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Blindness and Human Brain Plasticity

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Abstract

Early blindness causes fundamental alterations of neural function across more than 25% of cortex—changes that span the gamut from metabolism to behavior and collectively represent one of the most dramatic examples of plasticity in the human brain. The goal of this review is to describe how the remarkable behavioral and neuroanatomical compensations demonstrated by blind individuals provide insights into the extent, mechanisms, and limits of human brain plasticity.

INTRODUCTION

The sensory experience of a blind individual is very different from our own. When, fed up with Palatino 11 point, I look up from my computer screen, I notice my cluttered desk, gray skies, and raindrops rolling down the window pane. When I close my eyes my world changes; I become aware of the sound of the downpour. Suddenly the heated debate between my husband and child impinges and is no longer, perceptually, in another room. Yet, despite a sensory experience that is continuously different from our own, blind individuals do not have difficulties understanding sighted language and concepts, and many navigate fluently in a sighted world.

As shown in **Figure 1*a***, the neurophysiological changes that result from blindness (see the sidebar titled Blindness) are driven by two interrelated environmental components: the lack of vision and the resulting need to rely more heavily on remaining senses. Consequently, early blindness causes fundamental alterations of neural function across more than 25% of cortex—changes that span the gamut from metabolism to behavior and collectively represent one of the most dramatic examples of plasticity in the human brain.

WHY STUDY BLINDNESS?

Since the 1960s, blindness has been a classic model system for studying neuroplasticity (Wiesel & Hubel 1963, 1965). Animal models of blindness are easy to generate, and the lack of direct

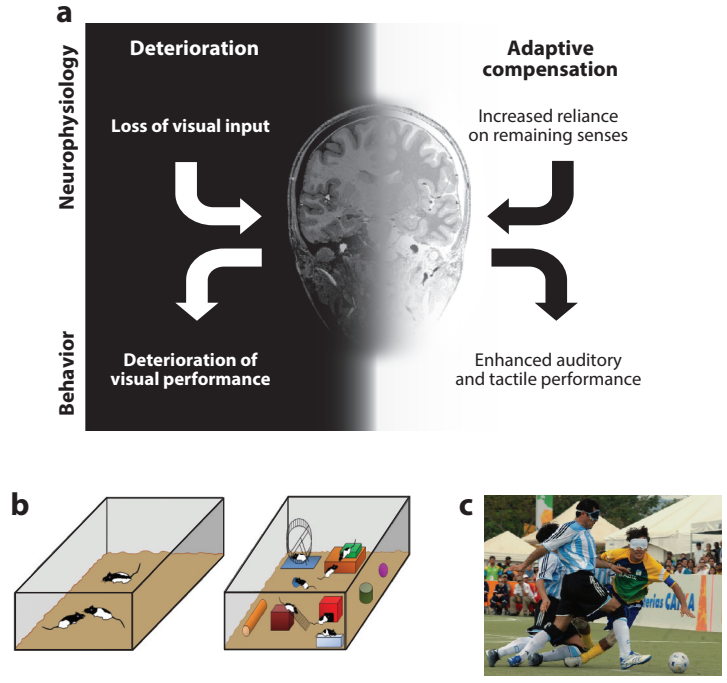

Figure 1

(*a*) Early blindness has widespread neurophysiological consequences. These include deterioration of neural function and visual function resulting from loss of visual input and compensatory alterations that enhance the ability of blind individuals to make sense of auditory and tactile input. Many of these compensatory alterations may be driven by the need to interact with the world. (*b*) Animal models suggest that the basic neuroanatomical consequences of dark rearing can be entirely different when animals must learn to solve tasks like navigation and food finding using their remaining senses. Panel *b* adapted with permission from Bengoetxea et al. (2012). (*c*) Brazil plays Argentina in a soccer final at the 2007 Parapan American Games.

BLINDNESS

Blindness is an extremely general term. Individuals can become blind at any age, and the extent of their visual loss can vary widely. When it comes to assessing very low vision that falls below measurable Snellen acuity, the following terms are in standard use. For this review the term blindness refers to vision of light perception or below, unless otherwise specified. The common terms that refer to visual loss are defined as follows:

- Legally blind, in the United States, means vision of 20/200 or less in the better eye or a field of view smaller than 20°.
- Finger counting means an individual can tell how many fingers the ophthalmologist is holding up.
- Hand motion means an individual can tell that the ophthalmologist is waving a hand in front of their eyes.
- Light perception means an individual can tell if the lights in a room are on or off, which is roughly equivalent to a normally sighted individual's perception with their eyes closed.
- No light perception means an individual cannot tell whether the lights in a room are on or off.

cortical damage provides an elegant model system for examining the role of experience on the development and maintenance of neuroarchitecture and function. These animal models provide an extraordinarily rich literature to complement the investigation of the effects of blindness in humans.

Of course, care must be taken in generalizing from animal models to humans. Blindness occurs at a variety of stages of development in humans (see the sidebar titled Blindness Occurs at Many Stages of Development), whereas animal models rely heavily on enucleation or dark rearing. There are large neuroanatomical differences between primate and nonprimate visual systems. Humans are born with relatively mature visual systems compared to most animals, and the human visual system contains a larger number of visual sensory areas than the nonprimate visual system (van Essen 2005). In addition, the primate neuronal organization, even within early visual areas, shows substantial differences from rodent models (Disney & Aoki 2008, Disney et al. 2006).

