

Visual maps and adult cortical plasticity: Revision of ideas

Human MRI

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*This is a draft document of a talk I will present at a meeting in London. The text and images here will eventually be transitioned into a new section of **Foundations of Vision (2nd Edition)**. Your comments and suggestions are very welcome.*

1 Introduction

Today I will tell two stories about how meso-scale imaging has improved our understanding of the human brain.

The first story describes advances in mapping visual field maps in human cortex. Over the past 30 years, a large group of investigators has significantly advanced our understanding of the organization of these maps. While the organization of human visual cortex shares similarities with macaques, there are important differences that I will enumerate. Furthermore, the large field of view provided by human neuroimaging has revealed that these maps are organized in clusters. I will suggest that these discoveries warrant a revision of the widely used Felleman and Van Essen diagram, which emphasizes macaque data, blends the concepts of areas and maps, and does not capture the cluster organization of human maps.

The second story focuses on measurements of adult cortical plasticity in the visual system. The idea of large-scale adult

cortical plasticity, which generated much excitement around 1990, does not appear to hold true in sensory areas. A large body of human MRI work now shows that adult visual cortex is relatively stable and does not undergo large-scale reorganization in response to changes in retinal input. I will also discuss the cellular mechanisms that may underlie this stability, particularly their relationship to perineuronal nets. Recognizing this stability allows us to focus on mechanisms that might genuinely repair cortex after injury, avoiding the distraction of trying to explain non-existent large-scale reorganization in the healthy adult brain.

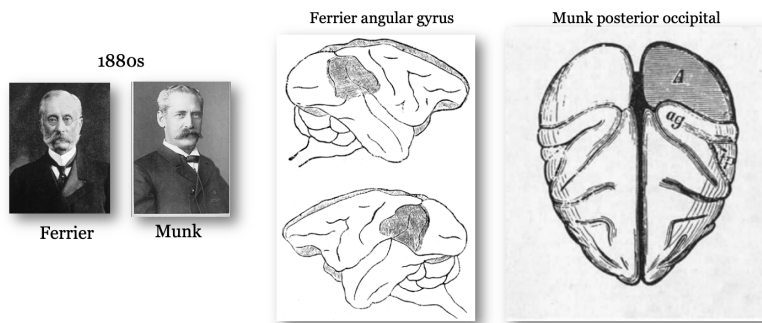
I plan to incorporate the material from this presentation into the second edition of my book *Foundations of Vision*, which is currently in preparation. Elements of each story will likely be familiar to many of you, particularly those who have studied visual neuroscience. My goal is to ensure the ideas and data are clear, accurate, and comprehensive, and that the figures are informative. I welcome your comments on any aspect of this talk, including the text, figures, and references.

2 Visual Field Maps - Historical Perspective

The discovery of visual field maps in the cortex is a fascinating history (Fishman 1995; Glickstein 1985; Wandell and Winawer 2011). The debates between Ferrier and Munk in the late 19th century about the location of visual cortex were heated. The disagreements were not just about the data, but also about the interpretation of the data and the implications for our understanding of brain function.

Ferrier performed lesion studies in monkeys and proposed that primary visual cortex was located in the angular gyrus. The German physiologist Hermann Munk disagreed with Ferrier's anatomical localization and argued that visual cortex was in the occipital region — a critical correction that set the stage for a more accurate understanding of retinotopic organization.

Identifying human visual cortex (1880-1920)



Glickstein, M. 1988. "The Discovery of the Visual Cortex." *Scientific American* 259 (3): 118-27.

Figure 1: Nineteenth-century neuroscientists, neurologists, and ophthalmologists who discovered the localization of visual signals in animal models (Ferrier, Munk) and the presence of a retinotopic map in human visual cortex (Henschen, Holmes, Inouye).

i Note 1: Ferrier and Munk

No need to wonder what Munk thought about Ferrier's work. Here are his own words:

In my first communication on the physiology of the cortex which I made in March of last year I did not say anything about Ferrier's work on the monkey because there was nothing good to be said about it. But asked in the subsequent session I had to say that Mr. Ferrier's declarations that the visual center in the monkey was situated in the angular gyrus [... and other claims ...] that all these statements and what followed from them as far as the character and restitution of disturbances set by the operation are concerned, are worthless and gratuitous constructions since the operated animals were examined by Mr. Ferrier in quite an insufficient manner and only at the time of general depression of brain function.

If I have gone too far in this statement which is based on a general survey of Mr. Ferrier's experiments it was up to me to restore the injury, the sooner the better. However, as the experiments show now I have said at that time rather too little than too much, Mr. Ferrier had not made one correct guess, all his statements have turned out to be wrong.

Commenting on the debate from the other side of the ocean, William James wrote, "Munk's absolute tone about his observations and his theoretic arrogance have led to his ruin as an authority" (James 1890).

James went on to write about Munk:

But he did two things of permanent value. He was the first to distinguish in these vivisections between sensorial and psychic blindness, and to describe the phenomenon of restitution of the visual function after its first impairment by an operation; and the first to notice the hemiopic character of the visual disturbances which result when only one hemisphere is injured. Sensorial blindness is absolute insensibility to light; psychic blindness is inability to recognize the meaning of the optical impressions, as when we see a page of Chinese print but it suggests nothing to us. A hemiopic disturbance of vision is one in which neither retina is affected in its totality, but in which, for example, the left portion of each retina is blind, so that the animal sees nothing situated in space towards its right.

James also noted, "The quarrel is very acrimonious; indeed the subject of localization of functions in the brain seems to have a peculiar effect on the temper of those who cultivate it experimentally. Each observer is sure that he is right, and is ready to explain away the adverse results of his rivals..."

Many of us have enjoyed Charles Gross’s book, which is filled with interesting histories of neuroscience discoveries (Gross 1998). Both his book and James’s work offer detailed insights into these early investigations on localization (James 1950).

It was the Swedish neurologist, Henschen, who first carefully observed the visual loss in **human** patients with occipital lesions. He concluded that at least part of the visual field, the upper and lower portions, were represented in cortex in an orderly map with the lower visual field in the dorsal occipital lobe and upper visual field in the ventral occipital lobe. His findings were met with objections by many, and subsequently confirmed by many more. He expresses his feelings on the matter in the opening of a 1923 review paper (Salomon Eberhard Henschen 1923).

In fact, Henschen’s observations about the organization of the visual cortex in the human were confirmed and extended by two clinicians working at opposite ends of the world: Gordon Holmes and Tatsuye Inouye. Both were studying visual field losses from soldiers injured in their countries’ wars, Holmes in Europe and Inouye in Japan. In that era, the guns were not always lethal, and the helmets would permit bullets to enter and exit the posterior skull, effectively lesioning a portion of occipital cortex. Such lesions could cause a permanent but partial visual field loss. By accumulating data from a number of different cases, they deduced the retinotopic organization of the human visual cortex. In addition to the upper-lower field representation, they both reported on the eccentricity map as well as the fact that the central portion of the visual field occupied more cortical territory (per square degree) than the peripheral portion. This phenomenon is called ‘cortical magnification’ (though perhaps it should be called ‘foveal magnification’).

Building on these early observations, modern measurements have since shown that the total surface area of V1, as well as the magnification factor, vary greatly between people with typical vision—by as much as a factor of 2.5 (Dougherty et al. 2003; Benson et al. 2022).

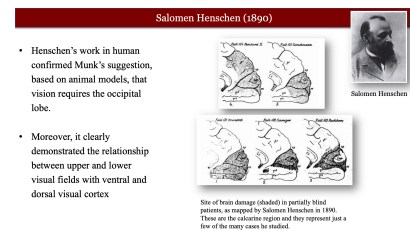


Figure 2: Henschen’s findings mapping the upper and lower visual field representations onto the human visual cortex.

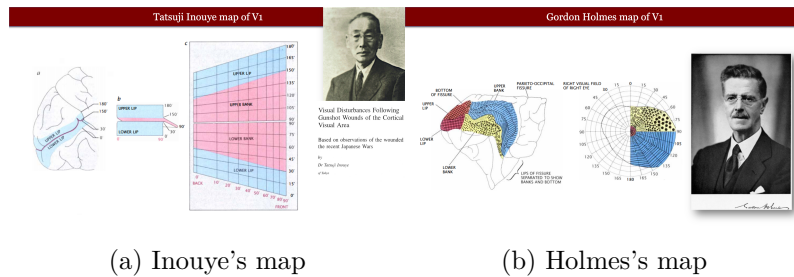


Figure 3: Early maps of human visual cortex by Inouye and Holmes, demonstrating foveal magnification and topological organization.

