Plasticity of the Visual Cortex after Injury: What's Different about the Young Brain?

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■ REVIEW

Plasticity of the Visual Cortex after Injury: What's Different about the Young Brain?

BERTRAM R. PAYNE AND STEPHEN G. LOMBER

The repercussions of localized injury of the cerebral cortex in young brains differ from the repercussions triggered by equivalent damage of the mature brain. In the young brain, some distant neurons are more vulnerable to the lesion, whereas others survive and expand their projections to bypass damaged and degenerated structures. The net result is sparing of neural processing and behaviors. This article summarizes both the modifications in visual pathways resulting from visual cortex lesions sustained early in life and the neural and behavioral processes that are spared or permanently impaired. Experiments using reversible deactivation show that at least two highly localizable functions of normal cerebral cortex are remapped across the cortical surface as a result of an early lesion of the primary visual cortex. Moreover, the redistributions have spread the essential neural operations underlying orienting behavior from the visual parietal cortex to a normally functionally distinct type of cortex in the visual temporal system, and in the opposite direction for complex-pattern recognition. Similar functional reorganizations may underlie sparing of neural processes and behavior following early lesions in other cerebral systems, and these other systems may respond well to emerging therapeutic strategies designed to enhance the sparing of functions. NEUROSCIENTIST 8(2):174–185, 2002

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In functional terms, the young brain can be quite resilient to early focal injury of the cerebral cortex, and the resiliency contrasts with the frequently severe and permanent impairments in neural performance and behaviors that accompany equivalent damage of the mature cerebrum. For example, damage of the mature primary visual cortex results in blindness, whereas equivalent damage incurred early in life spares visual functions, and the overall constellation and magnitude of deficits may be greatly attenuated.

But what types of neural processes and behaviors are spared, and what functions are permanently impaired? What are the repercussions of early lesions on neurons, brain pathways, neuronal properties, and activity levels? Are cerebral functions redistributed to accommodate the functional compensations? Is there a functional price to pay for the sparing of neural functions? Do the repercussions produce a different brain? Finally, what is it about the young cerebral cortex that makes it different from the mature cerebral cortex in the way that it responds to focal damage? These are some of the questions that we attempt to answer.

The central focus of the article is concentrated on data gathered from cats. These data are highly relevant to understanding the repercussions of early focal lesions in humans because, in broad terms, there are many aspects of brain connections, layout, and function that are similar to those of monkeys, and by extension humans (Payne 1993; Payne and others 1996b; Lomber and others 1996a). Moreover, there are also great similarities in the developmental program of cats, monkeys, and humans (Rakic 1977; Payne and others 1988; Williams and others 1989), yet the developmental tempo of the cat brain is considerably faster than that of both monkeys and humans. This greater tempo has distinct advantages for scientific investigations because it means that studies can be carried out over a reasonable period of years, rather than over a period of decades that it would take to investigate the broad long-term consequences of early lesions in monkeys or human infants and children. Consequently, studies in the cat continue at a pace substantially faster than those of either monkeys or humans.

One enormously important aspect of the work on cats is its relevance to the clinical arena and the understanding of the repercussions of focal cerebral lesions sustained by the premature or neonatal brain. This view obtains because the maturational status of the newborn cat approximates that of the early third trimester human fetus and is of particular significance because of its relevance to comprehending the repercussions of focal lesions in the growing numbers of fragile, premature infants born each year with a birth weight of ≤ 1.5 kg.

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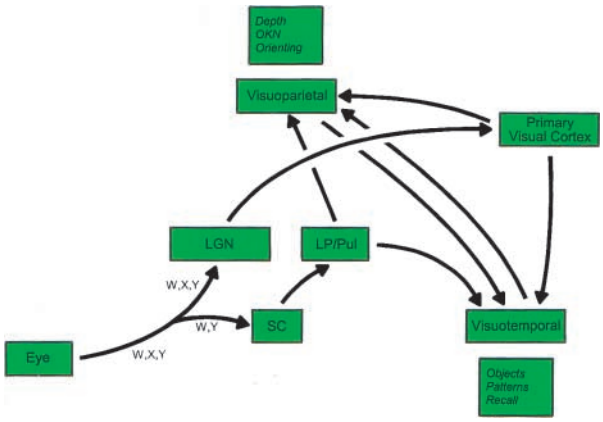


Fig. 1. Summary diagram of major visual pathways. LGN = lateral geniculate nucleus; LP/Pul = lateral posterior/pulvinar complex; SC = superior colliculus. Major destinations of retinal signals are identified by type, as are the contribution that visuoparietal and visuotemporal cortices make to visually guided behaviors (*italics*). Green symbolizes normal structures and functional performance of neurons and the individual. OKN = Optokinetic nystagmus.

They are the youngest of the group of viable infants born, and some estimate that between 40% and 60% of them suffer from some form of cerebral damage (e.g., Volpe 1994; Vohr and Ment 1996).

So far, what has emerged from the data on cats is the new perspective that the repercussions of early damage of the primary visual cortex, designated areas 17 and 18 (Payne and Peters 2002),[1] spread throughout the entire visual system (Payne and Cornwell 1994; Payne and others 1996b). They shape pathways and circuits into new and useful forms that underlie functions that are retained into adult life, and optimize the individual's interactions with the environment under the new conditions, and they are considered adaptive. In our view, such positive features are a distinguishing characteristic of the plastic capacities of the brain, and they should be distinguished from the nonspecific and disordered alterations in pathways and function that may also be induced by lesions, but that have no useful function. However, there may also be some permanent deficits that can be linked to degeneration of specific subsystems within the visual system.

