Plasticity and stability of visual field maps in adult primary visual cortex

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Abstract | It is important to understand the balance between cortical plasticity and stability in various systems and across spatial scales in the adult brain. Here we review studies of adult plasticity in primary visual cortex (V1), which has a key role in distributing visual information. There are claims of plasticity at multiple spatial scales in adult V1, but a number of inconsistencies in the supporting data raise questions about the extent and nature of such plasticity. Our understanding of the extent of plasticity in V1 is further limited by a lack of quantitative models to guide the interpretation of the data. These problems limit efforts to translate research findings about adult cortical plasticity into significant clinical, educational and policy applications.

Cytochrome oxidase staining
A technique that visualizes metabolically active neurons. If one eye is surgically removed from an experimental animal, cytochrome oxidase staining will selectively stain V1 neurons that receive input from the intact eye.

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Early life experiences significantly influence brain development — the neural and behavioural effects of developmental plasticity have been observed in systems serving perception, movement, language, and emotion[1–4]. Distinct neural systems have different requirements for plasticity versus stability across the lifespan. Several systems require cortical plasticity. Sensory system signals typically remain plastic in response to changes in environmental inputs throughout the lifespan (adaptation[5–8]) (BOX 1). Neural processes mediating learning and forgetting also require neuronal plasticity in adulthood. Adult plasticity is also required at the interface between sensory and motor systems, to cope with changes that occur as muscles fatigue or sensory transducers change with age (for example in the vestibulo-ocular reflex arc[9–14]).

Stability of cortical networks is also needed. For example, pathfinding for long-range projections between brain areas is challenging, and once paths are established re-routing could cause havoc. Excessive plasticity could disrupt the function of computational circuitries for stereoscopic depth perception, motion detection or object identification, and may change the correspondence between visual and cortical space. These changes would require downstream circuits — such as those that control visually guided reaching — to continuously update their interpretation of sensory signals. Consequently, several molecular mechanisms exist for stabilizing neural pathways after development[15–17].

There can be no serious debate as to whether the brain is plastic or not: it is both. It is more worthwhile to investigate distinct systems and understand the conditions under which each system is plastic or stable. It is also important to learn whether the degree or even the nature of brain plasticity is influenced by specific types of injury or specific attempts at rehabilitation.

This Review summarizes the conflicting literature on plasticity in adult primary visual cortex (area V1). Area V1 is the dominant cortical relay station distributing visual sensory input to the rest of the neocortex, and its proper functioning requires a balance between stability and plasticity. Many reports argue that adult V1 is highly plastic, but inconsistencies among these reports suggest that the data adduced in support of plasticity have not been interpreted correctly and that adult V1 in fact has only limited plasticity. For example, modelling may show that deletion of one component of the visual network is expected to change responses in other network components, even in the absence of plasticity. We stress the need to resolve these important inconsistencies.

V1 input from the two eyes

Ocular input to V1 is plastic during development. In experiments of lasting importance, Hubel and Wiesel demonstrated that depriving one eye of retinal contrast (by eyelid suture) during development reduces the number of neurons responsive to contrast presented to that eye[18–20]. The reduced V1 representation of the deprived eye can be detected in various ways. For example, a distinctive pattern of light and dark bands on the cortical surface of monocular-deprived animals can be visualized using cytochrome oxidase (CO) staining. The dark and light bands represent neurons that

receive their dominant input from different eyes. (The eye preference of a band extends to an extent through the cortical layers, and these regions are therefore called ocular dominance columns.) Visual deprivation of one eye reduces the proportion of cortex dominated by input from that eye. Amblyopia can be caused by this experience-dependent process.

Developmental plasticity also influences V1 binocular inputs at spatial scales finer than the ocular dominance columns[21,22]. Adams and Horton[21] explained that the photoreceptors that lie directly beneath (that is, 'in the shadow of') one eye's blood vessels "are condemned to a life of idleness owing to their location". As a consequence, projections from these shadowed photoreceptors yield their V1 territory to their industrious counterparts from the other eye.