2.1 Discovery of multiple maps

The discovery of visual maps beyond V1 began with animal models in the 1940s and extended to non-human primates by the 1960s. These early reports sparked a surge of studies identifying additional maps, as well as distinct patches of visually responsive cortex. Much of this history is summarized by Semir Zeki (1993). Over time, regions containing visually responsive neurons and distinctive response properties came to be broadly known as “visual areas”—a term often applied whether or not the region contained a strict, topographically organized map.

i Note 2: Discovery of multiple maps

The effort to discover and map multiple visual areas in animal models expanded enormously between the 1940s and the 1990s. The major milestones include:

- **1940s (V2 in cats and rabbits):** The discovery of multiple visual field maps began when electrophysiological measurements revealed a second visual map (V2) adjacent to the primary visual cortex (V1). These early discoveries were spearheaded by Talbot, Marshall, and Thompson (see review by Thompson, Woolsey, and Talbot (1950)) from the Wisconsin laboratory established by Woolsey.
- **1960s (V2 and V3 in monkeys and cats):** Mapping successfully extended to non-human primates

when Cowey identified a second map in the squirrel monkey (Cowey 1964). The following year, Hubel and Wiesel described a third map in the cat (D. H. Hubel and Wiesel 1965).

- **1970s–1990s (V4, MT/V5, and beyond):** Investigators focused heavily on parcellating the extrastriate cortex of non-human primates, causing the number of identified visual regions to grow rapidly. A major breakthrough was the discovery of V4 and the motion-sensitive MT/V5 map in the owl monkey by Allman and Kaas in 1971. Around the same time, Semir Zeki conducted pioneering anatomical and single-unit studies that established a framework for the concentric organization of these maps in macaques (S. M. Zeki 1969; S. Zeki 1974) and sought to associate specific functional (perceptual) properties to individual areas (S. Zeki 1978; Semir Zeki 1993).
- **Methodological challenges:** Identifying these early maps relied heavily on single-unit electrophysiology and very detailed anatomical work. Because the field of view for these technologies is relatively small, establishing the existence of a map was a notoriously difficult process that Hubel and Wiesel (D. H. Hubel and Wiesel 1977) famously likened to “a dismaying exercise in tedium, like trying to cut the back lawn with a pair of nail scissors”.

- The burst of activity identifying new visual regions was summarized in an influential article by Felleman and Van Essen (Felleman and Van Essen 1991). Figure 4 shows an iconic diagram from that paper, illustrating the proposed hierarchy of visual areas with signals flowing from the bottom (retina, LGN, V1) to the top (peri-hippocampal regions). Although the data supporting this specific hierarchy were initially sparse, the underlying measurements have been significantly augmented over the last decade, particularly by work from Henry Kennedy’s lab (Markov and Kennedy 2013; Markov et al. 2014). I will discuss a proposed update to this diagram at the end of this section.

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i Note 3: FACT: Definitions

An entire generation of scientists was taught a specific definition for a “visual area.” Van Essen proposed that a cortical visual area is a region that can be distinguished from its neighbors by a convergence of evidence across four criteria (FACT), rather than by any single criterion alone:

- **F — Function:** Neurons in the region share distinctive response properties (e.g., motion selectivity, color bias, disparity tuning).
- **A — Anatomy (architectonics):** The region has distinguishable microstructure (e.g., cytoarchitecture, myeloarchitecture, laminar patterns).
- **C — Connections:** It has a characteristic pattern of inputs and outputs (afferent/efferent connectivity distinct from neighboring cortex).
- **T — Topography:** It contains an orderly map of the visual field (retinotopy), often with clear field boundaries (e.g., meridian reversals).

The *visual area* terminology was highly influential, but in my view—and that of several others—it has proven to be an arbitrary and sometimes incoherent term (Wandell, Dumoulin, and Brewer 2007; Hayden, Heilbronner, and Yoo 2025). When identifying a distinct region of cortex, it is important to clarify exactly *why* it is being distinguished: does it contain a retinotopic map, neurons with common functional responses, similar cellular properties, or common connection targets? Grouping all of these distinctive properties under the single concept of an “area” without a clear rule is less helpful than scientists originally hoped.

2.2 Human retinotopic maps

Most scientists assumed that the retinotopic maps found in non-human primates would be a good model for human visual cortex. But even as late as 1991, Horton and Hoyt observed that there was no proof of even two maps in human visual

cortex (Horton and Hoyt 1991b, 1991a). The need for guessing changed with the introduction of functional magnetic resonance imaging (fMRI). That technology enabled investigators to identify retinotopic maps in the living human brain at the resolution of a few millimeters in experiments lasting less than an hour. Over time, spatial precision has increased and the time required for experiments has decreased dramatically.

Steve Engel and I—helped by many others—developed a technique to measure eccentricity and angle maps that was widely adopted (S. A. Engel et al. 1994; S. A. Engel, Glover, and Wandell 1997). The stimulus and cortical responses (fMRI) for measuring eccentricity are shown in Figure 5. The main feature is a wave of activation traveling from the occipital pole in the anterior direction, tracking the expanding ring stimulus. There is also a secondary ripple on the ventral occipital-temporal surface that emerges when the stimulus is near the fovea and fades as the ring expands to about 10 degrees. This secondary ripple reflects a second eccentricity map on the VOT surface, confined mainly to the perifoveal visual field and distinct from the primary map near the calcarine sulcus.

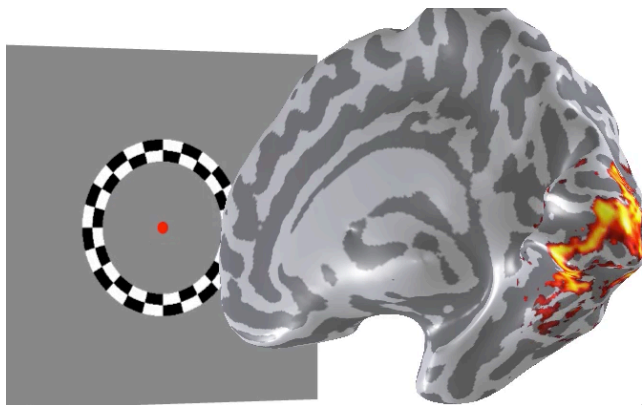


Figure 5: Eccentricity mapping using an expanding ring stimulus (20 deg) in the calcarine and ventral occipital region.

We also made measurements using a rotating wedge stimulus to measure the most effective angular position for each voxel. The angular responses subdivide the eccentricity map into different visual field maps. The data from the video are summarized in

two pseudo-color maps showing the most effective visual field eccentricity for each cortical location

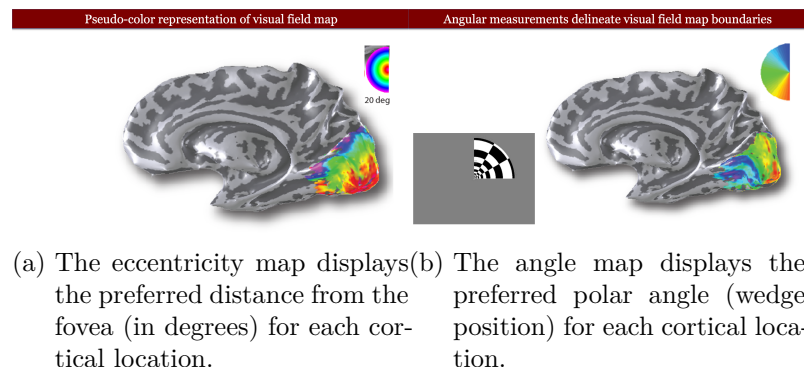


Figure 6: Eccentricity and angle measurements, combined, are used to define a retinotopic map.

Summarizing the information from the maps, we can label an entire retinotopic map using a single color, as in Figure 7. Notice that these maps are not simply adjacent to one another. Rather, the V2 map surrounds V1, and it is surrounded, in turn, by the V3 map. Thus, the dorsal and ventral portions of the V2 and V3 maps—which represent the lower and upper visual fields, respectively—are well-separated from one another.

Alyssa Brewer noticed the secondary foveal representation on the ventral occipital surface and decided to explore it further (Brewer et al. 2005). To see the two clusters distinctly, she used a much smaller field of view for the expanding rings, moving them slowly through the central 3 deg. You can see the two eccentricity maps—plainly distinct from one another—in Figure 8.

2.3 Map Clusters

Over time, it became clear to us that there were multiple distinct eccentricity maps, illustrated in these two brief videos. These eccentricity maps can be subdivided into different individual visual field maps by also considering the angle representations, just as V1-V3 can be separated from the unified eccen-

Early visual cortex

- Type of information
- Spatial scale of the information
- V1 surface area varies by 2.5 to 1
(Andrews et al. 1997; Dougherty et al. 2003)

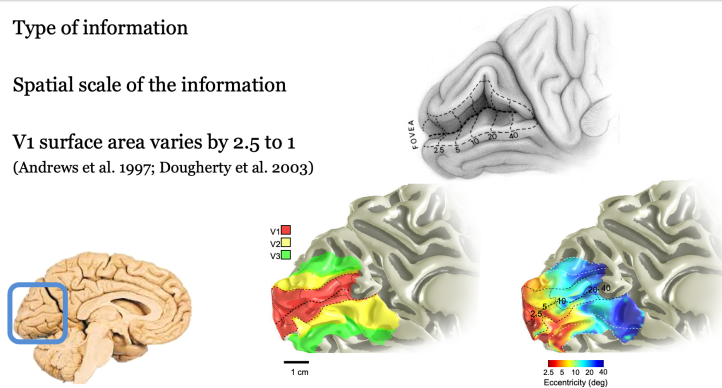


Figure 7: A medial view of the locations of three visual field maps (V1-V3) on the calcarine sulcus. The eccentricity map is overlaid to emphasize the large portion of cortex devoted to the central visual field (cortical magnification). This magnification roughly matches the higher density of cone photoreceptors in the fovea compared to the visual periphery.