These sequelae spread to all other major components of the highly interconnected visual system from the retina, through the nuclei in the thalamus (lateral geniculate, lateral posterior, and pulvinar), to regions of parietal and temporal cortices (Fig. 1). These repercussions have a substantial impact on neural function and behavior. Lesion-induced alterations include regressive sequelae such as the death of distant neurons normally highly connected with the damaged region, and consequent reduction or elimination of brain pathways, as well as permanent degradations in neural and behavioral performance.

1. While the lesions always include areas 17 and 18, they also include portions of area 19 to ensure completeness of the removals of areas 17 and 18. For the sake of brevity, we will refer to the lesions as being of the primary visual cortex.

Box 1.

By definition, competent neural and behavioral performance is characterized by highly accurate neural processing and action. It is this level of performance that provides the normative basis for measuring lesion-induced modifications in neural and behavioral performance, which we have grouped into three main types:

1. **Residual** function describes the neural and behavioral performance levels that remain after lesions are sustained by the mature brain. This performance level may be greatly impaired or not at all, if the function is unrelated to the brain region damaged. It is the severely impaired functions that are relevant to this article.

2. **Recovered** function describes the neural and behavioral performance levels that remain after focal lesions, if these capacities emerged from, and are superior to, the impaired residual functions. The magnitude of recovery may vary, but it is rarely complete. Embodied in the term *recovery* is a prior presence of a given behavior. There is little or no evidence for gross rewiring of brain pathways to support the recovery.

3. **Spared** functions describe the capacities that are present after lesions incurred in the earlier part of life before faculties have fully matured. Spared functions are always greater than both impaired-residual and recovered, neural, or behavioral performance levels, and result from altered development of brain pathways. Embodied in the concept of "sparing" is a prior *absence* of a given behavior and the notion of altered brain connections. In this regard, the concept of sparing differs in a fundamental way from the concept of recovery. The magnitude of any sparing identified may vary according to the age that a focal lesion was sustained, or according to extent of the lesion.

The nonregressive sequelae form the platform for progressive changes such as the expansion of pathways that bypass damaged and degenerated regions, and they form the substrate for neural compensations that result in sparing of neural performance and behavior (Box 1).

Impact of Lesions of the Primary Visual Cortex

Table 1 summarizes the results of studies on spared and impaired cat behaviors.

Table 1. Spared and Impaired Behaviors.

Summary of spared and impaired visual performance following lesions of the primary visual cortex sustained in adulthood or during the first postnatal week. Tasks are grouped according to neural structure that contributes most fully to the neural operations. ✚✚✚✚ = high level of performance; ↓↓↓ = great reduction in performance (severe deficit); ↓↓ = lesser reduction in performance (moderate deficit); ↓ = slight reduction in performance (minor deficit). Green shading represents normal high levels of proficiency on tasks. Yellow shading represents impaired performance. Red shading represents partial or complete sparing (see Box 1).

	1	2	3	4	5
	Visual Region	**Visual Property**	**Intact**	**Adult Lesion**	**P1 Lesion**
		Basic Property			
1	Retina	Acuity[1]	✚✚✚✚	↓↓↓	↓↓↓
		Reflex, Action, Space			
2		Depth[2,3]	✚✚✚✚	↓↓↓	↓
3	Parietal	OKN[3]	✚✚✚✚	↓↓↓	↓
4	Cortex	Orienting			
5		Visual[3-5]	✚✚✚✚	↓↓↓	↓
6		Auditory[4,5]	✚✚✚✚	✚✚✚✚	✚✚✚✚
		Form, Learning, Memory			
7		Objects	✚✚✚✚	↓	✚✚✚✚
8	Temporal	Patterns			
9	Cortex	Simple[6,7]	✚✚✚✚	↓↓	✚✚✚✚
10		Masked – Surround[6,7]	✚✚✚✚	↓↓↓	↓↓↓
11		Overlain[6,7]	✚✚✚✚	↓↓↓	↓*

* = no or lesser deficit following two stage lesions. OKN = Optokinetic nystagmus.

Studies cited are limited to those that employed comparable stimuli and testing procedures in assays of performance of the different groups of cats. 1) Mitchell (2002); 2) Cornwell and others (1978); 3) Shupert and others (1993); 4) Payne and others (2000); 5) Payne and Lomber (2001); 6) Cornwell and others (1989); 7) Cornwell and Payne (1989).

Lesions Incurred in Adulthood

Lesions of the primary visual cortex sustained in adulthood have a broad and substantial detrimental impact on a host of visually guided behaviors (Table 1, column 4). The impacts extend from basic visual functions such as visual acuity, through largely reflexive, action-based, and spatial functions, which are normally associated with the visual regions of the parietal cortex, through two-dimensional form, learning and memory operations, which are normally associated with the visual regions of the temporal cortex (yellow cells). However, simpler visual operations such as learning and recognizing simple three-dimensional forms (row 7) and neural operations underlying orienting to an auditory stimulus (row 6) are largely or completely unaffected by the lesions (green).

The broad spectrum of the behavioral deficits reflects principally the removal of the primary visual cortex and its signal processing functions, and the disconnection of the extrastriate cortical regions from large numbers of visual signals that enter the cortical network via the lateral geniculate nucleus and primary visual cortex (Fig. 2*A*). The most prominent disconnection is from the numerically dominant β retinal ganglion cells that survive and continue to transmit X signals, but they are not connected in any significant way to cerebral structures. The absence of these signals from cerebral circuits severely reduces acuity among other visual measures (Table 1, row 1, column 4). Consequently, the signals derived from them are not processed and they do not contribute to behavior. Moreover, there is a severe degradation of sophisticated receptive field properties and neural activities in the visuoparietal cortex (Fig. 2*A*, yellow shading), whereas activities assayed in the retina with electrophysiological methods or in the visuotemporal cortex with metabolic markers appear to be unaffected (green). The lesion has no detectable impact on the composition of pathways from the retina to LGN or those pathways that bypass the primary visual cortex, such as those from the thalamus or visuotemporal cortex to the visuoparietal cortex.

