New Approaches to Visual Rehabilitation for Cortical Blindness: Outcomes and Putative Mechanisms

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Abstract

Cortical blindness is a chronic loss of vision following damage to the primary visual cortex (V1) or its postchiasmal afferents. Such damage is followed by a brief period of spontaneous plasticity that rarely lasts beyond 6 months. Following this initial phase, the visual deficit is thought to be stable, intractable, and permanent. Cortically blind subjects demonstrate spontaneous oculomotor adaptations to their deficits that can be further improved by saccadic localization training. However, saccadic training does not improve visual sensitivity in the blind field. In contrast, recent studies by a number of independent groups suggest that localized, repetitive perceptual training can improve visual sensitivity in the blind field, although mechanisms underlying the observed recovery remain unclear. This review discusses the current literature on rehabilitative strategies used for cortical blindness with emphasis on the use of perceptual training methods. The putative mechanisms that underlie the resulting, training-induced visual improvements are then outlined, along with the special challenges posed to their elucidation by the great variability in the extent and sometimes nature of the V1 damage sustained in different individuals.

Keywords

visual training, perceptual learning, plasticity, visual cortex damage, hemianopia

Cortical blindness occurs as a result of damage to the primary visual cortex (V1) or its immediate afferents, producing a loss of conscious vision in the contralateral visual hemifield (Cowey and Stoerig 1991, 1995; Holmes 1918; Teuber and others 1960; Weiskrantz and others 1974). This loss is usually unilateral and homonymous, which implies that the visual deficit affects the same region of the visual field through both eyes. Damage to the primary visual cortex occurs most often (in 40%-90% of cases) as a result of stroke in the territory of the posterior cerebral artery (Fujino and others 1986; Lawton Smith 1962; Trobe and others 1973; Zhang and others 2006a), although trauma, infection, or tumors also contribute to the etiology of adult-onset cortical blindness (Trobe and others 1973; Zhang and others 2006a). In spite of the fact that the human brain possesses multiple visual cortical areas (Tootell and others 1996), damage to V1 is more frequently reported than damage to higher level visual cortical areas. Perhaps this is related to the fact that V1 damage is more devastating because V1 is the primary gateway for visual information transfer into the cortex. Some studies suggest that as many as 30% or more of all stroke survivors have some form of visual disability and that the incidence of homonymous visual field defects in the general, noninstitutionalized population appears to hover between 0.5% to 0.8% (Geddes and others 1996; Gilhotra and others 2002; Taylor and others 1997). Patients with cortical blindness are impaired in many day-to-day activities such as driving, reading, and navigating complex visual environments. Given this heavy burden of disability, there are remarkably few options for rehabilitation and recovery in this population. However, recent developments that use psychophysical methods to retrain visual perception in the blind field have had a fair level of success. This review will highlight some of these recent developments and discuss the possible mechanisms underlying the resulting functional recovery.

Effect of V1 Damage on Visual Perception and Function

Understanding the complex organization of the primate visual system offers insight into why insults to V1 have such severe consequences. The majority of primate retinal ganglion cells project to the dorsal lateral geniculate

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nuclei (dLGN) and then to V1 (Felleman and Van Essen 1991) through the optic radiations. This is termed the retino-geniculo-striate pathway and represents the major route of visual information transmission between the eye and cortex (Fig. 1). V1 is thought to be critical for perceptual processing of basic visual features orientation, contrast, and location (reviewed in Hubel 1982). V1 is also the primary source of visual information for a multitude of higher order, extrastriate visual cortical areas. Thus, damage to V1 or its postchiasmatic inputs causes dense blindness because V1 is the main source of feedforward visual information to higher order visual cortical areas. Because the visual system is one of the largest sensory systems in the primate brain, V1 damage essentially deprives a large part of the brain of bottom-up sensory information. Furthermore, V1 damage also causes retrograde degeneration in retinotopically corresponding regions of the dLGN and, in long-standing cases, in corresponding areas of each retina (Cowey and Stoerig 1991, 1995; Teuber and others 1960; Weiskrantz and others 1974). Finally, V1 damage deprives several subcortical centers, such as the superior colliculi, of feedback information.

However, cortically blind individuals do not lose all visual abilities within their blind field (Weiskrantz 1986; Weiskrantz and others 1974). Some have been found to possess a small amount of residual sensitivity to visual motion, form, and even color (e.g., Blythe and others 1987; Cowey and Stoerig 1995; Pasik and Pasik 1982; Weiskrantz and others 1991; Zeki and Ffytche 1998). Unlike normal vision, however, this preserved sensitivity often occurs without consciousness, and as a result, it was originally termed "blindsight" (Weiskrantz 1986; Weiskrantz and others 1974). Blindsight is more narrowly tuned in the spatiotemporal frequency domains than normal vision, with optimal spatial frequencies ranging around 0.5 to 2 cycles/deg and temporal frequencies around 10 Hz (Morland and others 1999; Sahraie and others, 2003). However, residual visual functions vary considerably among affected individuals in terms of the proportion of the visual field affected, the quality of residual visual processing taking place within the blind field, and the degree of consciousness associated with this processing (Danckert and Rossetti 2005). Most likely, this variability is directly related to the amount and precise location of damage sustained by the visual system (Blythe and others 1987; Morland and others 2004). However, in spite of residual visual processing abilities in the blind field, cortically blind subjects are still severely impaired when trying to use vision in their everyday life. For instance, they have difficulty reading (Leff and others 2000; McDonald and others 2006) and navigating in unfamiliar, complex visual environments (Marigold and others 2007; Turano and others 2004). These 2 visually guided functions are so pervasive in daily life that their impairment may be primarily responsible for the significant decrease in the quality of life reported by V1-damaged patients.

Before we delve into externally administered strategies for inducing recovery of visual function in cortical blindness, we will first review what we know on the topic of endogenous visual plasticity after V1 damage—the extent to which it occurs and how useful it is.

