrum known as mental deficiency? Fortunately, a combination of more sophisticated morphologic techniques, along with quantitative imaging studies, is beginning to answer these clinical dilemmas.

SYNAPTIC CIRCUITRY AND MENTAL RETARDATION

Cytoarchitectonic techniques have helped to delineate better the large group of brain malformations commonly labeled neuronal migration disorders (NMDs), which are associated with mental retardation (Barth, 1987). These abnormalities are diffuse and more severely involve the neocortex, and are characterized by a combination of anomalous neuronal density, laminar organization, heterotopic tissue, and aberrant cytodifferentiation (Friede, 1989; Warkany, Lemire, & Cohen, 1981). Milder forms of NMDs (microdysgeneses) that are not detected grossly, and that include heterotopias and cortical dysplasias, are seen at a higher frequency in persons with mental retardation when compared to other neurologic disorders (Rorke, 1994). By contrast, in individuals without macro- or microscopic malformations, such as most of those with an unclassified etiology, only morphometric techniques have showed cytoarchitectonic anomalies as aberrant distribution and orientation of small pyramidal neurons that are involved in local circuitry (Logdborg & Brun, 1993). Cytoarchitectonic findings such as microdysgeneses frequently are characterized poorly and are reported as minor anomalies in routine diagnoses. To understand the significance of these cytoarchitectonic abnormalities, it is important to consider that discrete areas of NMD also are seen in small numbers in neurologically normal subjects (Kaufmann & Galaburda, 1989). Therefore, microdysgeneses would be functionally significant only when they cover large or critical areas, or both, of the cortex and hippocampus. Cytoarchitectonic abnormalities imply disarrangements of brain circuitry in terms of spatial relationships between neurons; for instance, they can reflect aberrant numbers of a particular cell population or anomalous laminar and columnar orientation of a neuronal type. In addition, they indirectly show abnormal neuronal processes, particularly those arising from the neuronal soma (dendrites). All these parameters have pathophysiologic implications to the extent that they evidence aberrant morphology of the basic neural unit: the synapse. In this regard, the introduction of more sophisticated histologic techniques, principally Golgi impregnations that reveal, in detail, neuronal processes and therefore the synaptic surface, has been the single most important advance in approaching the neurobiology and neuropathology of mental retardation.

The staining by Golgi methods of autopsy and biopsy samples from individuals with mental retardation is the consequence of the re-introduction, in the 1970s, of these techniques in experimental neuroanatomy. Studies of normal cortical structure and development (Greengrough, 1984; Petit, LeBoutillier, Gregorio, & Libstug, 1988) and animal models relevant to mental retardation (Hohmann, Kwiterovich, Oster-Granite, & Coyle, 1991; Nigam & Labar, 1979) and learning disabilities (Adaro, Fernández, & Kaufmann, 1986) have provided an important base and stimulus for extension of these methods to human developmental disorders. Although many technical issues, such as fixation, postmortem interval, and selection of appropri-
ate controls (Buell, 1982; Huttenlocher, 1991; Williams, Ferrante, & Caviness, 1978), have brought into question the results of many investigations, there are general conclusions to be made.

There are dendritic anomalies in a wide variety of mental retardation-related conditions (Jagadha & Becker, 1989) (Table 1). Four groups of brains from individuals with mental retardation have been studied in a more systematic way: those with unclassified mental retardation, chromosopathies, malformations (NMDs), and metabolic disorders. The findings in unclassified mental retardation are prototypic in the neocortex and hippocampus: decreased dendritic arborizations (apical and basilar branches) and sparse dendritic spines (Huttenlocher, 1970, 1974; Purpura, 1974, 1975). Moreover, qualitative changes of dendritic spines, characterized by long and thin processes, suggest a developmental arrest at early stages of dendritic spine formation (Purpura, 1974). These dendritic spine anomalies, termed dysgenesis, have been studied extensively in chromosomal disorders by Marin-Padilla (1972, 1974, 1976), and, although not specific to these forms of mental retardation, they seem to be characteristic of each chromosomal syndrome. These investigations have included Down syndrome (Fábregues & Ferrer, 1983; Marin-Padilla, 1976; Suetsugu & Mehraein, 1980; Takashima, Becker, Armstrong, & Chan, 1981), perhaps the most extensively studied form of mental retardation (Barth, 1987). In this syndrome, quantitation of dendritic branches has suggested that anomalies are present in an age-dependent pattern, with infants and older individuals showing definitive abnormalities while fetuses and neonates show

<table>
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<tr>
<th>Disease/condition</th>
<th>Abnormality</th>
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<td>Diffuse NMDs (lissencephaly, pachygyria)</td>
<td>Abnormal neuronal density</td>
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<td>Anomalous lamination</td>
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<td>Distorted neuronal orientation</td>
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<td>Major dendritic aberration</td>
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<td>Reduced dendritic spines</td>
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<td>Focal NMDs (polymicrogyria, heterotopias)</td>
<td>Abnormal neuronal location</td>
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<td>Anomalous lamination</td>
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<td>Down syndrome</td>
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<td>Reduced dendritic tree</td>
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<td>Aberrant dendritic spines</td>
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<td>Aberrant perisomatic processes</td>
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<td>Immature synapses</td>
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<td>Rett syndrome</td>
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<td>Decreased dendritic tree</td>
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<td>Unclassified mental retardation</td>
<td>Reduced dendritic tree</td>
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<td>Aberrant dendrites and spines</td>
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<td>Decreased spine density</td>
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Note: NMD, neuronal migration disorder.