Impact of Lesions of the Primary Visual Cortex: Postnatal Week 1

Lesions of the primary visual cortex sustained during the first postnatal week result in both sparing and permanent impairments in visually guided behaviors. The impairments parallel the severity of impairments induced by equivalent lesions sustained in adulthood.

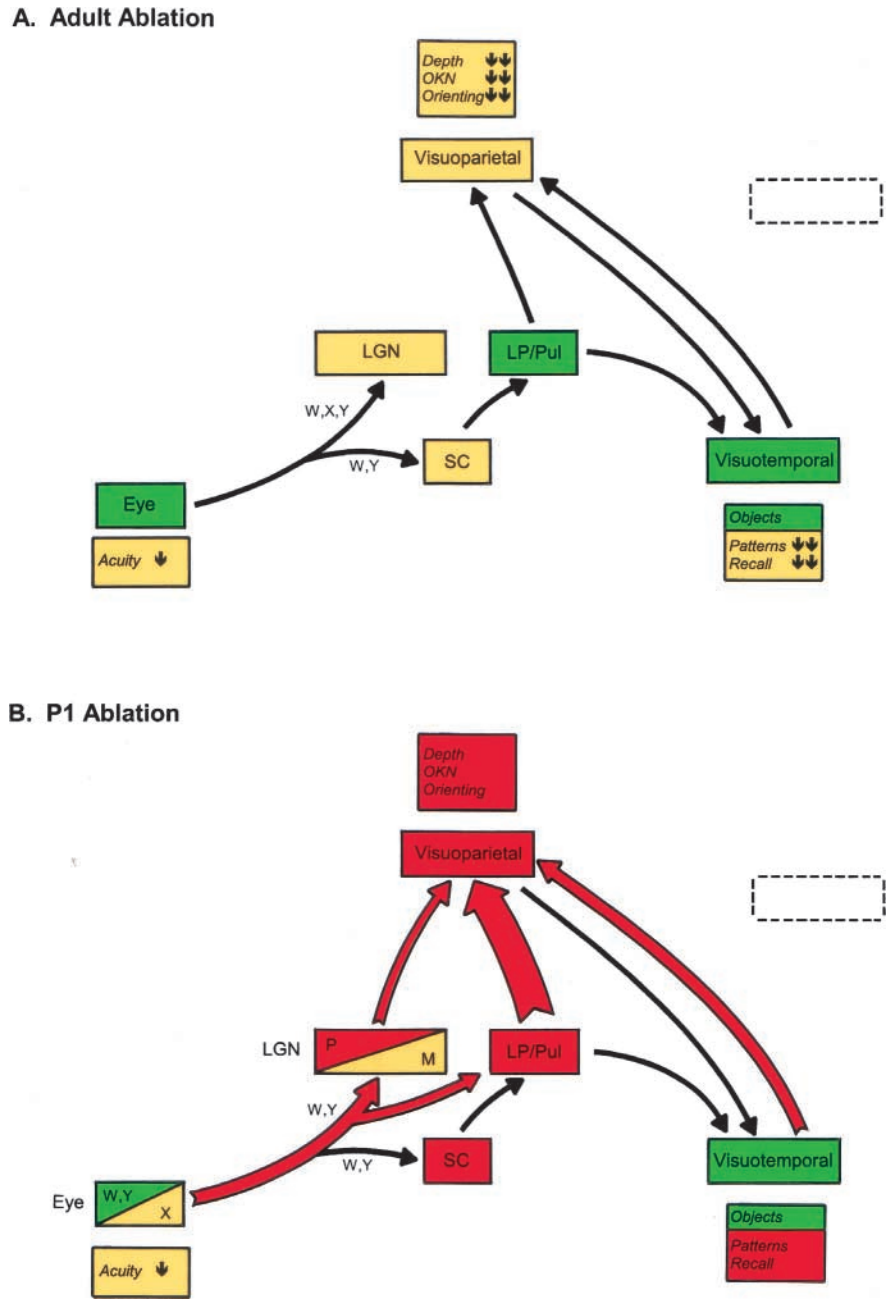


Fig. 2. Restructuring of visual pathways and impact of lesions of the primary visual cortex sustained in adulthood (*A*) or on the day of birth (*P1*). Yellow identifies neuron degenerations, degraded neuronal properties, lowered activity levels, and impaired visually guided behaviors. Red identifies spared neurons, expanded pathways, neural compensations (receptive field properties or activity levels), and sparing of visually guided behaviors. For clarity, cortical projections to superior colliculus are not shown. OKN = Optokinetic nystagmus; LGN = lateral seniculate nucleus; LP/Pul = lateral posterior/pulvinar complex; SC = superior colliculus.

Data are drawn from Berman and Cynader (1976); Callahan and others (1984); Cornwell and Payne (1989); Cornwell and others (1978, 1989); Doty (1961, 1973); Guido and others (1990a, 1990b, 1992); Kalil and Behan (1987); Kalil and others (1991); Labar and others (1981); Lomber and others (1993, 1995); Long and others (1996); MacNeil and others (1996, 1997); Mendola and Payne (1993); Murphy and Kalil (1979); Payne and Lomber (1996, 1998); Payne and Rushmore (2001); Payne and others (1984, 1991, 1993, 1996b); Rowe (1990); Spear and Baumann (1979); Spear and others (1980); Sun and others (1994); Tong and others (1982, 1984); Tumosa and others (1989).