Wiesel and Hubel[23] recognized that experience-dependent plasticity can be harmful: "One may reasonably ask whether mechanisms in which neural connexions become impaired through abnormal experience can possibly serve any use, or possess any survival value." They go on to point out that in some cases developmental plasticity can be helpful. A recent example comes from the neurological literature. In adults, loss of the occipital lobe has devastating and permanent consequences, typically leading to complete blindness in half of the visual field. Yet some children in which an occipital lobe fails to develop[24] or who have a hemisphere removed[25,26] still develop visual sensitivity and awareness in the entire visual field.

Ocular input to V1 is stable in adulthood. In adulthood the system shifts to favour stability. Adams *et al.*[27] measured the width of the ocular dominance columns in six V1 samples of adult humans (FIG. 1). In five of the subjects an adult eye was enucleated (removed). After these subjects died — which in this sample ranged from 5 days to 22 years after enucleation — V1 was processed by flattening and CO staining. Even after many years of monocular vision, the staining pattern showed the normal pattern of ocular dominance columns; that is, the loss of an eye in adulthood did not reduce the width of the columns from the enucleated eye. The sixth case demonstrated that the CO staining technique is sensitive enough to measure a developmental change in the width of ocular dominance columns[27]; this individual, a 94-year-old man whose right eye was injured in childhood, showed a difference in the width of ocular dominance columns between the left (wider) and the right (narrower) eyes.

Interventions reactivate plasticity of ocular input to V1. There is interest in finding pharmacological and behavioural manipulations of the nervous system that enhance adult plasticity. One approach is to identify molecules that promote stability, and then selectively eliminate them. Degradation of chondroitin sulphate proteoglycans, components of the extracellular matrix that inhibit axonal sprouting, reactivates plasticity in ocular dominance columns[28]. Similarly; knock-out mice lacking functional paired immunoglobulin-like receptor B (PirB) display enhanced ocular dominance plasticity[17,29,30] at all ages.

Another approach is to modulate the neurotransmitter environment. The timing of the critical period for ocular dominance in mice, which normally begins 3 weeks after birth and achieves maximal sensitivity a week later, can be significantly delayed by modifying genes that are essential for neurotransmitter development and release[31]. Reduced inhibition (in *GAD65*-knockout mice) early in life prevents experience-dependent ocular dominance plasticity, but plasticity can be rescued by treatment with benzodiazepines[32].

Adult plasticity can also be influenced by experience. For example, the critical period can be prolonged by dark rearing[33–36] or even reactivated by housing adult animals in a completely dark environment[37,38]. Engaging plasticity mechanisms during development seems to enhance adult plasticity; hence, juvenile behavioural training might be effective for expanding the capacity for adult plasticity[39–41]. Discovering pharmacological agents and behavioural protocols that increase adult plasticity offers hope of finding more effective treatments for amblyopia.

V1 ocular dominance columns
Most V1 neurons respond preferentially to inputs from one eye or the other. Cells with common preference are organized into columns that alternate with columns of neurons with the opposite preference.

Amblyopia
A developmental disorder of the visual nervous system. The amblyopic eye has decreased visual acuity that is not explained by structural abnormalities of the lens or retina.

Critical period
A period after birth during which neural connections have a large capacity for plasticity compared with adulthood.

Box 1 | **Adaptation and plasticity**

Neuronal activity patterns frequently adjust to changes of input statistics as well as to shifting demands on their outputs. For example, the neural response to a flash of light differs depending on recent exposure to light or the ambient lighting context. Similarly, eye movements and temperature sensitivity depend on events in the recent past. These adjustments occur throughout the lifespan, and neuroscientists have carried out many studies of this phenomenon, called sensory or motor adaptation.

Cortical plasticity or reorganization also refers to a change in neural properties as the input statistics change (for example, after a retinal lesion) or the output demands change (for example, after muscle mass loss). Although the distinction between the terms adaptation and plasticity is not sharp, there are several phenotypic characteristics that are commonly used to differentiate adaptation and plasticity (see the table).

Adaptation is a relatively short-term adjustment that is often made in response to fluctuations in the dynamic range of inputs or outputs. A prototypical example is the change in the cone photocurrent after exposure to a bright light (light adaptation). This change reverses in minutes after some time in the dark (dark adaptation). In this case, it is not thought that the neural circuits are transformed by the light or dark exposures.

Plastic reorganization typically describes a long-term change in the neuronal circuit. In the case of deafferentation, for example, the growth of new axons and dendrites to form new circuits to process or store information is considered plasticity.