Spontaneous Visual Improvements after V1 Damage

An important aspect of understanding the degree of plasticity inherent in the adult visual system is the realization that V1 damage (like damage to almost any part of the adult brain) is usually followed by some amount of spontaneous recovery. This has been fairly well documented in the context of homonymous visual field defects, which display 50% to 60% probability of spontaneous visual improvements occurring in the first month after the insult (Zhang and others 2006b). Unfortunately, little improvement is observed after 3 months, and almost none is expected after 6 months postlesion (Zhang and others 2006b). Most of the recovery observed is thought to be due to the resolution of inflammation and edema around the lesion and to the re-activation of partially damaged perilesional tissue (Poggel and others 2001; Sabel 1997). Animal studies also support the notion that some of the spontaneous recovery seen after permanent V1 damage might be due to changes in the properties of perilesional neural circuits (reviewed in Eysel 1997), which can include changes in excitability (Eysel and Schmidt-Kastner 1991), receptive field size (Eysel and Schweigart 1999), neurochemistry and channel properties (Barmashenko and others 2003; Rumpel and others 2000). Alterations in long-term potentiation and membrane permeability could in fact mediate the observed changes in receptive field size and neuronal excitability around the lesion site (Eysel and others 1999). This, in turn, could contribute to disinhibition of long-range horizontal connections within V1 (Darian-Smith and Gilbert 1995; Das and Gilbert 1995), sprouting of new horizontal connections (Darian-Smith and Gilbert 1994), and/or changes in the functional interactions between intact regions of V1 and higher level visual cortical areas (De Weerd and others 1995; Mendola and others 2006; Mendola and others 1999).

Aside from frank spontaneous recovery of lost visual functions within the blind field, there are also reports in the literature of cortically blind patients who develop a distorted perception of the visual world. Dilks and colleagues (2007) recently reported on one such patient who had sustained damage to postchiasmal afferents to V1 (rather than V1 itself), resulting in a quadrantanopia. Stimulation

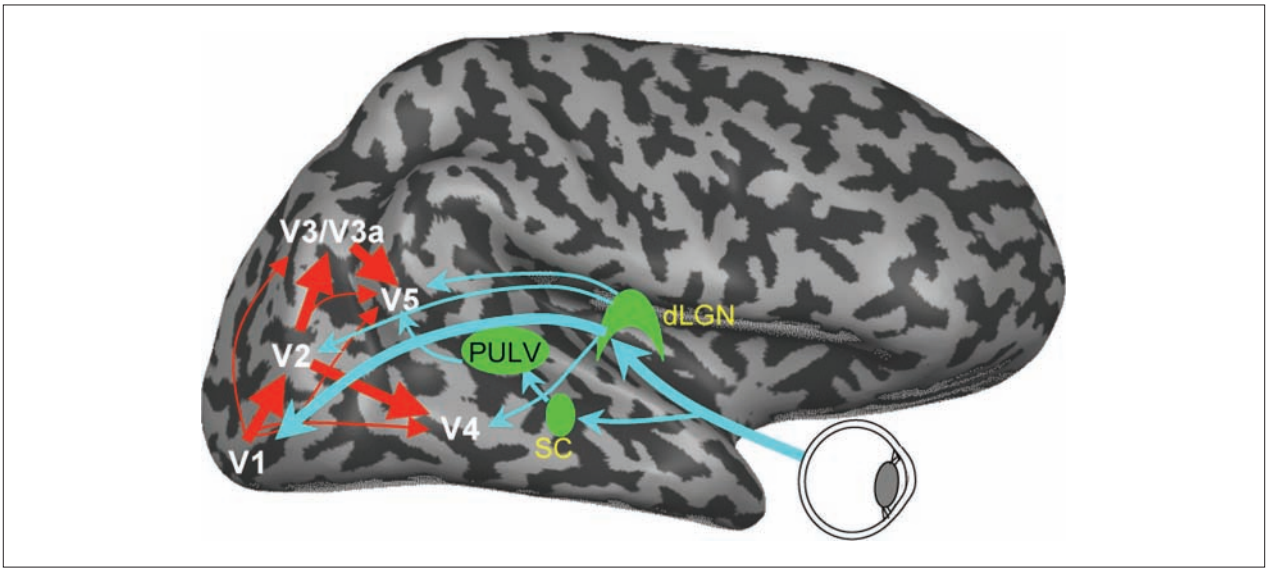

Figure 1. Basic anatomy and connectivity of the human visual system. Schematic diagram illustrating the main connections of the standard feed-forward model of visual information processing in the human brain. Connections originating in the retina (blue arrows) travel through the optic nerves and chiasm, synapsing in the dorsal lateral geniculate nucleus of the thalamus (dLGN) and the superior colliculus (SC). From the dLGN, most of the visual information travels via the optic radiations to the striate or primary visual cortex (V1). The major feed-forward pathways from V1 are indicated with thick, red arrows and show the significant divergence of information sent from V1 to different areas making up the extrastriate visual cortex (V2, V4, V3/V3a, V5, or hMT+, etc.). Note that most of these corticocortical connections are reciprocal, although for the sake of simplicity, this is not indicated on the diagram. Several alternate pathways are known to transmit information directly to extrastriate visual areas, effectively bypassing V1. These are indicated in thinner blue lines. These alternate pathways process visual information that is more narrowly tuned in terms of spatial and temporal frequencies, relative to the main retinogeniculostriate pathway. They are, however, hypothesized to underlie residual visual processing capacities in blindsight and may provide a mechanism for eliciting improvements in visual perception through targeted perceptual retraining following V1 damage.

of the intact quadrant (in the same hemifield) near the border with the blind quadrant caused distorted object perception in the blind field (Dilks and others 2007). Specifically, the subject perceived objects near the border of the anopic field to be elongated, extending into the blind portion of the visual field. In a sense, this highlights the fact that postlesion spontaneous plasticity in the adult brain can take many forms. What determines the form of plasticity elicited is not yet understood, but again, this may be related to the extent and type of damage sustained.