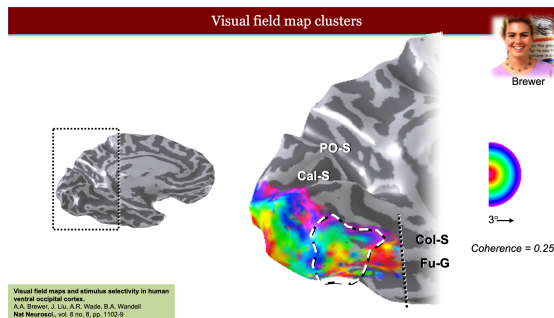


Figure 8: Eccentricity map emphasizing the central 3 deg. This highlights two different confluent foveal representations: one in the calcarine, and a second on the ventral occipito-temporal (VOT) surface. From Brewer et al. (2005).

tricity map around the posterior pole and calcarine cortex in humans.

Here are two different visualizations of the clusters. In Figure 9 they are shown on a slightly inflated cortical surface.

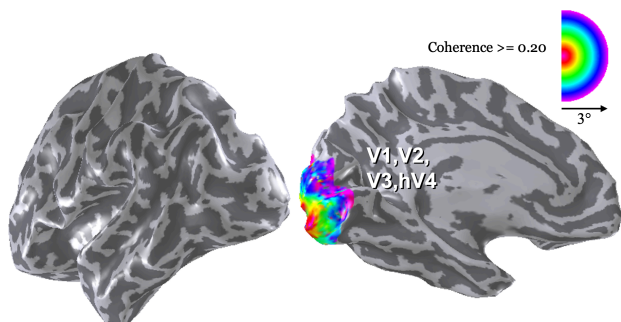


Figure 9: The visual field map clusters shown on the cortical surface (slightly inflated) (Wandell, Brewer, and Dougherty 2005).

In Figure 10 the eccentricity maps of the clusters are represented on a flattened cortical surface; the video oscillates between the measured eccentricity and a cartoon overlay that emphasizes the pattern.

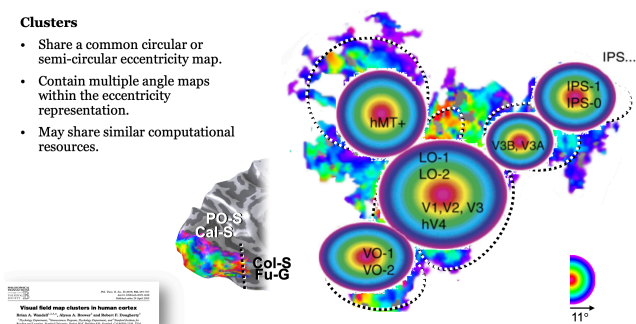


Figure 10: Visual field map clusters emphasized on a flattened representation of the posterior cortex (Wandell, Brewer, and Dougherty 2005).

The clustering of cortical retinotopic maps has been confirmed by multiple groups. The clusters have been identified in posterior and anterior cortex (Mackey, Winawer, and Curtis 2017), non-human primates (Kolster et al. 2009, 2014; Barton and

Brewer 2017; Meyer et al. 2025), and also in the pulvinar (Arcaro, Pinsk, and Kastner 2015). The retinotopic map cluster appears to be a basic functional organizational principle that may have implications for development and plasticity.

i Note 4: Clusters in the Human Brain

Frontoparietal Clusters (Mackey, Winawer, and Curtis 2017) Expanding the cluster model into higher-order cortex, this study identified multiple representations of polar angle and eccentricity in the human frontoparietal cortex. They discovered that these maps are organized into clusters sharing a confluent fovea, mirroring the organization of the visual cortex to facilitate efficient sensorimotor and cognitive processing.

The Pulvinar Cluster (Arcaro, Pinsk, and Kastner 2015) In a significant extension of the theory, Arcaro and colleagues identified two visual field maps in the human ventral pulvinar (vPul1 and vPul2). They proposed that these maps form a distinct visual field map cluster because they share an eccentricity representation and exhibit similar cortical connectivity patterns with early extrastriate areas.

The pSTS “Cloverleaf” Cluster (Barton and Brewer 2017) This 2017 work introduces a new cloverleaf cluster in the posterior superior temporal sulcus (pSTS). They characterized four distinct maps (pSTS-1 through pSTS-4) organized around a central foveal representation, suggesting this “radially orthogonal” structure is a fundamental principle for high-level visual and potentially multimodal processing.

Macaque Motion Clusters (Kolster et al. 2009) The Kolster and Vanduffel work is the primary reference for clusters in non-human primates, specifically identifying the MT cluster (MT, MST, FST, and V4t). Their work demonstrated that the cluster principle—minimizing wiring length between processing modules—is not unique to humans but is a general feature of the Old World primate visual system.

Probabilistic Map Atlases (Wang et al. 2015) The

Kastner group developed a probabilistic atlas of the human visual system that largely validates the cluster-based organization for more than 20 maps. This work is a large-scale confirmation of the cluster model across a large subject population in addition to being a very useful tool, widely used in neuroimaging.

2.4 Comparative anatomy

Initially, human fMRI groups relied on the macaque model—almost slavishly—to guide our interpretation of the retinotopic maps. Over time, investigators developed more confidence in the human fMRI data, and it became apparent that there are significant differences between the species. Some of these differences are discussed in Note 5.

Here are some of the agreed-upon differences:

- Human visual cortex contains a much larger number of neurons and a greater overall surface area, even though the human optic nerve contains roughly the same number of axons as the macaque's.
- The ratio of the surface area of human V2/V3/hV4 relative to V1 is much larger than the similar ratio in macaque (Figure 11); in general, the visual cortical maps and clusters are all larger in humans.
- The position of the nominal fourth visual map differs substantially between human and macaque—sufficiently so that I named it hV4 rather than V4, and spent years arguing this point with others.
- The functional responses to motion in human and macaque V3 and V3A do not match.

A recent paper used fMRI for a comparative anatomical analysis of human and macaque visual cortex (Meyer et al. 2025). They report that the number of maps and their cluster-like organization are strikingly similar across species, suggesting that the cluster is an evolutionarily preserved unit. Figure 11 shows a measurement of the relative sizes of the V2/V3 portion of the V1 cluster in human and macaque.

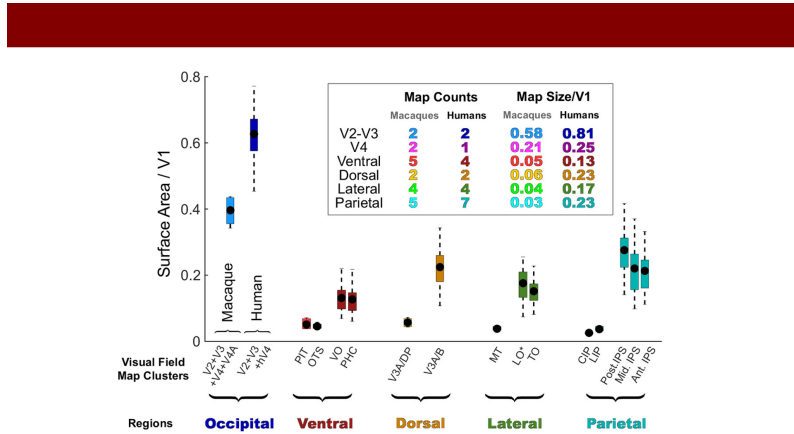


Figure 11: Comparative anatomical sizes of maps and clusters (Meyer et al. 2025). Note the expanded relative size of V2 and V3 in humans.

i Note 5: Humans and monkeys

This is an expanded commentary on the more obvious differences between human and non-human primate clusters and retinotopic maps.

Overall Size and Neuron Count: Human visual field maps are substantially larger overall than those in the macaque, with human V1 estimated to be roughly two to four times larger. The human visual cortex correspondingly contains a much larger number of neurons, which is thought to reflect the increased processing required for human-specific cognitive demands, such as language and reading. Derived from: “Visual Field Maps in Human Cortex” (Wandell, Dumoulin, and Brewer 2007) and “Imaging retinotopic maps in the human brain” (Wandell and Winawer 2011). The larger number of human cortical neurons contrasts with the similar number of ganglion cell axons in the human and macaque optic nerves (Fortune et al. 2014; Mikelberg et al. 1989; Kolb, Nelson, and Fernandez 2011).