In cases in which neural tissue is injured, the two processes typically operate at overlapping timescales in a way that makes them difficult to separate. For example, suppose half of the input signals to a neuron are suddenly silenced. This will alter the statistical structure of the neuron's input and change its input resistance. Properties such as synaptic gain are likely to change in the short term. In the long term, this may become very difficult or impossible to reverse, and the adaptation may be followed by dendritic sprouting and the formation of new synapses or long-term strengthening of existing synapses, conferring potentially new properties to neuronal circuits.

Measurement	Plasticity	Adaptation
Temporal scale of cause	Longer than inciting factor	Short (~tracking input statistics)
Temporal scale of effect	Long	Short (~tracking input statistics)
Anatomical connectivity	Likely to change	Unlikely to change
Receptive field: space	May change	May change
Receptive field: gain	May change	May change
Reversibility	Not typical, or takes long	Yes

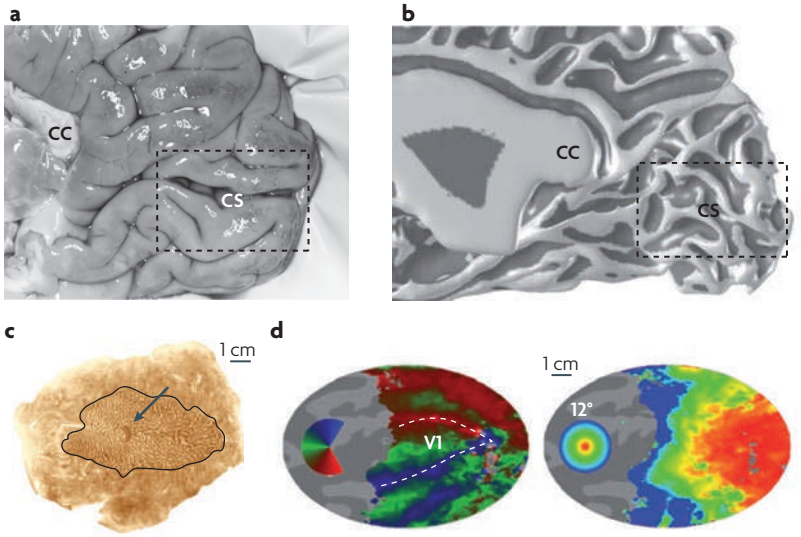

Figure 1 | **Ocular dominance columns and visual field map in primary visual cortex (V1). a** | A medial view of the posterior right hemisphere of a postmortem human brain. Human V1 is located principally in the calcarine sulcus (CS), although its full extent frequently reaches the occipital pole on the ventrolateral surface. **b** | The white and grey matter surface measured using MRI in a living subject. The surface rendering is inflated to increase the visibility of the sulci; it is shaded to emphasize the sulcal (dark) and gyral (light) regions. **c** | Part of a flattened postmortem brain from a subject with an enucleated left eye, showing the right calcarine and surrounding cortex. The outlined region is V1. The cytochrome oxidase staining forms light and dark bands that reveal the ocular dominance columns. The dark spot (arrow) is the projection zone from the left eye's blind spot (optic disk). **d** | Calcarine and surrounding cortex computationally flattened from the structural MRI-derived surface mesh. The colour overlays identify the stimulus angle (left) or eccentricity (right) that most effectively stimulates each cortical location (measured using functional MRI). Angle and eccentricity (up to 12° from the fovea) are measured with respect to fixation. The angle and eccentricity maps together define the V1 visual field map[86]. The boundary between V1 and V2 can be identified in the angle map from the locations that respond best to the vertical meridians (dashed white lines). CC, corpus callosum. Parts **a** and **c** are reproduced, with permission, from REF. 27 © 2007 Society for Neuroscience.

V1 receptive fields

An important approach for understanding experience-dependent plasticity in adulthood is to measure V1 spiking activity after localized retinal lesions. Many V1 neurons are selective for stimuli of a particular orientation, and some are motion–direction selective; some receptive fields span several millimetres (in cortical coordinates), and others span mere fractions of a millimetre. The variety of properties and receptive field sizes of V1 neurons is partly a consequence of the diversity of V1 inputs (FIG. 2); these arise from distinct cell classes in the lateral geniculate nucleus (LGN) and from within V1 (through horizontal connections)[42,43], extrastriate cortex[44,45] and thalamic nuclei such as the pulvinar[46–48]. Hence, deafferentation of the retinogeniculate input is expected to change — although not necessarily to eliminate entirely — the response of the sampled V1 population to visual stimuli.