For example, visual performance based on acuity and form-learning and -memory tasks that require discrimination of patterns with surround masking distractors is no better in the cats with early lesions than in cats that sustained the same lesion in adulthood (Table 1, column 5, rows 1 and 10, yellow cells). This latter, cognitive deficit reveals permanently impaired cerebral functions. However, the same cats have high proficiencies discrim-

inating simpler forms or figures obscured by an overlain masking grid, and they are superior to the diminished performances of cats that sustained primary visual cortex lesions as adults (column 4, rows 9 and 11, red). Sparing on this set of pattern discriminations with overlain grids is also complete, or almost complete, if the lesions incurred in infancy are made in two stages with 3 days between operations (row 11 *). These tasks are normally associated with the visuotemporal cortex (column 1). There is also overall superior performance on tasks normally associated with the visuoparietal cortex such as judging depth, optokinetic nystagmus, and reorienting of visual attention (rows 2–5). On some tasks, such as orienting, the same cats benefit from additional training (Payne and Lomber 2001). The superior performance by cats on the visuotemporal and visuoparietal tasks, compared to cats with lesions sustained in adulthood, is strong evidence for sparing of a constellation of visually guided behaviors and underlying neural operations, and they must be accompanied by significant adjustments in brain connections. Like cats with lesions sustained in adulthood, there is little detectable impact of earlier lesions on the ability to discriminate between highly dissimilar objects or on auditory orienting (rows 6 and 7).

Many neurons in structures distant from the lesion die, whereas others survive. For example, 90% or more of the X-cells in both retina and LGN die (Fig. 2*B*, yellow shading), whereas W and Y cells survive and they form the platform for pathway expansions and neural compensations (Fig. 2*B*, green and red shading). The surviving W and Y ganglion cells increase the density of their projections to the parvocellular (P) layers of LGN and establish a new projection to the lateral posterior nucleus (LP; Fig. 2*B*). In addition, the spared neurons in the magno-(M) and parvo-cellular layers of LGN contribute to increased projections to the visuoparietal cortex. Their numbers, though, are surpassed by the expansion of an already significant projection from the medial component of the lateral posterior/pulvinar complex (LP/Pul) that receives substantial visual signals fed forward from the superior colliculus. In toto, they provide a massive expansion of visual projections into the visuoparietal cortex. This expansion has a parallel in the increased numbers of neurons in the visuotemporal cortex that also project to the visuoparietal cortex, and probably in the reciprocal pathway. All of these expansions are accompanied by at least maintenance, if not an increase in overall level of neural activity in brain pathways (green and red shading, respectively), and sparing of receptive field properties of binocularity and direction selectivity in the cortex. Together, they provide additional measures of neural compensations induced by early lesions of the primary visual cortex.

Linkages—Behavior, Neuronal Properties, and Anatomy

The data summarized above become more fully comprehensible in the context of experimental results showing that there is no evidence for sparing of visually guided behaviors when the early lesion includes visuoparietal and visuotemporal regions in addition to the primary visual cortex, because performance in the early lesion group is inferior to that of cats with lesions limited to the primary visual cortex, and it is as poor as performance in the adult-lesion group (Cornwell and others 1978; Shupert and others 1993). The poor performance is understandable because these larger lesions eliminate all, or virtually all, of the cerebral cortical machinery for the processing of visual signals. From these data we conclude

1. that an appropriate system-substrate needs to remain for neural compensations to emerge and
2. that the substantial expansion of pathways into and out of the visuoparietal cortex, and possibly the visuotemporal cortex, are obligatory components of the neural compensations that overcome numerous otherwise profound deficits in neural performance and behavior.

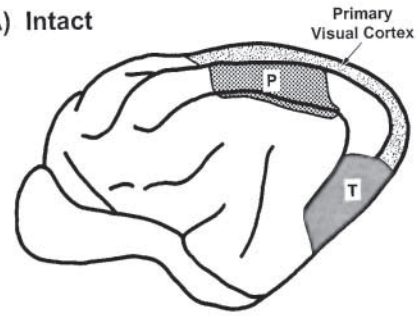
However, the compensations are not complete because the magnitude of the sparing does not equate with the highly proficient performances by intact cats and because neurons in the visuoparietal cortex do not adopt properties of neurons eliminated by the ablation of the primary visual cortex (Guido and others 1992). Thus, it appears that the visuoparietal cortex is able to compensate and establish a normal set of properties, but it cannot adopt attributes of eliminated cortices. Evidence for neuronal compensations in the retina and lateral geniculate nucleus are currently lacking.

Although it is straightforward to comprehend how pathway expansions are adaptive and contribute to the neural compensations, the contribution of neuron death and elimination of neural circuits to the compensations is less comprehensible. We interpret the deaths as purging the brain of poorly connected and largely superfluous neurons that may otherwise interfere or dilute signal processing. The net outcome, then, of the degenerations is a more efficient and accurate processing of signals in the remaining circuits, which we speculate are prerequisites for more normal levels of neuronal processing and accurate performance on a number of perceptual and cognitive functions by cats with early lesions.

A Different Brain?

