Review article

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Albert M. Galaburda, MD a,b, *
Bradley C. Duchaine, PhD c
a Division of Behavioral Neurology
Harvard Medical School
25 Shattuck Street
Boston, MA 02115, USA

b Beth Israel Deaconess Medical Center
330 Brookline Avenue
Boston, MA 02215, USA

c Department of Psychology
Harvard University
33 Kirkland Street
Cambridge, MA 02138, USA

* Corresponding author. Beth Israel Deaconess Medical Center, 330 Brookline Avenue, K-274, Boston, MA 02215

E-mail address: agalabur@caregroup.harvard.edu

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Developmental disorders of perception and cognition result from a difficulty during growth and development and are contrasted with those that are acquired during life or result from degeneration of skills already acquired. Some are progressive and some improve with age, whereas others remain relatively stable, taking into

account the effects of learning and maturation. The term "developmental" does not define the cause of the condition. Genetic conditions include those in which the gene(s) with the phenotype are inherited from one or two parents (who could be carriers), those that represent a new mutation in the offspring, and a third group that affects only the germ cells of the parent and expresses the phenotype only in the offspring. Other developmental conditions are not genetic and instead represent the consequence of brain injury (mechanic, infectious, traumatic, and so forth) in utero or early in life, before a behavior or a structural phenotype has been acquired fully. Thus, some developmental conditions are congenital, whereas others manifest themselves after birth, at a time when the affected genes or phenotypes normally are expressed. In developmental disorders of cognition and perception, the effects of early environmental interventions and learning can have the effect of exacerbating or altogether obscuring the phenotype. In some cases, the cultural environment itself influences the degree of clinical expression (eg, dyslexia in Italian as contrasted with English or French native speakers [1] [2]). Finally, given the enormous plasticity of the developing brain, the usual distinctions between systems can become blurred; thus, it is difficult to be certain where a perceptual or cognitive phenotype has its origin (eg, in a malformation or lesion involving the visual, auditory, or motor system). Some of these principles are illustrated in the examples discussed later.

Normal development and consequences of early injury

Cellular and molecular events and circuit formation in the developing brain

Normal development and injury to the brain, particularly ischemic injury, are accompanied by changes in excitatory neurotransmitter activity. There is a wealth of evidence supporting the role of excitatory glutamate and inhibitory gamma amino butyric acid (GABA) receptor function in activity-dependent circuit formation. Blockade of excitatory N-methyl-D-aspartate (NMDA) receptors

in kitten visual cortex, for example, disrupts ocular dominance column formation and affects neuronal size in the lateral geniculate nucleus (LGN), suggesting that postsynaptic activation of cortical neurons is required for competitive changes in lateral geniculate cell size [3] .

Neurotrophic factors, which are released during growth and learning and after injury, are expressed in a temporally and spatially distinct manner during development. There is a postnatal increase of neurotrophin-4 (NT-4) mRNA in cerebral cortex and thalamus [4] . At birth, track-B (trkB) mRNA (the common receptor for NT-4/5 and brain-derived neurotrophic factor [BDNF]) are strongly expressed in various regions, with the thalamus and cerebral cortex showing the strongest expression [5] . There is a transient and spatially distinct increase of NT-3 and nerve growth factor (NGF) during development, with the most striking example an increase in NT-3 in most of the dorsal thalamic relay nuclei, whereas NGF mRNA is increased transiently mostly in the posterior, anteroventral, ventrolateral, and ventromedial nuclei. These results suggest distinct and overlapping functions for NT-3 and NGF in early developmental processes, including involvement of NT-3 in cerebellar development and of NGF in the development and maintenance of visual afferents to thalamus [6] .

These temporally and spatially distinct patterns of neurotrophin expression have led researchers to suggest that neurotrophins also mediate the activity-dependent control of axonal branching during development of the CNS. The formation of ocular dominance columns by the invasion of the axons from the LGN into eye-specific patches within layer 4 of the primary visual cortex has proved a useful system for investigating this question. This process of ocular dominance column formation is a direct result of activity-dependent synaptic competition between axons representing the two eyes. Researchers found that infusion of NT-4/5 and BDNF, but not NT-3, inhibits column formation locally [7] . It also has been shown that the effects of monocular deprivation can be halted by introduction of neurotrophic factors. Thus, exogenous supply of NGF completely prevented the shift in ocular dominance distribution of visual cortical neurons [8] and the shrinkage of neurons in the LGN [9] induced by monocular deprivation.