Dendritic shaft and spine abnormalities are important in understanding mental retardation for several reasons. First, they also are seen in disorders affecting cerebrocortical lamination focally (e.g., polymicrogyria) (Richman, Stewart, & Caviness, 1974; Williams, Ferrante, & Caviness, 1976) or diffusely (e.g., lissencephaly or agyria/pachygyria) (Ferrer, 1984; Ferrer & Fernández-Alvarez, 1977; Jagadha & Becker, 1989; Robain & Deonna, 1983; Stewart, Richman, & Caviness, 1975; Williams, Ferrante, & Caviness, 1975). These malformations correspond to the category of NMDs even though four-layered polymicrogyria would most likely be the result of postmigrational necrosis (Barth, 1987; Humphreys, Rosen, Press, Sherman, & Galaburda, 1991). Based on correlations of cytarchitectonics with dendritic patterns by Golgi impregnations in NMDs, we can draw several conclusions. First, dendritic anomalies are more subtle signs of neuronal pathology, often overlooked in regions with minor laminar disturbances, such as those adjacent to conspicuous lesions. In fact, Golgi studies of cortical tubers in tuberous sclerosis have underscored the anomalous architecture of the cortex in this syndrome (Ferrer, Fabregues, Coll, Ribalta, & Rives, 1984). Consequently, brains of individuals with mental retardation that show only dendritic aberrations would represent the opposite end to gross malformations in the spectrum of cerebrocortical anomalies associated with these disorders. Second, most of these studies point to a decrease in dendritic length, which represents a decrease in overall postsynaptic surface. It is intuitive to associate this feature with hypofunction of the cerebral cortex, a presumed cause of cognitive impairment. Third, there are qualitative and quantitative changes involving dendritic spines in typical cases of mental retardation. This is the more generalized and direct evidence of synapse pathology in mental retardation, considering that dendritic spines are excrescences that represent postsynaptic sites for axodendritic synapses. Hence, not only decreased available synaptic sites but also aberrant ones would underlie cortical dysfunction in mental retardation. Fourth, the introduction of immunocytochemical techniques to the study of developmental disorders has confirmed the value of Golgi data in assessing neuronal differentiation and synaptic components (Takashima, Chan, Becker, & Kuruta, 1991) and promises to expand the spectrum of tools to assess neuropathologic changes in mental retardation. Finally, data from well-characterized models of mental retardation and learning disabilities (Adaro et al., 1986; Hohmann et al., 1991; Nigam & Labar, 1979) have shown results similar to the pathology of mental retardation and proved the feasibility of these methods in evaluating dynamics of developmental processes and their functional implications.

Is the reduction and distortion in the cortical postsynaptic surface a hallmark of mental retardation? Despite the consistency of Golgi impregnation findings in mental retardation, several troublesome issues remain. Long postmortem interval and agonal changes (Buell, 1982; Williams et al., 1978), as well as confounding variables, mainly the presence of cardiac malformations in chromosomal syndromes (Huttenlocher, 1991), are factors that preclude considering dendritic changes as specifics of mental retardation. In this regard, discrepancies among investigations could be the consequence of technical variables or methodology of assessment (qualitative vs. quantitative) (Huttenlocher, 1974; Williams, Ferrante, & Caviness, 1979; Williams, Hauser, Purpura, DeLong, & Swisher, 1980). Furthermore, in several metabolic disorders affecting primarily the cerebral cortex, there are dendritic abnormalities similar to those seen in typical mental retardation (Bau-
man & Kemper, 1982; Della Giustina, Goffinet, & Landrieu, 1981; Takashima, Chan, Becker, Houdi, & Suzuki, 1991). Nevertheless, the fundamental defect in these disorders—that is, the accumulation of storage material in neuronal somata and proximal dendrites and axons (Friede, 1989)—leads to a somewhat different Golgi pattern. The anomalies are more pronounced in axons, especially in the proximal segments, which are markedly distended (Braak, Braak, & Goebel, 1983; Goldman, Katz, & Rapin, 1981; Paula-Barbosa et al., 1981; Purpura, 1978; Purpura & Suzuki, 1976; Takashima, Becker, Chan, & Augustin, 1985;
Williams, Lott, & Ferrante, 1977). Therefore, dendritic aberrations in classic storage disorders such as gangliosidoses and neuronal ceroid lipofuscinoses affect predominantly axons (the presynaptic domain) and include anomalous spatial configurations of cortical neurons (Purpura & Suzuki, 1976).

Are these findings an indication that, in mental retardation there are also presynaptic disturbances? Not necessarily; although the cognitive profile of children with storage disorders may resemble that of classic mental retardation, these metabolic conditions are not stable but rather progressive (Dyken & Krawlecki, 1983). The clinical picture at a particular stage can be comparable with mild mental retardation and, at a later time point, with severe mental retardation. In fact, there are Golgi data showing progression of dendritic pathology in a case of gangliosidosis (Jagadha & Becker, 1989). It is possible to conclude that metabolic–degenerative disorders show qualitative and quantitative alterations of dendritic and axonal morphology that correlate with cognitive impairment as in mental retardation; however, these are dynamic changes and share with mental retardation their diffuse and severe magnitude. The pathogenesis of these abnormalities in metabolic disease is usually postnatal when the basic cytoarchitecture of the cortex is already established, and they can be considered as secondary processes. By contrast, in mental retardation, an earlier disturbance of cortogenesis is suspected, probably dating to the beginning of neuronal differentiation.

An extremely interesting situation is represented by autistic syndromes, a group of heterogeneous disorders that have been correlated with a variety of neuroanatomic anomalies (Lotspeich & Ciaranello, 1993; Williams et al., 1980). Mental retardation is a frequent manifestation in autistic individuals and, of particular interest, is the condition known as Rett syndrome. This entity affects almost exclusively girls, with a progressive course during early childhood that resembles a degenerative disorder. Nevertheless, by late childhood and adolescence, neurologic deficit, including cognitive dysfunction, stabilizes as in typical cases of mental retardation (Hagberg, 1989). Pathologically, cytoarchitectonic analyses demonstrate an increased cell packing density, particularly marked in the neocortex and hippocampus. These changes reflect a reduced dendritic tree, probably caused by developmental arrest, as has been corroborated by preliminary Golgi studies (Armstrong, 1992). These reports have shown no age dependency of these anomalies, as expected from clinical observations. Hence, reduced dendritic trees seem to be an indicator of cognitive impairment and not of evolution of developmental anomalies in this form of mental retardation. This is not surprising if one considers that a decrease in dendritic arboreizations also has been demonstrated in most neurodegenerative disorders associated with aging, such as Alzheimer’s disease (Catalá, Ferrer, Galofré, & Fábregues, 1988; Jagadha & Becker, 1989; Kaufmann, 1992). Therefore, it is necessary to analyze Golgi studies in mental retardation in the context of, and complementing, other sophisticated morphologic techniques in order to discern their specificity and pathophysiologic role.

