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# Probing Human Visual Deficits with Functional Magnetic Resonance Imaging

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## Keywords

V1 lesion, fMRI, scotoma, visual perception, visual field perimetry, rehabilitation

## Abstract

Much remains to be understood about visual system malfunction following injury. The resulting deficits range from dense, visual field scotomas to mild dysfunction of visual perception. Despite the predictive value of anatomical localization studies, much patient-to-patient variability remains regarding (*a*) perceptual abilities following injury and (*b*) the capacity of individual patients for visual rehabilitation. Visual field perimetry is used to characterize the visual field deficits that result from visual system injury. However, standard perimetry mapping does not always precisely correspond to underlying anatomical or functional deficits. Functional magnetic resonance imaging can be used to probe the function of surviving visual circuits, allowing us to classify better how the pattern of injury relates to residual visual perception. Identifying pathways that are potentially modifiable by training may guide the development of improved strategies for visual rehabilitation. This review discusses primary visual cortex lesions, which cause dense contralateral scotomas.

## INJURIES OF THE VISUAL SYSTEM: BRIEF OVERVIEW

Impairment of visual function can occur at any point along the visual pathway, from the eye to the cortex, causing different visual deficits.

### Eye Injuries

Eye or retinal lesions typically cause loss of acuity or dense monocular scotomas over a part of the visual field. Typically, it is not possible to recover visual information inside a scotoma caused by dense retinal lesions because the light detection apparatus is irreversibly damaged. Even when the eye pathology can be repaired, this does not necessarily result in full reconstitution of visual function. This is particularly true when the visual cortex is exposed to abnormal visual input for a prolonged period of time at a young age. Amblyopia is perhaps the most obvious example. In amblyopia, eye misalignment early in life causes the degradation of visual perception arising from the lazy eye, and this is mediated by cortical malfunction (Levi 2013). Delayed repair of eye misalignment results in permanent visual deficit. An even more striking example is the delayed repair of bilateral corneal lesions occurring in early childhood. Bilateral corneal injuries result in markedly decreased visual acuity, consisting of light perception but an inability to perceive shapes. Even though eye transparency can be restored by corneal transplantation later in life, significant visual dysfunction persists in such cases (Fine et al. 2003, Huber et al. 2015). In sum, restoring visual function in adult patients who suffered significant eye injury early in life requires repairing not just the eyes but cortical visual processing also.

### Primary Visual Cortex (Area V1) Injury

Posterior circulation infarcts, hemorrhages (Zhang et al. 2006), or traumatic brain injury (Bruce et al. 2006, McKenna et al. 2006) often produce varying degrees of injury to visual cortical networks, including area V1. V1 is the chief relay of visual input to higher (extrastriate) cortical areas. Therefore, V1 lesions produce dense, contralateral, homonymous visual field defects, or scotomas, within which visual perception is severely impaired. Scotomas caused by vascular area V1 lesions often involve half of the contralateral visual field (hemianopia) or a contralateral visual field quadrant (quadrantanopia). The resulting visual deficit is thought to be highly resistant to rehabilitation, essentially irreversible (Balliet et al. 1985; Horton 2005a,b; Riggs et al. 2007) (but see section Potential for Recovery After Lesions of the Adult Visual System: Role for fMRI below), and leads to significant disruption in the patient's life (Ajina & Kennard 2012, Kerkhoff 2000).

However, some residual visual function often persists inside scotomas induced by V1 lesions. An example of this is blindsight—that is, visual perception in the absence of conscious awareness of the visual stimulus (Cowey & Stoerig 1991, Weiskrantz 2004). Recent studies have suggested that some recovery of visual function is possible inside the scotoma (Das et al. 2014, Huxlin et al. 2009, Sahraie et al. 2006, Trevethan et al. 2007), raising the hope that with appropriate patient selection and targeted therapy, a degree of success in visual rehabilitation may be possible. This issue is fraught with controversy and is returned to in more detail in the section The Biggest Challenge: Restoring Conscious Visual Perception below.

### Extrastriate Visual Cortex Injury

Pure damage to extrastriate areas, sparing the primary visual cortex, is more infrequent, and often results in more specific and milder visual deficits, such as prosopagnosia, achromatopsia, akinetopsia, and others (Stasheff & Barton 2001). The particular nature of the deficit depends on

the area involved. For example, lesions of the ventral stream can lead to deficits in color perception (achromatopsia); defects in visual recognition, such as prosopagnosia (the inability to recognize familiar faces); or, sometimes, the inability to read (alexia) (Stasheff & Barton 2001). Lesions of the dorsal stream, involving the occipito-temporo-parietal region, lead to the inability to perceive aspects of visual motion (akinetopsia) (Vaina 1994; Vaina et al. 2000, 2005) or the inability to perceive simultaneously different parts of the visual stimulus (simultagnosia, Balint's syndrome) (Stasheff & Barton 2001). Focal injuries of the extrastriate visual areas are generally, although not always, felt to be easier to rehabilitate.

## **FUNCTIONAL MAGNETIC RESONANCE IMAGING CAN BE USEFUL FOR BETTER CHARACTERIZING VISUAL SYSTEM INJURIES**

### **Visual Field Perimetry Is Not Enough**

The standard way to characterize visual field deficits after injury to the visual system is by using visual field perimetry. Typically, this involves presenting visual stimuli of different sizes and brightness to different parts of the visual field while the patient is fixating, and then scoring stimulus visibility. Many different types of perimetry exist that cannot be reviewed here. Most patients with visual field lesions are evaluated and followed on the basis of Goldmann or Humphrey perimetry, including several more sophisticated variants (e.g., Tuebinger perimetry) (Cohen & Kawasaki 1999). Sophisticated perimetry mapping of visual field deficits is essential in order to assess the degree of injury and to document recovery.

Although it provides important information, visual field perimetry as currently performed is not sufficient to fully characterize the type of visual system injury. This is especially true for visual system injuries distal to the eye. For example, a dense, homonymous visual field scotoma could result from a number of different lesions, ranging from pure lesions of the optic radiation or area V1 to mixed lesions involving V1 and extrastriate areas or even to pure lesions of extrastriate areas (Horton & Hoyt 1991). In fact, different regions of the same anopic visual field that yield essentially indistinguishable perimetry maps may correspond to different patterns of neural injury (**Figure 1**). This makes it difficult to classify appropriately lesions that may have different potential for visual rehabilitation. Furthermore, such classification cannot proceed purely on the basis of anatomical imaging, whose resolution is often not sufficient to characterize the pathways involved or the completeness of the injury. Therefore, it is important to image visual circuit function in order to improve the characterization of visual system injuries.

### **fMRI Provides Information Complementary to Visual Field Perimetry**

Functional magnetic resonance imaging (fMRI) can be used to quantitatively measure the response of visual areas to standardized visual stimulation and to map (Engel et al. 1994, Wandell 1999) how surviving visual areas represent the topography of the visual field following injury. Recently, fMRI methods (Dumoulin & Wandell 2008; Lee et al. 2013, 2015; Zuiderbaan et al. 2012) have been developed to obtain voxel-based, neuronal population receptive field (pRF) estimates, yielding the receptive field center, size, and shape for the constituent voxels of spared visual areas. Standard retinotopic topographical maps can then be computed, borders of early visual areas identified, and magnification factors measured and followed over time.