The literature describing the effect of retinal lesions on LGN and V1 neuronal responses contains many conflicting reports. One possible reason for these different results is that properties of V1 receptive fields are typically compared between populations of neurons observed at different times; until recently there was no opportunity to monitor the same cell pre- and post-lesion. Another reason is the limited ability to measure cells of a particular type, as it is possible that the degree of adult plasticity depends on the particular type of V1 cells. New methods in volume imaging and chronic implantable electrode arrays should make more sophisticated measurements possible within the next few years[49–54].

Binocular retinal lesions in adulthood. Kaas *et al.*[55] used a laser pulse to create a photoreceptor lesion 500 μm in diameter in the retina of one eye in adult cats. The corresponding ~4 mm lesion projection zone (LPZ) in V1 consequently received only monocular input (from the other, intact eye). Measuring the single-unit responses in the LPZ at various times after the lesion, the authors observed "no notable change in retinotopic organization".

V1 was further deprived of input by removal of the second eye. After 2–6 months, the authors found neurons at the border of the monocular V1 LPZ that responded to visual stimuli. The photoreceptors that were the principal inputs to these neurons had been destroyed; however, the neurons now responded to input from intact photoreceptors located adjacent to the lesioned receptors (that is, they received ectopic input). The authors concluded that "the present results, together with those from the somatosensory system, imply that basic neuronal properties such as receptive field location are maintained in a dynamic state in sensory-perceptual systems of adult mammals. Such adult plasticity may be important, not only in recoveries from brain damage and adjustments to other impairments, but also in our abilities to maintain, alter, and improve sensorimotor and perceptual skills." The authors did not investigate whether the new input also improved behavioural responses to stimuli.

A similar experiment was subsequently performed in monkeys[56]. Binocular lesions covering the central 2° of the visual field resulted in an unresponsive V1 LPZ immediately following the lesions. But 75 days later around half of the neurons sampled in the LPZ did respond to a stimulus. These responses were weak and the receptive fields were unusually large, with "diffuse borders that were difficult to map precisely". In addition, the response latencies in these neurons had doubled. Moreover, CO staining "revealed depressed activity in the foveal region, especially in layers IVa and IVc compared to surrounding cortex with intact retinal input"[56]. Subsequent CO measurements confirmed that "CO levels in cortical scotomas remained severely depressed for months after retinal lesions, even when the other eye was enucleated."[57] Thus, at least at the spatial scale of CO measurements, there was no substantial adult plasticity.

Gilbert and colleagues[58,59] made binocular, localized photoreceptor lesions in cats and monkeys. In monkeys these lesions had around 1 mm diameter on the retina, centred 1 mm below the fovea; such a lesion creates a 3–5° scotoma in the visual field, creating a cortical LPZ with 8 mm diameter. Properties of the receptive

GAD65-knockout mice
Mice with knockout of the gene coding for GAD65 (one of the main two glutamic acid decarboxylase isoforms). They are used to study the effects of inhibition on visual system plasticity during the critical period for ocular dominance.

Receptive field
The region in the visual field in which presentation of a stimulus influences a neuron's activity.

Fovea
A small central depression (pit) in the primate retina that has very high photoreceptor density and is used for high-acuity vision.

Scotoma
A blind spot in the visual field.