Another, often overlooked, factor is that many of the compensations that occur because of blindness are likely driven by the need to navigate and interact with the world. Yet most animal

BLINDNESS OCCURS AT MANY STAGES OF DEVELOPMENT

Anophthalmia is an extremely rare condition where the eye fails to develop. As such, individuals lack retinal waves, and the input from the optic nerves to the thalamus and midbrain either never exists or exists only temporarily early in development before the embryonic eyes degenerate.

Congenital blindness is defined as a condition where retinal waves persist in utero, but there is loss of visual information to the brain at or very shortly after birth (within one month). Common causes of congenital blindness include retinopathy of prematurity and optic nerve hypoplasia. In the latter two conditions individuals generally retain light perception vision.

Early blindness refers to individuals blinded after birth but before age 16. Although this may appear to be a wide age range, evidence suggests that the early teenage years do represent a critical period after which large-scale cross-modal plasticity is less likely to occur.

Late blindness refers to individuals blinded after the age of 16. Most cases of late blindness are due to retinitis pigmentosa, macular degeneration, and glaucoma. It should be noted that late-blind individuals generally suffer from a slower progression of vision loss than early-blind individuals, and often retain light perception vision.

deprivation studies are carried out using animals in restricted environments **(Figure 1*b*)**. The effect of environment can be dramatic; for example, dark-reared animals in standard cages show a striking reduction in the number of astrocytes compared to controls. In contrast, dark-reared animals in enriched cages have more astrocytes than control animals (Bengoetxea et al. 2013). These results suggest that even the basic neuroanatomical consequences of dark rearing can be very different when animals must learn to solve tasks like navigation and food finding using their remaining senses.

Finally, normally sighted humans depend far more heavily on vision than most nonprimate animals. It is difficult to behaviorally distinguish early-blinded cats or monkeys from sighted animals when they are in familiar environments; the same cannot be said of early-blind individuals, even those adept with cross-modal technologies. Individuals who are blind do not simply rely more heavily on their remaining senses; across almost every interaction with the world, blind people must rely on senses that in a sighted person would play a far more minor functional role.

Although blindness has traditionally been used as a model system for examining sensory plasticity, in recent years it has become increasingly apparent that blindness may also be an excellent way of studying human cognitive plasticity. My sighted sons in their (occasionally excruciatingly) prolonged developmental periods are learning to carry out a vast number of tasks that lie far outside normal evolutionary demands: reading, chess, algebra, and soccer (Dehaene & Cohen 2007). All these tasks have a strong visual component and presumably involve either the development of novel cortically specialized areas (e.g., reading) or involve developing hyperabilities within existing areas. A blind child can learn all these skills, but she or he will learn them very differently (**Figure 1*c***). There are good reasons to believe that much of the plasticity that occurs because of early blindness reflects the development or hyperdevelopment of cognitive rather than sensory processes. Blind individuals show enhanced capacities and/or neural plasticity within many tasks that are clearly cognitive, including language, reading braille, numerical processing, and memory. It is also worth noting that the critical learning period for early blindness extends into the teenage years (Sadato et al. 2002) when sensory processes are adult-like but cognitive processes are still developing. Thus, gaining traction on how the brain responds to early blindness is likely to provide important insights into the mechanisms that underlie the complex developmental plasticity that governs not only sensation but also cognition.

NEUROANATOMY

As schematized in **Figure 2**, the effects of early blindness can be seen across multiple neuroanatomical scales, from molecules to function.

Neurotransmitter Regulation

In normal development, the onset of visually evoked activity alters the balance between excitatory cholinergic phospholipid and inhibitory GABA-ergic pathways toward a state of greater inhibition that is associated with the closure of the critical period (Bavelier et al. 2010). Animal models suggest that visual deprivation delays or prevents this shift in inhibitory/excitatory balance (Hensch & Bilimoria 2012). Magnetic resonance spectroscopy studies in adult early-blind humans similarly find reduced levels of γ-aminobutyric acid (GABA) and enhanced levels of choline and possibly glutamate/glutamine (Coullon et al. 2015, Weaver et al. 2013) in occipital cortex. One interesting unanswered question is whether human blind individuals retain greater excitability or plasticity in occipital cortex in adulthood.