Anatomical Location of V1: In macaques, a large portion of the primary visual cortex (V1) is located on

the operculum, extending posterior and lateral to the medial position of the calcarine sulcus. In humans, V1 is located largely within the calcarine sulcus, extending partially onto the lateral surface of the occipital pole. The human lateral extension is not as large or typical as it is in the macaque. Derived from: “Imaging retinotopic maps in the human brain” (Wandell and Winawer 2011).

Proportional Size of Area V3: A highly salient difference between the species is the relative size of area V3. In macaques, V3 occupies a very small surface area compared to V1 and V2. In humans, V3 is proportionately much larger, meaning the scale factor difference between human and monkey V3 is even greater than the difference between their V1 maps. This difference in the V3/V1 surface area ratio likely reflects a functional divergence between the visual systems of the two species. Derived from: “Imaging retinotopic maps in the human brain” (Wandell and Winawer 2011), “Visual field representations and locations of visual areas V1/2/3 in human visual cortex” (Dougherty et al. 2003; Benson et al. 2022), and “Visual field map clusters in human cortex” (Wandell, Brewer, and Dougherty 2005) and (Meyer et al. 2025).

Motion Sensitivity in Area V3A: Although the map topographies of V3A are similar between humans and macaques, their functional sensitivities are completely different. Human V3A is highly responsive to motion, whereas macaque V3A is not strongly motion-selective. Derived from: “Visual Field Maps in Human Cortex” (Tootell et al. 1997; Wandell, Dumoulin, and Brewer 2007) and “Imaging retinotopic maps in the human brain” (Wandell and Winawer 2011).

V4 / hV4 and Color Processing Locations: In the macaque, area V4 spans both the dorsal and ventral portions of the occipital lobe, and color-exchange experiments produce responses in both components. In humans, investigators have not reliably found a dorsal component for the fourth visual map; instead, the human map (hV4) and the regions critical for color vision (and those associated with cerebral achromatopsia) are confined almost entirely

to the ventral surface. Derived from: “Mapping hV4 and ventral occipital cortex: The venous eclipse” (Winawer et al. 2010). “Imaging retinotopic maps in the human brain” (Wandell and Winawer 2011), and “Visual Field Maps in Human Cortex” (Wandell, Dumoulin, and Brewer 2007). There is considerable variability within species in both the optic nerve axon count and the surface area of the visual field maps (Stensaas, Eddington, and Dobelle 1974; Dougherty et al. 2003; Benson et al. 2022).

2.5 Modern summary of map clusters

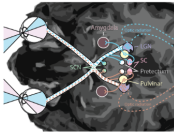
Over time, I have found the Felleman and Van Essen diagram less helpful for four reasons. The diagram

- makes no distinction between retinotopic maps and “visual areas”—a terminology I find to be fraught.
- omits the modern functional specializations that have since been identified in human visual cortex.
- emphasizes the hierarchy concept, but I am not confident about the implied flow of information.
- omits the subcortical systems, which have become increasingly important in teaching, particularly with the discovery of ipRGCs.

In Figure 12 I try to address these four issues. I separated the retinotopic maps from the functional specializations (Rosenke et al. 2021), relying entirely on human data. The diagram suggests a coarse hierarchy, from sub-cortical to cortical clusters, to specializations but does not imply a strict hierarchy (Jacques et al. 2025; Markov and Kennedy 2013). Finally, the sketch includes subcortical connections to remind the reader of their importance.

3 Cortical remapping

As early as Henschen, who first localized the human visual cortex, scientists wondered what factors might impact the size



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(surface area) of the visual cortex representation S. E. Henschen (1893) reported that the size of visual cortex was smaller in blind people, but at that time, very little was known about the natural size variation in the population. We now know that the variation in surface area in the sighted population is quite large; a factor of 2.5 in surface area has been confirmed by a number of modern authors (Stensaas, Eddington, and Dobelle 1974; Dougherty et al. 2003; Benson et al. 2022). Thus, a case study finding a smaller V1 in a blind person than in a sighted control is not definitive proof of experience-dependent plasticity.

Another framing on the general issue of adult cortical plasticity—a framing that influenced many decades of science—came from Cajal. He spent years trying to find evidence of axonal regeneration in the adult brain and spinal cord, famously reporting that his efforts were met only with failure (Ramón y Cajal 1928):

“In the adult centers, the nerve paths are something fixed, ended, and immutable. Everything may die, nothing may be regenerated. It is for the science of the future to change, if possible, this harsh decree.”
(Ramón y Cajal 1928)

There was never any doubt that the brain undergoes massive change during development. It increases dramatically in size and myelination during the first year of life, and these are only the two most obvious and easily observed changes. But Cajal’s assertion about the adult brain established a level of skepticism regarding adult plasticity that persisted for decades.

The story of brain plasticity took on new importance when Hubel and Wiesel reported that, at very young ages, cortical responses could be influenced by visual experience. They found that the width of ocular dominance columns (ODC) in the primary visual cortex could be altered by early visual experience. The period of this experience-dependent plasticity seemed to close around 8 years of age in humans. They named this window of significant experience-dependent plasticity the *critical period* (David H. Hubel and Wiesel 1970). Beyond this intermediate scale and timeframe, Cajal’s stability seemed to hold.

3.1 Animal models of map reorganization

In the 1980s, a series of papers from leading neuroscience groups reported a type of experience-dependent cortical plasticity in the adult, well beyond the critical period. They reported that there could be a reorganization of the visual and somatosensory maps in adult cortex (Merzenich et al. 1984; Jon H. Kaas et al. 1990; Gilbert and Wiesel 1992; Recanzone et al. 1992; Jenkins et al. 1990; Chino et al. 1992, 1995). This plasticity, termed *remapping*, occurred when a cortical region was deprived of its input—such as following a retinal lesion or finger amputation. The extent of the reported remapping was several millimeters or more.

The extent of the remapping was a surprise. Few scientists would have been surprised at the idea that synapses come and go, that synaptic strength changes, or even that there might be adjustments in dendritic and axonal arbors over small (e.g., 100-micron) distances. But the possibility of a large-scale reorganization in adult cortex—spanning many millimeters or even centimeters—was extremely exciting. This excitement motivated a set of new commercial ventures premised on the idea that adult plasticity could keep us forever young. Prominent examples in the 1990s and 2000s include **Scientific Learning Corporation** (founded in 1996 by Michael Merzenich and colleagues to produce *Fast ForWord*), **Posit Science** (founded in 2003 by Merzenich, creating *BrainHQ*), and others like **Lumos Labs** (*Lumosity*, 2005) and **Cogmed** (2001), all of which capitalized on the public enthusiasm for using neuroplasticity to train and reshape the brain.

Nikos Logothetis and I thought understanding adult remapping in the visual cortex would be an excellent target of investigation, particularly one that could yield useful health applications. It was possible to measure the retinotopic maps routinely in humans and macaques. By working with macaques, we thought it might be possible to discover the molecular mechanisms that governed this plasticity, which could then lead to helpful treatments for stroke and other neurological conditions.

We were fortunate to recruit Stelios Smirnakis to lead the project. He performed a series of experiments looking for

significant reorganization in adult macaque V1 after binocular lesions in corresponding locations of the two retinae. We expected to find an initially unresponsive zone in V1 that would fill in with activation over time. We used functional MRI to measure the remapping, as it is relatively non-invasive and permits many repeated measurements.

We easily measured both the typical retinotopic maps and the expected unresponsive zone in macaque V1 following the lesions (Figure 13). This unresponsive zone is called the *lesion projection zone* (LPZ).

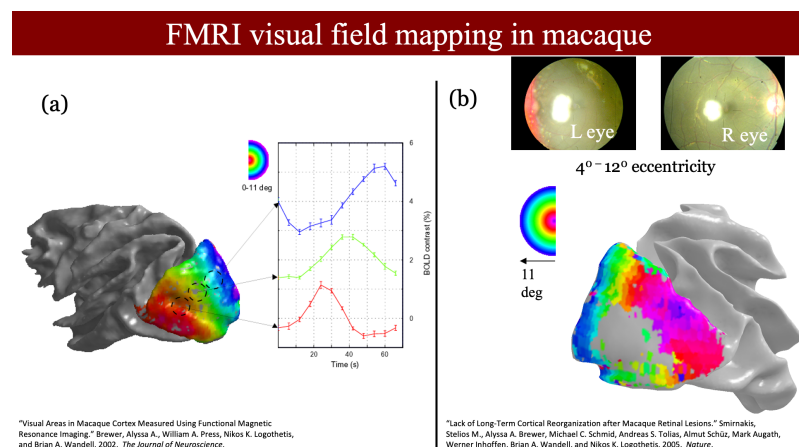


Figure 13: Initial functional MRI and electrophysiological measurements define the lesion projection zone (LPZ), an unresponsive area in macaque V1 matching the induced binocular retinal lesions.