It is still unknown whether dendritic tree reductions in most mental retardation–related conditions represent a true developmental arrest, as it has been demonstrated in Rett syndrome by morphometry showing decreased neuronal body surfaces (Armstrong, 1992). Therefore, more comprehensive qualitative and morphometric examinations, using Golgi and other techniques, that cover a wider spectrum of cases of mental retardation are essential. This approach has been successful in other conditions such as Huntington disease and human immunodeficiency virus encephalopathy, where it has resolved long-term dilemmas by disclosing a primary cortical involvement accompanied by peculiar plastic (compensatory) responses (Kaufmann, 1992; Sotrel, Williams, Kaufmann, & Myers, 1993). Likewise, more electron microscopic studies, which have been circumscribed almost exclusively to Down syndrome, directly examining synapses would help to clarify contradictory information. There are reports of both decreased (Wisniewski, Laure-Kamionowska, Connell, & Wisniewski, 1985) and increased (Cragg, 1975) synaptic density as well as of arrest in synaptic development (Petit,
LeBoutillier, Alfano, & Becker, 1984). Finally, neuropathologic studies in mental retardation present another difficulty in their interpretation. A few studies, which have compared individuals with mild to those with severe mental retardation, have found dendritic anomalies only in the most profoundly affected individuals (Huttenlocher, 1974; Williams et al., 1980). A bias toward severe forms of neurologic disease is not unusual because of the wider availability of specimens for neuropathology. Nevertheless, the experience in conditions such as dyslexia (Galaburda, Sherman, Rosen, Aboitiz, & Geschwind, 1985) has shown that at least some features found in severe cases (e.g., symmetry in the planum temporale) are also detected by MRI in vivo in more typical individuals (Hynd et al., 1990). Therefore, careful quantitation of Golgi staining combined with immunocytochemistry or other advanced methods most likely would be revealing even in milder cases of mental retardation.

CEREBROCORTICAL DEVELOPMENT AND MENTAL RETARDATION

As stated in the two previous sections, there are two relatively consistent types of anatomic abnormalities associated with mental retardation: malformations of the cerebral cortex and related structures and dendritic/synaptic anomalies in otherwise well-formed brains (Table 1). Although NMDs are seen almost invariably in severe mental retardation, dendritic pathology can be seen in milder forms. How can we explain this wide range of anomalies in severe mental retardation? A better understanding of the basic processes of cerebrocortical development and the techniques employed in their study can be helpful. The traditional view of CNS developmental abnormalities correlates phenotype with a fundamental developmental process. Thus, it is possible to categorize anomalies in a few groups: induction disorders (e.g., anencephaly); proliferation and migration anomalies, or NMDs (e.g., lissencephaly); and cytodifferentiation abnormalities (e.g., failure in myelination or dendritic growth) (Gabriel, 1974). Recently, it has become evident that this simple approach is accurate only in general terms. For instance, in most NMDs, including those relatively minor types, there is also a disorder of neuronal differentiation and programmed cell death (Rorke, 1994). The consequence of this multiple process anomaly is that the fine architecture of the cerebral cortex is distorted substantially not only by deficient synaptic structures but also by “extra” and aberrant neuronal circuitry. At this time, there is no technology available to distinguish, functionally, a neuron with normal morphology that is part of a minor aberrant circuit from one appropriately connected. Indeed, Golgi impregnations have revealed normal dendritic trees in neurons that clearly are situated abnormally (Williams et al., 1975). It is likely that normal dendritic staining in mild mental retardation (Huttenlocher, 1974) and other conditions (Williams et al., 1979, 1980) represents the limitations of Golgi methods in detecting aberrant synaptic relationships when dendritic patterns are otherwise normal.

Regressive events such as cell death and synapse elimination play a critical role in shaping normal brain wiring. Failure of neuronal death in the cerebral cortex could have significant cognitive and behavioral consequences, and it has been suggested in conditions such as schizophrenia (Akbarian et al., 1993); its role in mental retardation is unknown. Disturbances in synapse pruning might be present in mental retardation, as implied by growth-arrested dendritic spines in chromosomopathies and unclassified mental retardation (Marin-Padilla, 1972; Purpura, 1974). Consequently, a subtle but diffuse involvement of neuronal architecture and circuitry of the cerebral cortex eventually can lead to cognitive impairment similar to that produced by a major cortical malformation. The role of subcortical nuclei in mental retardation is still unknown. In severe NMDs, anomalies of the basal ganglia and thalamus are not unusual (Barth, 1987). Even in the absence of malformations, as in Rett and Down syndromes, macroscopic (Reiss et al., 1993) and histologic (Armstrong, 1992; Casanova, Walker, Whitehouse, & Price, 1985) anomalies in basal ganglia, substantia nigra, and basal forebrain strongly support the involvement of pathways from and to the cortex. Moreover, the clear association between perinatal pathology, which
usually involves subcortical nuclei and connections to the cortex (Friede, 1989), and mental retardation in a significant proportion of cases (Chaney, Givens, Watkins, & Eyman, 1986; Hagberg & Kyllerman, 1983) emphasizes a subcortical role in the pathogenesis of mental retardation. A schematic representation of the relationship between abnormal anatomic circuitry and mental retardation is provided in Figure 1.