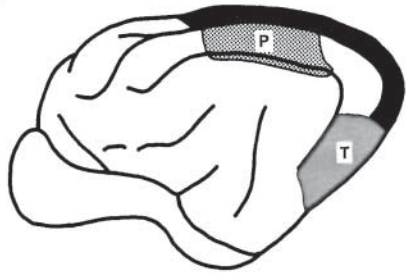
In the intact brain, each region of the cerebral cortex is unique in terms of its architecture, connectional signature, functional maps, inventory of receptive field properties, and its contributions to neural processing and behavior. But the multiple repercussions of the early lesions of the primary visual cortex modify all of these attributes, and we conclude that the early lesion triggers the development of a different brain, and we are prompted to ask: Is there a redistribution of functions across the modified expanse of the cerebral cortex? For example, functions normally localized to one region may become

A) Intact



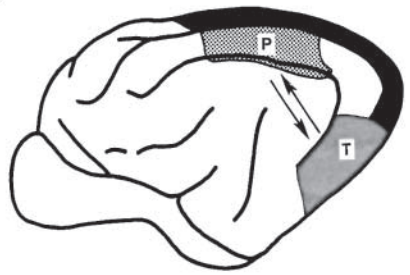
	Visual Orienting	Pattern Recognition	Object Recognition	Auditory Orienting
Performance	++++	++++	++++	++++
Parietal Deactivation	↓↓↓↓	0	0	0
Temporal Deactivation	0	↓↓↓↓	↓↓↓↓	0

B) Adult Ablation



	Visual Orienting	Pattern Recognition	Object Recognition	Auditory Orienting
Performance	+	+	+++	++++

C) Infant Ablation



	Visual Orienting	Pattern Recognition	Object Recognition	Auditory Orienting
Performance	+++	+++	+++	++++
Parietal Deactivation	↓↓	↓	0	0
Temporal Deactivation	↓	↓↓	↓↓↓	0
Parietal & Temporal Deactivation	↓↓↓	↓↓↓	↓↓↓	0

Fig. 3. Performance of Intact (*A*), Adult lesioned (*B*), and infant (*P1*)-lesioned (*C*) cats on 1) visual orienting, 2) complex-pattern recognition, 3) object recognition, and 4) auditory orienting tasks, and the impact of cooling deactivation of visual parietal and visual temporal cortices. Color conventions are summarized for Table 1. In addition, for impact of cooling deactivation: light blue = maximum deficit; intermediate blue = substantial deficit; dark blue = lesser deficit. Behavioral performance: ++++ = highly proficient performance; +++ = competent performance; ++ = modest performance; + = poor performance. Impact of cooling: ↓↓↓↓ = Proficiency on task is abolished or reduced to chance levels; ↓↓↓ = severe reduction in performance; ↓↓ modest reduction; ↓ = minor reduction. In *C*, note should be made of initial proficiency prior to cooling. For example, on the orienting task there is considerable sparing of function, but performance is not at normal levels, and it is designated "+++". During combined cooling of visuoparietal and visuotemporal regions, the cat is unable to reorient its attention, and the reduction in performance is designated "↓↓↓" and impact of the cooling is maximal.

Data drawn from Lomber and others (1996a, 1996b); Lomber and Payne (1996, 2001); Payne and others (1996a); and unpublished data.

dispersed across a broader region of the cerebral cortex as signals are redistributed. Anatomical evidence to support this view is provided by the expanded projection from the visuotemporal cortex to the visuoparietal cortex and in the reciprocal direction (Fig. 2*B*), as well as by the expanded projection from the visuoparietal cortex that reaches the visuotemporal cortex via the superior colliculus and LP/Pul (not shown). Thus, it may be that the processing of signals in the visuoparietal cortex is altered in significant ways by the signals arriving from the visuotemporal cortex and vice versa.

The first experiments to test this proposition have been carried out. The tests have used localized cooling, via subdurally implanted cooling loops, to reversibly deactivate the visuoparietal and visuotemporal cortices in behaving cats in conjunction with four tasks: 1) visual orienting, 2) pattern recognition, 3) object recognition, and 4) auditory orienting (Fig. 3). In intact cats, visual orienting is completely abolished by cooling deactivation of the visuoparietal cortex (Fig. 3*A*, column 1, light blue cell) but is completely unaffected by cooling deactivation of the visuotemporal cortex. In contrast,

pattern- and object-recognition processes are completely disabled by cooling deactivation of the visuotemporal (Fig. 3*A*, columns 2 and 3, light blue cells), but not the visuoparietal, cortex, and deactivation of neither region has an impact on orienting to a sound stimulus (Fig. 3*A*, column 4, open cell). Following visual cortex lesion in adulthood, performance on both the visual orienting and pattern recognition tasks is severely impaired (Fig. 3*B*, yellow cells), but without significant impact on object recognition or auditory orienting (Fig. 3*B*, green cell). As indicated earlier, the early lesion of the primary visual cortex largely spares visual orienting and complex-pattern recognition and has only minor impact on object recognition and no impact on auditory orienting (Fig. 3*C*, red cells). Cooling deactivations reveal that visual orienting remains strongly dependent upon the visuoparietal cortex. However, the dependence is not complete, because full deactivations, as revealed by modified 2DG uptake, do not completely abolish orienting, as it does in intact cats (Fig. 3*C*, column 1, intermediate blue cell). In the very same cats, independent cooling deactivation reveals a new essential contribution of the visuotemporal cortex to high proficiency on the task (column 1, dark blue cell). Moreover, the impact of combined visuoparietal and visuotemporal deactivations does not exceed the impact of the sum of the independent deactivations (column 1, light blue cell). This result suggests that no other region than the visuotemporal cortex acquires a role in guiding visual orienting movements.