Although subsequent research found that only NT-4 rescued neurons in the LGN from the dystrophic effects of monocular deprivation [10] , it is certain that neurotrophins play an important role in circuit formation in the developing brain.

In the rat, a spatial and temporal gradient of differential neurotrophin expression can be seen. NT-3 mRNA is seen transiently in the occipital cortex of the neonate, whereas BDNF and NGF mRNAs increase during the first three weeks of life. In the LGN, NT-3 mRNA also is transiently expressed, whereas NGF and BDNF mRNAs do not vary significantly during development. Whereas trkB and trkC (high affinity NT-3) receptors are expressed in the developing LGN and in the occipital cortex at birth, there is little change during subsequent development. In contrast, trkA mRNA, which encodes the high-affinity NGF receptor, is undetectable in either region. NGF mRNA is slightly increased after three weeks of light deprivation, whereas BDNF mRNA expression in visual cortex is lowered significantly in rats dark-reared from birth. Decreased BDNF expression after sensory deprivation is reversible by exposure to light [11] .

Connectivity changes in response to early injury

Damage to the brain during development affects typical patterns of neuronal connectivity. In neonatal hamsters, unilateral lesions of the superior colliculus result in restructuring of afferent connections [12] [13] [14] . Specifically, these lesions cause optic fibers to cross the midline where they compete successfully for available terminal space in the intact superior colliculus. In monkeys, prenatal unilateral removal of portions of the frontal cortex results in significant displacement of callosal connections [15] [16] .

Not all anomalous events occurring during brain development affect the eventual patterns of connectivity, however. The reeler mouse, whose cerebral cortex is characterized by the inversion of the normally inside-out disposition of the cortical layers because of a disturbance of neuronal migration, has efferent connections that arise from appropriate neuronal types irrespective of their laminar location [17] [18] [19] [20] [21] [22] . Thus, medium-sized pyramids

located in the superficial layers of the cortex of the normal mouse, but in the deepest layer of the cortex of the reeler mouse, are the cells of origin for callosal projections in both cases.

It would be reasonable to conclude, then, that disorders affecting neuronal migration have little effect on the patterns of inherent connectivity of the brain. There is evidence, however, that neuropathologic events during the period of neuronal migration to the cortex could have profound effects on the eventual laminar disposition of neurons and on the patterns of intrinsic connectivity. For example, injection of ibotenic acid into the visual cortex of cats on postnatal days 2 and 3 causes death primarily of infragranular neurons and the subsequent formation of microgyric-like cortex [23] . This microgyric cortex receives abnormal projections from auditory areas AI and AII—projections that normally are transient and eliminated during development [24] .

In summary, much information has been acquired regarding the normal development of the mammalian brain, described at the systems, cellular, and molecular levels. Genetic or environmental injury to the developing brain often triggers mechanisms of growth and plasticity that, however, are not designed to cope with repair or rebuilding and lead instead to abnormal brain and behavioral development. Of these developmental disorders, three prominent examples discussed here are dyslexia, Williams syndrome (WMS), and prosopagnosia. Space limitations do not permit discussion of other developmental disorders of vision, although they do present with some frequency to the clinic (eg, visual perception in children who had congenital cataracts, strabismus, or amblyopia and children with developmental disorders such as Down syndrome, Asperger syndrome, or Rett syndrome).

Developmental dyslexia

JB (age 7) manifested a serious delay in the acquisition of reading skills. He was very slow to learn the alphabet and to acquire phonetic skills. His sight-reading (used for words with irregular orthography such as “enough”) evolved more rapidly than his sounding-out abilities (used for regular words, such as “rebuff”),

despite allegedly equal training in both forms of reading. Still, his sight-reading also was delayed for his age. This particular difficulty with reading regular words is consistent with the diagnosis of phonologic dyslexia, the most common form of developmental dyslexia. Phonologic dyslexia contrasts [25] with surface dyslexia [26] , where the more pronounced difficulty occurs in reading orthographically irregular words, and with deep dyslexia [27] , where the problem is deeper in the processing pathway and where meaning is attached to the visual word form (eg, in deep dyslexia, a word such as "chair" might be read as "bench"). All these types have been reported in developmental and acquired cases of dyslexia.