**NEUROPATHOLOGY OF LEARNING DISABILITIES**

Our limited knowledge about neurobiologic bases of developmental cognitive disorders is even more evident in the field of learning disabilities. Neuropathologic studies have been infrequent because of the difficulty in identifying cases for postmortem examination and because surgical specimens have been available only oc-

![Figure 1.](image)

*Figure 1.* Disrupted cortical cytoarchitecture, and its dendritic correlates, in mental retardation and learning disabilities. A, Normal. All six neocortical layers are well defined, and pyramidal and nonpyramidal neurons display rich apical and basilar dendritic trees. B, Learning disability. Microdysgenetic cortex, as seen in dyslexia and NF 1. There are ectopic neurons in layer I and laminar disarrangement beneath this abnormality (cortical dysplasia). Dendritic anomalies are focal in nature. C, Mild mental retardation. Cortical laminar organization is relatively well preserved; however, moderate reduction in dendritic arborizations is widespread. D, Severe mental retardation. Typical cortical disorganization seen in generalized NMD. Neuronal density, typology, orientation, and differentiation are affected. There are major qualitative and quantitative changes in dendritic arborizations. Other cases of severe mental retardation, without malformations, show only dendritic anomalies. (ML, molecular layer, cortical surface; WM, white matter; NMD, neuronal migration disorder.)
casionally for more sophisticated methods such as Golgi impregnations and immunocytochemistry. Of all learning disorders, the best characterized is developmental dyslexia (Duanne, 1989). In this situation, neuropathology not only has provided specific information regarding affected areas of the brain, but also has allowed for the development of a research program on neurobiologic bases that extends from animal models to clinical evaluations (Galaburda, 1991). Neurofibromatosis type 1 and ADHD, without association to dyslexia, are two other learning disabilities to be considered in more detail in this analysis.

**Developmental Dyslexia**

Developmental dyslexia is associated with several consistent and characteristic anatomic anomalies. First, there is a deviation from the usual pattern of asymmetry of the planum temporale, which is larger on the left side (Galaburda, 1991, 1993; Galaburda et al., 1985, 1987). The planum temporale corresponds to a triangular region of associative neocortex located immediately behind the primary auditory cortex. Dyslexic individuals exhibit a symmetric planum, which seems more similar to the standard larger left side. Magnetic resonance imaging studies have confirmed plana symmetry (Rumsey et al., 1986); however, the direction of this deviation is still a controversial issue (Galaburda, 1993; Hynd et al., 1990). Radiologic studies have detected other anomalies in hemispheric symmetry involving the right frontal, insular, right parietal opercular, and right occipital cortices (Galaburda, 1993). These changes have not yet been demonstrated in pathologic specimens and require further confirmation. A second neuropathologic feature in dyslexic brains is the presence of multiple foci of microdysgenesis in the frontal and temporal lobes. These developmental anomalies are distributed mainly in the left perisylvian region (Galaburda et al., 1985, 1987), although multiple lesions are still found on the right and ventral aspects of the cortex (Humphreys, Kaufmann, & Galaburda, 1990).

The specificity of these two types of anatomic anomalies in dyslexia is underscored by MRI investigations in children with language and learning impairment, who were not selected on the basis of reading disability. These children also demonstrated deviation of normal asymmetry in the posterior perisylvian region (Jernigan et al., 1991). Also, MRI comparisons of individuals with dyslexia with normal and ADHD subjects corroborated the consistent association of dyslexia and planum temporale symmetry (Hynd et al., 1990). Furthermore, a preliminary neuropathologic investigation of a case of developmental dysphasia, a language disorder that usually precedes dyslexia, demonstrated microdysgenetic lesions, consistent in cortical dysplasia or laminar disorganization, in the medial (insular) left temporal cortex in association with symmetry of the planum temporale (M. Cohen, Campbell, & Yaghai, 1989). From these studies and others evaluating cortical function (Rumsey et al., 1992), we can conclude that anomalous development of the left perisylvian and posterior temporal cortex seems to be a consistent anatomic substrate for developmental language deficits, such as those seen in dysphasia and dyslexia. Figure 1 shows a representation of microdysgenetic cortex in learning disability and its dendritic correlates.

Nevertheless, the cerebral cortex is not the only brain structure involved in dyslexia. More subtle anomalies have been found in subcortical nuclei in dyslexic subjects. Cytoarchitectonic/morphometric analyses of both lateral and medial geniculate nuclei show a shift in neuronal size toward smaller cells (Galaburda & Livingstone, 1993; Galaburda, Menard, & Rosen, 1994). These two centers, which are the thalamic-specific nuclei for the visual and auditory pathways, respectively, are essential in the processing of these sensory modalities. Reduction in neuronal size is correlated with decreased speed of neural transmission; therefore, information carried by these affected thalamic nuclei would arrive with delay to the respective cortical regions. In the case of the visual pathway, it is the magnocellular division of the lateral geniculate that displays these anomalies. The magnocellular system, which is segregated from the parvocellular pathway from the retina to the visual cortex, is responsible for processing fast, low-contrast visual stimuli. As expected, children with dyslexia have difficulties in the per-
ception of these stimuli (Galaburda, 1993). Moreover, a study of visual evoked potentials confirmed that perception of magnocellular-mediated and not parvocellular-dependent stimuli (slow, color selective, contrast sensitive) is slowed in people with dyslexia (Livingstone, Rosen, Drislane, & Galaburda, 1991). Similarly, people with dyslexia show impairment in fast auditory processing that may correlate with less well-defined changes in the auditory thalamus (Galaburda, 1993; Galaburda et al., 1994). In summary, in dyslexia there are anatomic abnormalities that involve different levels of the central neural pathways of at least two critical sensory modalities: vision and audition. These features suggest that the substrate of this learning disability is a combination of inappropriate cortical input and altered cortical processing by defective cortical organization.

Are these findings in dyslexia a model of the neuroanatomic substrate for specific cognitive deficits/learning disabilities in general? Because of the limited information available on other developmental learning disabilities, we do not have a definitive answer to this question. However, there are some sparse experimental, radiologic, and pathologic data on other types of learning disability that tend to support, as in dyslexia, a corticosubcortical defect.