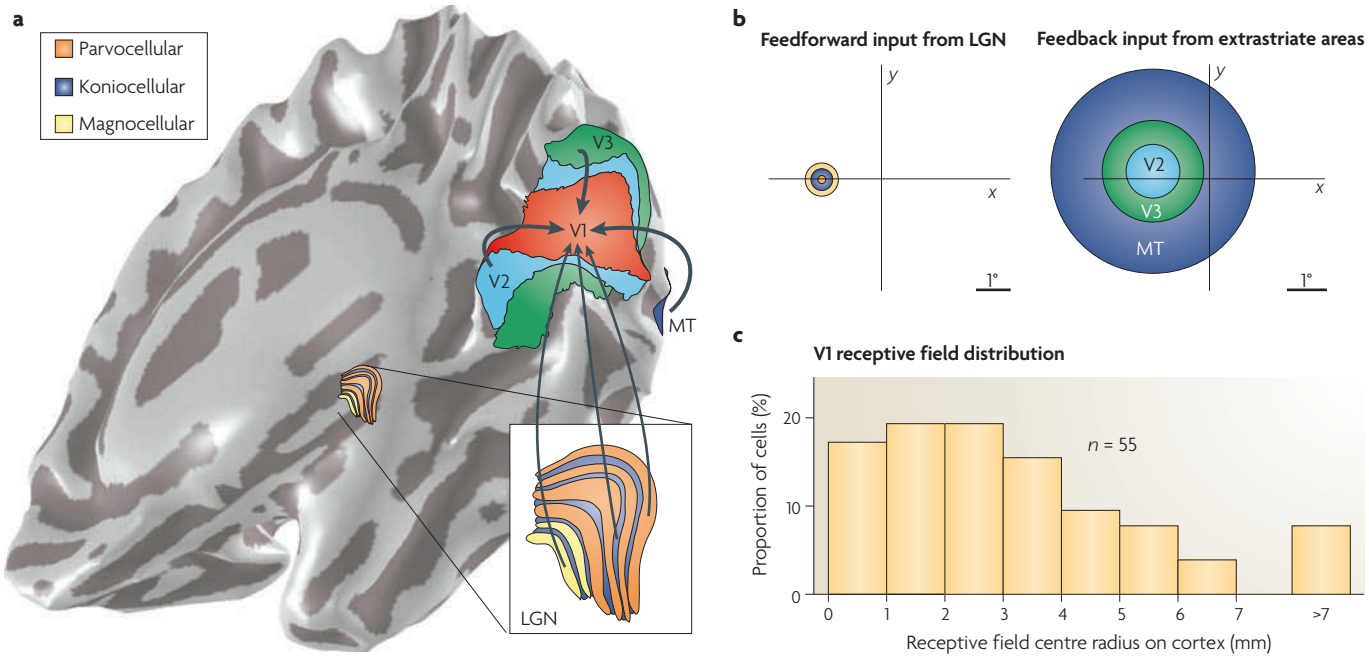

Figure 2 | **Primary visual cortex (V1) neurons receive diverse inputs. a** | A V1 neuron can receive input from the lateral geniculate nucleus (LGN), extrastriate cortex (V2, V3, middle temporal (MT) and other extrastriate sources), lateral connections between V1 neurons, and the pulvinar, a large nucleus in the thalamus (not shown). In healthy V1, the reported receptive field (RF) size can vary fourfold depending on the nature of the mapping stimulus[44]. **b** | The different inputs to V1 neurons have a wide range of RF sizes. The RF size of centre-surround LGN inputs (left) is small compared with the RF size of extrastriate sources (right). Extrastriate sources have RF sizes that vary and can be larger than 5° in diameter[125]. V1 neurons can also receive input from other V1 neurons with RF centres separated by a degree or more. The variations in estimated RF size of V1 neurons probably result from different contributions from the pathways that deliver the input signals to the V1 neuron. **c** | From the V1 visual field map, it is possible to express estimates of the RF centre radius on the cortical surface. The radius of V1 RFs is often larger than 3 mm, and more than 10% of the neurons have a radius exceeding 5 mm. The surround influence generally extends beyond 7 mm. Part **c** is reproduced, with permission, from REF. 124 © 2002 The American Physiological Society.

field were sampled at fixed V1 sites before and following the lesion. The authors reported a fivefold expansion in mean receptive field size immediately after the lesion; this remained a "several fold" expansion 2 months later: "At the end of this period [2 months] all cortical sites could be activated by visual stimuli." The responses within the LPZ differed from those within normal cortex, being more 'bursty' (C. Darian-Smith, personal communication). The authors did not specify what fraction of the neurons were responsive. A later study[60] reported increased sprouting of long-range laterally projecting axons near the border of the V1 LPZ, suggesting that this sprouting may be the anatomical basis for putative signal spreading from nearby (non-deafferented) V1 regions to the interior of the LPZ.