In the opposite direction, visuotemporal-unique representations spread to the visuoparietal cortex. For example, cooling deactivation of the visuotemporal cortex in cats that sustained early lesions of the primary visual cortex impairs performance on pattern discriminations as it does in intact cats. However, in the cats with early lesions, the reduction is less profound and does not reach chance levels exhibited during visuotemporal cooling in intact cats (cf. blue cells in columns 2 and 3, Fig. 3*A* and *C*). However, in the very same cats, there is also a reduction in proficiency of performance on the pattern recognition task when the visuoparietal cortex is deactivated (dark blue cell). Moreover, during the visuoparietal deactivation, the cats can relearn the task, whereas there is no evidence that performance can improve during visuotemporal deactivation. The visuoparietal cortex does not contribute to visual discrimination of three-dimensional objects, which remain critically dependent upon the visuotemporal cortex alone, as it does in intact cats (column 3). Thus, following the early lesion of the primary visual cortex, the visuoparietal cortex also contributes to the recognition and discrimination of complex, masked patterns that require processing of signals across extensive regions of the cortex. Presumably, in intact cats, a significant fraction of this essential processing is carried out in the primary visual cortex. These observations demonstrate a functional reorganization of neural substrates contributing to visually guided behaviors; there is a muted role of the visuoparietal cortex and a heightened role of the visuotemporal cortex in guiding orienting behavior with the converse pertaining to the neural bases of complex pattern discriminations. Nevertheless, the visuotemporal cortex remains critical for the relearning of overlearned and simpler pattern discriminations.

These data show that at least two highly localizable functions of the normal cerebral cortex are remapped across the cortical surface as a result of an early lesion of the primary visual cortex. Moreover, the redistributions have spread the essential neural operations underlying orienting behavior from the visual parietal cortex to a normally functionally distinct type of cortex in the visual temporal system, and in the opposite direction for complex-pattern recognition. However, it is not known if there is a "price" to pay for the redistribution, or if functions normally associated with respective regions are reduced, displaced, or "crowded out" as proposed by Teuber (1975), as the regions make contributions to new aspects of visually guided behavior not normally represented. This change in function is a possibility because it is known that visuospatial abilities are reduced when sparing of language functions can be demonstrated in humans (Milner 1974; Teuber 1975).

Parallel Sequelae of Early Visual Cortex Lesions in Monkeys and Humans

The knowledge gained in the studies on the cat visual system are matched by compatible, although much less comprehensive, data collected on the repercussions of early visual cortex lesions in monkeys and humans.

Monkeys

To our knowledge, only two studies have specifically investigated the behavioral sequelae of early visual cortex lesions in monkeys. Both show a level of performance that is superior to that of monkeys with the same size and location of lesion sustained in adulthood. For example, monkeys that sustained lesions at 5 to 6 weeks of age can detect and localize stimuli within a cortical "scotoma" with a greater level of accuracy than monkeys with later acquired lesions, and performance does not depend upon the type of testing paradigm as it does after adult lesions where forced-choice methods are essential for revealing residual visual capacities (Moore and others 1996a). Moreover, for the early-lesioned monkeys extensive testing benefited performance, which eventually approached normal levels (Moore and others 1996b). This sparing of visual functions and benefit of training are akin to the results on detection and orienting tasks applied to cats (Shupert and others 1993; Payne and others 2000; Payne and Lomber 2001). The early-lesioned monkeys were also effective at discriminating differences in the direction of motion of dot fields, but only when the size of the moving field is large (Moore and others 2001). These results suggest that the monkeys with early lesions develop a visual system that differs in fundamental ways from that remaining after a lesion sustained in adulthood, a conclusion concordant with data on cats.

The anatomical data gathered from monkeys are focused on neuron degenerations in retina and LGN, and no studies have attempted a comprehensive analysis of pathways modified by visual cortex lesions. Overall, the neuron degenerations broadly parallel those identified in cats. For example, pathways characterized by high connectivity with the primary visual cortex, such as LGN and certain classes of retinal ganglion cells, are largely eliminated from the brain following the visual cortex lesion (Dineen and Hendrickson 1981; Weller and Kaas 1989), and there is virtually complete retraction of retinal projections from both the parvocellular and magnocellular layers of the LGN (Weller and Kaas 1989). The only relevant data on pathway expansions shows that residual neurons in the LGN hypertrophy following early damage of the primary visual cortex (Hendrickson and Dineen 1982), and this observation suggests that the neurons expand their dendritic arbors in the LGN, to accept greater numbers of retinal inputs, and expand their axon arbors in the extrastriate cortex to contact greater numbers of target neurons. However, it is not known if the early lesion triggers a recruitment of neurons to the direct projection from the LGN to extrastriate cortex. Such a recruitment is a possibility because evidence suggests that some LGN neurons project transiently to parts of the extrastriate cortex early in life (Webster and others 1995; Sorenson and Rodman 1996, 1999). If correct, such an expansion would resemble the expansion of the projections from the LGN to the visuoparietal cortex triggered in cats by early lesion of the primary visual cortex (Kalil and others 1991; Lomber and others 1995). Regardless of pathway modifications, the residual visual capacities of the monkeys are derived from both W and Y ganglion cells, as they are in the cat. However, whatever visual capacities are spared, they are likely to be counterbalanced by the large loss of X ganglion cells, which greatly attenuate other types of functions, such as discrimination of fine details, reduced contrast sensitivity (Miller and others 1980), and substantial impairments in color vision (Schilder and others 1972).

Humans

Tests of visual performance of humans that have incurred lesions of the primary visual cortex in infancy or childhood are as limited as those in the monkey, and reports are largely confined to case studies. Even so, they do reveal visual capacities that are superior to those of individuals that sustained damage of the primary visual cortex when mature.