Spontaneous Behavioral Adaptation after V1 Damage

In addition to exhibiting a small level of spontaneous visual improvement, cortically blind patients also demonstrate spontaneous behavioral adaptations to their deficit. Carefully controlled clinical and laboratory studies have shown that these patients compensate for their loss of vision with gaze strategies that are both abnormal and biased toward the affected visual hemifield (Gassel and Williams 1963; Ishiai and others 1987; Pambakian and others 2000). For instance, when presented with point light targets at different, randomly chosen positions along the horizontal meridian of their field of view, cortically blind subjects rarely fixated the targets directly (Meienberg and others 1981). When target duration and position were predictable, they performed a series of hypometric saccades that incrementally approached each target until it was found. Once target positions were learned, the saccades became hypermetric, overshooting the target by a few degrees of visual angle, followed by a short, corrective saccade. A similar pattern of hypometric saccades was noted when cortically blind subjects searched static images for a small target (Zangemeister and others 1995). These patients also prefer to explore the side of space associated with their seeing hemifield first before scanning the side corresponding to their visual deficit (Chedru and others 1973). However, cortically blind individuals spend most of their time looking toward their blind hemifield, a bias that is not due to visual or attentional neglect (Ishiai and others 1987) and has been observed in numerous tasks, including counting dots (Zihl 1995), viewing natural and degraded images (Pambakian and others 2000), detecting sudden-onset,

moving targets in a 3-dimensional virtual environment (Riley and others 2007), and constructing wooden models from individual pieces laid out on a table top (Martin and others 2007). It is very likely that the gaze bias toward the blind hemifield is a compensatory strategy that develops naturally following homonymous visual field loss, allowing those afflicted to partially overcome the loss of visual input from the affected side of space (Zihl 1995).

In summary, spontaneous neural plasticity is likely a ubiquitous phenomenon following damage to the adult primary visual cortex and its afferents. However, the consequences of this spontaneous plasticity for perception appear to be relatively limited, both in magnitude, time course, and impact on visual functions in everyday life. Spontaneous behavioral adaptations to the deficit have been well documented, but they are largely restricted to changes in oculomotor behavior. While this ameliorates the disability suffered by cortically blind patients to a small extent, persistent loss of visual perceptual abilities and impaired quality of life persists in the long term in the majority of patients with V1 damage. Our next section discusses the results obtained from attempts to actively stimulate and enhance plasticity within the damaged visual system.

"Forcing" Plasticity after V1 Damage: the Case for Rehabilitation

When patients suffer motor deficits due to stroke, trauma, or tumors in the adult motor cortex, they are almost uniformly sent to undergo physical rehabilitation, which is aggressive and relatively successful (Hallett 2001; Taub and others 2002). In contrast, restoration of vision after postchiasmal brain lesions remains controversial and, to date, is still rarely attempted clinically (Horton 2005; Pambakian and Kennard 1997). Only in the last few decades have more principled rehabilitative strategies begun to emerge for cortical blindness, with some demonstrated successes and hopes for further improvements. So far, these strategies have fallen into 2 major categories: oculomotor compensatory training and perceptual retraining of the blind field.

Training Compensatory Behaviors

Some of the earliest attempts to rehabilitate vision in cortically blind fields involved saccadic training. Primate studies were the first to provide evidence that targeted visual training had any degree of success in adult animals with V1 damage. Monkeys with striate cortex lesions were trained to detect and saccade to a point of light presented within their blind field. Following training for about a month, monkeys regained the ability to detect and localize visual stimuli within their blind field (Cowey and Weiskrantz 1963; Mohler and Wurtz 1977). Interestingly, this recovery of function was restricted to trained regions of the blind field and did not occur spontaneously (Cowey and Weiskrantz 1963; Mohler and Wurtz 1977). Subsequent lesions to both the superior colliculus and the striate cortex precluded recovery even after 15 weeks of training (Mohler and Wurtz 1977).

Similar saccadic training was subsequently attempted in humans with cortical blindness, improving the "usable" field of view in these patients (Zihl 1981; Zihl and von Cramon 1985). However, the authors also claimed that there was a reduction in the size of the blind field, a finding that was questioned because the study did not properly control for variables such as compensatory shifts in fixation or eye movements that could affect blind field size (Bach-Y-Rita 1983; Balliet and others 1985). More recently, a different set of cortically blind patients were trained on a modified visual search paradigm (Nelles and others 2001) in which they were asked to localize a square defined by 4 red lights. The patients viewed the stimuli on a large training board that spanned almost the complete visual field. After 4 weeks of training, patients showed shorter reaction times and were more accurate at saccadic localization of the target. However, saccadic training did not improve performance in a detection task while patients maintained fixation, nor were there any significant changes in visual perimetry, that is, the size of the blind field (Nelles and others 2001).

Saccadic training is important because it seems to strengthen the ability of cortically blind patients to compensate for their deficit using eye movements. However, it is not clear that this technique brings about any significant reversal of visual deficits induced by the cortical damage. The question, therefore, remains as to whether such a reversal is possible. Given recent evidence from several groups using psychophysical methods to retrain visual perception in particular locations within cortically blind fields in humans, it appears that the answer is yes.

Retraining Perception in the Blind Field

The first major attempt to rehabilitate visual perception in the blind field was reported almost 15 years ago and led to the development of the first commercial product for the treatment of cortical blindness—Visual Restitution Therapy or VRT, marketed by NovaVision Inc. (Kasten and others 2000; Kasten and Sabel 1995; Kasten and others 1998; Sabel and Kasten 2000). VRT requires participants to press a button when they detect a bright point of light presented on a computer monitor in front of them, in one of 500 locations along the border between the blind and sighted fields. Detection accuracy appears to significantly improve as a function of training, and visual perimetric enlargements averaging around 5° of visual angle were reported (Kasten and others 2000; Kasten and others 1998).

Patients also showed significant improvement in activities of daily living, which was corroborated by their subjective testimonials (Pambakian and others 2004; Sabel and others 2004). Unfortunately, these claims were later challenged when apparent visual fields improvements failed to be replicated using a scanning laser ophthalmoscope (SLO) that tightly controlled for fixation accuracy during performance of the test (Reinhard and others 2005). Reinhard and colleagues (2005) concluded that patients trained on the VRT detection task learned to make small, rapid eye movements towards the targets to be detected. This statement was disputed by Sabel and colleagues (2005), who suggested that the stimuli used in the SLO differed from the other perimetric tests that were used to measure recovery following VRT. However, if VRT did cause an absolute perimetric expansion of the blind field, this should generalize to an improved ability to detect any sufficiently salient stimulus within the trained region. Although the SLO stimuli were sufficiently high contrast, no perimetric changes were observed.