Giannikopoulos *et al.* reported that the likelihood of encountering a spiking unit was reduced in cat V1 following binocular, central retinal lesions (see figure 2B in REF. 61): 12 weeks post-lesion the probability of encountering a spiking cell more than 3 mm inside the LPZ was reported as less than 10% per millimetre of penetration length. This probability remained unchanged for at least 3 months, contrasting with reports of significant reorganization by this time[55,58]. A year later, this probability had increased to 40% (see figure 2B in REF. 61), but the increase cannot be interpreted unambiguously because the authors also reported that the probability of identifying a spiking unit in normal cortex also increased significantly (from ~60% to ~90%) during that time.

A dispute: responses following monocular lesions. Several investigators have found no reorganization of V1 receptive fields following monocular lesions[55,62–64]. Others have reported a zone of activity extending 2.5–5 mm beyond the initial border of the LPZ[65–67]. Indeed, Schmid *et al.* reported a zone of reactivation up to 3.6 mm from the border of such lesions, and no further effect following subsequent removal of the other eye[67]. An initial hypothesis to explain these striking differences was that the retinal ganglion cell layer had been destroyed in some studies[55,62–64] but not others[67]. To test this idea, Calford *et al.*[66] performed a complete retinal lesion and confirmed the results of Schmid *et al.*[67] The difference between the results from these two studies and the other experimental reports remains unexplained.

Murakami *et al.*[64] made electrophysiological measurements in alert, behaving macaques following monocular deafferentation. They reported no significant V1 reorganization, but the macaques showed evidence of

perceptual filling in; that is, perceptual completion of missing information such as occurs across the retinal blind spot. This suggests that the observed behavioural filling in is not likely to be mediated by V1 neurons, in agreement with REF. 68.

Following lesions that deafferent the monocular crescent of cat V1, which represents the far periphery of the visual field, "most neurons in the deprived peripheral representation remained unresponsive to visual stimuli even more than 1 year after treatment"[69]. This contrasts with reports from the same authors showing significant changes in response following relatively central deafferentation[65,67,70].

A dispute: receptive field sizes and orientation. Chino *et al.*[63] used long-duration (0.5 s) laser pulses with 1 mm diameter to lesion both the photoreceptors and the cells in the inner retinal layers of one eye. They made a corresponding, but larger, lesion in the second eye to completely deafferent the LPZ. Sampling the neural populations in V1 90 days following the second lesion, the authors found that the "overall responsiveness under optimal stimulus conditions was clearly reduced", but observed "strikingly normal orientation tuning, direction selectivity, and spatial frequency tuning when high-contrast (< 40%) stimuli were used". Giannikopoulos *et al.*[61] contradicted this report. Working in cats with a 10° lesion centred on the area centralis, they reported that "orientation tuning was found to be significantly decreased at distances >1 mm inside the LPZ, and it deteriorated with increasing distance from the border irrespective of recovery time". Chino *et al.* further reported an average receptive field size of 2.8° for neurons in the LPZ, compared with 2.19° for neurons in the adjacent cortex (see table 1 in REF. 63); this receptive field expansion is much smaller than that described by Gilbert and Wiesel[58].

A dispute: time course of plasticity. Heinen and Skavenski reported no neural activity inside the LPZ until 3 weeks after a retinal lesion[56]. Gilbert and Wiesel[58], as well as Darian-Smith and Gilbert[71], reported responsive units in the LPZ within minutes of a binocular lesion, but larger changes were seen ~2 months post-lesion. Schmid *et al.*[67,70] and Calford *et al.*[65] reported large-scale reorganization minutes to hours following monocular retinal lesions, whereas Chino *et al.*[62] found that the receptive fields of neurons in the LPZ are stable following monocular lesions and then reorganize within hours following enucleation of the other eye.

Pettet and Gilbert[72] described V1 as being so dynamic and mutable that large-scale reorganization can be induced by simply depriving the retina of stimulus contrast. Specifically, they reported that occluding a portion of the retina while stimulating the surround (inducing an 'artificial scotoma' in V1) induced a five-fold expansion of receptive fields centred in the artificial scotoma. However, DeAngelis *et al.*[73] reported that such an artificial scotoma causes no change in either the size or the internal structure of V1 receptive fields but only a short-term increase in responsiveness in some cells (see also DeWeerd *et al.*[68]). Using intracellular recording methods, Nowak *et al.*[74] reported "no significant difference between adaptation to a scotoma and adaptation to a gray screen".