In grade one, JB exhibited serious difficulties with visual planning. His written letters collided into each other, he had problems staying on the line, and thus sentences also collided. JB was reported as reading words in isolation far better than reading them in sentences. He often skipped words or entire lines. A speech and language assessment at the age of six revealed articulation difficulties in several sound clusters, weak phonologic knowledge, and difficulty remembering sound-sequence information. Language comprehension in most areas was average. Intelligence measures taken at age seven revealed low average verbal and performance IQs with no significant difference between these scores. Memory tests revealed average recall of meaningful and organized information (eg, stories and pictures) while showing dramatic difficulty recalling auditory digits and letters, particularly in their proper order. JB also had poor performance when attempting to recall visual information in an ordered sequence. Gross motor skills developed normally, whereas fine motor skills were delayed somewhat. Basic speech and language milestones allegedly were reached at normal times. JB had a long history of ear infections beginning at six months of age and had tubes placed in his ears from four to six years of age. A visit to the audiologist at age six indicated no difficulties in hearing, and no problems with vision were noted. There was a family history of learning difficulties on the maternal line.

Dyslexia is a relatively common developmental disorder (around 5% of the school age population) that often results in school failure

[28] [29] [30] . There is a strong genetic predisposition [31] [32] [33] . Most studies reveal more boys than girls affected. There is no racial imbalance in prevalence, but native languages affect the clinical expression of the biologic risk [2] . In this condition, the child exhibits difficulties learning to read, hence the term "dyslexia." There are other symptoms, however, that seem to indicate that there also are problems with language in general, some aspects of visual and auditory perception, motor control, and some aspects of memory. As reading clearly involves participation of the visual system, it was tempting during the early history of dyslexia research to assume that the problem was primarily visual. A deeper look, however, quickly shows that dyslexia results from developmental involvement of multiple systems.

Multisensory deficits in fast processing systems

Developmentally language-impaired children (a large subset of whom are later diagnosed with dyslexia) suffer from rapid auditory processing deficits affecting even nonlinguistic sounds [34] [35] [36] [37] . Researchers in the visual system [38] [39] [40] [41] [42] [43] [44] [45] [46] [47] and somatosensory system [48] have shown similar deficits affecting temporal and spatial processing of stimuli in dyslexics, indicating that multiple sensory modalities are involved. Livingstone and colleagues [42] , for example, found that the magnocellular component of the visual system, which is responsible for processing fast, low-contrast information, was impaired in dyslexics. The physiologic response of this system is slowed in comparison with controls, and the magnocellular neurons of the LGN are smaller than normal [42] . Moreover, examination of the dyslexic medial geniculate nucleus (MGN) found more small and fewer large neurons in the left MGN, whereas there is no side difference in neuronal size in controls [49] . These findings complement previous reports of anomalies in the dyslexic MGN [50] and are consistent with reported behavioral findings of a left hemisphere–based phonologic defect in dyslexic individuals [51] [52] .

The brains of dyslexics show focal cortical dysplasia in the form of focal microgyria or glioneuronal heterotopias (ectopias) in perisylvian regions affecting left and right hemispheres, Fig. 1) and

cell changes in the auditory and visual thalamus consisting of a shift toward fewer large neurons and an excess of small neurons. It is not possible to say from the examination of human brains whether or not the anatomic findings are related causally to the dyslexic deficits. Experiments in newborn rats, however, have found that induction of focal cortical dysplasias mimicking those seen in dyslexia also leads to thalamic changes and behavioral deficits comparable to those seen in the dyslexics [53] .

http://home.mdconsult.com/das/article/body/35445500-2/jorg=journal&source=MI&sp=13788844&sid=247730687/N/361771/I18.fig - top **Fig. 1.** Photomicrograph of a section of dyslexic cerebral cortex showing an example of a minor migrational anomaly called a glioneuronal heterotopia, or ectopia (enclosed by *black arrows*). They are usually less than 500 _m in diameter, but disturb the underlying architecture and connectivity (see text).