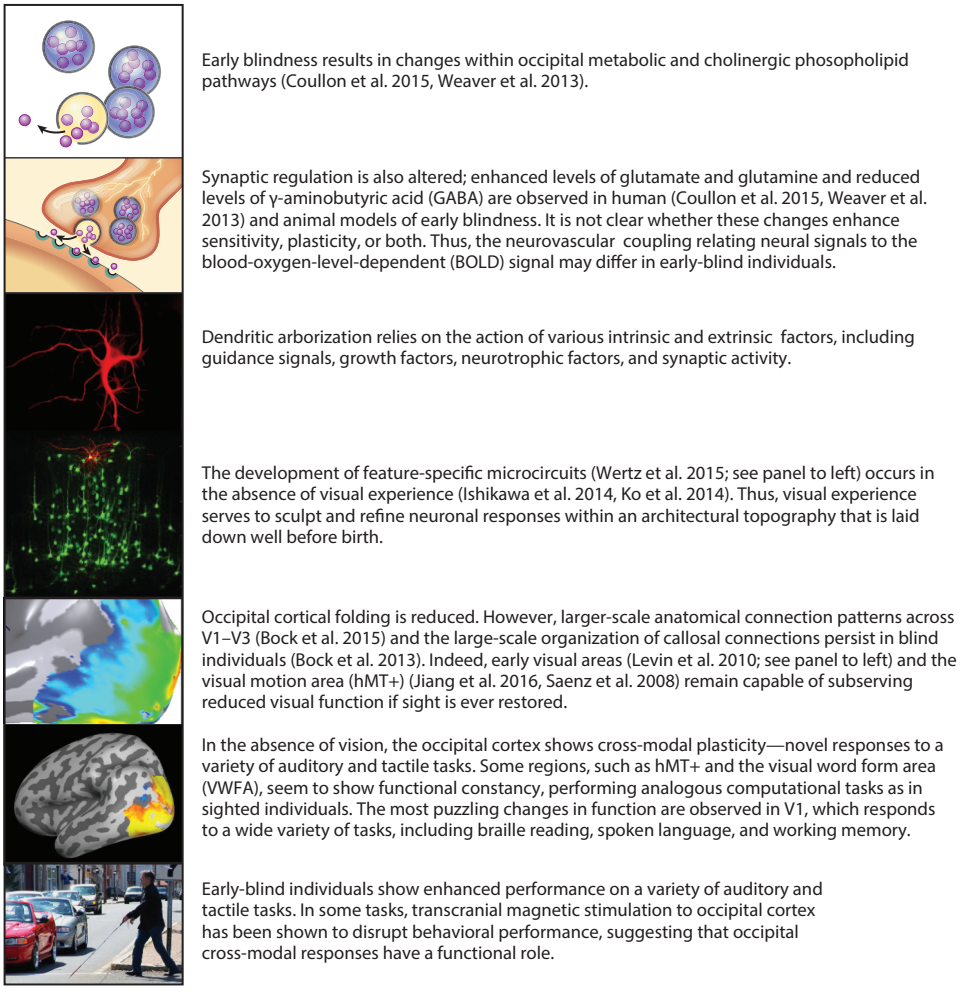

Figure 2

Blindness changes brain organization across multiple scales, from molecules to function: These alterations include neurotransmitter regulation, metabolic function, white matter pathways, cortical expansion and pruning, local synaptic connectivity, functional responses, and behavioral abilities.

Metabolic Pathways

As far as metabolism is concerned, in the 1990s positron emission tomography studies demonstrated that early-blind subjects exhibit greater levels of glucose metabolism and regional cerebral blood flow within the occipital cortex than sighted subjects (De Volder et al. 1997, Veraart et al. 1990, Wanet-Defalque et al. 1988), suggestive of metabolic upregulation. More recently, using magnetic resonance spectroscopy, it has been shown that early blindness leads to elevated levels of creatine (Coullon et al. 2015, Weaver et al. 2013), further supporting the possibility that early blindness leads to chronic upregulation of occipital metabolism. One possibility is that these increased metabolic demands are due to the increased resting-state firing that has been observed

in occipital cortex as a result of dark rearing (Benevento et al. 1992). Somewhat surprisingly, given this metabolic upregulation, dark rearing reduces occipital vascularization compared to control animals (Bengoetxea et al. 2008); however, this reduction in vascularization is less salient for animals in enriched cages.

The effects of early blindness within occipital metabolic and neurotransmitter pathways are not only significant in and of themselves, but are also an important consideration when interpreting group differences in blood-oxygen-level-dependent (BOLD) responses. In Alzheimer's disease, the importance of considering potential metabolic differences between groups when interpreting BOLD signals has already been demonstrated: Disease-related metabolic downregulation has effects on neurovascular coupling that in turn influence task-related BOLD activity (Herminghaus et al. 2003, Lecrux & Hamel 2011, Nicolakakis & Hamel 2011). Group differences in neurotransmitter levels are also likely to have substantial effects on neurovascular coupling: GABA-ergic and cholinergic pathways directly affect the coupling between neuronal and vascular responses (Donahue et al. 2010)—for example, via perivascular astrocytes (Cauli et al. 2004, Hamel 2006, Kleinfeld et al. 2011, Muthukumaraswamy et al. 2012).

White Matter Tracts

The anatomical effects of early blindness can best be interpreted in the context of normal development (see **Figure 3**). The early wave of migrating neurons provide a first rough blueprint of cerebral organization that is primarily governed by intrinsic signaling, controlled in part by graded expression of transcription factors (Dubois et al. 2014). These pathways begin to form well before the onset of visual experience, during the second trimester of pregnancy. This means that