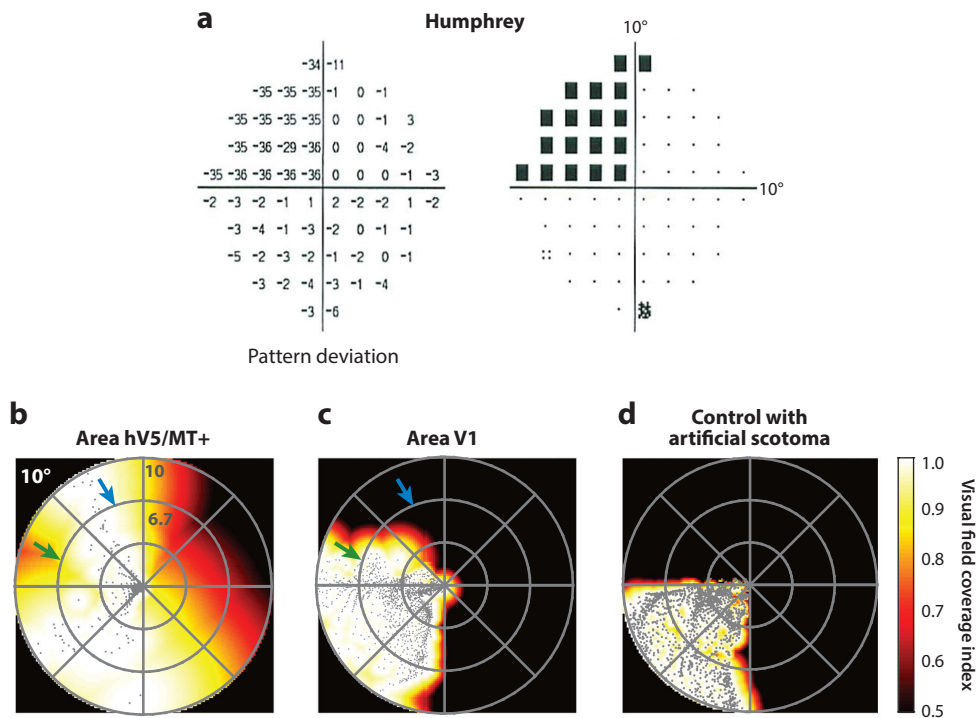
From the pRF maps, the part of the visual field that can activate a visual area can be estimated, and this is called the visual field coverage map for that area (Amano et al. 2009). Visual field coverage maps can be compared across visual areas and with visual field perimetry. Papanikolaou

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**fMRI:** functional magnetic resonance imaging

**pRF:** population receptive field

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**Figure 1**

Visual field coverage maps of spared visual areas. (a) Humphrey visual perimetry map showing a participant with left upper quadrantanopia. Each black square in the left upper quadrant corresponds to visual sensitivity loss  $\gg 20$  dB, indicating a dense scotoma. (b) The right area hV5/MT+ visual field coverage map (Amano et al. 2009, Papanikolaou et al. 2014) shows the visual field locations that evoke significant responses from the right area hV5/MT+. At each visual field location, the highest population receptive field (pRF) value of all normalized pRFs that cover this location is plotted. Note that area hV5/MT+ can respond to stimuli presented in the left upper quadrant, although the participant is blind there. (c) Visual field coverage map of right area V1 shows that there is a residual area of V1 activity that arises from the left upper quadrant (green arrow) even though the scotoma is dense there (a). This activity may arise in surviving islands that are partially active following the V1 lesion or could be due to ectopic V1 receptive fields. The blue arrow points to a region of the visual field that cannot elicit activity in V1. The blue versus green arrow regions of the visual field elicit different patterns of activity in the visual cortex, despite giving the same signature of a dense scotoma on Humphrey perimetry. It is possible that visual motion rehabilitation may be easier in regions of a scotoma for which the visual field coverage maps of area V1 and hV5/MT+ are congruent (green arrow) compared with those that are incongruent (blue arrow). (d) Visual field coverage map from the right area V1 of a normal participant with an artificial scotoma simulating left upper quadrantanopia. The control visual field coverage map does not encroach into the left upper quadrant. Figure modified from Papageorgiou et al. (2014) with permission.

et al. (2014) recently used fMRI to measure area V1 pRFs in patients with dense, chronic scotomas resulting from postchiasmatic lesions and found that the functional properties of spared V1 cortex are not necessarily predicted by standard visual field perimetry mapping. Two different patterns were described: First, spared V1 visual field coverage maps overlapped significantly with dense regions of the perimetric scotoma, suggesting that even regions with a dense perceptual scotoma can sometimes elicit activity in spared primary visual cortex. This pattern might occur if there is damage downstream of area V1, interrupting communication between V1 and

extrastriate areas, or, perhaps, from injury to the extrastriate areas directly (Horton & Hoyt 1991). However, this pattern was also detected in a patient whose lesion was exclusively located in the optic radiation, interrupting lateral geniculate nucleus (LGN) inputs to layer V1 but sparing the visual cortex (Papanikolaou et al. 2014). In this case, visually driven fMRI [blood oxygen level-dependent (BOLD)] activity could be seen in both area V1 and higher extrastriate areas, but it was not sufficient to drive visual perception, suggesting that the activity generated was too weak or too disorganized to elicit a percept. Given that the pathways from area V1 to higher extrastriate areas were intact and islands of activity were present in the V1 cortex, it is reasonable to speculate that this patient may have a high potential for visual rehabilitation. Second, spared V1 visual field coverage maps sometimes failed to cover sighted locations in the perimetric map that overlapped with the visual field coverage maps of higher areas, indicating the potential existence of V1-bypassing pathways that are able to mediate useful vision. This is in agreement with prior reports in humans (Goebel et al. 2001, Schoenfeld et al. 2002) and primates (Rodman et al. 1989, 1990; Schmid et al. 2009, 2010, 2013).

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**LGN:** lateral geniculate nucleus

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These examples suggest that fMRI pRF measurements in patients with cortical lesions yield information complementary to standard visual field perimetry. These and other observations (Barleben et al. 2015, Goebel et al. 2001, Raposo et al. 2011, Schoenfeld et al. 2002, Striem-Amit et al. 2015) suggest that fMRI analysis can be used to subclassify patients with otherwise identical perimetric scotomas into categories that may potentially have different implications for prognosis and the capacity for visual rehabilitation. Future studies of patients with lesions of the visual pathway that incorporate careful retinotopic visual field mapping and pRF measurements are clearly warranted to improve understanding of visual processing in the context of injury and to carefully select patient populations for rehabilitation trials. It will also be interesting to study whether one can devise new, comprehensive methods of perimetry, which may be better able to subclassify the different patterns of visual cortical injury seen by fMRI.

## **POTENTIAL FOR RECOVERY AFTER LESIONS OF THE ADULT VISUAL SYSTEM: ROLE FOR fMRI**

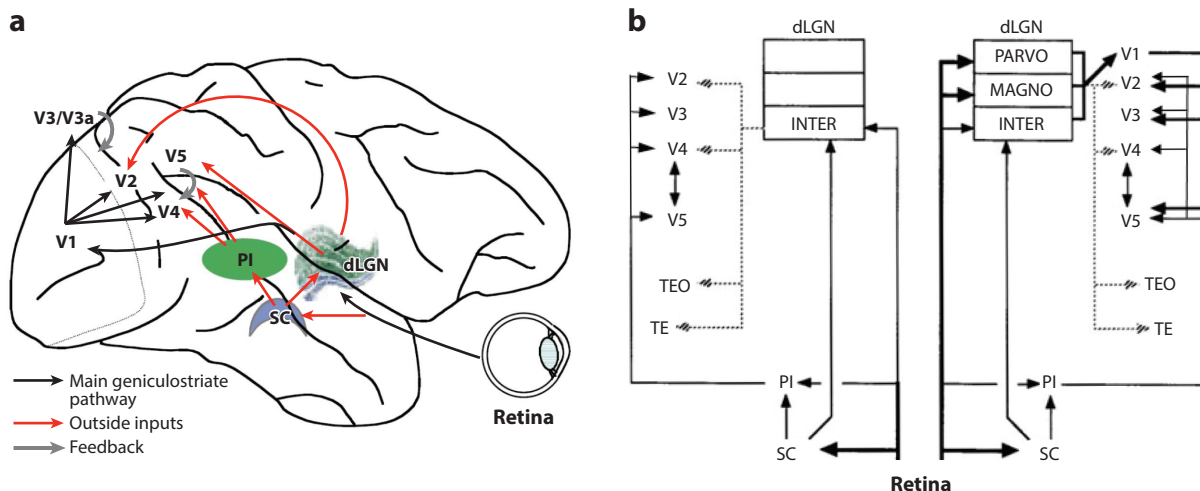
The potential for recovery after visual system injury has been the subject of controversy for many years. This topic has been reviewed extensively, so it is only briefly summarized here. Spontaneous short-term recovery of visual perception typically occurs 1–2 months following injury, essentially never beyond 6 months (Urbanski et al. 2014), and is chiefly related to perilesion repair processes, such as decreases in edema and inflammation (Ajina & Kennard 2012, Tiel & Kolmel 1991). After this period, spontaneous recovery reaches a steady state and, without training, visual field defects remain essentially stable. It is this latter period that is discussed here.