For example, there are varieties of changes in the rat cortex associated with the microgyria consistent with excessive excitation and diminished inhibition [54] [55] [56] [57] [58] [59] and alterations in axonal connectivity adjacent to the malformation and at a distance, including interhemispheric connections [60] [61] [62] . Furthermore, animals with induced cortical malformations, but not their sham-operated littermate controls, show a wide variety of behavioral deficits involving rapid auditory processing [63] [64] [65] and other deficits that can be classified as more cognitive in nature (eg, changes in visual working memory [66] [67] [68]). These deficits have been demonstrated in operant conditioning tests, event related potentials, and oddball paradigms, all of which indicate that dysplastic animals are abnormally slow when processing rapidly changing sounds and make more errors in some maze tests. A comparable study of the rat visual system has not been carried out.

A consistent observation in the induced-dysplasia model in rodents is that only males display changes in the thalamus and alterations in auditory/perceptual behavior [69] , although both sexes show the cognitive problems [67] [68] . Cell stains of affected cortex do not show any sex differences in the size or severity of the focal dysplasias themselves, but the sexes do differ in the thalamic

changes. This suggests that the cognitive changes could be related to the cortical changes and that the auditory temporal deficits instead probably are related to the secondary thalamic changes. Furthermore, the data can be interpreted to indicate that response in the thalamus to cortical malformation induction is maladaptive in males but not in females. Although this is the case for the auditory thalamus, the LGN has not shown this type of gender difference.

In summary, developmental dyslexia is associated with cortical malformations, which, albeit focal, are capable of affecting wide areas of cortex and subcortical structures. Among these structures, the thalamus has been studied and found abnormal in the lateral and in the medial geniculate nuclei [42] [49] [70] [71] [72] , possibly explaining some of the perceptual problems seen in this population affecting visual and auditory function.

Williams syndrome

WMS is a rare (1:20,000 live births) neurogenetic condition that typically results from a hemideletion in the q11.23 region of chromosome 7, losing one copy each of approximately 20 genes [73] [74] [75] . The resulting phenotype presents a broad spectrum of unique physical and behavioral characteristics. The physical features of WMS include distinct facies, hypercalcemia in infancy, widely-spaced teeth, strabismus, and narrowing of the vasculature, particularly supravalvular aortic stenosis (SVAS) [76] .

What is perhaps most interesting in WMS, however, is a truly unusual profile of behavioral features [77] [78] . The cognitive hallmark of WMS is dissociation between relatively preserved linguistic ability and profoundly impaired visual-spatial ability. For example, a study that compared WMS children with children with Down syndrome of equivalent IQs showed that WMS patients were able to produce longer, more flowery sentences with rich vocabulary, whereas they accomplished much more impaired drawings of animals and houses [77] . Additionally, a preserved social drive and enthusiasm and love of music characterize WMS. Increased anxiety and attentional problems also are common in this

condition [79] [80] [81] .

Research into the underlying neuroanatomic features of WMS reveals patterns of alteration that are concordant with current understanding of functional neuroanatomy and the behavioral phenotype of WMS. Although autopsy and MRI studies show that the overall brain size of persons with WMS is decreased substantially relative to typically developing controls, comparable to the reduction seen in Down syndrome, certain regions are relatively spared [70] [71] [82] . As expected from the observation of preserved language and musical abilities in this condition, the temporal lobe, specifically the superior temporal gyrus (STG), is relatively preserved in volume. Additionally, the cerebellar size is preserved. Given recent studies implicating the cerebellum in higher cognitive and social abilities [83] [84] , a disproportionately preserved cerebellum may be related to the hypersociability seen in this condition. In contrast, regions of the brain that play a large role in visual-spatial ability (eg, parietal and occipital lobes) are disproportionately decreased compared to expectations based on total cranial volume (Fig. 2).

http://home.mdconsult.com/das/article/body/35445500-2/jorg=journal&source=MI&sp=13788844&sid=247730687/N/361771/I19.fig - top **Fig. 2.** Surface rendering of an MRI from a patient with WMS syndrome showing two common gross anatomic features: the black arrow points to a dorsally foreshortened central sulcus, implicating the development of the dorsal forebrain; the white arrowhead points to the vertically curved and reduced size of the occipital region, possibly a part of the neural substrate for the described visual deficits in this condition (see text).