Post-lesion blood oxygen level-dependent (BOLD) responses in the V1 LPZ of adult macaques are small or absent. Using functional MRI (fMRI), Smirnakis *et al.*[75] monitored responses in the V1 LPZ in adult macaques for several months following bilateral retinal lesions. They did not observe any change in fMRI signal activity across the LPZ border. These results agree with those of Yinon *et al.*[76], who reported little reorganization following deafferentation of V1 in adult cats by interrupting geniculo-cortical afferents. The fMRI measurements also agree with earlier results from studies measuring CO activity, another metabolic marker[57].

Smirnakis *et al.*[75] also performed multi-unit electrophysiological recordings following the fMRI experiments using a linear electrode array spanning the border between the V1 LPZ and adjacent, healthy cortex. In healthy cortex, all the electrodes measured powerful stimulus-driven multi-unit activity. But in the V1 LPZ, classical receptive fields could not be found; the responses were absent, weak or atypical (transient and driven by stimuli located far outside the typically small receptive field), as previously reported[56]. Further, the weak V1 LPZ responses had a longer latency (93 ms) than the responses just outside the LPZ (68 ms). The relative difference in timing is qualitatively consistent with those reported in REF. 56, and the difference in absolute latency between the two studies might be due to differences in the stimulus contrast. Smirnakis *et al.* concluded that "neuronal responses in the LPZ do not recover to anything approaching their normal state".

Different views of reorganization in the LGN. Eysel and colleagues measured responses in the cat LGN following peripheral (~18–22°) retinal damage[77–81]. Neurons receiving input from cells at the border of the lesion had receptive field positions that were shifted "up to five degrees" from the expected location. Only a small number (33) of such cells were found in a study involving 244 electrode penetrations[78].

Eysel *et al.*[80] suggested that "the cells with displaced receptive fields after long-term deafferentation received fibres of the fast-conducting (Y) type according to stimulus response latency criteria, after electrical stimulation near the optic chiasm". These Y cells might correspond to the axons of the retinal parasol cells in primates, the dendritic arbors of which normally cover a larger portion of the visual field than those of colocalized parvocellular neurons[82]. These responses in the LGN LPZ could therefore be functional changes that enhance the effectiveness of existing synapses, or they could simply reflect the residual inputs from the Y cells. But in other reports Eysel *et al.*[79] discount changes in the LGN as the source of cortical recovery because comparable lesions performed in the area centralis in cats resulted in "no deviation from the normal retino-geniculate

Monocular crescent
A crescent-shaped region in primate primary visual cortex that receives input from only one eye (the contralateral eye).

Area centralis
A central retinal region with relatively higher photoreceptor density that serves high-acuity vision; it exists in many species lacking a retinal fovea (pit).

Y cells
Ganglion cells in the cat retina exhibiting nonlinear spatial summation. They may be homologous to the primate parasol cells.

Parasol cells
A class of primate retinal ganglion cells identified by their large dendritic arbors. These cells comprise 10% of the retinal ganglion cells and project to the magnocellular layers of the lateral geniculate nucleus.

Visual field map
The receptive field centres of nearby neurons in visual cortex generally represent nearby positions in the visual field, forming an orderly map of at least a portion of the visual field.

Macula
The central portion of the primate retina that is covered by a yellow pigment (macular pigment). It includes the fovea.

Binocular neurons
Neurons that respond to stimulation of either eye.

Stereo-blindness
The inability to combine information from the two eyes to perceive depth. Stereo-blindness is a typical result of strabismus (eye misalignment) that was not corrected in early childhood.

topography and no receptive field displacements." This is not a very sensitive measurement, however, because the expected size of the visual receptive field displacement in the LGN representation of the cat area centralis (~0.3°) is very close to the detection limit in LGN recordings. In V1 the effects of a foveal lesion are easier to detect because the foveal representation is expanded relative to that in the LGN.

Subsequently, authors generally dismissed the possibility that differences between the pre- and post-lesion V1 LPZ responses have a thalamic origin[58,71]. For example, Gilbert and Wiesel[58] emphasized that "at a time when the initial cortical scotoma had disappeared … there was still a large unresponsive area in the LGN (about 1 mm in diameter, corresponding topographically to the size of the retinal scotoma)." However, a small surface area in the LGN projects to a large area in V1, so this observation does not eliminate the possibility that a significant fraction of the post-lesion V1 responses may originate in the LGN.