**Neurofibromatosis Type 1**

Neurofibromatosis type 1 (NF 1) is a genetic disorder that long has been associated with a variety of developmental cognitive disorders, including mental retardation and learning disabilities (Berg, 1991; Riccardi, 1981). Although most of the neuropathologic literature on NF 1 has focused on tumors, several studies have demonstrated the presence of multiple NMDs (pachygyria, polymicrogyria, cortical dysplasias, neuronal heterotopias in deep white matter, glial nodules) involving mainly the cerebral cortex (Lott & Richardson, 1981; Rosman & Pearce, 1968; Rubinstein, 1986). In one of the few comprehensive analyses on the subject to date, Rosman and Pearce (1968) showed a positive correlation between the extent of the cortical microdysgenesis and the cognitive impairment in terms of IQ. They found fewer lesions in intellectually normal subjects with NF 1, but more than in normal subjects without NF 1. Limited characterization of the subjects in neuropsychological terms, lack of precise topographic data, and application of only conventional pathologic methods impair generalization of these results. Furthermore, a large number of NF 1 cases do not exhibit the global and severe cognitive involvement reported in the mentioned study. In fact, learning disability in the form of visuospatial or visuomotor impairment, without significant language or reading difficulties (Elison, 1986) or left shift in the normal range of IQ (Eldridge et al., 1989), which occurs in 30%–45% of children with NF 1, seems to be the predominant type of cognitive disorder in NF 1 (Riccardi, 1981).

The recognition of this specific learning disability occurred at a moment when great interest and controversy were originated by descriptions of a high frequency of bright abnormal images on MRI present only in children with NF 1. These prolonged T2-weighted images are located subcortically mainly in the deep cerebral white matter, basal ganglia (globus pallidus), brain stem, and cerebellum (white matter) (Duffner, Cohen, Seidel, & Shucard, 1989; Dunn & Ross, 1989; Goldstein, Curless, Post, & Quencer, 1989; see also Chapter 22, Volume 1). Their incidence in the pediatric NF 1 population ranges from 43% to 79% (Aoki et al., 1989; Duffner et al., 1989; Dunn & Ross, 1989), similar to the proportion of children with NF 1 who are affected by mental retardation or learning disabilities. Several questions arose about these MRI abnormalities. First, what is their nature? It was speculated that they corresponded to hamartomas or microdysgeneses (Dunn & Ross, 1989). Only one preliminary study has correlated MRI with histology, and it showed that these abnormalities are areas of atypical glial infiltrate and perivascular gliosis with microcalcifications, dysmyelination, and spongy degeneration of the white matter in the pallidum and midbrain (Zimmerman et al., 1992). This study, on two pediatric NF 1 cases, must be expanded to cover a wider age spectrum.

A second issue related to these subcortical abnormalities deals with their temporal dimension: Are they a transient phenomenon because of their rare occurrence in patients older than 20
years (Aoki et al., 1989)? The limited prospective information indicates that these lesions tend to decrease over time, but they do not disappear by 16 years (Sevick et al., 1992). Based on the pathologic data, it is difficult to understand how glial changes of an astrocytic proliferation type can be reversible. It is more likely that anomalies in extracellular fluid composition and myelin biochemistry could generate aberrant MRI images that can return to normal after brain maturation is finished.

Finally, the third critical question regarding these MRI anomalies concerns their functional significance. Lack of correlation between MRI lesions and neurologic manifestations initially was reported (Duffner et al., 1989; Dunn & Ross, 1989). Nevertheless, a later larger scale study has shown a negative correlation between MRI abnormalities and several neuropsychological parameters, including IQ, language scores, and visuomotor integration and coordination (North et al., 1994). Indeed, according to the authors, MRI abnormalities divide pediatric NF 1 into two clearly distinct groups in terms of cognitive development.

In conclusion, a combination of cortical and subcortical, perhaps transient, abnormalities underlies mental retardation and learning disabilities as seen in NF 1. It is not clear whether specific pathways connecting the cortex with subcortical nuclei are critical in NF 1 learning disability, as in dyslexia, but this is a likely possibility. In this regard, the association of visuomotor impairment and MRI anomalies in the basal ganglia and related structures support a distinct corticosubcortical model. Contrasting the left cortex/thalamic pattern seen in dyslexia, NF 1 would show a right cortex/basal ganglia-deficient axis. At this point, only clinical data indicate right hemisphere pathology in NF 1 learning disability (B.H. Cohen, 1991), as well as the nature of subcortical lesions, which is an issue that deserves further neuropathologic study.

Attention-Deficit/Hyperactivity Disorder

Attention-deficit/hyperactivity disorder is one of the most prevalent forms of learning disability. Unfortunately, there are no direct neuropathologic data on this disorder because of the difficulties in premortem characterization of this condition. Nevertheless, analyses of both subjects with selective developmental language impairment and dyslexics with ADHD are informative regarding the likely neurobiologic bases of ADHD. (For more comprehensive reviews on the subject, see Kaufmann [1993] and Zametkin & Rapoport [1987].) Comparative analyses of brain symmetry, using MRI scans, in subjects with dyslexia and subjects with ADHD have demonstrated that, whereas symmetry of the planum temporale is a feature associated with dyslexia, a rather symmetric prefrontal region is common to both dyslexia and ADHD. Specifically, the two groups show smaller right anterior width measurements in comparison with controls, who show an asymmetry in favor of the right side (Hynd et al., 1990). These results are intriguing if one considers that the brains of people with dyslexia exhibit multiple dysgenetic lesions in the dorsolateral and orbital frontal cortex, particularly on the right side (Humphreys et al., 1990). These abnormalities have not clearly implicated a cognitive substrate in dyslexia and might contribute to attentional deficits, at least in this population. As mentioned above, in general terms, a left temporal developmental anomaly would be a base for selective language disorders, and an aberrant formation of the right anterior frontal cortex would predispose for attentional disturbances. Frontal cortex dysfunction in ADHD is also supported by a variety of functional studies, including evaluations of blood flow (Lou, Henriksen, & Bruhn, 1984), glucose utilization (Zametkin et al., 1990), and cognition/behavior (Benson, 1991). These investigations not only have confirmed a frontal cortex abnormality, particularly on the right side, but also indicate an involvement of subcortical regions such as the striatum (more on the right) and the midbrain (Lou et al., 1989; Lou, Henriksen, Bruhn, Borner, & Nielsen, 1989).