A different approach was taken by Raninen and coworkers, who trained 2 cortically blind patients on a flicker detection task and a flickering letter identification task deep in their blind field (Raninen and others 2006). Flicker frequencies ranged between 1 to 35 Hz. The stimuli were presented at 10° or 30° eccentricity along the horizontal meridian. After a year of intensive training, flicker sensitivity and letter recognition at the trained blind field locations became comparable to those in the subjects' intact hemifields (Raninen and others 2006).

A third group of researchers specifically targeted residual spatial channels in blindsight for training (Sahraie and others 2006). Twelve cortically blind subjects were trained on a 2-interval detection task, wherein they indicated the interval in which the stimulus was present. The stimulus, a vertical sinewave grating on a luminance matched background, was optimized to fall within the narrow spatial and temporal frequency channels of sensitivity previously described to be preserved in the blind field (Sahraie and others 2003). The subjects trained daily for 3 months. At the end of the training period, and even in the presence of stringent eye movement monitoring, all had significantly improved in their ability to detect low-contrast stimuli at their trained blind field locations. The subjects also displayed increased sensitivity as measured by Humphrey perimetry, although not all subjects reported increased awareness for visual stimuli presented in their blind field.

Most recently, Huxlin and colleagues trained 5 adult humans with stroke-induced V1 damage to discriminate the global direction of moving random dot stimuli in their blind field (Huxlin and others 2009). Initially, although they could detect the visual stimuli presented in their blind field, the patients were completely unable to discriminate their global motion direction. After training at a single location for 6000 to 30,000 trials, they slowly recovered the ability to correctly discriminate global motion direction when dot motion was coherent, and they also attained normal direction integration thresholds. These thresholds were verified in the laboratory with controlled fixation procedures, which ensured that eye movements towards the targets were not responsible for the improvements. Moreover, while the recovery was limited retinotopically to retrained blind field locations, it generalized to contrast sensitivity for direction and the ability to extract motion signals from noise at the trained blind-field locations (Fig. 2). This was interesting because the subjects had not been specifically trained on a contrast sensitivity or motion coherence task. In addition, the spatial and temporal frequencies at which the greatest posttraining improvements in contrast sensitivity were attained hovered around 0.5 to 1 cycles/deg and 10 Hz (Huxlin and others 2009). This matches the known spatiotemporal frequency channels thought to mediate blindsight (Barbur and others 1994; Sahraie and others 2006; Sahraie and others 2003) rather than the broad spatiotemporal frequency content of the random dot stimuli used to train these patients. It is thus conceivable that the spatiotemporal frequency channels that define residual vision in the blind field both mediate and limit the type of training-induced visual recovery that can be elicited after V1 damage.

A number of questions arise from these studies. First is the issue of generalization to different categories of visual stimuli. All 4 retraining paradigms trained one or at most 2 kinds of stimuli and saw improvements within the same category of or to closely related visual stimuli (e.g., Fig. 2). The visual world is complex; thus, the extent to which training on the simplistic, artificial stimuli used in laboratory psychophysics can transfer to other visual modalities or even tasks is both functionally relevant and as yet relatively undetermined. Another issue is that the studies described above all involved intensive, repeated, retinotopically specific stimulation that lasted from several weeks (Sahraie and others 2006) to many months (Huxlin and others 2009; Raninen and others 2006) before significant improvements were seen. This is a much longer time frame than usually required for most instances of visual perceptual learning in visually intact humans (e.g., Ball and Sekuler 1986). To understand why this happens, we need to better define the anatomical and functional substrates that underlie training-induced improvements in visual perception following V1 damage.

Putative Mechanisms of Visual Recovery after V1 Damage

The adult visual system exhibits a high degree of anatomical and functional plasticity following both injury and experience (reviewed in Huxlin 2008). Thus, it should be

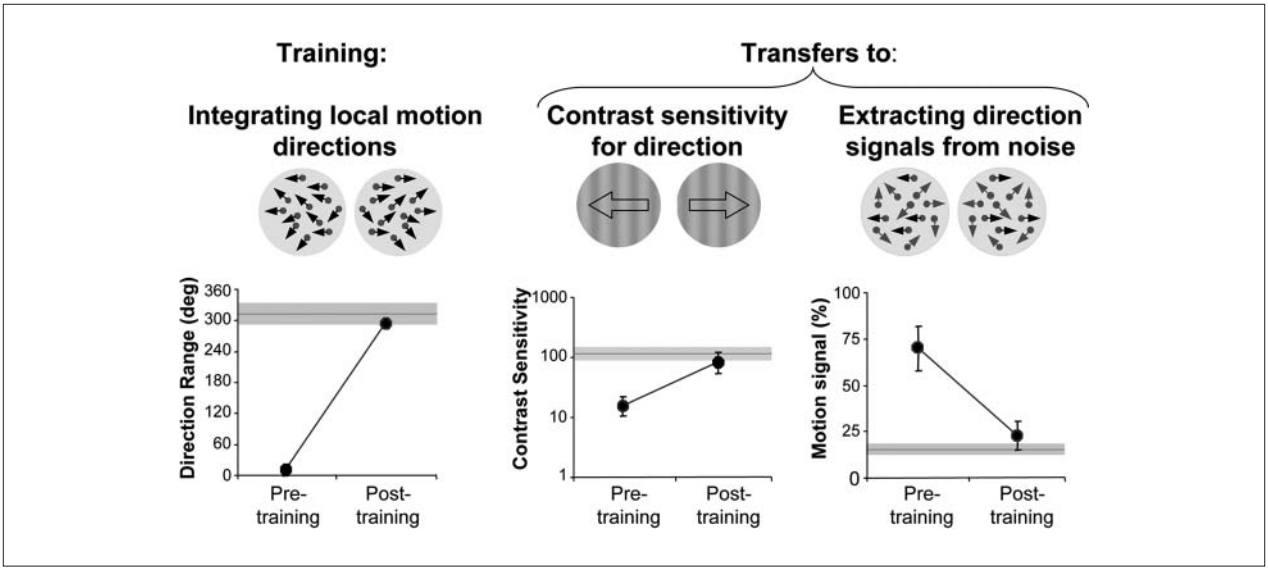

Figure 2. Global motion discrimination training generalizes to improved contrast sensitivity and motion signal thresholds. The first graph illustrates the training task (global direction discrimination) and its effect on direction range (DR) integration at the trained blind field locations in 5 cortically blind subjects. The next 2 graphs illustrate the transfer of global direction discrimination training to contrast sensitivity for discriminating the direction of motion of drifting sinewave gratings and for extraction of motion signals from noise at the same trained, blind field locations. Contrast sensitivity was measured using luminance-modulated, drifting sinewave gratings (spatial frequency = 0.5 or 1 cycle/deg; temporal frequency = 10 Hz). Mean performance in the intact visual field for all 3 tasks is indicated by a dark gray line, with the standard errors of the mean in shaded gray around this line.