More detailed investigations of WMS also have been performed on a few autopsy specimens, which allows for a much higher resolution of cortical anatomy than that permitted by MRI studies [82] [85] . Gross examination of the WMS brain shows that there is an overall decrease in brain weight, with parietal and occipital hypoplasia common. Other than focal changes suggestive of immaturity of development, no consistent differences were found in the cytoarchitectonic organization of the cerebral cortex of

subjects with WMS. Motor and sensory association areas are easily identifiable by architectonic features typical of these areas. At the histologic level, however, changes are seen in cell packing density and cell size, suggesting abnormal neuronal development and connectivity [86] .

The shape of the WMS brain also is unique. Overall, the brains of subjects with WMS are dolichocephalic and have some anomalous gyral patterns. The most consistent gross anatomic observation is a foreshortening of the dorsal central sulcus [87] . Unlike most typical brains in which the central sulcus extends fully to the interhemispheric fissure, in WMS the central sulcus usually terminates prematurely on the dorsal, but not ventral, end. The second common shape difference is a bilateral foreshortening of the parieto-occipital region, effectively a curtailment in the superior-inferior dimension posteriorly in the telencephalon.

Gross morphologic differences observed in autopsy specimens have been supported by several recent structural MRI studies that confirmed in larger samples autopsy findings of abnormal central sulcus morphology, posterior curtailment, and anomalous gyri [71] [87] [88] [89] . Observations made on necessarily small numbers of autopsy specimens direct attention to specific brain areas that can be assessed in large numbers of living subjects. MRI provides highly automated, in vivo evidence with sample sizes that provide more statistical power than is usually obtained in autopsy studies. Conversely, observations made on MRI can lead to more detailed studies in autopsy specimens at the architectonic and histologic levels. The authors found that this cross-level combination of histology, gross anatomic observation, and MRI analyses is a productive strategy for furthering neurogenetics research.

Despite the relatively small size of the WMS deletion region, it includes several genes that likely have roles in brain development or synaptic functioning. The gene STX1A encodes for syntaxin 1A, a member of a gene family that has role in neurotransmitter release [90] . A second gene, LIM-kinase 1, has been shown to play a role in growth cone formation and axon guidance [91] [92] , which partially might underlie the abnormal white matter volume demonstrated by MRI in WMS. Hemizygosity for LIM-kinase 1

has been correlated with visuospatial impairment for subjects with WMS and subjects with microdeletions of only the elastin (ELN) and LIM-kinase genes [93] . Another gene in the WMS critical region, FZD9 (formerly known as FZD3, the human homologue of Drosophila's frizzled gene), is expressed strongly in adult brains and seems to play a key role in global brain development [94] . FZD9 is related to the Wnt gene family, which encodes for secreted signaling glycoproteins and are known to be involved in controlling early cell development, tissue differentiation, segmentation, and dorsal-ventral polarity [95] .

Neuroanatomic studies of WMS suffer from some methodologic limitations typical of complex behavioral phenotypes. Specifically, the broad array of neuroanatomic differences seen in WMS makes interpretation of relationships to genetics and behavior difficult. Fortunately, there is a limited number of genes in the critical WMS deletion region (approximately 20, compared with over 200 in Down syndrome), although several of these have prominent roles in brain development. Additionally, as with other developmental disorders of known genetic origin, WMS is a rare condition, which can lead to difficulties in gathering a statistically powerful sample, particularly for studies requiring tissue samples. Finally, as with other mental retardation syndromes and developmental disorders affecting emotional behavior, the noisy and relatively stressful environment of the MRI lab can be a barrier to research.

Study of the WMS neuroanatomic phenotype also raises the ever-present question regarding the validity of correlations between relative anatomic and functional effects in neurodevelopmental conditions. For example, although the STG is relatively preserved in WMS, can it be assumed that this volume preservation is related to the relative preservations in language in this condition? First, there is a strikingly phrenologic quality to this form of reasoning, whereby volume of brain tissue is assumed causally related to quality of performance. Second, this argument assumes that the STG in WMS serves the same function as in normal individuals. Third, regional measurements assume a greater degree of functional localization than is evident from contemporary studies using activation approaches, such as functional MRI and positron emission tomography. Alternatively, regional measurements

provide clues for focusing other types of studies, and it is only through convergent evidence derived from various methodologies that a clearer picture of structure–function relationships begins to emerge.