Various strategies have been adopted for visual system rehabilitation following injury. Chief among them (Das & Huxlin 2010, Pelak et al. 2007, Pouget et al. 2012, Schofield & Leff 2009) are (a) relocating the visual field via prismatic correction, (b) teaching compensatory strategies for oculomotor exploration of the blind field, and (c) improving residual detection capability and recovering lost visual function (improving visual perception). Recovery induced by compensatory strategies (a) and (b) is not discussed in this review, but instead the focus is on the recovery of visual perception.

Improvement of visual function has been shown in a number of species to require repeated training, which induces plasticity and alters neural physiology (Ahissar et al. 2009; Huxlin 2008, 2009; Salazar et al. 2004; Yang & Maunsell 2004). This has been corroborated in cats and macaques, chiefly with extrastriate but also with striate lesions of the visual cortex (Cowey & Weiskrantz 1963, Huxlin & Pasternak 2004, Newsome & Pare 1988, Pasternak & Merigan 1994, Rudolph &

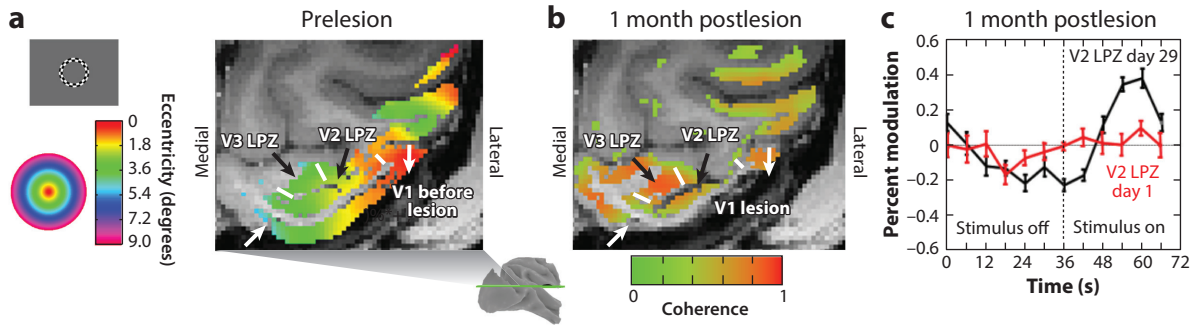
Pasternak 1999). However, it remains controversial whether in adult primates or humans training can induce significant recovery in visual field scotomas resulting from area V1 lesions (against this possibility are Balliet et al. 1985; Horton 2005a,b; Reinhard et al. 2005; Riggs et al. 2007; and for this possibility are Huxlin 2007, Huxlin et al. 2009, Sabel 2006, Sabel & Kasten 2000, Sabel et al. 2011, Sahraie et al. 2006, Zihl & von Cramon 1985). Part of the reason for the controversy is that (a) it is often not possible to determine with certainty whether the injury is complete, (b) light scatter into the seeing field, if not controlled, may spuriously improve performance, and (c) eye movements, if not rigorously controlled, may contribute to the recovery in a trivial way by shifting the stimulus from the blind to the seeing field.

Remarkably, under carefully controlled conditions, a limited capacity to process visual attributes such as motion (Weiskrantz 2004, Zeki & Ffytche 1998) often persists inside scotomas induced by V1 lesions, both in humans (Poppel et al. 1973, Weiskrantz et al. 1974) and in monkeys (Covey & Stoerig 1995). This phenomenon is known as blindsight because visual perception in the scotoma is generally lost despite above-chance performance on testing. Several pathways to the extrastriate cortex bypass area V1 (Figures 2 and 3) and can potentially mediate the residual visual function (Bruce et al. 1986; Covey & Stoerig 1991; Moore et al. 2001; Rodman et al. 1989, 1990; Schmid et al. 2009, 2010; Weiskrantz 2004). Blindsight performance has been shown to improve with training (Stoerig & Covey 1997, Weiskrantz 2004), raising the hope that better rehabilitation strategies may one day be able to increase the strength of V1-bypassing pathways to partially



**Figure 2**

Extrageniculostriate pathways bypassing area V1. (a) Sketch of some of the projections from the retina to the early extrastriate cortex. (b) This diagram, adapted from Stoerig & Covey (1997), shows the main retinofugal pathways to the early extrastriate cortex. On the right, the pathways are shown with V1 intact. The left illustrates the chief surviving pathways after area V1 has been lesioned. Feedforward and feedback projections from the extrastriate cortex (V2 to V5) and higher areas are not shown. Two pathways stand out as potentially mediating the residual activity observed in the extrastriate cortex as well as related aspects of blindsight behavior: First, the koniocellular pathway (dotted lines), from the intercalated layer of the thalamus directly to extrastriate areas, receives both direct input from the retina and indirect input from the retinotectal (superior colliculus) pathway. Second, the projection from the inferior pulvinar to the extrastriate cortex also receives direct retinal, as well as retinotectal (superior colliculus), input. A third pathway, not illustrated, that potentially contributes consists of the parvocellular and magnocellular neurons that survive degeneration after area V1 injury, likely because they project directly to the extrastriate cortex (Covey & Stoerig 1989). Abbreviations: INTER, intercalated layer; dLGN, dorsal lateral geniculate nucleus; MAGNO, magnocellular neurons; PARVO, parvocellular neurons; PI, inferior pulvinar; SC, superior colliculus. Figure adapted from Stoerig & Covey (1997) with permission.



**Figure 3**

V1-bypassing pathways visually modulate area V2 and V3 in the absence of V1 input in the macaque. (a) Phase-encoding retinotopic map of a slice through the right posterior hemisphere of a macaque, whose V1 is intact. White arrowheads indicate the extent of the V1 region that is going to be lesioned. The regions between the small white bars indicate the domains in areas V2 and V3 that correspond retinotopically to the V1 area between the arrowheads. These areas are labeled, respectively, V2 LPZ (lesion projection zone) and V3 LPZ. Note that only V2 and V3 regions located in the same slice are shown, explaining why the part of the V3 LPZ shown does not contain the full range of eccentricities seen in the corresponding V1 region (between the white arrowheads). (b) Because the animal has a permanent head post, it was possible to obtain the exact same slice >1 month later. It is illustrated here with an overlaid color map corresponding to the strength of visually driven modulation (coherence) elicited by a full-field stimulus alternating with the background. A threshold has been applied at the noise level of coherence to allow visualization of the underlying anatomy. Note that the V1 area between the white arrowheads, which has been lesioned, shows no activity. In contrast, the corresponding regions in the V2 LPZ and V3 LPZ show robust visual modulation (strong coherence signal). (c) The mean temporal profile of the response of the V2 LPZ to the visual stimulus. Note that on day 1 the response is flat, but by day 39 significant visual modulation is seen. It turns out that the strength of this visual modulation is about 20% of what it was prior to the V1 lesion (Schmid et al. 2009). Electrophysiological experiments presented in Schmid et al. (2009) indicated that the source of the input driving the visual modulation is subcortical. More recent experiments by Schmid et al. (2010) point more specifically to the lateral geniculate nucleus as a source of the visual modulation. Figure adapted from Schmid et al. (2009) with permission.

compensate for the loss of V1 input. This possibility has been underscored by recent results from Huxlin et al. (Huxlin 2008, Huxlin et al. 2009) and others showing that, with intense training, behavioral thresholds to certain stimuli can recover inside the scotoma of human hemianopes with V1 lesions (Raninen et al. 2007, Sabel et al. 2011, Sahraie et al. 2006). Sabel et al. (2011) have also argued that it may be possible for malfunction due to partial injury to visual pathways to be rehabilitated by training, especially at the border of the scotoma. However, despite these promising results, training to improve visual perception has not produced consistently practical benefits (see controversy between Sabel et al. 2011 and Horton 2005a,b) and, therefore, it is not widely accepted as an effective method of visual rehabilitation.