no great surprise that intensive visual training is able to improve visual function in cortically blind fields. Both human and animal studies of cortical damage suggest that after the initial short period of spontaneous plasticity, further visual recovery does not occur without some form of training (e.g., Huxlin and Pasternak 2004; Huxlin and others 2009; Sahraie and others 2006; Yamasaki and Wurtz 1991). The exact mechanisms of visual recovery and the reason why training is so essential remain to be elucidated. The following sections consider several hypotheses: 1) that training stimulates pre-existing, intact islands of cortex within V1 (suggested by some to mediate blindsight); 2) that training induces plasticity in perilesional, spared V1; 3) that training reactivates damaged V1 cortex; 4) that training strengthens extrageniculocalcarine pathways to more effectively transfer information directly to extrastriate visual areas such as V4 or MT; and 5) that training either recruits or inhibits visual areas in the intact hemisphere.

Intact Islands of Cortex within V1

It has been suggested that spared islands of cortex in V1 may mediate blindsight (Fendrich and others 1992; Scharli and others 1999a, 1999b; Wessinger and others 1997, 1999). A number of independent studies have performed functional imaging while cortically blind subjects viewed stimuli in intact and blind portions of their visual field. Stimuli have ranged from pattern reversals (Kleiser and others 2001; Morland and others 2004; Radoeva and others 2008) to moving gratings (Kleiser and others 2001; Morland and others 2004; Radoeva and others 2008). The results have been variable at best, a characteristic of the cortically blind population in general. Each of the 3 studies mentioned above included at least one subject who demonstrated activity within (Morland and others 2004; Radoeva and others 2008) or just outside the damaged zone in V1 (Kleiser and others 2001). All of these patients had some form of residual vision within their blind field. However, not all patients with residual vision in the blind field were found to have activity that might correspond to "islands" of spared V1 (Kleiser and others 2001), suggesting that this is clearly not the only way by which residual vision might occur. Nevertheless, spared islands in V1 do exist in some patients. If they do, it is possible that they could mediate blindsight and that they might be able to mediate training-induced perceptual recovery in the blind field if such training was administered.

Plasticity of Spared, Perilesional V1

Demonstrating the existence of spared islands of cortex within an area of V1 damage is difficult. It is much easier

to identify patients who have large "chunks" of spared V1 cortex adjoining their V1 lesion, both from structural MRIs and inferentially from visual perimetry. In such cases, intensive visual training could work by remodeling connections and/or changing synaptic weights in this region, allowing it to take over portions of vision normally subtended by damaged V1 cortex. In essence, this would mean a change in the retinotopic map of the spared portion of V1. In fact, the findings of Dilks and colleagues (2007) suggest that such plasticity might occur to a small degree even spontaneously. Retinotopic mapping of their quadrantanopic patient revealed that the deafferented cortex originally representing the upper-left visual quadrant was now sensitive to stimuli presented in the lower left, intact visual quadrant (Dilks and others 2007). With specific, intensive training, it is conceivable that an even greater degree of remapping could occur within intact portions of V1, although this remains to be documented.

Reactivation of Damaged Visual Cortex

Remarkably, it has also been suggested that in some instances (prevalence unknown), parts of the blind field may be represented by underperfused visual cortex (Benzel and Mirfarkhraee 1987; Holbach and others 1977; Roski and others 1979). If this were true, then vision might be restored by reperfusing the damaged cortex. In support of this notion, there have been several case reports of reversal of homonymous hemianopia following arterial bypass to reperfuse the occipital cortex (Benzel and Mirfarkhraee 1987; Holbach and others 1977; Roski and others 1979). Reperfusion has also been observed without surgery, over a longer period of time, in motor-related brain regions following motor therapy (Kononen and others 2005). The extent to which this might occur following visual retraining remains to be determined. Our own preliminary fMRI results show, in some cortically blind patients, a lack of significant visually induced BOLD signal changes in parts of V1 that appear structurally spared by the stroke (see VC pretraining images in Fig. 3). However, after global motion discrimination training, these same regions now exhibit significant, visually induced BOLD signal changes (see VC posttraining images in Fig. 3) (Martin and others 2009). This could be interpreted to signify a reperfusion event. However, it could also be due to simple neural re-activation, and currently, we have no means of distinguishing between these 2 mechanisms.