Congenital prosopagnosia

TA is a 42-year-old developmental prosopagnosic who recalls incidents early in childhood when he could not recognize close family members, and he has failed to recognize nearly all his relatives at times. TA's son, mother, and grandmother also have prosopagnosia; it clearly has a genetic basis. Although there were signs during childhood, it was not until TA entered the army that he realized that something serious was wrong. The uniform appearance of fellow servicemen left him unable to differentiate between people, and he likens his time in the army to a prison sentence. In addition to failing to recognize others, TA often falsely recognizes strangers as acquaintances. As a result of his difficulties, he tends to avoid situations in which he might encounter people he is not expecting. In lieu of the face, TA relies primarily on hair, body shape, head shape, movement patterns, and clothing, and when he encounters acquaintances in typical contexts, he can recognize others fairly effectively using these cues.

Despite the complexity and within-class similarity of human faces, most people are adept at recognizing faces. Proficiency with such a difficult task suggests that humans have procedures that are specialized for this task, and many lines of evidence support this possibility. Evidence has come from single-cell recordings in monkeys [96] [97] and humans [98] , neuroimaging [99] [100] , and cognitive and psychophysical experiments [101] [102] [103] [104] . Investigations of individuals with neuropsychologic conditions, however, provide strong support of the theory that at least some of procedures used to recognize faces are different from those used to recognize other classes of objects [75] [105] [106] [107] .

Given the apparent existence of dissociable procedures for face recognition, one might expect that developmental problems could

lead to specific problems with face recognition. Until recently, nearly all published cases of prosopagnosia were the result of brain damage acquired after the development of normal face recognition abilities. Within the past decade, there have been many reports of developmental prosopagnosia, and studies of many more individuals are underway. The authors' discussion of developmental prosopagnosics is confined to individuals without any history of head trauma or visual deprivation, leaving eight case reports of congenital prosopagnosia [78] [79] [81] [108] [109] [110] [111] [112] and one brief report of a family of congenital prosopagnosics [113] . This excludes individuals with face recognition impairments resulting from brain damage in their early years, infantile cataracts [106] , and other etiologic events occurring after birth. Although these individuals are interesting, congenital prosopagnosics provide a unique opportunity to explore whether or not face recognition involves procedures built by developmental procedures separate from those constructing other visual processes.

The paucity of cases of congenital prosopagnosia in the literature suggests that it is a rare condition. This may not be the case, however. Several laboratories are contacted regularly by congenital prosopagnosics, and there is an Internet discussion group that has included approximately 150 to 200 purported prosopagnosics in the last six years. One of the reasons for its apparent rarity is that many congenital prosopagnosics do not recognize their problem until well into adulthood [81] [110] [114] . Unlike acquired prosopagnosics, they cannot compare their abilities to previously normal abilities, thus their deficit is sometimes not noticeable to them. Whereas this may sound incredible to individuals with normal face recognition, it raises the possibility that significant numbers of individuals have congenital impairments for various psychologic abilities that are undetected. Congenital prosopagnosics, and developmental prosopagnosics more generally, often report that the realization that their difficulties stem from a neurologic condition is a relief, because they finally understand their social difficulties and no longer attribute them to lack of effort or interest.

Not surprisingly, congenital prosopagnosia can be a socially troubling or even devastating condition [115] [116] . Without the

ability to track identity, prosopagnosics commonly find interpreting social situations overwhelming. They often have trouble maintaining friendships, because their failure to identify and acknowledge friends is interpreted as rude. These problems often lead prosopagnosics to restrict social interaction to manageable situations or avoid it altogether. They often rely on alternative routes to recognition, such as hair [81] [108] [110] , gait [81] , context [115] , and other information, but these alternative routes usually are not as fast or reliable as face recognition. As discussed later, many congenital prosopagnosics commonly have other face and object processing problems that further complicate social interaction; one congenital prosopagnosic reported that his problems with emotion recognition are more troubling than those with identity recognition.

The parallels between congenital prosopagnosia and acquired prosopagnosia are striking. The authors discuss many characteristics of congenital prosopagnosia and compare these characteristics with acquired prosopagnosia. The similarity of the disorders suggests that their underlying impairments are similar, in contrast to the difference between acquired and developmental reading disorders.