The most common cortical injury that leads to significant deficits in human patients involves V1 lesions (Bruce et al. 2006, Zhang et al. 2006), which are the most difficult to rehabilitate. This is compounded by the fact that following V1 lesions there is significant (>90% in the macaque) retrograde degeneration of the parvocellular and magnocellular pathways going back to the retina (Covey & Stoerig 1989). It is likely that an even greater degree of retrograde degeneration occurs in the human (Polyak 1957), suggesting that perceptual aspects of vision are likely to be permanently and markedly changed post-V1 lesions, even under the best-case scenario of successful rehabilitation. However, all hope may not be lost. In the LGN, the koniocellular pathway survives, as well as scattered parvocellular and magnocellular neurons (perhaps as many as 10%), likely because they project directly to the extrastriate cortex (Covey & Stoerig 1989, Sincich et al. 2004). This raises the possibility that, if strengthened appropriately, these surviving projections may mediate a degree of visual perception.

Several V1-bypassing pathways have been shown to mediate neural activity and, sometimes, useful perception. For example, the circuit involving the superior colliculus (SC), inferior pulvinar, and extrastriate cortex is strengthened (Stoerig & Cowey 1997) and has been shown to mediate residual motion perception in macaques with V1 lesions (Moore et al. 2001; Rodman et al. 1989, 1990). Recently, the surviving pathway from the LGN to the cortex has been shown to be involved in activity generated in macaque areas V2 and V3 that have been associated with blind-sight performance (Schmid et al. 2009, 2010). In humans, multiple observations have suggested that extrastriate areas can be activated following dense primary visual cortex lesions (Goebel et al. 2001, Henriksson et al. 2007, Papanikolaou et al. 2014, Raninen et al. 2007, Schoenfeld et al. 2002), presumably taking advantage of surviving subcortical projections from the SC–pulvinar or LGN, or both. Additionally, it has also been suggested that in the case of focal lesions, the contralesional hemisphere may also be able to mediate residual function through transcallosal or intertectal connections (Baseler et al. 1999, Henriksson et al. 2007).

In spite of these encouraging observations, clinical efforts at rehabilitating visual perception have yet to convincingly demonstrate significant practical benefits (benefits arising from a change in oculomotor strategy or by using prisms to remap the blind onto the seeing visual hemifield are not discussed). Part of the problem may be that the ability of patients to recover following visual rehabilitative training is not uniform. Some patients show strong recovery following visual rehabilitative training and others show no recovery at all (Sabel et al. 2011). It remains unclear what criteria one might use to select patients who are more likely to recover. A problem faced in studies of visual rehabilitation is that patients often have heterogeneous lesions, even though the extent and density of their perceptual scotomas may match when measured by standard perimetry approaches (Papanikolaou et al. 2014). This reinforces the notion that visual field perimetry mapping, as currently performed, does not necessarily provide a sufficient indicator of the capacity for rehabilitation, although these maps are paramount for following recovery that has practical significance. A measure of the ability of visual stimuli presented inside the scotoma to elicit subthreshold activity in spared visual cortex would add valuable information.

fMRI can be used to characterize the functional implications of a lesion by identifying which sectors of the visual field scotoma are still able to transmit visual information to spared regions of the visual cortex. A reasonable hypothesis is that regions of the scotoma able to convey visual information to spared parts of area V1, or to higher visual areas bypassing the area of cortical injury, may be more amenable to visual rehabilitation. It is important to keep in mind that fMRI does not simply give information about a patient's classification, but can be used as a biomarker to study how different rehabilitative strategies enhance visual responses across the network of visual areas. Apart from the obvious use of such information in delineating the mechanisms of recovery, it may well be possible to observe changes in the pattern of visual responses on fMRI before these become evident in behavioral performance, and this may prevent us from prematurely discarding potentially useful rehabilitative approaches. Over time, enough information will be gathered to relate the observed patterns of activity measured by fMRI to the improvement in visual perception induced by rehabilitation, helping to guide the intelligent design of more effective rehabilitative strategies.

## **POTENTIAL FOR RECOVERY AFTER VISUAL SYSTEM INJURY IN DEVELOPMENT: ROLE FOR fMRI**

The ability of the nervous system to reorganize after injury decreases with age. The weight of the evidence suggests that injuries occurring early in development recruit mechanisms of plasticity that are unavailable later in life, and these can result in much better functional improvement. The topic is large and deserves a brief mention even though it cannot be reviewed in detail here.



In the 1940s Kennard & Fulton (1942) showed that timing is important for neural plasticity, and Teuber (1975) observed that visual recovery was inversely correlated with age at the time of trauma. The incidence of abnormal visual function in children with cortical infarction is lower than in adults with corresponding lesions, suggesting an increased capacity of the visual system for reorganization at earlier ages (Guzzetta et al. 2001a, 2010; Payne & Lomber 2002; Werth 2008). There are several reports of partially spared visual function in children with damaged optic radiation and visual cortex (Amicuzi et al. 2006, Giaschi et al. 2003, Guzzetta et al. 2010). These observations support the notion that the capacity of the young brain for plasticity is high. Guzzetta et al. (2010) recently reviewed the topic of plasticity in the visual system after early injury and discussed the mechanisms of plasticity that are operating in the young. It should be noted, however, that even though visual outcomes are better, visual field defects often remain in children with large cortical lesions suffered in early childhood. Koenraads et al. (2014) reviewed 45 children with epilepsy who underwent hemispherectomy at a median age of 2.1 years and found that they all had a remaining homonymous hemianopia on visual field perimetry, despite having near normal visual acuity and ability to fixate. It is likely that even earlier lesions, perhaps incurred prenatally or perinatally (Guzzetta et al. 2010, Seghier et al. 2005), are necessary in order to observe significant visual field recovery.

New brain imaging modalities, such as anatomical MRI imaging, diffusion tensor imaging (DTI), and fMRI, allow us to evaluate and follow in detail the functional reorganization of the visual system, from the time of injury to adulthood (Guzzetta et al. 2001b, Haak et al. 2014, Seghier & Huppi 2010, Seghier et al. 2005). This has the potential to markedly improve our understanding of which plasticity mechanisms can, in principle, lead to recovery. Guzzetta et al. (2010) listed the following possible mechanisms of recovery in patients with congenital V1 lesions: (a) partially functional tissue is still present within or at the border of the V1 lesions (Dumoulin et al. 2007, Knyazeva et al. 2002), (b) primary visual cortex function is subsumed by reorganized extrastriate cortex (Kong et al. 2000), or (c) the geniculostriate pathway reorganizes to bypass the lesion (Seghier et al. 2005). Although some of these mechanisms may operate only in the young, it is not inconceivable that appropriate manipulations may eventually potentiate them in adulthood, leading to improved outcomes in adults with lesions. It is, therefore, important to study in detail carefully selected developmental series of visual system injuries, as they will potentially teach important lessons on how to approach the problem in adults. However, the interpretation of these studies should be done with care, and appropriate controls should be used. In particular, it is important to consider the possibility that changes may be due to the arrest of normal development by the injury rather than to active remapping (see Haak et al. 2014). It is also important to ensure careful visual perimetry mapping has been performed, which is notoriously challenging in children.

## **THE BIGGEST CHALLENGE: RESTORING CONSCIOUS VISUAL PERCEPTION**

Lesions of the primary visual cortex alter the quality of visual perception. Conscious vision typically disappears in the interior of the scotoma, and perceptual distortions occur near the border of the blind field (Dilks et al. 2007). It is important to investigate the neurophysiological mechanisms that underlie these phenomena, because finding a way to restore conscious visual perception is likely to be strongly linked to practical benefit.