Strengthening of Extrageniculocalcarine Pathways

An intriguing question in the context of V1 damage is what happens when all (or the great majority) of V1 is damaged in a given hemisphere. Do such patients exhibit blindsight, and can they undergo training-induced visual improvements in the blind field? We recently studied one such patient (VC3 in Huxlin and others 2009) (see Fig. 4 for structural MRIs), who even before the onset of training, was able to point to and detect (but not discriminate the direction or motion of) a moving random dot stimulus in the upper-right quadrant of his blind field (Fig. 5). The fact that we were able to elicit training-induced visual recovery of global motion discrimination at that location, albeit after 90 training sessions (i.e., 27,000 trials), suggests that recovery in this case did not involve residual V1. Instead, training probably recruited and strengthened function in extrageniculostriate pathways that carry visual information directly from either the dorsal lateral geniculate nuclei (dLGN) or superior colliculi (via the pulvinar) to extrastriate visual areas (Fig. 1). For instance, cells in koniocellular layers of the dLGN project directly to extrastriate visual areas V2, V3 (Hendry and Reid 2000; Schmid and others 2009), V4 (Cowey and Stoerig 1989), and MT/MST (Sincich and others 2004). The superior colliculus projects via the pulvinar nucleus in the thalamus, primarily to dorsal stream areas MT/MST (Benevento and Rezak 1976; Cragg 1969). The size of the known extrageniculostriate pathways, however, is considerably smaller than the classic geniculocalcarine pathway. A consequence of this is that extrageniculostriate activity is unlikely to provide the full range of visual information provided by the geniculocalcarine pathway. Several studies in V1-damaged humans have actually taken advantage of this fact (Leh and others 2009; Tamietto and others 2009), based on the observation that in nonhuman primates, the superior colliculus does not receive short wavelength cone input from the retina (Marrocco and Li 1977; Schiller and Malpeli 1977). Tamietto and others (2009) tested the famous V1-damaged patient G.Y. on a detection task using achromatic red (L/M cone) or purple (S cone) stimuli. G.Y. had significantly shorter reaction times to achromatic and red stimuli presented bilaterally but showed no such effect for purple stimuli. This phenomenon has been termed bilateral gain wherein blindsight patients demonstrate shorter reaction times to stimuli presented bilaterally than to the good field alone (Corbetta and others 1990; de Gelder and others 2001). fMRI showed concomitant activity in his superior colliculus and extrastriate visual areas for achromatic and red stimuli, which decreased when purple stimuli were used (Tamietto and others 2009). Leh and others (2009) found similar results with hemispherectomized patients using achromatic and S cone–isolating chromatic checkerboard stimuli. Of the 2 patients in the study, only one demonstrated blindsight and was subsequently found to have ipsilateral hMT+ and FEF activity in response to achromatic stimuli but not to S cone–isolating stimuli presented to the blind field.

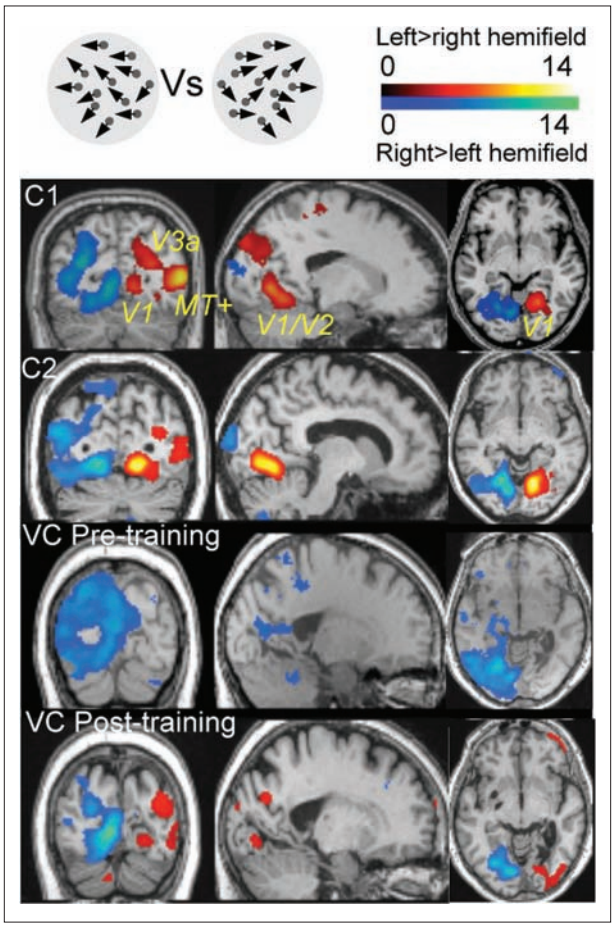

Figure 3. Training reactivates early visual cortex and extrastriate visual areas in some cortically blind subjects. Functional MRI reveals a stereotypical pattern of activity in 2 control subjects (C1 and C2) while they perform a left-right global direction discrimination task in the scanner. Areas significantly more activated in response to stimuli presented in the contralateral versus ipsilateral visual hemifields include V1/V2, V3, and hMT+. Functional MRI on a cortically blind subject with visual cortex damage (VC) reveals extensive hyperactivity in the intact hemisphere following intact hemifield stimulation relative to control subjects. However, before training, no significant voxels are seen in the damaged hemisphere in response to blind field stimulation. Following intensive global direction discrimination training in the blind field, activity in the intact hemisphere begins to resemble the pattern seen in intact controls. Furthermore, stimulation of the trained blind field location results in significant BOLD signal changes in perilesional tissue (V1/V2), as well as locations likely corresponding to V3a and hMT+ in the damaged hemisphere. All voxels are viewed with an uncorrected threshold of $P < .001$. All slices across subjects are coplanar and viewed at x, y, z = 15, –84, –8.

Aside from these observations, several groups have also reported activation of extrastriate cortical areas in the V1-damaged hemisphere following blind field stimulation in humans (Baseler and others 1999; Morland and others 1999; Ptito and others 1999; Rausch and others 2000; Slotnick and Moo 2003; Slowik and others 1997; Vanni and others 2001). However, several other studies failed to find such activation, describing instead extrastriate areas that were underactive or showed aberrant patterns of activation following a V1 lesion (Girard and others 1992; Nelles and others 2002), a phenomenon that can be described as "diaschisis." In summary, it is likely that extrageniculostriate pathways are instrumental in mediating blindsight and even training-induced visual recovery in the blind field of at least some individuals with V1 damage, particularly when V1 is completely destroyed. However, it remains to be determined how widespread this phenomenon is in the general population of cortically blind subjects, who exhibit an almost infinitesimal degree of variability in the extent of their brain damage. Perhaps the extent and nature of the brain lesion (i.e., its location, the amount of gray versus white matter damage, and the presence of any spared V1 cortex) are indeed the most critical determinants of an individual's propensity to recover vision via any given mechanism or pathway. It is also probable that several different mechanisms act in concert rather than being mutually exclusive. However, just as different types of blindsight (action, attention, and agnosopsia) are likely mediated by different residual visual pathways (reviewed in Danckert and Rossetti 2005), it is also possible that visual training may work via different pathways in different subjects. If this were the case, it would be of interest to contrast the type of visual recovery that can be attained via spared regions of V1 versus the extrageniculocalcarine pathways. Similarly, it remains to be determined whether targeted training on static form discriminations (as opposed to motion discriminations) modulates or biases the extent to which different brain pathways (in dorsal versus ventral stream, for instance) are recruited to mediate the resulting visual perceptual improvements.