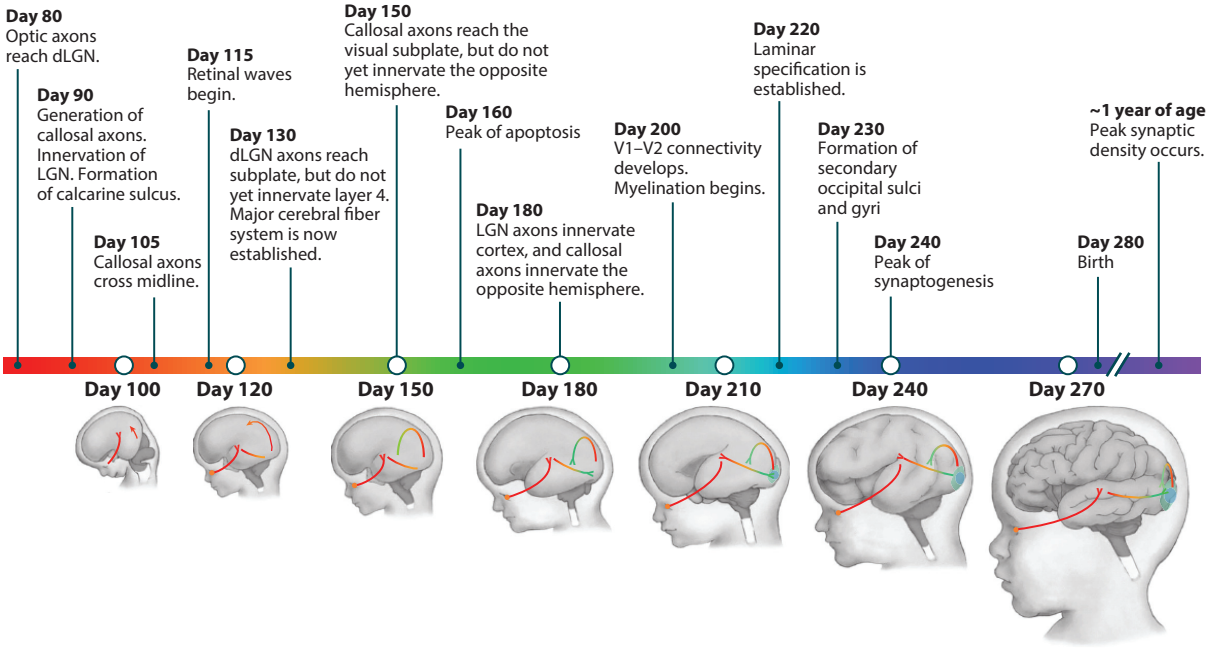

Figure 3

Time line for major events within the development of the human visual system. Event times are generally based on animal models, with conversion into human pre- and postnatal development based on the translating time model of Workman et al. (2013). Abbreviations: dLGN, dorsolateral geniculate nucleus; LGN, lateral geniculate nucleus.

the major cortical pathways have formed well before visual input reaches the cortex. For example, callosal axons cross the midline around prenatal day 105, well before input from the lateral geniculate nucleus (LGN) innervates the cortex (prenatal day 180). By prenatal day 120, the major cerebral fiber system is established.

Even though these pathways are established well before eye opening (Stellwagen & Shatz 2002), early blindness leads to significant reduction in visual subcortical white matter connections, including atrophy of the optic nerve and tract (from the eye to the lateral geniculate nucleus) (Bridge et al. 2009, Shimony et al. 2006, Shu et al. 2009). This atrophy extends to the optic radiations (from the LGN to V1) (Bridge et al. 2009, Noppeney et al. 2005, Shimony et al. 2006, Shu et al. 2009). Given that most cases of congenital blindness have onset after prenatal day 210 (except in the case of anophthalmia), it can be presumed that this reduction of white matter in visual subcortical pathways is due to atrophy after these pathways have formed.

Within early visual cortex, there is evidence that the topographical organization of white matter fibers in early blind individuals retains retinotopic organization. The large-scale topographical organization of visual fibers in the corpus callosum can be observed even in anophthalmic individuals (Bock et al. 2013). Similarly, enucleate animal models still show topographical organization of interhemispheric callosal fibers even though the local precision (on the order of microns) of arborization into gray matter lacks refinement (Bock & Olavarria 2011).

There is surprisingly little evidence for either reorganization or atrophy within corticocortical white matter pathways as a result of visual deprivation. The cortical connectome between the occipital cortex and other areas seems to be largely unaffected by blindness (see Bock & Fine 2014 for a review), though there is some evidence of a weakening of connections between the occipital and temporal cortex (Ptito et al. 2008, Shu et al. 2009). The lack of significant atrophy or reorganization in occipitocortical pathways (as compared to the pathways between the retina and V1) suggest that these connections play a functional role of some kind in early-blind individuals.

Recent evidence in neurotypical children suggests that white matter tract development both precedes and predicts the eventual location of functional responses within the ventral occipital cortex (Osher et al. 2016, Saygin et al. 2016). Thus, intracortical white matter tracts may help determine how cortical functionality is reorganized as a function of blindness (Bedny 2017). Bedny has argued that these white matter connections may determine function because gray matter is pluripotent. As described in the section titled The Reverse Hierarchy below, although gray matter may be surprisingly functionally pluripotent, this functional flexibility may exist within the context of a highly constrained local anatomical microstructure.

Cortical Expansion

Early blindness results in a reduction in cortical folding and an increase in cortical thickness in early-blind (Anurova et al. 2015, Jiang et al. 2009) and anophthalmic (Bridge et al. 2009) individuals. This increase in cortical thickness has generally been attributed to a lack of experience-dependent cortical pruning after birth.

However, Reillo et al. (2011) have proposed an alternative model. Cortical expansion relies heavily on a special type of progenitor cell that generates a fiber scaffold (at around prenatal day 120), which promotes tangential dispersion of radially migrating neurons and thereby facilitates surface area growth within the cortical sheet. This cortical expansion has a prolonged developmental time line; for example, in humans, the area of V1 does not reach its adult size until more than two years of age. Enucleation in ferrets reduces the density of these progenitor cells, and the resulting lack of tangential dispersion leads to a reduction in cortical surface area. This leads to an increase in cell density and cortical thickness (Reillo et al. 2011).

Human anatomical imaging shows that increases in cortical thickness are more pronounced in anophthalmic (~18% reported by Bridge et al. 2009) than early-blind individuals (~8% reported by Jiang et al. 2009), suggesting that both a prenatal reduction in progenitor cells and a reduction of postnatal pruning may contribute to increases in cortical thickness.