A combined cortical/subcortical anomaly in ADHD has been suggested by numerous animal studies of normal and abnormal attention (Colby, 1991; Heilman, Voeller, & Nadeau, 1991). Although anatomic data on subcortical anomalies are not available in humans, experimental investigations have provided valuable information that must be evaluated in post-
mortem material. Several discrete subcortical regions, mainly components of dopaminergic pathways (e.g., ventral tegmental area) have been implicated in hyperactivity and deficient attention in adult animals (Kaufmann, 1993). Based on these results, and clinical studies demonstrating abnormal dopamine metabolism in ADHD (Shaywitz, Cohen, & Bowers, 1977), a murine neonatal model of decreased dopamine with hyperactivity was generated (Shaywitz, Yager, & Klopper, 1976). From these and other reports, it was established that disruptions of mesocortical dopaminergic systems play a critical role in the most salient manifestations of ADHD (Clark, Geffen, & Geffen, 1987; Miller, Heffner, Kotake, & Seiden, 1981). Future directions in the neuropathology of ADHD require the evaluation of these brain regions and other monoaminergic systems, as pointed out by clinical observations (Zametkin & Rapoport, 1987). Striatal lesions also are correlated to hyperactivity, as well as to some of the cognitive manifestations (e.g., motor impersistence) of ADHD (Kaufmann, 1993). Moreover, studies on neurobiology of normal attentional processes have emphasized their distributed nature, involving not only multiple cortical regions (Mesulam, 1981) but also nuclei in the brain stem, diencephalon, and basal ganglia (Colby, 1991). Finally, experimental data on primates emphasize the role of frontal cortex dysfunction in virtually all the signs associated with ADHD (Kaufmann, 1993).

**Tourette Syndrome and Tuberous Sclerosis**

There are two other learning disability syndromes that are not so well characterized as dyslexia or NF 1, but can provide an insight to the neurobiology of learning disabilities in general. Tourette syndrome is a movement disorder condition characterized by motor and vocal tics. Although intelligence is normal, there is an increased incidence of ADHD and learning difficulties (B.H. Cohen, 1991). Neuropsychological data indicate that Tourette syndrome learning disability is similar to NF 1 learning disability in its visuomotor/visuospatial impairment profile (Matthews, 1988). Interestingly, it long has been recognized that there is an increase in dopamine activity in Tourette syndrome, considering that drugs that reduce dopamine production or block its receptors alleviate symptomatology (B.H. Cohen, 1991). Recently, the nature of the biochemical defect has been pinpointed to a deficiency in dopamine reuptake in the striatum (Singer, Hahn, & Moran, 1991). This involvement of the basal ganglia is not surprising, given the fact that the most prominent symptom in Tourette syndrome is a movement disorder. Moreover, MRI volumetric analyses have shown a deviation from the normal pattern of asymmetry of the putamen, normally left sided, with increased incidence of right-sided asymmetry. Tourette syndrome cases with ADHD typically had this putaminal right-sided asymmetry, and also a significant reduction in left globus pallidus volume when compared with Tourette syndrome cases without ADHD and controls (Singer et al., 1993). Cortical pathology has not been described in Tourette syndrome; however, it cannot be excluded until comprehensive studies are performed. These findings in Tourette syndrome emphasize the association of developmental anomalies of the basal ganglia with learning disabilities, particularly of the nonverbal type.

Tuberous sclerosis is a neurocutaneous syndrome also associated with mental retardation and learning disabilities in a high proportion (Berg, 1991). Tubers, the characteristic lesions in this syndrome, usually are located in the cortex, but they can be found in the basal ganglia, where they are smaller. They are more or less circumscribed lesions characterized by large and bizarre cells with glial and neuronal features. Similar abnormal cells are seen in the two other typical subventricular or subependymal lesions, subventricular nodules and giant cell tumors. Golgi impregnations have clarified that, at least on morphologic grounds, the tubers are composed of astrocytes and small neurons. These neurons are primitive in appearance, stellate or pyramidal, with short dendrites and a few aberrant spines and an anomalous dendritic orientation that forms neuronoglial contacts (Ferrer et al., 1984; Machado-Salas, 1984). Cytotarchitectonic evaluations demonstrate a lack of laminar organization in the region of the tubers (Ferrer et al., 1984), and Golgi preparations reveal reduced dendritic trees in adjacent
and, to a lesser extent, in distant cortices (Huttenlocher & Heydemann, 1984). These findings stress the multifocal nature of the distortion of circuitry in the cerebral cortex with tuberous sclerosis. Although no correlations between magnitude of cortical involvement by tubers and cognitive profile have been made (Huttenlocher, 1991), difficulties in detection of small tubers, particularly beneath the cortex, may prevent this assessment. It is likely that large numbers of lesions underlie mental retardation and a few cortical and subcortical tubers are present in patients with learning disabilities and cognitively typical patients.