Full conscious vision relies on the integrity of the pathway between the retina and the primary visual cortex (Felleman & Van Essen 1991). Substantial recovery of conscious visual perception does not occur within the scotoma of adults with dense lesions of the primary visual cortex (Bouwmeester et al. 2007). Early in development, this is not necessarily the case. Injury to the

optic radiation or the primary visual cortex before birth may spare conscious vision (Blythe et al. 1987, Giaschi et al. 2003, Payne & Lomber 2002, Ptito & Leh 2007). The reason for this is not well understood, but contributing mechanisms may include reactivation of residual spared V1 tissue (Knyazeva et al. 2002), strengthening of subcortical pathways that bypass V1 (Seghier et al. 2005), and reorganization of extrastriate areas (Kong et al. 2000). The early timing of the insult allows the brain to take advantage of specific time-dependent strategies of cortical reorganization not available in adulthood. Mechanisms of plasticity that can support the restoration of conscious vision appear to be available up to the third trimester of prenatal development and then decrease markedly following birth (Guzzetta et al. 2010). Even postnatally, however, the young brain is more plastic and has higher capacity for reorganization than the adult brain.

In adulthood, injury to the primary visual cortex generally causes loss of conscious visual perception in the contralateral hemifield (Weiskrantz et al. 1974) even though the ability to process visual information does not always completely disappear (blindsight) (Riddoch 1917) (reviewed in Stoerig 2006 and Cowey 2010). The division between blindsight and conscious vision is not necessarily sharp, as some patients that exhibit blindsight also report partial visual stimulus awareness in the blind hemifield (Dancerkert & Rossetti 2005, Sahraie et al. 2006, Zeki & Ffytche 1998). However, spontaneous recovery is not sufficient to return conscious vision to the large majority of adult patients with primary visual cortex lesions. Interestingly, training has been reported to increase the subjective sense of visual stimulus awareness inside the blind field (Chokron et al. 2008, Payne et al. 2000, Sahraie et al. 2006, Treveltham et al. 2007, Weiskrantz et al. 1991) and, therefore, offers some hope that future interventions may be able to restore a modicum of phenomenal vision in adults with injuries of the primary visual cortex.

To optimize interventions designed to decrease the threshold for conscious visual perception, it may well be important to take into account information about the functional integrity of the visual circuits downstream from the lesion. Such information is provided by fMRI in conjunction with resting-state connectivity analysis. It remains an open question whether fMRI signatures will be sufficient for developing a reliable biomarker for the presence of conscious visual perception following lesions of the primary visual cortex. For instance, the magnitude of the fMRI signal recorded in response to a visual stimulus from spared extrastriate cortex following V1 lesions is not, by itself, a reliable predictor of whether the stimulus is perceived. Visually driven BOLD signal activity can be obtained throughout the extrastriate cortex of monkeys with dense V1 lesions, even though the monkeys exhibit only blindsight (Schmid et al. 2009, 2010, 2013). It is not clear why it is that, even though extrastriate areas can be visually driven post-V1 lesions (Barleben et al. 2015, Papanikolaou et al. 2014; Schmid et al. 2009, 2010, 2013), subjects do not perceive the visual stimulus. For example, the strength of visual modulation elicited by high contrast stimuli in macaque areas V2 and V3 following V1 lesions is approximately 20–30% of what it was prior to the lesion, but the monkeys are capable only of blindsight (Schmid et al. 2009, 2010). When V1 is intact, low contrast stimuli that elicit the same BOLD level of activity in the early extrastriate cortex are clearly visible. This suggests that either (*a*) area V1 activity is itself essential to visual perception or (*b*) V1 input is needed to coordinate directly, or indirectly via feedback loops, the temporal profile of extrastriate activation needed to give rise to visual perception.

The literature discussing the neurophysiological correlates of conscious perception is large and it cannot be done justice here (see reviews by Moutoussis & Zeki 2002, Silvanto 2015, Stoerig & Cowey 1995). Suffice it to say that reports of conscious visual experience in the absence of V1, rare as they may be, argue against the possibility that the primary visual cortex is the only gateway to awareness (Barbur et al. 1993, Ffytche et al. 1996, Silvanto 2015, Silvanto & Rees 2011). Silvanto (2015), in a recent review, has argued that the need for global coherence of neural activity across

areas at short temporal time scales may be necessary to yield the conscious percept of vision. If that is the case, reestablishing coherence across extrastriate areas in the absence of V1 input may potentially return a degree of conscious visual perception (Silvanto et al. 2007).

Complementing fMRI data with data collected using other imaging modalities that have much higher temporal resolution—such as magnetic encephalography (MEG), electrocorticography (EcoG), or electroencephalography (EEG)—will likely be needed to make progress in this area. Transcranial magnetic stimulation (TMS) may also be a valuable adjunct in the effort to establish causality. This has been illustrated by Silvanto et al. (2007) who demonstrated that with bilateral, but not unilateral, V5/MT+ TMS stimulation, a patient with hemianopia could experience phosphenes in his blind field. Because Cowey & Walsh (2000) had previously shown that ipsilesional V5/MT+ stimulation elicited no phosphenes, Silvanto et al.'s observations suggest that a contribution from the patient's intact hemisphere is necessary for extrastriate activation in the lesioned hemisphere to reach visual awareness. New creative approaches are necessary to tackle this difficult, but probably not insurmountable, problem.

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**EcoG:** electrocorticography  
**EEG:** electroencephalography  
**TMS:** transcranial magnetic stimulation

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## THINGS fMRI HAS TAUGHT US

fMRI can measure quantitatively the topography of the retinotopic organization across visual areas. It is, therefore, a powerful method for measuring abnormalities of the cortical representation of the visual field in patients with visual defects and for following them over time to document plasticity as a function of rehabilitation (see also the recent review in Urbanski et al. 2014).

### Extrastriate Visual Areas Can Be Visually Modulated in the Absence of Retinotopically Corresponding V1 Input

There is strong evidence that subcortical pathways can activate extrastriate areas in the absence of V1 input. This arises from both animal and human studies. Early work by Rodman et al. (1989, 1990) demonstrated that macaque area V5/MT could be visually modulated in the absence of V1 input via pathways involving the SC. More recently, Schmid et al. (2009) used fMRI and electrophysiology in macaques to study activity patterns in areas V2 and V3 from 1 to 22 months after lesioning in area V1. Visually driven responses were found to persist inside the V1 lesion projection zones of areas V2 and V3, reduced in strength by 70% on average compared with prelesion levels. This visual modulation appeared to emerge without specific training within 1 month postlesion, and it remained stable thereafter. The retinotopic organization inside the lesion projection zones of areas V2 and V3 remained similar to that of the nonlesioned hemisphere, suggesting that V2 and V3 activity is not the result of input arising from nearby (nonlesioned) V1 cortex. Cross-hemispheric callosal connections did not appear to make a significant contribution because restricting the stimulus to the intact visual hemifield produced no significant BOLD modulation inside the V2 and V3 lesion projection zones. Follow-up work demonstrated that this activity was mediated via V1-bypassing geniculol-extrastriate projections (Schmid et al. 2010, 2013), likely involving the koniocellular pathway and perhaps the small fraction (<10%) of magno and parvo cells that do not degenerate following the V1 lesion, presumably because they project directly to extrastriate cortex.

Extrastriate cortex activation in the absence of V1 input has also been reported in humans (Bridge et al. 2010, Goebel et al. 2001, Nelles et al. 2002, Papanikolaou et al. 2014, Schoenfeld et al. 2002, Stoerig et al. 1998). Goebel et al. (2001) reported sustained extrastriate cortical activation in the absence of visual awareness during stimulation of the blind field in two participants with hemianopia. Schoenfeld et al. (2002) reported similar findings in one patient with hemianopia

examined with MEG, suggesting that activity arose earlier in areas V5 and V4 compared with areas V2 and V3 of the ipsilesional hemisphere. Nelles et al. (2002) reported bilateral extrastriate cortex activation with stimulation of the blind field in a group of seven patients with partial hemianopia. Papanikolaou et al. (2014) also reported patients with early visual cortex activity in the absence of retinotopically corresponding V1 input (supplementary information from Papanikolaou et al. 2014). Bridge et al. (2010) reported hV5/MT+ activation in a patient with no V1 activity because of bilateral occipital strokes, suggesting subcortical pathways are involved.