Local Synaptic Connectivity

Early enucleation has strong effects on local connectivity in subcortical pathways, leading to atrophy of the LGN in both animal models (Dehay et al. 1996a,b; Karlen & Krubitzer 2009; Wiesel & Hubel 1963) and individuals with anophthalmia (Bridge et al. 2009), atrophy of cortical input layer 4 (Dehay et al. 1996a, Karlen & Krubitzer 2009, Rakic et al. 1991), and a failure of layer 4 pyramidal cells to remodel into spiny neurons (Callaway & Borrell 2011).

However, many aspects of cortical synaptic microstructure develop relatively normally in the absence of visual experience. For example, the retinotopic organization of local connections across V1-V2-V3, whereby a region in V1 precisely connects with regions in V2 that eventually represent the same region of the retina (and so on though V3), occurs around prenatal day 200, only shortly after LGN axons innervate the cortex (prenatal day 180). This topographical organization seems to be primarily driven by molecular signaling (Abbott & Dayan 1999, Banton et al. 2001). Retinotopic maps in the dorsal LGN and cortex still exist when retinal waves are disrupted, but precision is reduced (Cang et al. 2005, Grubb et al. 2003, McLaughlin et al. 2003). Resting-state BOLD data also suggest the persisting existence of V1–V3 retinotopic organization in early-blind and anophthalmic individuals (Bock et al. 2015, Striem-Amit et al. 2015).

More recently it has been shown that feature-specific microcircuits in layers 2 and 3 develop even in the absence of visual experience (Ishikawa et al. 2014, Ko et al. 2014, Rizzi et al. 2014). Cells sharing the same stimulus preferences are preferentially connected to each other even in dark-reared animals (Ko et al. 2014). Visual experience serves to refine these circuits, consistent with earlier data suggesting that experience sculpts and refines the formation of ocular dominance columns and the size and orientation of receptive fields, as well as the spatial frequency, direction, and disparity tuning of V1 neurons (Ackman & Crair 2014; Movshon & Van Sluyters 1981; Raviola & Wiesel 1978; Sherman & Spear 1982; Wiesel & Hubel 1963, 1965). These animal model data are consistent with findings in sight-recovery subjects: Relatively normal (albeit low acuity) retinotopic and motion-selective responses can be measured in V1–V3 and the visual motion area (hMT+) in these individuals. Interestingly, these visual responses seem to coexist with auditory responses, suggesting that the auditory motion responses observed in blind individuals coexist with a neural architecture that can support visual processing if sight is ever restored (Jiang et al. 2014, Saenz et al. 2008).

Thus, visual experience does not establish neural response selectivities but rather sculpts and refines neural microcircuits that are established well before visual experience. These neural microcircuits may be analogous to complex-instruction-set processors in computers, which are designed to carry out a fixed sequence of computations that are applicable to a wide range of tasks. The innate structure of prenatal gray matter neural microcircuits may be designed to carry out canonical neural computations, such as addition (neural summation), subtraction (opponency), exponentiation, linear filtering, adaptation, and divisive normalization, which are assigned a functional role only with the onset of sensory experience.

FUNCTIONAL RESPONSES

One of the most extraordinary effects of early blindness is that individuals show large amounts of cross-modal plasticity. Large regions of occipital cortex that primarily process visual information

in sighted individuals show novel responses to auditory and tactile stimuli in individuals who become blind early in life (Sadato et al. 1996). These novel responses in occipital cortex are found for a bewilderingly wide range of auditory and tactile stimuli and tasks, including verbal working memory (Amedi et al. 2003), language (Bedny et al. 2011, Burton et al. 2003, Lane et al. 2015, Watkins et al. 2012), and mathematics (Kanjlia et al. 2016). Despite considerable effort, the principles underlying these changes in function remain mysterious.

Metamodal Plasticity

In 2001, Pascual-Leone & Hamilton (2001, p. 427) suggested that "the brain might actually represent a metamodal structure organized as operators that execute a given function or computation regardless of sensory input modality." Thus, the role of hMT+ is determining the motion of objects in space, the role of the visual word form area (VWFA) is decoding structured spatial information for reading, and the role of the fusiform face area is identifying the presence and identity of individuals. In sighted individuals, visual input provides the best source of information for these tasks, so vision becomes the primary input. According to the metamodal hypothesis, in blind individuals the neuroanatomical architecture of these areas should generalize to carrying out highly analogous computational tasks using auditory or tactile input.

Numerous studies have looked for tight homologies of function within well-established visual areas. hMT+ has been associated with auditory motion (Bedny et al. 2010, Jiang et al. 2014, Lewis et al. 2007, Poirier et al. 2006, Saenz et al. 2008, Wolbers et al. 2011). The VWFA has been associated with braille reading (Burton et al. 2002, Reich et al. 2011, Sadato et al. 1996), and the fusiform gyrus has been associated with voice processing (Gougoux et al. 2009, Hölig et al. 2014). Early-blind individuals taught to use auditory sensory substitution devices also seem to show activity in appropriate category-specific areas, including the extrastriate body area (Striem-Amit & Amedi 2014) and the VWFA (Striem-Amit et al. 2012a).

One concern is that the extent of the apparent similarity between early-blind and sighted individuals may be partly a consequence of experimental biases. Most experiments published so far have relied on measuring brain responses to stimuli and tasks that have been selected and categorized based on what makes intuitive sense to us as sighted scientists. Moreover, the metamodal hypothesis has led scientists to look for similarities rather than differences between early-blind and sighted individuals. Examining functional responses using a data-driven approach or selecting stimuli and tasks from a nonsighted perspective may yet reveal overlooked differences in the neural representations of blind and sighted individuals (Fine 2014).