Girl MS was studied by Innocenti and others (1999). She was born prematurely at 30 weeks gestational age and suffered bilateral ischemic damage of the primary visual cortex as a result of bacterial meningitis at 6 weeks of age. Longitudinal testing has shown that subject MS has grown out of initial deficits and she matches performance of children of her own age on a variety of tasks including spatial and contrast sensitivity measures, figure-ground segmentation based on textures, and vernier visual acuity. Performance is very high on the figure-ground tasks when figure and background differ in luminance, color, or motion, and different brain pathways are used to make the discriminations. However, she has maintained a severe impairment on "Poppelreuter" (1917) figures that require extraction of forms from multiple overlain outlines. These results reveal selective sparing on some visual cognitive tasks, but permanent deficits on others.

Lesions acquired somewhat later in childhood produce a different picture. For example, subject GY incurred unilateral destruction of the primary visual cortex when he was 8 years old as a result of head injury sustained in a traffic accident (Weiskrantz 1986). He makes saccadic eye movements into the blind hemifield, he is able to follow the path of a moving spot with arm movements, and he can discriminate between opposite directions of movement and between targets moving at different speeds, although he is not conscious of the presence of the stimulus (Barbur and others 1980, 1988, 1994). These features are shared with other subjects with lesions of the primary visual cortex, but sustained later in life.

What distinguishes GY from the other subjects is that he can switch to an aware mode where he is conscious of the presence of stimuli and can verbally report on stimulus position, aspects of spectral content, and the direction and velocity of stimulus movement providing that the size, contrast, displacement, and velocity are high enough (Barbur and others 1993; Brent and others 1994; Weiskrantz and others 1991, 1995). Regional cerebral blood flow studies indicate that high visually guided performance in the unaware mode is linked to activity in the superior colliculus (Sahraie and others 1997), whereas that in the aware mode is linked to activity in the cerebral areas V3, V5,[2] 7, and 46 (Barbur and others 1993; Sahraie and others 1997). In both modes, medial and orbital prefrontal cortices are also active (Sahraie and others 1997). These results show that visual signals reach visuoparietal (areas V5 and 7) and frontal (area 46) cortices along pathways that bypass the damaged the primary visual cortex and that these signals are sufficient in themselves for visual discriminations, conscious awareness, and ability to verbally report at least some stimulus attributes. These pathways may include limbs that pass through the superior colliculus and the pulvinar nucleus, or residual projections to surviving neurons in the LGN that project to visuoparietal regions as described above for the monkey, which seem to be able to activate visuoparietal visual cortices with a lag of only 20 mSec (Rossion and others 2000).

Functional MRI studies show that GY differs from subject FS who sustained a lesion much later in life at age 42 years (Goebel and others 2001). In GY, neural activity levels in the ipsilesional area V5 complex generated by stimuli presented within the scotoma matched activity levels in the contralesional area V5 complex

2. Primate area V5 complex is a topologue of the cat middle suprasylvian cortex, and both lie within visuoparietal cortex (Payne 1993).

generated by stimuli presented in the sighted hemifield. In contrast, the ipsilesional V5 complex in FS showed no significant activity when stimuli were presented within the scotoma. Largely congruent results were obtained for areas V4/V8 in the two subjects, and both subjects showed activation of area LO. Goebel and others (2001) suggest that the greater strength of ipsilesional activity in subject GY results from plastic changes of the system compensating for the loss of area V1, which is the normal major input to area V5 complex. Moreover, they suggest that the enhanced activation results from the much earlier lesion sustained by GY than by FS. The posited view builds upon an earlier suggestion and detailed enumeration of pathways (Payne and others 1996b) that might contribute to the spared visual capacities exhibited by GY relative to other subjects that sustained lesions of area V1 later in life. What is new from the study of Goebel and others (2001) is that there are areas in the visuotemporal system that are active following early damage of area V1, a result that may have been predicted from earlier work on the repercussions of early visual cortex lesions in cats (Doty 1961; Cornwell and others 1978; Payne and others 1996b).

Corroborating, but less expansive, data are available from other subjects (HW and RL), who also incurred damage of the primary visual cortex in childhood (ages 1 and 8; Blythe and others 1987). They both perform almost as well as GY on a visual localization task (Blythe and others 1987), which sets them apart from 20 other subjects included in the same study, who incurred their damage later in life. Unfortunately, there are no published data on whether or not patients HW and RL can report conscious awareness of stimuli in their defective fields, or on levels of activity in prestriate regions of the visual cortex.

Parallel Sequelae of Early Lesions in Other Systems

The observations made on the ramifications of early lesions of the primary visual cortex are corroborated in studies of the impact of early lesions in other cerebral systems. For example, studies of the repercussions of early lesions of the sensorimotor cortex also reveal functional reorganizations, but they involve the contralateral sensorimotor cortex rather than circuits in the damaged hemisphere. For example, fMRI- and somatosensory-evoked potentials reveal that both passive movement of a hemiplegic hand and median nerve electrical stimulation produce foci of activation in the ipsilateral sensorimotor cortex (Holloway and others 2000). Likewise, magnetic brain stimulation of the intact motor cortex evokes compound muscle action potentials in the ipsilateral upper limb that are consistently shorter in latency and larger in amplitude than the equivalent potentials evoked in patients with later acquired damage (Benecke and others 1991). In these studies, a possible transcallosal component to the pathway has been ruled out, and it is likely that the effects are mediated via expanded direct and disynaptic ipsilateral cortico-spinal pathways. Broadly compatible results have been obtained in studies on sensorimotor lesions in young monkeys and cats (Soltmann 1876; Leonard and Goldberger 1987; Murakami and Higashi 1988; Rouiller and others 1998; Liu and Rouiller 1999).