We expected that the area of the LPZ would shrink as we measured it over time. But over the ensuing months, we found very little—or perhaps no—remapping (Smirnakis et al. 2005). Surprised by this, Stelios made targeted electrophysiological measurements to find neural signals, but again he found no significant electrical response, mirroring the lack of fMRI response.

Our finding of map stability conflicted with prior reports, and its publication was met with a rebuke by several of the authors who had previously reported significant remapping (Calford et al. 2005). A principal objection to our work was that fMRI

The margins of the LPZ did not change systematically

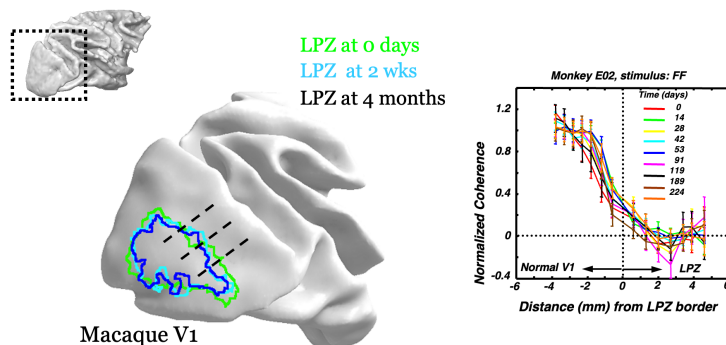


Figure 14: Over a period of 7.5 months, the boundaries of the lesion projection zone remained remarkably stable without significant functional filling-in.

was a poor measure of neural activity, which simply ignored the fact that we had also used electrophysiology.

We too were puzzled by the discrepancy and decided to restudy the literature, which we had previously accepted without intense scrutiny. Upon closer review, Stelios and I discovered many serious inconsistencies in the animal literature, which we then summarized in a review paper (Wandell and Smirnakis 2009). The concerns raised in that review remain unanswered to this day — none of the groups that reported large-scale remapping have provided a satisfactory resolution of the experimental conflicts we identified. A number of investigators told us privately that they too had failed to find remapping, attributing this to their own error rather than seeking a public reckoning. The scientific community has largely moved on without settling the question, which I find deeply unsatisfying.

Given what is known about cortical development, the idea of large-scale adult remapping seemed like a long shot (see Note 6)—which is exactly why so many people found it exciting. The anatomical infrastructure for the maps is laid down by white matter connections. The axons find their targets (the “correct neighborhood”) early in development (Feldheim 2000; McLaughlin, Hindges, and O’Leary 2003). This principle is

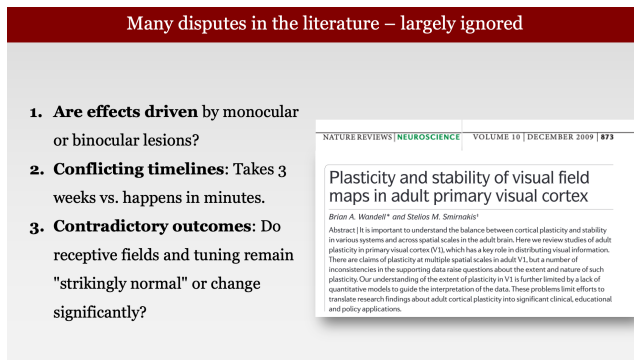


Figure 15: Wandell and Smirnakis (2009) describes a series of experimental conflicts in papers that found topographic remapping in adult visual cortex. These are discussed in detail in the review.

broadly true across the brain, not just for visual maps (Agmon et al. 1993; Huberman, Feller, and Chapman 2008; McLaughlin and O’Leary 2005).

Crowley and Katz (2000) showed that even finer anatomical inputs—the basis of the ocular dominance (OD) columns—are in place before the eyes open (in the ferret). They showed that even after removing the eyes during the period when retinal waves would normally occur (postnatal days 0 to 15 in the ferret; equivalent to embryonic days 42-57 in the cat), thalamocortical projections from the LGN still segregate into eye-specific cortical columns. Molecular cues that are part of the developmental program are sufficient to establish the ODC anatomy. The experience-dependent changes Hubel and Wiesel observed modulated ODC widths by a few hundred microns, but there was nothing on the scale of massive remapping.

i Note 6: How maps develop

To understand what would be required for remapping, it is useful to understand how the anatomy that supports the maps develops. The axonal connections develop through a series of critical stages that connect the axons carrying signals between the principal structures (retina, LGN,

V1).

Feldheim (2000) demonstrated that the retinotopic mapping onto the LGN and Superior Colliculus is guided by gradients of Ephrins and Eph receptors, which are part of the innate developmental programs. These molecular markers are expressed and guide axons in the optic nerve and optic radiation to their specific topographic coordinates (“spatial addresses”) well before photoreceptors are functional.

Molnár and Blakemore (1995) proposed that thalamocortical and corticothalamic axons meet in the subplate (the embryonic white matter) and use each other as scaffolding to establish topography. The topographic ordering in the white matter occurs extremely early, before the axons even penetrate the cortical plate to form Layer 4. Thus, retinotopic mapping is sorted in the white matter before any visual signal could possibly exist.

After the axons are in place, McLaughlin, Hindges, and O’Leary (2003) showed that this rough draft might be fine-tuned by spontaneous waves of activity in the retina that sharpen the retinotopic map, again before the rods and cones are even connected to the ganglion cells. And, of course, Hubel and Wiesel showed that aspects of the functional organization are experience-dependent as well (David H. Hubel and Wiesel 1970).

Striem-Amit et al. (2015) studied the functional connectivity of fMRI signals in the adult human cortex of the blind. Their findings support the idea that the large-scale organization remains fixed, despite drastically different life experiences. The functional connectivity of early visual cortex in the blind—individuals with no retinal input to the cortex—matches the connectivity in sighted controls.

More will be required to understand the full range of possible functional changes. Vision scientists have become increasingly aware that subcortical pathways are also part of the computational system, and some of the functional changes observed in cortex can be explained by changes in the signals within these structures. Jon H. Kaas and

Lyon (2007) suggests that some of the changes we observe after lesions can be explained by properties of the pulvinar and subcortical pathways. Any hope of understanding the functional changes will require a computational model, which is a main point in our review (Wandell and Smirnakis 2009).

3.2 Human measurements of map reorganization

The ability to measure retinotopic maps in humans affords the opportunity to evaluate map reorganization, both during development and in the adult. In the next section, I will briefly run through five different experimental measures of human map reorganization.

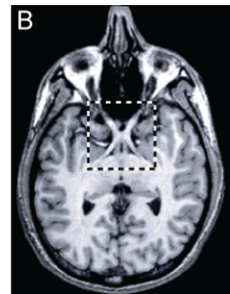
In summary, fMRI methods are capable of measuring and quantifying key aspects of map reorganization. The predominant finding from multiple types of measurements is that retinal lesions do not cause large-scale remapping in visual cortex. When a large portion of an adult visual cortical map is deprived of input, the lesion projection zone remains unresponsive.

3.2.1 1. Achiasmia

A particularly striking case of developmental plasticity in the visual system occurs when the retinal axons fail to find their way to the lateral geniculate. In most people, there is a standard crossing pattern in which the optic nerve axons from each nasal retina cross to the opposite hemisphere at the *optic chiasm* (Figure 16a). In a small number of people, the molecular guidance for this crossing fails and the optic chiasm never develops (Figure 16b). In these individuals, the retinal axons stay within the same hemisphere, so that the right eye projects to the right hemisphere and the left to the left (Victor et al. 2000; Prakash et al. 2010; Hoffmann et al. 2012).

The anatomical wiring governs the map organization. If all the axons from an eye project to the LGN and V1 on the same side,

The optic chiasm is easy to see in a T1-weighted MRI

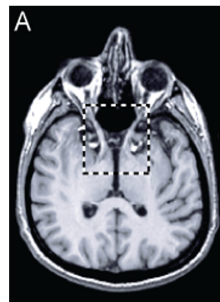


Conventional
optic chiasm



(a) Typical chiasm

This subject doesn't have an optic chiasm



Missing
optic
chiasm



(b) Missing chiasm

Figure 16: The optic chiasm is normally easy to find in a structural anatomical image (a). In some rare cases, the retinal axons do not cross and each eye projects to the LGN on its side of the brain (b).

then both the right and left visual fields will evoke a response in that hemisphere (Figure 17a).

Probing the organization in more detail using a methodology called population receptive field (pRF) mapping, we can also see how the two halves of the retina project through to V1. In typical development, the left hemisphere V1 voxels will only respond to stimuli in a small portion of the right visual field. This region is called the population receptive field (pRF). The population receptive field of a voxel in V1 of an achiasmic subject is quite different. It comprises two small, widely separated regions that arise from the nasal and temporal halves of the retina (Figure 17b).