Causes of congenital prosopagnosia

Congenital prosopagnosia results from brain damage in utero or from genetic deficits. In four of the congenital cases, the etiology in unclear [78] [108] [111] [117] , and it is possible that these individuals experienced a visual deprivation that led to their face recognition difficulties. In the other four reports [79] [81] [110] [112] , the prosopagnosics reported other family members with face recognition problems. De Haan [113] studied a family with many prosopagnosics and found that the father and two daughters showed clear impairments on a test of famous face recognition.

Recognition of facial identity

The defining characteristic of prosopagnosia is impaired recognition of facial identity. Most assessments of facial identity in congenital prosopagnosics have relied on two types of tests. In

tests of familiar face recognition, subjects are presented with faces of celebrities or close acquaintances and are asked to identify the faces. Congenital prosopagnosics usually perform much more poorly than control subjects [79] [81] [110] [118] , but many individuals are not completely unable to recognize familiar faces [78] [79] [110] [118] ; one individual was able to promptly name 20 photographs of acquaintances [81] . Many of the individuals who have been assessed reported that they require many exposures to a face before they can recognize it. For example, all but one of the 15 congenital prosopagnosics we recently tested recognized Bill Clinton, but some reported that they did not begin to recognize him until he had been in office for a few years.

Tests of unfamiliar face recognition usually require face matching (either simultaneous or delayed) or discrimination of previously presented faces from new faces. Four congenital prosopagnosics [78] [108] [110] [118] were tested on the Benton Facial Recognition Test (BFRT) [119] and two scored in the normal range [78] [110] , whereas two were borderline impaired [108] [118] [120] . Because the BFRT is a simultaneous matching test, it is possible to answer accurately with a feature matching strategy, and developmental prosopagnosics have reported that they used just such a strategy [78] [110] . In contrast, these four individuals scored out of the normal range on other tests of unfamiliar face recognition. As a result, normal scores on the BFRT should be interpreted with caution. Similarly, the other commercially available test, the Warrington Recognition Memory for Faces (WRMF), is vulnerable to nonfacial routes to normal performance [78] ; thus, normal scores do not necessarily demonstrate normal face recognition. When congenital prosopagnosics were tested with facial identity tasks other than the BFRT or the WRMF, they usually show impairments [78] [110] [117] [118] ; thus, well-designed tests of face recognition can be used to assess face recognition impairments in congenital cases.

Neural substrate

Currently, there is little understanding of the neural substrate of developmental prosopagnosia, but the results available suggest that similar brain regions are involved in congenital and acquired prosopagnosia. Structural MRI scans performed with four

congenital prosopagnosics failed to reveal any lesions [78] [79] [117] [120] ; thus, unreported brain trauma is not likely responsible for their disorder. In one of these four cases, volumetric analysis showed that YT's right temporal lobe was significantly smaller than the temporal lobes in the control group [79] . It is not clear that this difference is causally related to YT's prosopagnosia, but these results are consistent with lesion [121] [122] , neuroimaging [99] [123] , and neurophysiologic [96] [97] studies that indicate that face recognition involves the posterior temporal lobes, particularly the fusiform gyrus.

Electrophysiologic recordings have been performed with three subjects [79] [108] [119] , and all three have shown abnormal patterns of activity in posterior areas. YT, mentioned previously, showed an abnormal negative potential (N170) from a region at the posterior-inferior portion of the temporal lobe [79] . For normal individuals, this potential is generated in response to faces but not other objects. YT's response, however, showed a similar response to faces and objects. The investigators suggest that this indicates that YT is unable to select properly or represent face-specific information for relay to dedicated face recognition procedures. Thus, in this case at least, it seems that the impairment is at an early stage of face processing.

Covert recognition

Twelve cases of acquired prosopagnosia have shown covert recognition of faces [124] . When presented with familiar faces, these individuals claim to be unfamiliar with them, yet a variety of methods have demonstrated that the familiar and unfamiliar faces are distinguished unconsciously. Covert recognition has been investigated in congenital prosopagnosics, and, until recently [111] , no covert recognition had been found [79] [118] . This result was not surprising, because covert recognition in acquired prosopagnosia has been argued to rely on subthreshold activation of face memories acquired prior to brain damage. Because congenital prosopagnosics and developmental prosopagnosics [124] have never recognized faces normally, it seemed plausible that they would not be able to covertly activate these memories. Recently, however, experiments with a five-year-old developmental prosopagnosic

clearly showed the presence of covert recognition [111] . The boy was presented with faces of friends and family intermixed with faces of strangers. He was unable to recognize any of the familiar faces, but the difference in galvanic skin responses to the familiar and unfamiliar faces differed markedly and matched that of the control subject's (5.45 uS for familiar and 0.13 uS for unfamiliar). As a result, it is clear that he is able to store facial identity information and use it to recognize faces, but he does not become conscious of this recognition. It remains to be seen whether or not covert recognition is common among developmental prosopagnosics, but its presence in some individuals and absence in others parallels findings with acquired prosopagnosia.