Summary
In learning disability syndromes, there is variable neuroanatomic involvement of the cerebral cortex and subcortical nuclei. A pattern of left hemisphere–thalamus anomaly emerges in verbal learning disabilities, such as dyslexia. In contrast, nonverbal learning disabilities, such as NF 1 and Tourette syndrome, seem to have right cortical–basal ganglia disturbances. Frontal cortex–striatum–midbrain axis anomalies would predispose to attentional and motor inhibition deficits. In this regard, the direct role of the basal ganglia in cognitive processes should not be underestimated (Alexander, DeLong, & Strick, 1986). With respect to the pathogenesis of learning disability abnormalities, it is clear that they represent disorders of brain formation: NMD in dyslexia, NF 1, and Tourette syndrome and cytodifferentiation in tuberous sclerosis. ADHD-related pathology is still unclear in origin. Animal studies have pointed to genetic factors in NMDs associated with learning disabilities (Galaburda, 1991); however, perinatal damage—including prematurity, which involves the subcortical white matter (Gordon, 1991; Towbin, 1971), cortex, hippocampus, basal ganglia, and brain stem (Fuller, Guthrie, & Alvord, 1983)—has been associated consistently with learning disabilities. New etiologies of learning disability are emerging: prenatal exposure to drugs of abuse, such as cocaine, is one of them. Learning disabilities in the form of ADHD have been reported preliminarily in these children (Dow-Edwards, 1991; Volpe, 1992). Only one neuropathologic study, in infants, is available. Kaufmann and Cuello (1991) found increased neuronal density in subcortical white matter and retarded neuronal cytodifferentiation in the neocortex. Mild cytoarchitectonic disarrangements that resemble these human abnormalities also have been described in a rodent model of prenatal exposure to cocaine (Gressens, Kosofsky, & Evrard, 1992). More clinical and pathologic data are necessary to clarify whether or not prenatal drug exposure also is associated with corticosubcortical anomalies.

GENES, ENVIRONMENT, AND DEVELOPMENTAL COGNITIVE DISORDERS
In order to develop solid programs in prevention and treatment of mental retardation and learning disabilities, it is important to recognize factors involved in the predisposition to and genesis of developmental anomalies underlying these disorders. Traditional views of developmental conditions differentiate two distinct categories: genetic and environmental variables. In the first group, major alterations in quantity (e.g., Down syndrome) or quality (e.g., phenylketonuria) of genetic material would lead to an aberrant structural phenotype associated with mental retardation, learning disabilities, or both. The second category corresponds to factors whose presence or deficiency disturbs an otherwise normal genetic program (e.g., connatal infection, perinatal hypoxic–ischemic damage, postnatal malnutrition) (Dobbing & Smart, 1974; Jones, 1988; Kinsbourne, 1980). This simple categorization, although valid in very general terms, overlooks the complex interaction of gene expression and the environment occurring during brain development, as disclosed by advances in developmental neuroscience.

Brain development is characterized by an organized and stereotypic sequence of events—neural induction, proliferation, migration, and cytodifferentiation—that occur in a precise temporospatial sequence (Gabriel, 1974; McConnell, 1988). It has been postulated that these processes reflect also precise sequences of gene activation (Rorke, 1994). Some of the critical
regulatory genes (e.g., homeo genes) have been identified in early stages of embryonic formation, such as during hindbrain segmentation (Keynes & Lumsden, 1990). Since the late 1980s and early 1990s, gene expression in cognitively relevant areas during histogenesis has been reported. Multiple regulatory genes, including transcription factors (TFs), are expressed in the prenatal cortex, hippocampus, and basal ganglia in extremely complex patterns (Bulfone et al., 1993; He et al., 1989). Nevertheless, the precise role of these master genes in mammalian development is unknown and has been inferred from studies in invertebrates and in simpler systems, such as neural cells in culture. These investigations have demonstrated that growth factors, membrane potential changes, and neurotransmitters activate distinct gene programs (Bartel, Sheng, Lau, & Greenberg, 1989; Greenberg, Ziff, & Greene, 1986). Transcription factors, proteins that induce the expression of specific or target genes, are the best understood of these molecules (Sheng & Greenberg, 1990). Members of the Fos and Jun TF families (Smythe, Curran, & Morgan, 1992) and zinc finger TFs (Kaufmann, Yamagata, Andreasson, & Worley, 1994; Worley et al., 1990; Yamagata, Kaufmann, et al., 1994) are expressed at relatively high levels during critical stages of cerebrocortical development. These regulatory genes are important for understanding normal and aberrant cortical formation for several reasons. First, these TFs clearly are involved in programs of cell growth and differentiation (Nathans et al., 1991). Second, they are involved in long-term, or "plastic," changes in neural structures (Kaufmann et al., 1994; Montarolo et al., 1986). These synaptically dependent long-term changes share many features with cytodifferentiation of neural structures occurring during cerebrocortical development (Worley et al., 1990). In addition, TFs are induced by physiologic neural stimuli (Hunt, Pini, & Evan, 1987; Sheng & Greenberg, 1990) and seem to participate in complex activity-dependent changes in adult cerebral cortex (Chaudhuri & Cynader, 1993; Yamagata, Kaufmann, et al., 1994).

Cellular interactions play a critical role in "decision making" during brain development (McConnell, 1988). In addition to the well-known radial glial-neuroblast interaction, which allows the migration of the future cortical neuron to the right place (Gabriel, 1974), intercellular communication of the synaptic type or mediated by neurotransmitters is present from early stages of cerebrocortical development. Neuroblasts are electrically coupled in the germinial matrix (Lo Turco & Kriegstein, 1991) (the ventricular proliferation zone), are regulated in their migration by neurotransmitter receptor activity (Komuro & Rakic, 1993), and express these receptors shortly after their arrival at the cortex in formation (Blanton & Kriegstein, 1992). Moreover, postnatal neural activity-dependent modulation of neuronal maturation has been demonstrated clearly in experimental animals (Greenough, 1984; Kaufmann et al., 1994; Kleinschmidt, Bear, & Singer, 1987; Worley et al., 1990). These cellular interactions, synaptic or not, would constitute the microenvironment that triggers the expression of regulatory or effector genes essential for that particular phase of neural development. In other words, despite the existence of a genetic blueprint, cortical development can be modulated at every critical step by local factors. Indeed, the precise patterns of connectivity of many regions, including the cortex, are determined by neural activity (Goodman & Shatz, 1993). Therefore, NMDs and dendritic anomalies, already mentioned in the neuropathology of mental retardation and learning disabilities, can be explained in terms of an aberrant, local signal-gene induction process (Kaufmann et al., 1994; Rorke, 1994). The best characterized of these intercellular factors is the activation of a particular type of glutamate receptor, the so-called N-methyl-D-aspartate (NMDA). This receptor is involved, for instance, in cerebellar cortex neuronal migration (Komuro & Rakic, 1993) and visual cortex organization (ocular dominance patterns) (Kleinschmidt et al., 1987). Changes in NMDA activity by pharmacologic agents modulate regulatory gene expression, particularly of TFs (Kaufmann et al., 1994; Worley et al., 1990).