A second concern is that when data are compiled across multiple studies, the anatomical alignment between sighted and blind responses becomes less clear. In **Figure 4**, it is not obvious that auditory motion responses cluster near hMT+, braille clusters near the VWFA, and voice localization clusters near the fusiform face area. One possible reason for this apparent discrepancy is that these areas are close to each other. Moreover, there is significant individual variability in the location of these areas, especially when using nonsurface-based alignment techniques. This can lead to spurious overlap when comparing the location of BOLD activations using group averaging techniques (Jiang et al. 2015, Saenz et al. 2008). Recent progress in defining category-selective areas using sulcal landmarks (Dumoulin et al. 2000, Weiner et al. 2014) may make it possible to more rigorously quantify the alignment between blind and sighted functional areas.

Other groups have focused on demonstrating looser homologies of structure and function (van den Hurk et al. 2017). For example, regions associated with visual object processing are implicated in the processing of haptic and auditory information about objects (Amedi et al. 2001, 2007), and

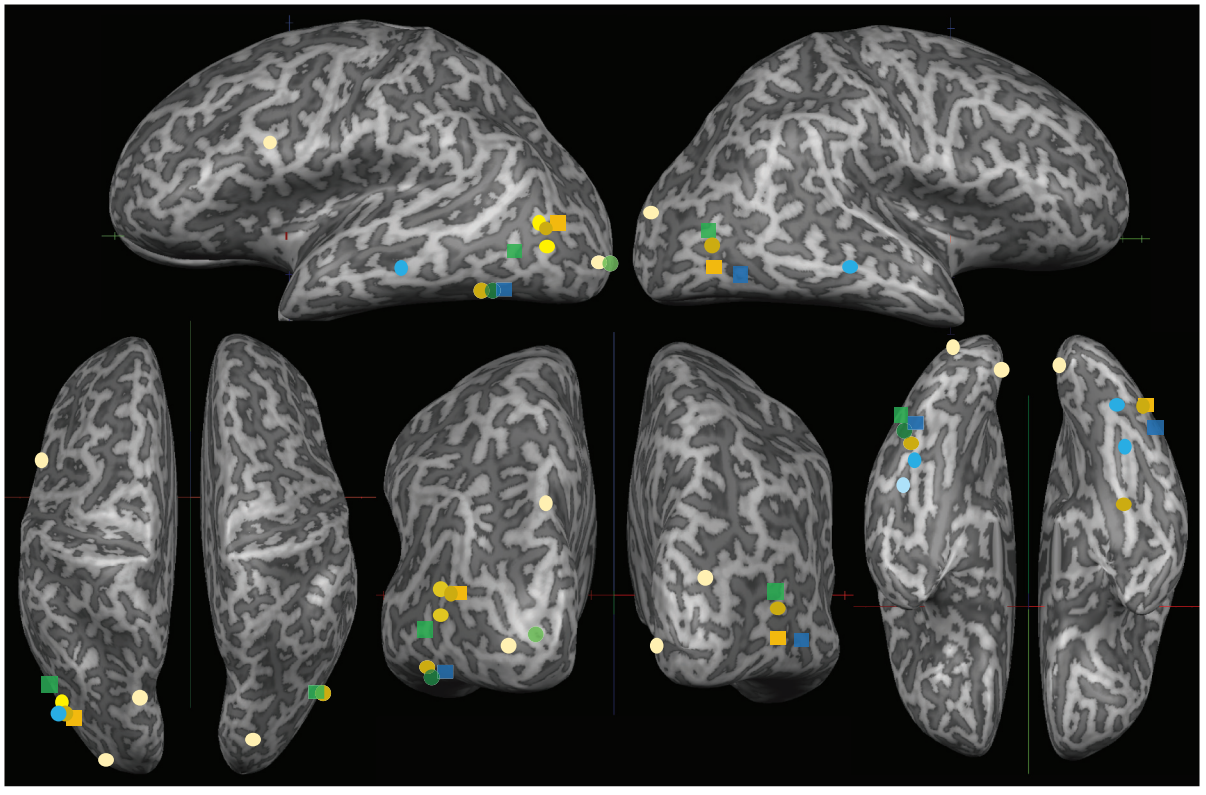

Figure 4

Examples of functional constancy in cross-modal plasticity. Square symbols show the expected stereotaxic locations (Talairach & Tournoux 1988) of the visual motion area (hMT+), the visual word form area (VWFA), and the fusiform face area (FFA). The circles show the center of mass of blood-oxygen-level-dependent (BOLD) responses in blind individuals in tasks designed to isolate auditory motion processing (*yellow* and *brown colors*), braille reading (*green colors*), and voice processing (*blue colors*). According to the metamodal hypothesis, the red, green, and blue symbols should be clustered. Abbreviations: EB, early-blind; MVPA, multivoxel pattern activation; SC, sighted control; VOC, vocalization.

regions within the occipital dorsal stream—whose activity is linked to visual spatial processing in sighted subjects—are preferentially active when blind subjects perform a task involving the spatial attributes of auditory and tactile stimuli (Collignon et al. 2011, Renier et al. 2010) as compared to identification (Striem-Amit et al. 2012b).

Is the Occipital Cortex Supramodal?