Associated conditions

Many conditions commonly are associated with congenital prosopagnosia. As is the case in acquired prosopagnosia, other types of face-processing abilities sometimes are impaired and sometimes are normal. In nearly all the cases discussed, face processing of information other than identity has not been the focus of investigation; thus, the reports are based on limited testing.

Two congenital prosopagnosics showed normal performance when tested on their recognition of facial expressions of emotion [78] [112] . This contrasts with four other individuals who had problems with emotion recognition [81] [108] [110] [118] . On gender discriminations, one congenital prosopagnosic showed normal performance [78] , whereas three other individuals had gender discrimination impairments [108] [111] [118] . There are fewer reports on age discrimination, but one case was normal [78] and two were impaired [108] [118] . In summary, identity recognition seems to dissociate from other types of face processing, but more work is needed in order to support inferences regarding the developmental independence of these different abilities.

As with acquired prosopagnosics [125] , congenital prosopagnosics often have trouble with nonface object recognition. Usually these problems are not apparent from tests of entry-level recognition (ie, recognition of a cat as a cat in general) [78] [110] [111] , but some

patients have shown such difficulties [108] [118] . Tests of individual item object recognition are similar to tests of facial identity in that they require recognition of individual items from within a category, and most cases of acquired prosopagnosia show impairments with individual item object recognition [125] [126] . There are only a few reports of nonface individual item recognition in congenital prosopagnosics, but the great majority of the individuals assessed by the authors' laboratory have shown problems with some categories of objects. Again, however, as with acquired prosopagnosia [105] [127] , there are cases of congenital prosopagnosia in which there are no apparent problems with individual item object recognition [78] [79] , and these cases suggest that face recognition relies on procedures that are computationally and developmentally separate from those used for other types of object recognition.

Although it has yet to be demonstrated formally, congenital prosopagnosics often report navigational problems [111] [112] . For example, approximately half the congenital prosopagnosics who contacted the authors' laboratory's Web site report having navigational problems. Many of the congenital prosopagnosics who have navigational troubles also have trouble with place recognition, but there may be additional cognitive problems impairing their navigational abilities. This reinforces the parallel with acquired prosopagnosia, which is often associated with topographagnosia, which manifests as losing one's way in familiar surroundings.

The complaint of abnormal social interactions by many patients with congenital prosopagnosia raises the question as to whether or not face-processing deficits is also found in patients with social developmental disorders, such as autism and Asperger syndrome [70] . Individuals on the autism spectrum have deficits in social interaction, and not surprisingly, many have shown impairments with a variety of face-processing tasks including identity recognition [120] [128] [129] , emotion recognition [129] , age determination [130] , and gender discrimination [130] . Neuroimaging studies found that individuals with autism and Asperger syndrome show abnormal fusiform activity in response to faces, and the investigators suggested that these individuals process faces in the

same manner as objects [131] . If an association between impaired face recognition and abnormal social development in autism and Asperger syndrome is found, however, it is not clear which way the causal link runs. It also has been hypothesized that, because the development of adult-level face expertise likely requires exposure and interest in faces after birth, early social dysfunction might lead to impaired face perception [132] . Therefore, it remains to be determined whether or not one of these conditions leads to the other condition [133] [134] , but it is an intriguing relationship.

Summary

This review of developmental disorders of vision focuses on only a few of the many disorders that disrupt visual development. Given the enormity of the human visual system in the primate brain and complexity of visual development, however, there are likely hundreds or thousands of types of disorders affecting high-level vision. The rapid progress seen in developmental dyslexia and WMS demonstrates the possibilities and difficulties inherent in researching such disorders, and the authors hope that similar progress will be made for congenital prosopagnosia and other disorders in the near future.

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