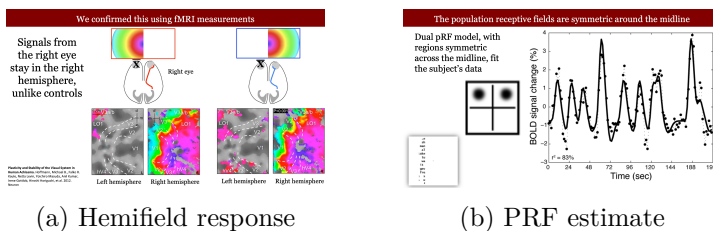


Figure 17: In achiasmic individuals, both the left and right sides of the visual field initiate a response in V1 (a). The population receptive field of a V1 voxel in an achiasmic subject has two distinct regions, arising from the nasal and temporal halves of the retina (b) (after Hoffmann et al. (2012)).

Even in the presence of such a large anatomical mis-wiring and the corresponding functional abnormalities, such individuals manage their visual perception in daily life effectively (Hoffmann et al. 2012; Kaule et al. 2014). These individuals can read, navigate, and even engage in sports. They do not have stereovision, and they generally have nystagmus. But many people have these disorders, and thus they are not specifically diagnostic of achiasmia. Furthermore, other individuals with albinism have a less extreme form of this disorder and still manage to achieve reasonable visual function (Hoffmann et al. 2003; Hoffmann and Dumoulin 2015).

3.2.2 2. Achromatopsia—rod monochromats

After learning how to measure human retinotopic maps, we began exploring potential cases of remapping in people. Heidi Baseler and I were aware of work by our colleagues at UC Berkeley with individuals who had a relatively rare condition: rod monochromacy. Heidi made measurements in three such individuals. A problem with our original study was that only one of the subjects was genetically screened to be a true rod monochromat. The other two had minimal, but some, cone function. We reported that the foveal representation was responsive in these individuals, suggesting that a developmental loss of cone function might produce a remapping. This finding was accepted and reported in subsequent authoritative reviews (Hoffmann and Dumoulin 2015).¹

Twenty years on, the matter was taken up again by Baseler and colleagues using much better screening methods (Molz et al. 2023). Contrary to our original report, they found that individuals genetically classified as having *only* rods had a silent foveal projection zone. In returning to the H. Baseler et al. (2002) paper, I could see that the one person we had securely identified as rod-only did seem different from the other two. He had no real filling-in of the foveal projection zone, while the other two we had emphasized did have filling-in.

In this developmental case, the cortical map organization—which is initiated before the retina is even functional (Molnár and Blakemore 1995)—is not altered. The absence of foveal input from the retina does not cause a major remapping.

Remapping of the cortical representation of the central visual field is not a general feature in achromatopsia. (Molz et al. 2023)

¹We thought acquired foveal lesions would not fill in, but that developmental lesions might be different. Alas, we were wrong—and fortunately, after a few years, Heidi straightened us out. “In adults, the deafferented cortical foveal representation in rod achromatopsia is not silent, but driven by parafoveal input (H. Baseler et al. 2002). In essence, the visual field maps are preserved, but only represent retina covered with functional photoreceptors, that is rods” (Hoffmann and Dumoulin 2015).

It is worth noting that this question already has practical clinical interest. The possibility that the adult human brain may regain or develop function following the correction of congenital deafferentation has fired the imagination of scientists over the years. In the visual domain, cases of recovery from congenital deficits are rare. Gene therapy for visual restoration of congenital *CNGA3*-achromatopsia, a disease caused by cone photoreceptor dysfunction, provided an opportunity to examine cortical function—to the best of our knowledge, for the first time—both before and after restorative treatment (McKyton et al. 2021).

Behaviorally only minor improvements were observed post-treatment. fMRI analysis (including population receptive field algorithms) revealed cortical changes, specifically a decrease in receptive field size in the treated eyes. This suggests that the adult cortex retains some capacity to encode new input. Importantly, these findings illustrate how plasticity can differ by spatial scale: while the large-scale map representation (centimeters) remains stable, localized functional fine-tuning (e.g., millimeter-scale changes in receptive field size) remains possible.

3.2.3 3. Macular degeneration

Further measurements of map plasticity have been made in the adult brain following the onset of different types of retinal disease that create retinal lesions. One might expect to see remapping in such individuals, perhaps by filling in the lesion projection zone (LPZ) corresponding to the disease.

Yet, publications on humans have found little support for cortical remapping in the adult subsequent to foveal disease (Sunness, Liu, and Yantis 2004; Masuda et al. 2008, 2021; Rosenau et al. 2008; H. A. Baseler et al. 2011). The human literature contains one series of papers from Baker and colleagues that reported large-scale reorganization (Baker et al. 2007; Baker et al. 2008; Dilks et al. 2007). However, our review raised several methodological concerns regarding those findings (Wandell and Smirnakis 2009).

One possible explanation for the Baker findings concerned the control of the observer’s attention. According to Masuda et al. (Masuda et al. 2008), the lesion projection zone (LPZ) was silent during passive viewing (Figure 18).

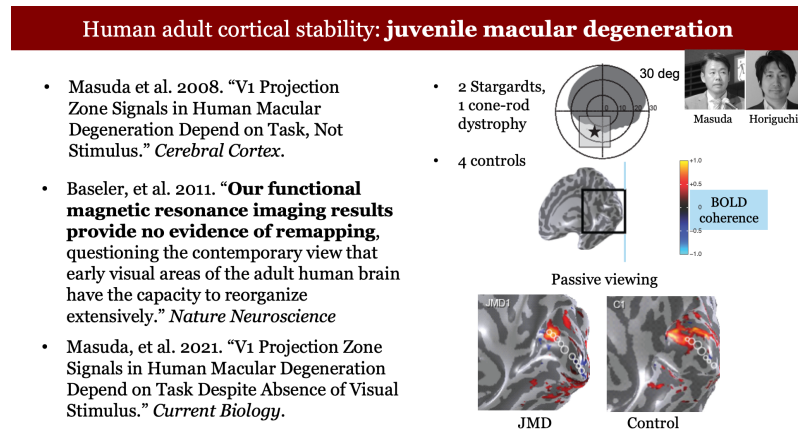


Figure 18: During passive viewing, the primary visual cortex lesion projection zone (LPZ) in JMD patients remains entirely unresponsive to visual input.

However, when the subjects engaged in a one-back memory task, a small signal could be detected in the LPZ (Rosenau et al. 2008; Masuda et al. 2021).

These findings suggest that there may typically be cortico-cortical signals present in V1 that are associated with task judgments. In sighted individuals, these feedback signals are masked by the retinal signal. If we remove the retinal signal but still maintain a task, we can measure the feedback signal. Figure 20 is a block diagram showing the concept.

A later study showed that the V1 lesion projection zone of JMD patients responds to tactile and auditory stimuli, but only in the one-back memory task, not in the passive condition (Masuda et al. 2021). The modality-independent, task-dependent LPZ responses suggest they reflect task-related feedback signals rather than reorganized feedforward signals. Masuda is currently performing these experiments in blind subjects, and preliminary reports suggest he has found the same kind of signals, further supporting the idea.

Human adult cortical stability: **juvenile macular degeneration**

- Masuda et al. 2008. "V1 Projection Zone Signals in Human Macular Degeneration Depend on Task, Not Stimulus." *Cerebral Cortex*.
- Masuda, et al. 2021. "V1 Projection Zone Signals in Human Macular Degeneration Depend on Task Despite Absence of Visual Stimulus." *Current Biology*.

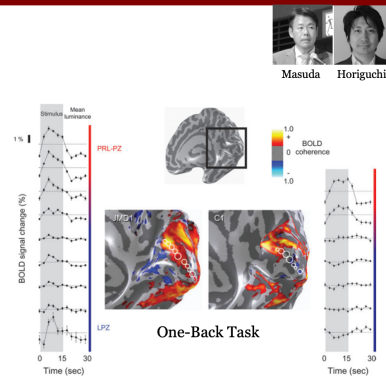


Figure 19: When JMD patients perform a cognitively demanding one-back memory task, a measurable fMRI signal emerges in the otherwise silent LPZ, exposing task-dependent cortico-cortical feedback. Conversely, this task does not elicit a signal in the corresponding region of healthy controls when the stimulus is restricted to their peripheral vision.

Human adult cortical stability: **retinitis pigmentosa**

- Masuda et al. 2008. "V1 Projection Zone Signals in Human Macular Degeneration Depend on Task, Not Stimulus." *Cerebral Cortex*.
- Masuda, et al. 2021. "V1 Projection Zone Signals in Human Macular Degeneration Depend on Task Despite Absence of Visual Stimulus." *Current Biology*.