Overall, both human and animal studies suggest that activation of the extrastriate cortex is possible following dense V1 lesions, and it is likely mediated by V1-bypassing subcortical pathways through the LGN and the SC–pulvinar. These likely represent preexisting pathways that are unmasked and become stronger in the absence of V1 input (**Figure 3** here, and supplementary figure 2 in Schmid et al. 2009). Without specific rehabilitative intervention, they are generally not sufficient to mediate visual perception. It remains an open question whether they can be induced to reorganize sufficiently to support residual visual function of practical significance.

### Capacity of the Visual Cortex for Reorganization After Retinal Lesions

As mentioned above, the capacity of the visual system for reorganization is large after early congenital lesions and then decreases drastically in adulthood (Guzzetta et al. 2010). This is reflected in the reorganization patterns that are seen in the primary visual cortex following retinal injury: No large-scale (~1-mm) reorganization occurs in area V1 following retinal lesions in adulthood (Baseler et al. 2011, Horton & Hocking 1998, Smirnakis et al. 2005, Wandell & Smirnakis 2009) (but see Baker et al. 2005, 2008; Gilbert & Wiesel 1992; Gilbert et al. 2009), although, in contrast, congenital eye disorders can lead to drastic primary visual cortex reorganization (Baseler et al. 2002). For example, marked cross-modal visual system plasticity occurs in patients with intact visual cortex who become blind at a young age. This is manifested by the fact that deafferented visual areas can be activated by somatosensory stimuli, such as Braille reading (Sadato et al. 1996). Moreover, this reorganization has functional significance, as disruption of visual cortex activation is seen to disrupt Braille reading (Cohen et al. 1997).

Extrastriate areas appear to have higher capacity for reorganization following retinal lesions than does the primary visual cortex (Shao et al. 2013). Furthermore, not all pathways projecting to the primary visual cortex have the same capacity for reorganization. Following retinal injury caused by juvenile macular degeneration, Masuda et al. (2008, 2010) argued that feedback pathways to the primary visual cortex are unmasked (or, perhaps, reorganized) to elicit visually driven activity inside the V1 lesion projection zone. The hallmark of this activity is that it depends on the performance of a visual task, as passive viewing of the same stimulus elicits no activity inside the V1 lesion projection zone. It remains to be seen whether this represents true reorganization—that is, an adjustment that requires structural changes and time (Wandell & Smirnakis 2009)—or the simple adaptive unmasking of existing feedback projections from higher areas that are triggered by the absence of feedforward inputs. Regardless of which is occurring, these observations suggest that top-down projections related to task performance have the ability to modulate the response of early visual areas in the absence of V1 input. These pathways, likely involving, in part, attentional networks, may be more amenable to rehabilitation than pure feedforward inputs.

### Capacity of the Visual Cortex for Reorganization After Cortical Lesions

Although there are no large, systematic, prospective studies, there have been several small series and case reports in the literature suggesting that various mechanisms of plasticity operate in

different patients. There have been reports of significant reorganization of the spared part of area V1 after stroke that were associated with distortion of visual perception near the border of the scotoma in a patient with V1 lesions (Dilks et al. 2007). However, a follow-up study by the same group found that similar changes occurred within seconds in the border of the blind spot when the eye contralateral to the stimulus presentation was closed, which suggests that this may be more of an adaptive phenomenon rather than a representation of structural reorganization (Dilks et al. 2009). Rather modest changes were seen in the pRFs of spared V1 cortex in patients with quadrantanopia as a result of lesions to area V1 or its input in the optic radiation (Papanikolaou et al. 2014). Papanikolaou et al. (2014) observed no large-scale changes in spared V1 topography; the V1 and V2 border remained stable; and pRF eccentricity versus cortical distance plots were similar to those of controls (participants with a simulated, or artificial, scotoma but no lesions). However, detailed observations did suggest limited reorganization: (a) the distribution of pRF centers in spared V1 was shifted slightly toward the scotoma border in two of five patients compared with the controls with artificial scotoma; (b) the pRF size in spared V1 was slightly increased near the scotoma border; and (c) the pRF size in the contralesional hemisphere was slightly increased compared with controls with artificial scotoma. These changes are not by themselves sufficient to confer significant visual recovery.

In general, more prominent changes occur in the extrastriate cortex and seem to increase with training. Henriksson et al. (2007) reported that in an adult with chronic hemianopia who underwent rigorous training in the blind hemifield for 2 years, the representation of the contralesional visual field gradually shifted into the ipsilateral (healthy) hemisphere as a result of training. So, in this case, stimuli in both the normal and the hemianopic visual fields appeared to be processed by the intact hemisphere following training. The reorganization reported by Henriksson et al. (2007) was prominent in the extrastriate areas, particularly the dorsal stream, but also included areas near the vertical meridian of the primary visual cortex. They argued that this may be mediated via strengthened, interhemispheric, SC commissural connections, which may be targeting the ipsilateral hemisphere via the pulvinar. This is in general agreement with prior reports by Bittar et al. (1999) and Marx et al. (2002), but differs from those of Goebel et al. (2001) and Vaina et al. (2014), who reported extrastriate cortex activation only in the lesioned hemisphere contralateral to the scotoma. Other studies (Nelles et al. 2002, 2007) have reported bilateral extrastriate cortex activation when the visual stimulus is presented in the anopic field. Most of these studies (except for Vaina et al. 2014) did not involve specific training, although in some cases the participants were experienced.

In summary, it appears that the patterns of activity elicited in the spared visual cortex of patients with V1 lesions can be quite variable across patients, but in at least some cases these involve ipsilateral or bilateral extrastriate cortex activation in a pattern that does not occur in subjects with normal vision. The degree to which this is due to the adaptive uncovering versus the plastic reorganization of latent subcortical or callosal interhemispheric pathways requires additional longitudinal studies to be definitively resolved.

## Dissecting Altered Visual Response Properties Following V1 Lesions

fMRI can provide information about how spared visual cortex responds as a function of particular stimulus parameters. For example, Ajina et al. (2015a) demonstrated that hV5/MT+ responses to visual motion coherence in the absence of primary visual cortex input resemble responses to local motion features rather than the global motion response. In addition, area hV5/MT+ response to contrast becomes linearized (similar to the V1 response) for stimuli presented in the blind hemifield (Ajina et al. 2015b). The observation that hV5/MT+ responses

resemble V1 responses after area V1 lesions suggests that in the absence of V1, hV5/MT+ is driven by subcortical inputs similar to the ones driving V1 input in the healthy cortex. Top candidates for these inputs would be the koniocellular pathway, as well as potentially surviving parvocellular and magnocellular projections from the LGN directly to the extrastriate cortex. It would be interesting to follow hV5/MT+ responses during training for global motion discrimination to study the mechanism of the reported behavioral improvement and how it generalizes across different sets of stimuli (Das & Huxlin 2010; Das et al. 2014; Huxlin 2007, 2009).

Overall, fMRI has a lot to teach us about the mechanisms by which learning occurs during visual rehabilitation. One important issue that has not been addressed in this review is the potential contribution of attentional mechanisms that increase the ability of the patient to focus on the task at hand. The ability of fMRI to globally cover both visual cortex and attentional networks is important for investigating whether these mechanisms contribute to recovery (Kelley & Yantis 2010, Umarova et al. 2011).

### **STUDYING VISUAL SYSTEM INJURIES BY fMRI: TECHNICAL PITFALLS**

Using fMRI to study the visual cortex of patients with lesions requires careful controls and analysis. This is particularly true when using fMRI measurements to infer visual system plasticity following rehabilitation. It is expected that following injury, the properties of visual processing in various areas will change, regardless of whether reorganization occurs (Binda et al. 2013; Haak et al. 2012, 2014; Papanikolaou et al. 2015; Wandell & Smirnakis 2009). The observed changes can be nonlinear, and it is not necessarily easy to design good control experiments for these a priori (Binda et al. 2013, Papanikolaou et al. 2015). The selection of tasks and stimuli is important, as they may differentially activate bottom-up versus top-down pathways, which likely have different potentials for plasticity (Masuda et al. 2010). It is essential to perform careful quantitative measurements repeatedly over time as a function of rehabilitative training to establish the mechanisms of recovery.