Some have taken the metamodal argument a step further by claiming that the cross-modal responses observed in early-blind individuals do not reflect qualitative differences but rather the unmasking or enhancement of cross-modal responses that exist even in sighted individuals (Pascual-Leone & Hamilton 2001, Ricciardi et al. 2014). According to this view, many cortical areas that are generally presumed to be visual should be considered supramodal, performing certain types of computation regardless of the sensory input modality. hMT+ has no innate predisposition toward visual input even in visually typical adults; rather, hMT+ computes object motion using the best available sensory information at hand and can use auditory or tactile input to perform the task if visual input is not available.

The evidence for supramodal responses within visual areas in sighted individuals is highly mixed. Merabet et al. (2008) examined recruitment of the occipital cortex for braille reading across sighted individuals who either were or were not blindfolded during a five-day period. Transcranial magnetic stimulation (TMS) to occipital cortex selectively disrupted braille reading in the blindfolded but not the nonblindfolded group. As far as BOLD imaging was concerned, a small region of enhanced activity within occipital cortex was found in the blindfolded versus nonblindfolded group. However, since this study was published, the cluster-based methods that were used to determine statistical significance have come under increasing scrutiny for having inflated false-positive rates (Bennett et al. 2011, Eklund et al. 2016).

Several studies have found BOLD responses to auditory or tactile motion stimuli within regions defined as hMT+ in sighted individuals (Beauchamp et al. 2007; Blake et al. 2004; Matteau et al. 2010; Poirier et al. 2005; Ricciardi et al. 2007, 2011; Sani et al. 2010; Summers et al. 2009). However, in most of these studies, the definition of hMT+ was based either on group averaged data or on anatomical coordinates despite the fact that the hMT+ location cannot be reliably identified in individuals using these methods (Dumoulin et al. 2000). Studies that identified hMT+ using individual visual localizers have generally failed to find auditory or tactile motion BOLD responses within hMT+ in either sighted (Alink et al. 2012; Bedny et al. 2010; Dormal et al. 2016; Jiang et al. 2015; Lewis et al. 2000, 2010; Saenz et al. 2008) or even late-blind (Bedny et al. 2010, Jiang et al. 2016) individuals.

Thus, although it is clear that the responses of the visual cortex can be modulated when sighted subjects are engaged in tasks that would benefit from visual imagery (Kourtzi & Kanwisher 2000, Senior et al. 2000), during cross-modal tasks (Blake et al. 2004) or when cross-modal attention is manipulated (Ciaramitaro et al. 2007), it is less clear whether passive auditory or tactile stimulation can elicit responses in occipital areas in sighted individuals, as would be predicted if these areas were genuinely supramodal.

Competition Across Areas as Well as Inputs

The metamodal hypothesis is generally couched in terms of competition across inputs: Areas such as hMT+, VWFA, or the fusiform gyrus select the sensory input signal that is most informative. However, the hypothesis also generalizes to competition between areas, predicting that cortical regions may compete for function based on their suitability for that role.

Recent data from early-blind individuals suggest that competition across cortical areas for functional role may occur, with the deprived occipital cortex usurping the function of nondeprived regions of the somatosensory or auditory cortex. The first hint of this was a study of Sadato et al. (1998), who found that secondary somatosensory areas were less activated by braille reading in blind individuals than in sighted controls. More recently, recruitment of hMT+ for

auditory motion processing in early-blind individuals was shown to be accompanied by a loss of selectivity for auditory motion in the right planum temporale (Dormal et al. 2015, Jiang et al. 2014). Thus, competition between areas may play a significant role in developmental cortical specification.

In general, the effects of early blindness on auditory and somatosensory areas are not well understood. These areas seem to show enhancement of function, perhaps because of an increased functional role, for some tasks (Elbert et al. 2002, Hertrich et al. 2013, Jafari & Malayeri 2014) even while showing decreased functional engagement, perhaps because of competition with occipital cortex, in others (Dormal et al. 2015, Jiang et al. 2014, Sadato et al. 1998).

The Reverse Hierarchy

Although the idea of functional constancy or metamodal reorganization seems to explain results in several studies, many other findings of cross-modal plasticity do not fit this framework. Cross-modal responses in early visual areas such as V1 and V2 are particularly mysterious. An increasing number of studies suggest that regions near the occipital pole may be involved in abstract cognitive tasks, such as verbal working memory, language, and mathematics (Amedi et al. 2003, Bedny et al. 2011, Burton et al. 2003, Kanjlia et al. 2016).

One model that has been put forward to explain these findings is the concept of a reverse hierarchy (Ahissar & Hochstein 2004, Bedny 2017). In the sighted brain, feedforward cortical responses in the LGN closely reflect the retinal stimulus. Responses gradually elaborate across the visual hierarchy; early occipital areas extract low-level features, and higher-level visual areas [e.g., the lateral occipital cortex (LOC)] contain more abstract representations that are relatively invariant to object-irrelevant properties, such as size, position, or viewpoint. These high-level representations provide the primary input into regions concerned with memory, decision, attention, and action. In sighted individuals, the primary role of the exuberant reciprocal connectivity between high- and low-level visual areas, the reverse hierarchy, is to focus selective attention and enhance learning within selected subgroups of lower-level neurons.

When the notion of a reverse hierarchy is applied to early-blind individuals, it is assumed that more anterior cortical areas like hMT+ and LOC continue to represent the objects of motion in space or the identity of objects (albeit based on auditory and tactile input) but that the exuberant feedback connections to early visual areas now perform a similar role as the feedforward connections from areas like LOC/hMT+ to higher-level cortex, further elaborating and abstracting information. Thus, early visual areas become involved in cognitive processes, such as verbal working memory, language, and mathematics.