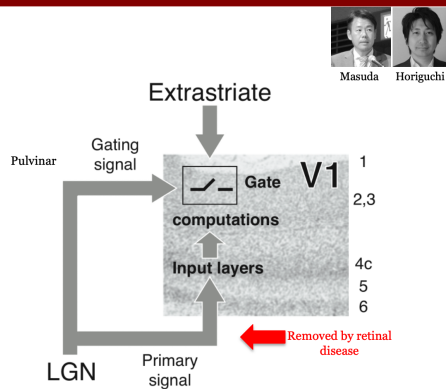


Figure 20: A conceptual diagram illustrating how strong feed-forward retinal signals typically mask task-related feedback in healthy vision, whereas retinal lesions unmask these cortico-cortical projections.

3.2.4 4. Retinitis pigmentosa

Masuda also made measurements in patients with retinitis pigmentosa, a disease that spares the fovea but damages the peripheral retina (Masuda et al. 2010). Once again, they found no significant reorganization in the adult cortex (Figure 21).

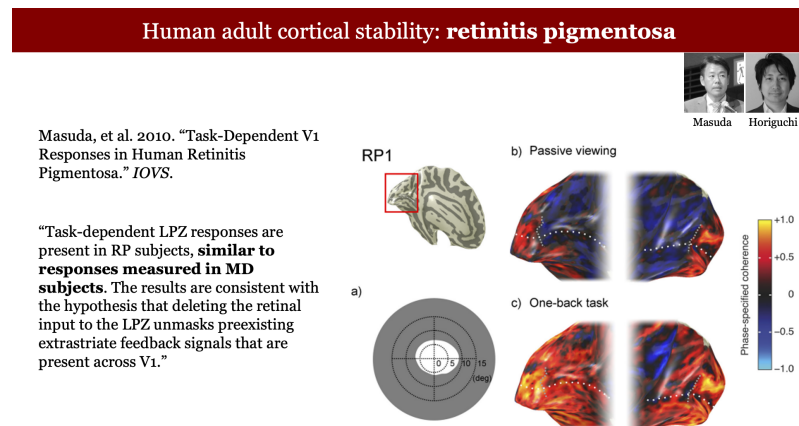


Figure 21: In retinitis pigmentosa, which damages the peripheral retina rather than the fovea, fMRI mapping matches the features in JMD. There is no significant feedforward remapping into the peripheral lesion projection zone, but there is a task-based signal that is not present in controls.

It is worth noting that in both retinal diseases, remapping cortical signals into the LPZ would not solve the problem caused by the retinal lesion: an expansion of cortical signals does not replace the missing retinal signal. It is unclear what functional purpose a remapping would serve. From the point of view of retinal prosthetics, the absence of remapping is good news: if we replace the missing retinal signal, the LPZ seems to be preserved and ready to receive signals from the blinded retinal region.

3.2.5 5. Case study: Mike May

People who are deprived of vision from birth—most often due to cataracts or other optical distortions—and later have their sight restored provide a natural experiment on visual development. The earliest documented case is from Cheselden (Cheselden 1728), and more recent cases (Gregory and Wallace 1963; Valvo 1971; Sacks 1993) tell a consistent story: restoring a clear retinal image rarely restores normal vision.

The case of Michael May is one of the most thoroughly studied. His story is told in the book *Crashing Through*, and it raises two sharp questions: Would surgery restore high-quality vision? And what would fMRI reveal about visual cortex after decades without contrast input?



Figure 22: Measurements of contrast sensitivity in MM following his sight restoration surgery showed a severe and persistent contrast sensitivity deficit at high spatial frequencies, despite the restored optical clarity.

At age three, Mike found a jar in his family's garage. It contained calcium carbide, a chemical used in miners' lamps that releases highly volatile acetylene gas on contact with water. When he brought the jar to the sink, the resulting explosion was catastrophic. He required roughly 300 stitches and spent six months in the hospital. Both corneas were destroyed, as was one retina. For the next 43 years, he had almost no con-

trast vision and only minimal light perception in his remaining eye.

Early attempts to replace the damaged cornea and lens failed. A new procedure developed by Dr. Holland—involving the transplantation of limbal stem cells—eventually made surgery feasible. In March 2000, corneal specialist Dr. Daniel Goodman performed the operation in San Francisco. It succeeded: the new cornea and lens delivered a clear image to the retina.



Figure 23: Following 43 years of blindness, Michael May’s vision was partially restored using a limbal stem cell transplant that repaired his damaged cornea. This image was captured at the moment MM opened the repaired eye and ‘saw’ his wife for the first time.

Yet, as Elizabeth Huber, Ione Fine, and their collaborators documented, restoring retinal image quality did not restore normal vision (Huber et al. 2015). Consistent with the historical literature, Mike’s contrast sensitivity function remained severely impaired despite years of follow-up.

The second question—what had happened to visual cortex after 43 years without contrast input?—required fMRI to answer. Mike generously gave his time for scanning, and Netta Levin led the analyses of his visual field maps and white matter pathways (Levin et al. 2010). Despite the long period of visual deprivation and the complete loss of one eye, the basic retinotopic map was preserved in Mike’s visual cortex, with a notable deviation

Contrast sensitivity functions remained stable 7 years after surgery

- MM has similar absolute contrast sensitivity to Controls at very low spatial frequencies
- Substantially worse sensitivity at spatial frequency above 0.25 cpd
- MM's sensitivity remained constant for the 7 years following surgery

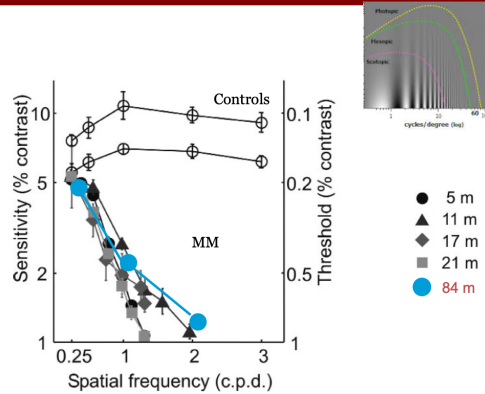


Figure 24: Even nearly a decade after surgery, Michael May's contrast sensitivity function remained highly attenuated compared to typical vision, consistent with phenomena seen in historical cases.

from normal. The central (foveal) region of his visual field, a region in which the retinal ganglion cells typically carry relatively high-resolution signals, seems to have been disrupted.

We interpreted these measurements as suggesting that the foveal receptive fields were larger than normal, and thus their centers were more peripheral (green) than what is found in the typical case. This hypothesis was supported by measurements of the relationship between eccentricity and pRF size in V1–V3.

The main graph shows MM's estimated population receptive field sizes as a function of eccentricity. Different symbols indicate estimates from V1, V2, and V3. For comparison, average pRFsize estimates from three control subjects are shown in the inset. Solid lines are fit to the points from each map. In controls and MM, pRF-size increases systematically from V1 to V3. MM's estimated receptive field sizes at eccentricities from 8-10 deg are larger than those in controls. The pRF sizes beyond 10 deg are similar or smaller compared to controls.

Levin's paper also examined various structural aspects of the white matter, suggesting that there is a significant change in the

MM has an unusual cortical map

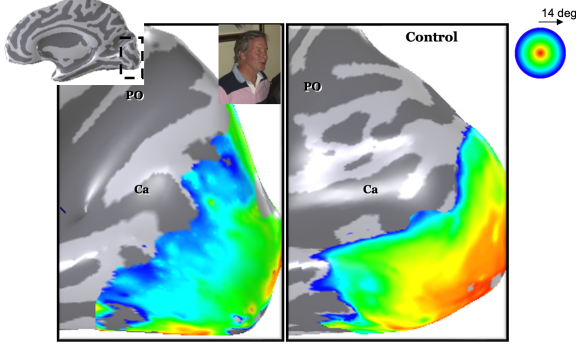


Figure 25: Functional MRI retinotopic mapping in Michael May shows a robust representation of the peripheral visual field, but reveals an extensive loss of coherent signals within the typically expansive foveal confluence.

Hypothesis: MM is selectively missing V1 neurons with small receptive

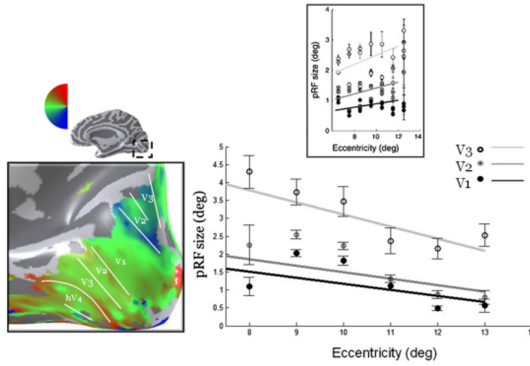


Figure 26: In controls, the population receptive field sizes measured across V1–V3 are systematically enlarged, particularly in the central visual field where the classical small-pRF foveal representation has deteriorated (inset). In MM, however, the ordering between V1–V3 is maintained but the increase in size with eccentricity is absent or perhaps reversed.

inter-hemispheric callosal fibers from the occipital lobe (Levin et al. 2010).