In taking these measurements, it is important to note that the standard phase-encoding and pRF mapping methods can give biased estimates of retinotopic maps near the boundaries of retinal or cortical scotomas, as pointed out by Binda et al. (2013) and others (Lee et al. 2013, Papanikolaou et al. 2015). Various strategies have been proposed for minimizing such biases (Binda et al. 2013, Lee et al. 2013, Papanikolaou et al. 2015), but it is safe to say that care should be taken in each case, as no method is perfect. At a minimum, when possible it is important to implement appropriate controls, using normal participants for which the stimulus presentation includes the so-called artificial scotoma—that is, excludes the part of the visual field that corresponds to the scotoma of the patients (Binda et al. 2013, Haak et al. 2012, Papanikolaou et al. 2015). Another important methodological modification that has been successfully used to minimize bias is to perform pRF mapping using a randomized stimulus presentation and then take the area of the scotoma into account when implementing the pRF fitting algorithm (Binda et al. 2013). Note that the presence of the artificial scotoma itself introduces real nonlinearities in the response of the visual areas to the stimulus, which is now truncated by the artificial scotoma (Papanikolaou et al. 2015). Such nonlinearities are not the result of plasticity but, rather, are properties of normal visual processing under the artificial scotoma stimulation condition. They should be carefully mapped and controlled for, in order to prove that that reorganization has occurred. Distinguishing pRF changes that occur as the result of true reorganization versus changes that occur as the result of different stimulus presentation conditions is important for studying visual cortex organization in patients with visual field defects.

## CORTICOCORTICAL RECEPTIVE FIELD MAPPING AND CONNECTIVITY ANALYSIS HOLD PROMISE

The relatively recent introduction of corticocortical receptive field mapping (Haak et al. 2013) and functional and effective connectivity analysis (Kaiser 2011, Van Dijk et al. 2010), often performed at resting state, open a new window for probing the strength of pathways that operate following visual system injury. Corticocortical receptive field mapping characterizes responses in a particular visual area as a function not of the stimulus, but of activity present elsewhere in the brain (Haak et al. 2013). The computed corticocortical receptive field (the connective field) predicts the response of a particular voxel in a given area as a function of activity in a different visual area. In principle, this approach allows us to measure and monitor the relationship between responses arising in different locations along the hierarchy of visual areas and how this changes in the context of injury or following rehabilitative training. A similar argument can be made about measurements of functional and effective connectivity. Such measurements have the potential to reveal important information about how different areas in the visual stream interact with one another following injury. They should be pursued via fMRI, MEG, or EEG to formulate hypotheses that could then be tested using other modalities (such as TMS) to establish causality. For example, Silvanto et al. (2009) used TMS to show that the functional connectivity between ipsilesional hV5/MT+ and the contralesional striate cortex is strengthened in blindsight. These findings were consistent with prior DTI results showing abnormal anatomical connectivity between these areas (Bridge et al. 2008). These methods show considerable promise, but have not yet been applied systematically to patients with visual system lesions.

## fMRI AS A POSSIBLE TOOL FOR INTERVENTION

Two decades ago, the real-time fMRI neurofeedback method (rt-fMRI NFB) was introduced (Cox et al. 1995) in the field of neurorehabilitation. This method extracts the BOLD signal from a region in the participant's brain in real time and uses it to provide feedback to the participant. Several studies have shown that rt-fMRI NFB can train participants to modulate the magnitude and spatial extent of the activity elicited in various cortical and subcortical areas (deCharms 2008, Papageorgiou et al. 2013, Shibata et al. 2011). The goal of this approach is to train participants to control the pattern of their brain activity in a way that boosts plasticity or promotes a desired behavior. Shibata et al. (2011) in a seminal study used rt-fMRI NFB to induce perceptual learning. Initially, participants performed an orientation discrimination task, and a decoder of activity in areas V1 and V2 was constructed to classify a pattern of the measured fMRI signals as corresponding to one of three orientations. Once the decoder was constructed, each participant was trained by rt-fMRI NFB to induce the pattern of activity corresponding to a target orientation in areas V1 and V2. Participants were instructed to maximize the signal delivered to them via feedback but did not know what was to be learned, nor were they told how to induce the desired pattern of activity. This strategy successfully induced visual perceptual learning specific to the target orientation. Learning occurred as a function of the participant's ability to elicit the particular pattern of activation corresponding to the target orientation in early visual areas. Remarkably, participants were able to generate this pattern simply by being given the instruction to maximize feedback, without being aware that the pattern to be elicited had anything to do with orientation. This demonstrated that rt-fMRI NFB can be used to induce highly specific activity patterns within a brain region and that repeatedly eliciting a desired pattern of activity can be sufficient to induce plasticity in early visual areas. Judicious pairing of "internally" generated patterns of activity (via neurofeedback) with appropriately timed target stimulus presentation shows particular promise for engaging adaptive learning mechanisms (Papageorgiou et al. 2014).

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### Effective

#### connectivity:

estimates the causal influence that one neural system exerts on another

### Functional

#### connectivity:

the statistical association or dependency among two or more anatomically distinct time series

**rt-fMRI:** real-time functional magnetic resonance imaging

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Shibata et al.'s (2011) findings suggest that rt-fMRI NFB training can be used to induce perceptual learning (plasticity) in a highly selective fashion in the intact visual system. In principle, this method could be applied to strengthen specific pathways hypothesized to mediate recovery in individual patients. The hope is that by providing specific feedback about relevant neural processes, rt-fMRI NFB training will be able to achieve stronger behavioral results than similar training without neurofeedback. Whether this tool can be applied effectively in rehabilitating visual system injury remains an open question (see also Papageorgiou et al. 2014 for other possible uses of fMRI as an intervention).

## LIMITATIONS OF fMRI: NEED FOR OTHER MODALITIES

A major advantage of fMRI-based methods is that they provide global coverage at high spatial resolution and can be tailored to study visual responses and functional and effective connectivity in a quantitative and topographic fashion. The biggest disadvantage is that fMRI measures neuronal activity indirectly and has low temporal resolution. The latter disadvantage makes it difficult to study processes that occur in subsecond time scales, which are likely to be important in eliciting conscious visual percepts (see section above entitled *The Biggest Challenge: Restoring Conscious Visual Perception*). Therefore, it is essential to complement fMRI data with data from other imaging modalities that have higher temporal resolution, such as MEG, EcoG, and EEG. This will permit the study of perceptual processes in real time, identifying potential abnormalities in the global coordination of activity across visual areas, and allowing the formulation of hypotheses about how they might be repaired.

Monitoring brain activity at high temporal resolution will be particularly valuable for neurofeedback training because it allows training of fast cognitive processes. Furthermore, EEG-based neurofeedback can be provided outside a magnet, making this approach to rehabilitation easier, efficient, and less costly.

It is also desirable to pair the above methods with a tool that allows causal manipulation of the networks under study. TMS is a useful tool for probing directly the strength of visual pathways to establish causality. This was illustrated by Silvanto et al. (2007), who demonstrated that bilateral, but not unilateral, hV5/MT+ TMS stimulation induced phosphenes in the blind visual field of a patient with hemianopia.

Approaches that combine these complementary methods should be designed to probe the visual system following injury and to devise new strategies for visual rehabilitation. Other tools that have not been reviewed here, such as DTI tractography, can also be brought to bear to correlate functional results with anatomical changes seen in underlying projection pathways.