The search for other neural activity-induced genes is very active (Nedivi, Hevroni, Naot, Israeli, & Citri, 1993) given their importance in brain physiology and development. Of partic-
ular interest are reports of activity-dependent genes expressed at very early stages of cortical development (e.g., neuronal migration), when TFs modulated by activity are virtually not expressed (Kaufmann et al., 1994; Yamagata, Kaufmann, et al., 1994). One of these novel regulatory genes, termed *rheb*, is also modulated by growth factors and NMDA-dependent activity. *rheb* encodes a Ras-related protein, and belongs, as does this oncogene, to the large category of G proteins. Intriguing is the fact that two conditions leading to mental retardation and learning disabilities, Miller-Dieker lissencephaly (Reiner et al., 1993) and NF 1 learning disability (Xu et al., 1990), are linked to G protein–like genes. Consequently, the neural manifestations of these two syndromes could be the result not only of general disturbances in development but also of specific alterations in brain formation.

Finally, the identification of nonregulatory-type activity–dependent genes (Qian, Gilbert, Colicos, Kandel, & Kuhl, 1993) has opened the possibility of a more direct influence of neural activity on brain physiology and development. *COX-2* is one of these genes, with high expression during the critical period of postnatal cortical development (Kaufmann et al., 1994; Yamagata, Andreasson, Kaufmann, Barnes, & Worley, 1993), similar to zinc finger TFs (Worley et al., 1990; Kaufmann et al., 1994; Yamagata, Kaufmann, et al., 1994). *COX-2* encodes the inducible form of cyclooxygenase, the enzyme that catalyzes the first step in prostaglandin synthesis. In the brain, prostaglandins are involved in modulation of synaptic activity and have direct actions in areas such as the hypothalamus. Their role in cortical function is unknown; however, *COX-2* is expressed predominantly in cognitive-related regions and is regulated by NMDA-dependent activity in developing and adult cortex (Yamagata et al., 1993). In conclusion, a better understanding of the specific role of genes expressed during cortical development, and their regulation by growth factors, neurotransmitters, and TFs, provides the opportunity for designing new strategies in prevention and amelioration of brain pathology associated with mental retardation and learning disabilities. Furthermore, the identification and characterization of these neural activity-dependent genes will help to develop improved histochemical markers for the study of these conditions.

CONCLUSIONS: COMPARATIVE NEUROPATHOLOGY OF MENTAL RETARDATION AND LEARNING DISABILITIES

It can be concluded that different, but not exclusive, neuroanatomic bases underlie mental retardation and learning disabilities. The latter show a consistent and characteristic combination of cortical and subcortical anomalies. In most learning disabilities, there is focal involvement of specific cortical regions (left perisylvian in dyslexia, prefrontal in ADHD, and perhaps right hemisphere in NF 1) while the rest of the cerebral cortex seems to be normal. These cortical areas, at least in dyslexia and ADHD, clearly are linked to the specific deficits of the particular learning disability. The left perisylvian cortex, which corresponds to the classic language areas of Broca and Wernicke, displays dysgenetic lesions and contributes to an anomalous planum temporale in dyslexia (Galaburda, 1993). Similarly, in ADHD, the prefrontal cortex, which has been implicated in attentional and executive skills (Fuster, 1989), shows functional abnormalities that seem to be more severe on the right. Nevertheless, the most characteristic neuropathologic feature of learning disabilities is the additional involvement of specific subcortical nuclei. In the case of dyslexia, thalamic nuclei that are part of sensory pathways are affected, causing an impairment in processing fast modalities of visual and auditory information. In NF 1 and tuberous sclerosis, at least the globus pallidus, which is the output nucleus for the basal ganglia, would be anomalous, leading to disturbed visuomotor integration. Finally, in ADHD, the striatum and other brain stem monoaminergic nuclei seem to be dysfunctional, causing disruption of circuits involved in attention and motor inhibition.

In mental retardation, the unifying feature is a disturbance in synaptic relationships or circuitry, or both, affecting the cerebral cortex. Abnormal architecture of cortical regions, aberrant
synaptic surfaces, or both occur in a generalized manner, leading probably to dysfunction in multimodal processing and integration. Although in mental retardation there is no clear selective cortical involvement or subcortical pathology in most instances, features common to learning disabilities should not be excluded. In fact, several NMDs affect preferentially some cortical areas; for instance, in polymicrogyria the perisylvian distribution is quite characteristic. In addition, subcortical heterotopias and other abnormalities are common in generalized NMD (Aicardi, 1991; Barth, 1987). Given the extent of the cortical pathology, it is not surprising that subcortical abnormalities have been greatly overlooked in mental retardation. A

Figure 2. Postulated patterns of involvement of corticosubcortical circuits in mental retardation and learning disabilities. A, Normal relationships between neocortex (CTX), basal ganglia (BG), and thalamus (TH). (S, sensory pathway.) B, In learning disability, there are selective abnormalities in connections between cortex and basal ganglia or cortex and thalamus. C, In severe mental retardation associated with malformations, major cytoarchitectonic disruptions originate aberrant corticosubcortical pathways. In addition, primary developmental abnormalities of basal ganglia and thalamus can contribute to these anomalous relationships.
schematic diagram of the postulated differential neuropathology of mental retardation and learning disabilities is represented in Figure 2.

In conclusion, aberrant synaptic arrangements of developmental origin that compromise brain regions critical for cognition are the neuroanatomic/neurobiologic bases of developmental cognitive disorders. Specific circuits in learning disabilities, and a more generalized disturbance in connectivity in mental retardation, are beginning to be characterized. An increased understanding of gene–environment interaction during brain development, especially of neural activity-dependent genes, may provide new approaches for prevention, diagnosis, and treatment of developmental cognitive disorders.

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