Mike’s experience echoes other well-documented cases of recovered sight. In his essay ‘To see or not to see’, Oliver Sacks describes a strikingly similar trajectory in his subject Virgil (Sacks 1993, 1995): Virgil could perceive colors and movement but could not make sense of objects or faces, experiencing the restoration of sight as a catastrophe rather than a miracle. Sacks attributed this to the visual cortex having stabilized in a non-visual state over decades — its “instructional window” for building functional maps long since closed.

3.3 The role of parvalbumin cells and PNNs

In recent years there have been substantial advances in our understanding of the molecular mechanisms that enforce local stability. There are two main principles.

First, Hensch showed that inhibitory parvalbumin interneurons are the primary modulators of cortical plasticity (Hensch 2005; Morishita et al. 2010; Hensch and Quinlan 2014).

Second, Maffei, Fawcett, and others identified the molecular structures called *perineuronal nets* (PNNs) — dense extracellular matrix coatings on the surface of parvalbumin neurons — as the physical substrate that stabilizes these circuits (Kwok et al. 2011; Fawcett et al. 2022; Jain et al. 2012, 2025). The existence of this external coating was first noted by Camillo Golgi (Figure 27), quoted by Celio et al. (Celio et al. 1998):

Eminent colleagues, ... In the group of preparations shown here, you will immediately recognize two different peculiarities in the organization of the nerve cells; peculiarities concerning: the external surface, on the one hand, and the interior or the thickness of the cellular body, on the other.

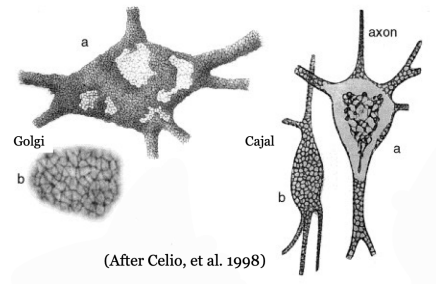
The specific molecules responsible — chondroitin sulfate proteoglycans including aggrecan — were later identified and shown to stabilize inhibitory circuits and suppress the local plasticity

- **Perineuronal Nets (PNNs):**

Lattice-like extracellular matrices enveloping specific neurons (mostly PV+ interneurons).

- **The "Molecular Brake":**

PNNs physically restrict receptor movement and axon sprouting, preventing adult reorganization.



Extracellular Matrix and Perineuronal Nets in CNS Repair

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Dev Neurobiol, 2011

Figure 27: The perineuronal net (PNN) is a specialized extracellular matrix structure that surrounds the cell body and proximal dendrites of certain neurons, classically observed by Golgi and Cajal.

seen in the juvenile brain (Sorg et al. 2016). Post-mortem analyses of the human brain reveal that PNNs are established at different times in different brain regions, with some stabilizing around 8 years of age, coincident with Hubel and Wiesel's critical period (Rogers et al. 2018; Mauney et al. 2013; Yew et al. 1997; Grateron et al. 2003; Fung et al. 2010).

More recently, we have learned that PNN formation is not simply a developmental clock running out, but is also activity-dependent: Nakayama et al. found that among PNN-related genes, aggrecan alone showed strong activity-dependent transcriptional regulation (Nakayama, Mubuchi, and Miyata 2025). This suggests a feedback loop in which neural activity drives PNN formation, which in turn reduces plasticity — a mechanism that may help explain why the critical period closes gradually rather than abruptly.

3.4 Speculation: MRI and PNNs

An interesting question for those of us who study the human brain is this: Can we help establish or contradict this role of the PNNs using non-invasive methods, such as MRI?

Why? Advances in understanding cellular and molecular properties

- **Developmental Timing:** They emerge late in development, coinciding precisely with the closure of plasticity critical periods.
- **Therapeutic Potential:** Enzymatic degradation (e.g., Chondroitinase ABC) and also less aggressive methods can re-open windows of plasticity.

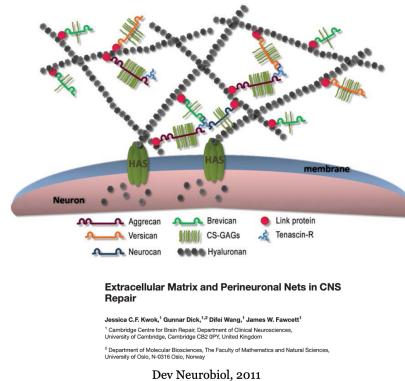


Figure 28: Aggrecan and other chondroitin sulfate proteoglycans form the structural core of perineuronal nets, which stabilize inhibitory circuits and restrict local plasticity after the critical period closes.

Point 8

A New Frontier

We should develop MR techniques to map the development and spatial distribution of PNNs in human cortex.

(Hint: Ask me about how hydration layer physics makes this possible!)

Figure 29: Could specialized quantitative MRI protocols, such as precise measurements of T_1 relaxation, detect the hydration layers associated with PNNs to map cortical plasticity and stability non-invasively?

We might be able to learn something about their development and spatial distributions in the human brain using MRI. The key determinant of the MR time constant, T_1 , is the interaction between spins near the cell surface membranes, referred to as the hydration layer. Perhaps through careful study, we might find that the PNN molecules at the cell membrane impact the T_1 value of in vivo measurements, and thus variations could be informative about the development of PNNs at different locations and times. These measurements might inform us about healthy development, plasticity, and stability. This is quite speculative of course, but this is just a talk amongst friends.

i Why MRI?

Even a speculation requires some justification. Here are some thoughts about why an attempt to map PNN distributions over space and time might work.

1. **The Molecular Composition of PNNs:** PNNs are dense extracellular matrix (ECM) structures. They are composed heavily of chondroitin sulfate proteoglycans (CSPGs), hyaluronic acid, and link proteins. These macromolecules are highly negatively charged and bind massive amounts of structured water (forming the hydration layers). It is plausible that the hydration layer formed by the PNN has an MR signature that differs from the hydration layer in cells without such an ECM.
2. **Precedents in MRI (Cartilage & MSK Imaging):** Musculoskeletal MRI images these molecules. Techniques like gagCEST (Glycosaminoglycan Chemical Exchange Saturation Transfer), $T_{1\rho}$ imaging, and Magnetization Transfer (MT) are used specifically to quantify proteoglycan concentration in cartilage by measuring the interaction between the macromolecular hydration layer and bulk water. If the MSK people can do it, why not the Neuro people?
3. **Application to the Cortex:** In neuroimaging, myelin has historically dominated the conversation

around T1 and MT because it is so highly concentrated in white matter. However, the ECM makes up roughly 20% of the brain's volume! (Nicholson and Syková 1998; Bonneh-Barkay and Wiley 2009). As PNNs condense during development (wrapping around PV+ interneurons and locking in stability), the local density of proteoglycans and structured water must change. This would alter local macromolecular tissue volume (MTV, (Mezer et al. 2013, 2016)) and change the relaxation times (T1, T2, and especially T1-rho or CEST contrast) in those specific cortical layers.

3.5 Summary

A working hypothesis about plasticity and stability is something like this: The relatively large scale (say, multiple centimeters) of axonal connections that determine the human visual field maps is established by the long-range axonal projections that develop from birth. These orderly representations are established during the earliest stages of development and are rather stable—except when they are not (e.g., achiasmia).

Activity-dependent fine-tuning impacts features at a smaller spatial scale, say 1–3 mm. This includes features such as receptive fields and local architecture (e.g., ocular dominance columns).

The role of activity-dependent fine-tuning is highest in early development and systematically reduced over time, as the PNNs form on the parvalbumin (PV) inhibitory neurons. The formation of the PNNs stabilizes the neuronal structural and functional properties. To recreate the activity-dependent plasticity, one would need to dissolve the PNNs, and then it would be desirable to recreate them after achieving some functional goal. PNN removal might enable local changes (mm), but it would be unlikely to adjust the long-range guidance cues that established the maps at centimeter scale. The larger structures emerge from the Ephrin gradients early in development, and they will not be changed by dissolving the PNNs.

With respect to adult cortical remapping, we should consider the likelihood that the topographic coordinates are fixed, but the local fine-tuning becomes fixed after the critical period, and could potentially be unlocked.

Term	Spatial Scale	Mechanism	Adult Status
Synaptic Plasticity	Microns	LTP/LTD, Gain Control	Highly Plastic
Local Refinement	1–2 mm	PNN Removal, OD Shifts	Reactivatable
Topographic Remapping	10 cm	Long-range Sprouting, Map Shifts	Stable/Fixed

- Agmon, Ariel, L. T. Yang, D. K. O’Dowd, and E. G. Jones. 1993. “Organized Growth of Thalamocortical Axons from the Deep Layers of Immature Rat Somatosensory Cortex.” *Journal of Neuroscience* 13 (12): 5365–82.
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