## CONCLUSIONS

Different outcomes occur in different patients with visual system injury (Urbanski et al. 2014). Outcomes depend on multiple factors, including the structural and functional anatomy of the pathways involved and the age at injury. Postlesion rehabilitative training can improve visual performance through mechanisms that remain largely unclear, but is a long way from reaching the level of practical significance. Studies pairing behavioral measurements with detailed anatomical and functional MRI imaging—including advanced methods, such as pRF analysis, functional and effective connectivity analysis, and axonal pathway mapping (such as DTI)—promise to yield a better understanding of the mechanisms of residual visual function following injury. Modalities with higher temporal resolution, such as MEG and EEG, are likely to be essential, particularly in efforts aiming to restore conscious visual perception. When incorporated judiciously in rehabilitative studies, these imaging biomarkers will likely help improve the design of visual rehabilitative approaches in the future.



In what follows we outline a proposed roadmap to consider in planning human research studies on visual system plasticity after injury. This is meant as a loose guideline for choosing research strategies and certainly not as a suggestion for studies to be pursued in the context of clinical evaluation.

The following are steps to consider for studying visual system plasticity following injury:

1. Make detailed characterizations of visual field deficits, including high-resolution ( $\leq 1^\circ$  resolution) perimetry. It would be useful to develop new methods of perimetry that are better able to discriminate between different causes of underlying visual system dysfunction. When available, optical coherence tomography should be combined with perimetry to map the degree and topography of retrograde degeneration in the retina.
2. Construct detailed anatomical and functional topographic maps of visual areas, including estimation of pRFs and visual field coverage maps. This should be performed at least twice after visual field deficits are stabilized to ensure a consistent intrasubject baseline. The use of random, multifocal stimulation paradigms rather than classical traveling wave-inducing stimuli should be considered to minimize artifacts. Rigorous eye-tracking during fMRI scanning is essential.
3. Conduct corticocortical receptive field mapping and functional and effective connectivity analyses at baseline and following injury.
4. Classify different types of visual system injury in the patient population to be studied based on the results of mapping parameters obtained in points 2 and 3. The relative overlap of visual field coverage maps in different areas provides an interesting dimension along which to pursue this classification.
5. Formulate hypotheses about the mechanism of visual system dysfunction and the most likely pathways that could contribute to recovery.
6. Design and implement an appropriate training and rehabilitation strategy using meaningful outcome measures for practical recovery. A degree of individualization will likely be necessary, as different patient groups are likely to benefit from different approaches, depending on the hypotheses generated in point 5.
7. Repeat the mapping procedures in points 1–3 over time as a function of recovery, studying visual areas as well as attentional networks that correlate with recovery.
8. Consider whether high temporal resolution data obtained by EEG, EcoG, or MEG can be incorporated in the analysis.
9. Consider whether TMS can be used to causally link observed changes to recovery.
10. Test performance in a realistic task or virtual environment that is designed to measure practical benefit.

In summary, the judicious use of fMRI and other imaging modalities will allow us to formulate hypotheses and to identify imaging biomarkers that correlate with improved performance following visual system injury. Access to such biomarkers will enable the design of targeted rehabilitative approaches with better chances of success in the future.

## SUMMARY POINTS

1. Visual field perimetry is not enough to fully characterize visual system injuries.
2. FMRI pRF mapping provides complementary information to visual field perimetry studies, leading to better characterization and classification of visual system injuries.

3. Area V1 lesions are the most common lesions of the visual system and lead to a dense contralateral scotoma within which visual perception is typically lost. Partial V1 injury can also result in dense perceptual scotomas despite activating extrastriate areas and may have different implications for rehabilitation.
4. Extrastriate areas can be visually modulated in the absence of V1 input, mainly via V1-bypassing subcortical pathways, which become stronger over time, particularly with training.
5. Rehabilitative training can improve some aspects of visual performance inside scotomas induced by area V1 injury, but attaining benefits with practical significance remains elusive.
6. Using fMRI measurements to follow changes that occur with training should enhance our understanding of (*a*) the capacity of visual pathways for reorganization and (*b*) the relation of the observed plasticity to recovery. The hope is that these measurements will eventually help design improved strategies for visual rehabilitation.
7. A number of technical pitfalls arise when imaging patients with lesions of the visual pathways, which can lead to results that masquerade as reorganization. It is important to avoid such pitfalls by using appropriate controls—for example, by studying normal participants with an artificial scotoma matched to the patient's visual defect.
8. There is considerable individual variability, so large, well-designed, carefully controlled studies need to be systematically undertaken in order to make progress.

## FUTURE ISSUES

1. Design large, standardized fMRI trials to better characterize and classify the different functional phenotypes of visual system injury.
2. Continue to develop increasingly sophisticated visual field perimetry methods that may be able to pick up the differences in visual system organization seen on fMRI.
3. Test whether visual system injuries with similar visual field perimetry but different fMRI phenotypes have different potential for rehabilitation.
4. Combine fMRI pRF mapping with connectivity analysis—such as corticocortical receptive field estimation, resting-state connectivity, and anatomical tractography—to further investigate visual system organization following injury.
5. Restoring conscious visual perception is a particularly difficult problem; it will likely require repairing global coordination across spared visual areas at relatively high temporal resolution.
6. High spatial resolution fMRI methods will need to be combined with high temporal resolution EEG or MEG methods and causality-probing TMS methods to identify and validate imaging biomarkers that correlate with recovery.
7. Having access to such biomarkers will make it faster and easier to test the promise of new rehabilitative approaches.

8. Use the information obtained to develop and test new rehabilitative paradigms. For example, behavioral training might be enhanced by (a) neurofeedback targeted to enhance plasticity in appropriate pathways or (b) discovering a way to reopen the developmental window of plasticity.

## DISCLOSURE STATEMENT

The author is not aware of any affiliations, memberships, funding, or financial holdings that might be perceived as affecting the objectivity of this review.

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Introduces corticocortical connective field modeling.

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Presents a human study arguing that intense training can improve visual motion discrimination thresholds inside dense, homonymous scotomas.

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Demonstrates that nonlinear changes in population receptive field maps do not necessarily imply reorganization.

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Argues that fMRI population receptive field analysis complements visual field perimetry in further classifying lesions of the visual pathways.

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Area V2/V3 can be visually modulated in the absence of V1 input via input from the LGN. This is correlated with blindsight performance.

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Argues that in the macaque, areas V2/V3 can be visually modulated in the absence of V1 input.

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Reviews the requirements for conscious visual perception.

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Reviews the use of brain imaging methods for mapping visual field defects.

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Critically reviews the evidence for visual field map plasticity in the adult primary visual cortex.

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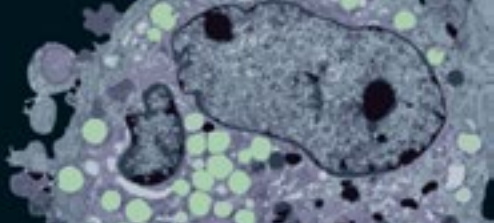
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Vista Lab Wiki (<http://web.stanford.edu/group/vista/cgi-bin/wiki/index.php/Software>): includes a number of software tools developed by the Wandell Lab and collaborators over the years, which support the quantitative analysis of neuroimaging data including population receptive field analysis



MGH/HST Athinoula A. Martinos Center for Biomedical Imaging (<https://www.nmr.mgh.harvard.edu/research/software>): software tools for image analysis and data processing

Serge O. Dumoulin's home page (<http://www.fss.uu.nl/psn/web/people/personal/dumoulin/Software.html>): provides software downloads for population receptive field analysis and early visual cortex segmentation



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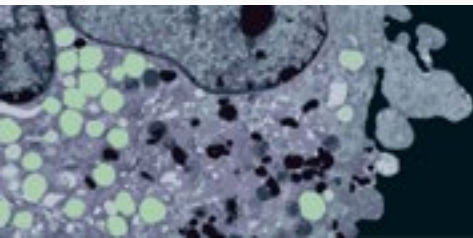
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- *Chimeric Antigen Receptors: A Paradigm Shift in Immunotherapy*, Michel Sadelain





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## Errata

An online log of corrections to *Annual Review of Vision Science* articles may be found at <http://www.annualreviews.org/errata/vision>