Contribution of Visual Areas in the Intact Hemisphere

Limited evidence suggests that in some cases, visual areas in the intact brain hemisphere might play a role in mediating both residual (Ptito and others 1999) and improved vision following visual retraining in the blind field after unilateral V1 damage (Henriksson and others 2007; Raninen and others 2006). Some of the best evidence for this came from fMRI and neuromagnetic recordings performed on a cortically blind subject following training with flicker stimuli; these showed that both blind field and intact hemifield stimulation activated the same group of areas in the intact brain hemisphere—V1, V2, V3, V3A, and hMT+ (Henriksson and others 2007; Raninen and others 2006).

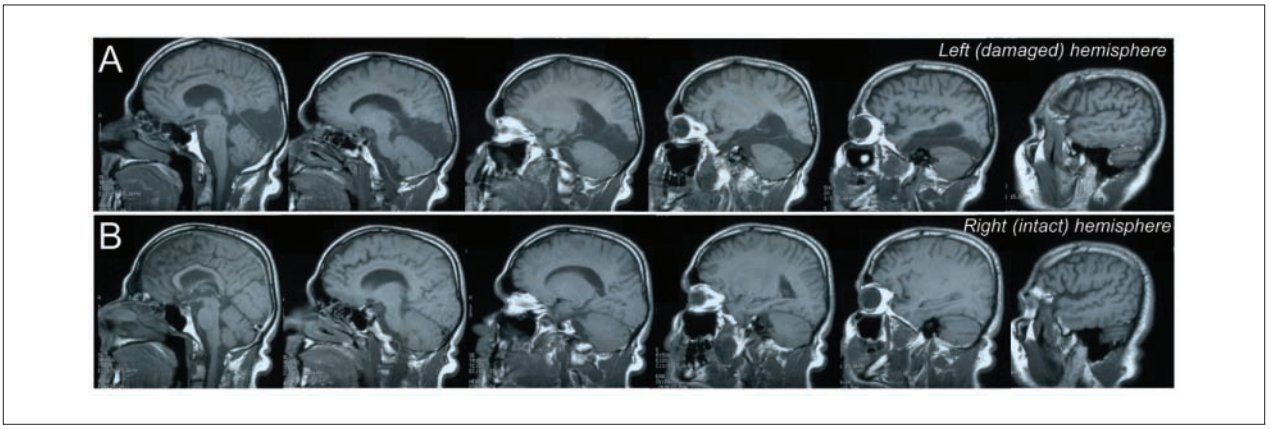

Figure 4. Example of "complete" V1 lesion. Poststroke structural MRI images in one patient with cortical blindness, showing damage (area of darker gray) completely surrounding the calcarine sulcus in the occipital lobe, which occurred as a result of hemorrhage secondary to a burst aneurysm. (A) Sagittal slices through the left hemisphere of the brain, showing the extensive area of damage that caused this patient's dense, right homonymous hemianopia (see Fig. 5A for Goldmann visual fields). The lesion comprises the entire calcarine sulcus and extends into the temporal lobe. However, the extrastriate visual cortex in the occipitoparietal lobe (where hMT+ is likely located) appears relatively intact. (B) Sagittal slices through the same patient's right hemisphere, shown for comparison, to illustrate the extent of the calcarine sulcus.