Language

There is substantial evidence for functional sparing in the neural system that subserves human language. The plasticity in this system is likely strongly linked to the highly distributed nature of the representation and control of language production and its inherent adaptability even in the intact brain. Numerous studies have provided evidence that the right hemisphere can take over many aspects of language function following lesions in the left cerebral hemisphere providing that the lesions are sustained prior to age 6 (Rasmussen and Milner 1977). Vargha-Khadem and others (1985) concur with this view and add that the crucial variables governing sparing of language functions are not severity of lesion but age at injury and hemispheric side of lesion.

Finally, one case report is worth commenting on because it reveals that we are only starting to grasp the plastic potential of the cerebral cortex, because it challenges the widely held view that early childhood is a particularly critical period for acquisition of speech and language. Subject Alex failed to develop speech and, as he developed, comprehension remained stagnant at an age equivalent of 3 to 4 years (Vargha-Khadem and others 1997). At 8.5 years of age, he underwent left hemispherectomy, and 6 months later anticonvulsants were withdrawn. Following these procedures, Alex started to acquire receptive and expressive speech and language, and these faculties improved markedly over succeeding years. He has not suffered any serious permanent disadvantage of his protracted period of mutism and severely limited comprehension because his language abilities are commensurate with his mental age, which is somewhat retarded. Even so, his case shows that clearly articulated, well-structured, and appropriate language can be acquired for the first time as late as age 9 years with the right hemisphere alone (Vargha-Khadem and others 1997).

Epilogue

Over the preceding 2 decades, we have learned a great deal about the plastic capacities of the connections in the young cat brain, shown that the wiring is adaptive and that it results in functional neuronal compensations and the sparing of visually guided behavior. These advances have been possible because of the great suitability of the cat, its visual system, and its developmental program to intervention by experimentalists. The advances have been particularly rapid in recent years with the sound application of experimental methods and the application of methods to quantify the lesion-induced changes. Although these studies have intrinsic merit, they also have a broader context and applicability for increasing our understanding of the repercussions of early lesions

in other parts of the cerebral cortex, and on their associated systems, and in humans.

Even with the progress that has been made in recent years, much more needs to be done. It is important to identify accurately the cerebral and subcortical functions that are spared or impaired by the early lesions so that we have a more accurate picture of the substantial flexibility of the immature brain. It is also important to localize functions in the rewired brains, just as attempts have been made to localize functions in the intact brain. Such studies have the potential to reveal much about the plastic properties of the cerebral cortex and associated systems. Initial studies point us in the right direction by showing that normally highly localizable functions of the cerebral cortex can become remapped across the cortical surface as a result of the early lesion. In so doing, the remappings produce a different brain. However, it is not known if there is a price to pay, or if functions are crowded out, when one lobe contributes to neural processing normally localizable solely within another lobe. Another extremely important avenue of investigation is the analysis of the rewired and massively depleted retina. This is an essential activity because the retina is the gateway through which all visual signals must pass to influence the brain and ultimately behavior.

The key element in the brain reorganization is the enormous potential of immature neurons to modify connections and to contribute to neural compensations, and the high neural performance characteristic of organized behavior. Yet, it is clear that a comprehension of the repercussions of early cerebral lesions requires the application of multiple approaches to elucidate the brain rewirings and neuron degenerations, to ascertain modifications in neural activity, and to link these repercussions to spared behavior. There is no doubt that in the coming years, comprehension of the repercussions of early cerebral lesions will benefit greatly from the cellular and molecular analytical approaches that are designed to elucidate why some neurons die whereas others survive, how neurons redirect axons to new targets whereas others do not, and how signals delivered by the redirected axons influence the activities of target neurons. These are all important and worthy avenues of investigation in experimental animals. In the human arena, identification of spared and impaired functions, as well as imaging of a battery of cerebral functions in individuals with circumscribed lesions acquired across a spectrum of ages, will be enormously beneficial.

Finally, we hope that future studies will also come to recognize the plastic capacities of the immature human brain that permit it to overcome major challenges to its normal development. We are optimistic about this possibility because studies on a variety of systems in laboratory animals and humans foster the view that the immature brain is highly plastic and that several neural functions severely impaired by lesions sustained in adulthood are spared, or partly so, following equivalent lesions sustained early in life. Once the sparing and plastic capacities are identified, we anticipate that enriched environments and training strategies may be usefully employed to potentiate the natural capacity of the brain to overcome the challenges and contribute to considerable neural compensations, sparing of neural functions, that result in relatively normal organized behaviors.

Medicinal, pharmaceutical, or biological treatments such as neural transplants may also be used one day to extend the therapeutic strategies further. The promise of these directions is pointed to by the observations that amphetamine attenuates the defects in depth discrimination by cats with visual cortical lesions (Feeney and Hovda 1985; Hovda and others 1989), and transplants of embryonic visual cortex or extracts of embryonic visual cortex slow the retrograde degeneration of LGN neurons after visual cortical lesions in rats (Cunningham and others 1987; Haun and others 1989; Eagleson and others 1992; Haun and Cunningham 1993). Moreover, instances in which the cortex may need to be removed surgically may benefit from procedures carried out in two or more stages. Multistage procedures afford a greater level of functional sparing compared to removals made in one stage (Cornwell and Payne 1989), presumably by allowing tissue remaining at each stage to contribute to compensatory adjustments that are not possible following large, single-stage removals. We hope that similar strategies can be employed to enhance the modification of pathways, slow the degeneration of neurons, and boost the faculties spared subsequent to lesions of the immature visual cortex. In the end, it is likely that multiple strategies may need to be adopted to attenuate deficits and maximize the natural capacity of the brain to minimize disruption to function following lesions.

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