Although conceptually elegant, one serious concern is that it is very difficult indeed to see how feedback connections could be co-opted to a feedforward role. Feedforward connections project to layer 4, and the local flow of information occurs between layer 4 and more superficial layers. Feedback connections project to superficial layers 1 and 2 or to deep layers 5 and 6 (Callaway 2004). Anatomical reconfiguration of this pattern of connectivity would be extraordinary given that this general laminar structure is highly stereotyped across the cortex and does not require visual experience (McConnell & Kaznowski 1991). Thus, development of a reverse hierarchy would either require anatomical reconfiguration of the laminar structure of visual cortex or require the existing pattern of laminar connectivity to take on a strikingly different computational role. From an engineering perspective, the idea of reversing the hierarchy is a little like playing a song to a radio and expecting electricity to flow into your wall.

The Potential Role of Feedback Connections in Occipital Cross-Modal Plasticity

If we assume that feedback connections to early visual areas in blindness cannot be dramatically repurposed, then it seems plausible that cross-modal plasticity in blind individuals might continue to reflect feedback. In sighted individuals, feedback connections to early visual areas seem to play three main roles. One is attentional modulation in which the responses of neurons in early visual areas are modulated based on whether they share featural or spatial properties with the attended stimulus. A second is predictive coding in which feedback connections contain a preattentive template of the predicted neural response (Muckli et al. 2015, Smith & Muckli 2010), and it is hypothesized that feedforward connections may carry an error signal reflecting the residuals between predictions and the neuronal signal (Rao & Ballard 1999, Joo et al. 2012). Finally, foveal early visual areas seem to provide task-dependent, position-independent representations of stimuli that are being imagined (Thirion et al. 2006), remembered (Serences 2016), or compared (Williams et al. 2008). Thus, early visual areas contain a multiplexed signal in which responses are driven not just by the visual input but also by what the individual is attending to, the expected stimulus (Hsieh et al. 2010), and visualizations of task-relevant stimulus content.

Interestingly, most of the tasks that have been associated with V1 occipital cortex responses in blind individuals have included a significant load on short-term working memory (Amedi et al. 2003, Bedny et al. 2011, Burton et al. 2003, Kanjlia et al. 2016, Lane et al. 2015, Watkins et al. 2012), suggesting that task-related feedback pathways involved with visualization may be the primary source of cross-modal plasticity.

SUMMARY

Although early blindness results in dramatic changes in neurochemistry and function, alterations in occipital neuroanatomical architecture are surprisingly subtle. Two insights may make this apparent conundrum less perplexing.

First, it is worth noting that from the very beginning it was presumed that metamodal constancy might be a consequence of an inflexible anatomical architecture (Pascual-Leone & Hamilton 2001). It was proposed that assignment of functional role might be the consequence of a competitive process whereby computational tasks are assigned to brain regions whose innate anatomical characteristics, including local cortical microstructure as well as global white matter connections, were well suited to those tasks (Jacobs 1997, Jacobs & Kosslyn 1994).

Second, if the fundamental structure of cortical microcircuits reflects canonical computational functions (such as summation or normalization) rather than specific functional roles (visual motion processing), then dramatic changes in function may occur without an easily observable change in neuroanatomy. The structure-function relationship for neural architectures that subserve cross-modal plasticity may be one to many; in other words, the same architecture can subserve both auditory and visual motion processing, making it difficult or impossible to infer changes in structure from changes in function or vice versa (Jonas & Kording 2017). Thus, the dramatic changes in occipital function that are observed in early-blind individuals may occur in the context of anatomical constancy.

Finally, one possible reason why cross-modal plasticity has been observed for such a confusing collection of tasks in early visual areas may be that most studies have focused on using whole-brain or region of interest–based analyses of group differences in mean BOLD response. It is worth remembering that much of the representational content of early visual areas in sighted individuals would be almost entirely opaque to these approaches: Early visual area BOLD responses remain

relatively constant as a function of varying orientation, spatial frequency, and eye of origin. If the general neural architecture of visual areas is inherited during cross-modal plasticity, then looking for regions that show group differences in BOLD responses across many voxels may similarly be blind to critical aspects of neural representational content in blind individuals. One promising future direction may be to move toward methods such as multivoxel pattern activation (MVPA) or voxel-wise encoding models, which are sensitive to representational content at a finer scale.

SUMMARY POINTS

1. The plasticity that results from early blindness is driven both by the lack of vision and by the resulting need to rely more heavily on remaining senses.
2. Early blindness results in dramatic changes in neurochemistry and metabolism.
3. Alterations in occipital neuroanatomical architecture because of early blindness are surprisingly subtle.
4. Early blindness results in dramatic changes in function—cross-modal plasticity—with much of visual cortex responding to auditory, tactile, or cognitive tasks.
5. The organizing principles underlying cross-modal plasticity are still unknown. There are significant difficulties with current theories such as metamodal reorganization and the reverse hierarchy.

FUTURE ISSUES

1. Investigators need to move from examining mean blood-oxygen-level-dependent (BOLD) responses to more sophisticated measures of neuronal representations, using methods such as multivoxel pattern activation (MVPA) and/or voxel-wise encoding models.
2. Computational models need to be developed that relate changes in brain activity to improvements in auditory and tactile perception.
3. Future research should examine alterations in auditory and somatosensory cortices as well as the occipital cortex.

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Contents

Errata

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