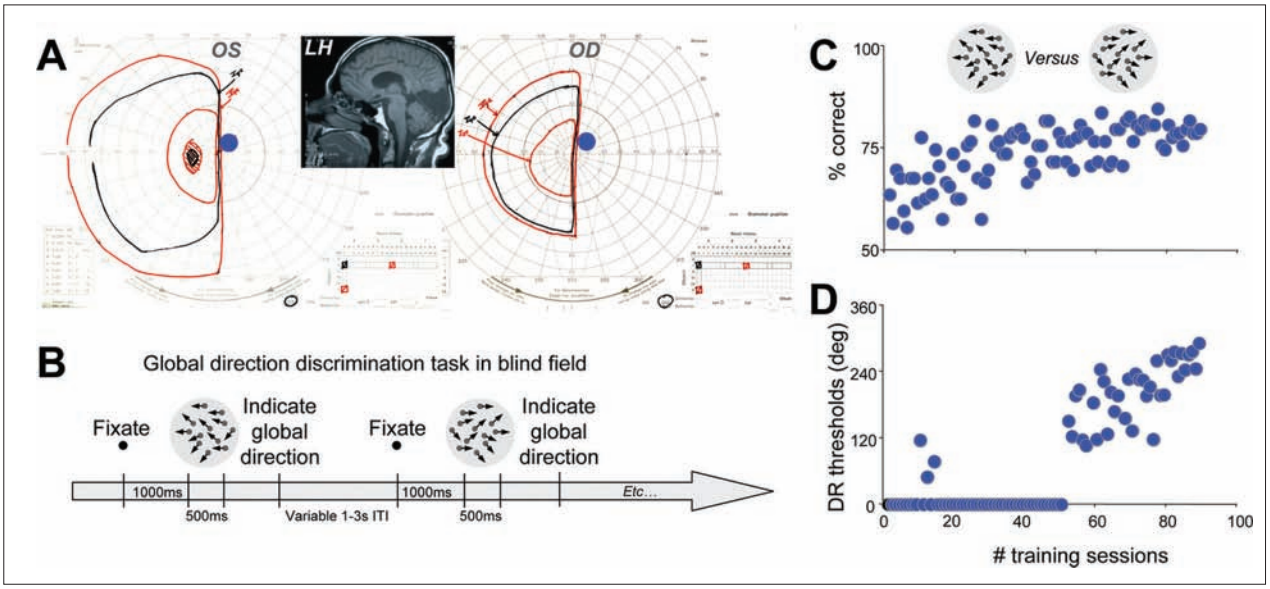

Figure 5. Training-induced recovery of global motion discrimination in the blind field following "relatively complete" damage to V1. (A) Goldmann perimetry of a patient whose MRIs are shown in Figure 4 reveals a dense, complete, right hemianopia. Red, black, and orange lines indicate the perimeter of the field of view attained with different intensity lights. The blue circle denotes one of the blind field locations at which this subject was retrained to perform global direction discriminations. OS, left eye; OD, right eye; LH, left hemisphere on MR image showing lesion around calcarine sulcus. (B) Sequential diagram of the global motion discrimination task on which the subject was trained in his blind field (blue circle location in A). (C) Plot of this patient's performance on a left-right global direction discrimination task using random dot stimuli presented at a single location in the blind field (blue circle in A). The graph plot's percentage correct performance in consecutive training sessions consisting of 300 trials each. Chance performance lies at 50% correct for this 2-alternative, forced-choice task. (D) Plot of direction range (DR) thresholds measured in these same training sessions illustrated in C. DR thresholds are measured by fitting a Weibull function to the percentage correct data at different DR levels and calculating the range of dot directions in the stimulus at which global direction discrimination performance is 75% correct. Note the dramatic improvement first in percentage correct performance, followed closely by improving thresholds, which reflect increased ability to integrate different motion directions in the random dot stimuli and extract a global directional vector from them.

Hemispherectomized subjects present a special opportunity to study the role of the intact hemisphere in visual recovery, although to our knowledge, this has not yet been done. In the context of blindsight, Ptito and colleagues tested several patients who underwent complete removal (decortication) or deafferentation of an entire cerebral hemisphere (reviewed in Ptito and Leh 2007). From an experimental point of view, the advantage of such patients is that they lack the majority of visual areas on the decorticated side. As a result, any residual visual ability within their impaired visual hemifield cannot be explained by spared striate or extrastriate cortex. Yet, such patients are able to detect a variety of stimuli in their blind field (Ptito and others 1991; Wessinger and others 1996). Moreover, they exhibit the same pattern of activation described by Henriksson and others (2007) when their blind field is stimulated with a moving grating presented on a background of random dots (Bittar and others 1999).

Diffusion tensor imaging in patient G.Y., who was rendered cortically blind following an automobile accident at 8 years of age, also reveals a strong connection between the intact hemisphere's dLGN and the damaged hemisphere's hMT+ (Bridge and others 2008). This connection was found to be absent in control, visually intact subjects. In addition, G.Y. also showed stronger corticocortical connections between his two hMT+ than control subjects (Bridge and others 2008). Although diffusion tensor imaging is primarily an anatomical technique, transcranial magnetic stimulation (TMS) can be used to test more precise hypotheses about functional connections between brain regions. In visually intact controls, TMS over the primary visual cortex elicits bright flashes of lights known as phosphenes in the contralateral hemifield, while unilateral stimulation of hMT+ elicits moving phosphenes, also in the contralateral visual field (Silvanto and others 2007). Bilateral stimulation of hMT+ produces a single, static phosphene that spans both visual fields that is explained by the cancellation of opposing directions of motion sensed in hMT+. Stimulation of G.Y.'s damaged V1 did not elicit any visual sensation (Cowey and Walsh 2000). However, bilateral stimulation of hMT+ in G.Y. produced bilateral, static phosphenes that differed from controls in that they were not joined centrally (Silvanto and others 2007). This experiment represented possibly the first instance of G.Y. having a conscious visual experience in his blind field. The fact that contralesional hMT+ was needed in order for G.Y. to have a conscious percept in his blind field, taken together with the aberrantly strong connectivity between visual areas in his 2 brain hemispheres, suggests that the intact hemisphere is functionally engaged in visual sensation within the blind field. As such, it is poised to also play a positive role in mediating training-induced visual improvements. An important consideration here is that G.Y. sustained his lesion in childhood. Other studies usually describe patients who sustained V1 damage in adulthood, although there is wide heterogeneity in the age of both the patients and of the lesion. At this stage, the relative implications of these factors for recovery are not known.

Summary and Conclusions

Cortical blindness is a disabling loss of vision that occurs following injury to V1 or its postchiasmal afferents. After an initial period of spontaneous plasticity, the visual deficit stabilizes and becomes permanent in the absence of specific intervention. Many of those afflicted develop spontaneous behavioral adaptations to their deficit, which may improve their quality of life. Intensive saccadic training can further develop and strengthen the patients' oculomotor strategies and further improve their ability to effectively use vision in everyday life. This finding has been verified using both objective scales and subjective reports. A disadvantage of saccadic training is the fact that it does not induce perimetric changes. On the other hand, several recently developed perceptual training methods have now shown success both at improving visual sensitivity for particular tasks/stimuli in the blind field and at reducing the size of perimetrically blind fields. The common theme in these methods is that they all used repetitive training, a classic approach to elicit perceptual learning in the intact nervous system. The outcome of such training is that after being forced to repeatedly discriminate visual targets in the blind field, the damaged visual system is able to slowly relearn to process and interpret what little visual information it receives. Significantly more research is needed to define the specific mechanisms at play here, but one possibility is that traditional mechanisms of perceptual learning such as improved template matching, channel reweighing, reduction in internal noise, increased external noise filtering (e.g., Dosher and Lu 1999; Dosher and Lu 2006; Dosher and Lu 1998), and changes in cellular and/or network sensitivities and specificities (e.g., Chowdhury and DeAngelis 2008; Ghose and others 2002; Law and Gold 2008; Schoups and others 2001; Yang and Maunsell 2004) are all invoked by training.

Part of the difficulty in defining mechanisms of training-induced perceptual improvements in cortical blindness is that this is not a homogenous condition; there is a huge variability in the extent and nature of the damage sustained by different individuals. Brain lesions in humans rarely respect functional or cytoarchitectonic boundaries. Nevertheless, systematic investigation of many additional patients with the specific goal of eliciting visual improvements in the blind field and correlating them with functional imaging or electrophysiological data collected during the retraining process should prove informative and allow us to eventually tease out the most likely substrates of the observed recovery of function.

We have come a long way from the days of thinking that the adult human brain was essentially devoid of plasticity or that cortical blindness was a permanent deficit with no hopes of improvement. However, we are still far from our ultimate goal of effectively rehabilitating this patient population. Defining mechanisms, limits, and characteristics of the plasticity attainable after V1 damage are all going to be important if we are to devise principled rehabilitation strategies for those who suffer from adult postchiasmal damage to the visual system.

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