Finally, it is possible that functional recovery at the border of the retinal lesion might contribute to the changes as retinal inflammation abates[57] or the retina itself reorganizes[83].

V1 visual field maps

In much of visual cortex neurons are arranged so that the centres of their receptive fields form an orderly map of the visual field: neighbouring neurons have overlapping receptive fields, the centres of which represent neighbouring locations in the image[84–86] (FIG. 1). These visual field maps, also called retinotopic or topographic maps, are created by a precise developmental process. fMRI has made it possible to quantify visual field maps in macaques[87,88] and humans[86], and several studies have investigated the stability of these maps.

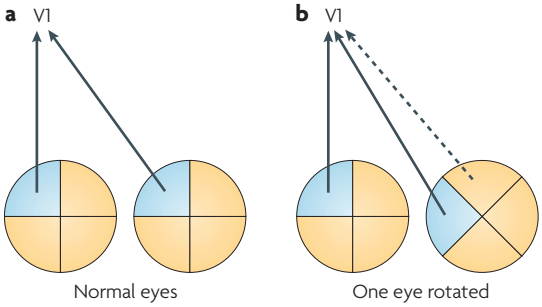

Figure 3 | **No reorganization of the primary visual cortex (V1) visual field map after eye rotation.** **a** | Normally, the locations in the two eyes that receive corresponding images (blue quadrants) send their signals to corresponding locations in the cortex. This is indicated by the convergence of the arrows in V1. **b** | Following surgical rotation of one eye, V1 inputs from the two eyes no longer represent corresponding visual field locations (solid lines). In principle, developmental plasticity could compensate for this misalignment by reconnecting retina and cortex (dashed line). However, developmental plasticity does not correct the inappropriate mapping caused by eye rotation; the original, and now incorrect, mapping is preserved (solid lines).

Developmental plasticity of visual field maps. Developmental plasticity of the V1 visual field map was demonstrated in humans born with a genetic defect that causes a malfunction in cone phototransduction[89] (such individuals develop as rod monochromats). The normal eye has a pure cone (rod-free) region in the central 0.6° of the macula called the fovea; a predominantly cone region extends to at least 1° radius[90,91]. In rod monochromats, however, no cone signals are present in this region; consequently, the 1 cm^2 V1 projection zone of signals from the fovea should receive no input[27,92]. Indeed, in normal subjects rod-initiated signals produce no BOLD fMRI response in this large area[93]. In some rod monochromats, however, the entire zone is responsive[89]; in others, a small silent zone remained. Developmental plasticity therefore creates rod-driven receptive fields in a cortical location that, in control subjects, is a cone-only projection zone (see figure 1C in REF. 89 and REFS 94–96).

There is no evidence that the defective cone phototransduction in rod monochromats[97–101] directly influences cortical structure or ganglion cell morphology[101,102]. One report assumed that the unusual cortical responses in rod monochromats must be explained by the development of novel functional connections — such as new projections — from rod-initiated signals[89]. However, other mechanisms might also explain the results. For example, rod signals could normally be present in this zone but suppressed by cone signals; failure of cone development could eliminate this suppression, unmasking the rod signal.

V1 map stability despite large eye misalignments. In healthy V1, binocular neurons receive inputs from the left and right eye that represent corresponding visual field locations. Following surgical rotation of an eye, V1 inputs from the two eyes no longer represent corresponding visual field positions (FIG. 3). After Hubel and Wiesel's work on developmental plasticity of binocularity, other investigators asked whether surgically rotating one eye in a kitten could invoke mechanisms that alter the retinotopic maps to compensate for the eye rotation[103,104]. They reported no experience-dependent plasticity in response to eye rotation; the V1 maps from the two eyes remained misaligned.

The maps also fail to realign following experimental deviation of one eye (strabismus). Strabismic cats have a few binocular neurons, although these animals are stereo-blind[105]. In these binocular neurons, neither developmental nor adult plasticity brings the visual field representation from the deviated eye into register with the normal eye[106]. However, for modest amounts of misalignment (<10°) the maps from the two eyes can be brought back into register further downstream, in an extrastriate visual map[106,107].

In summary, V1 maps develop an abnormal organization in certain developmental cases (such as in rod monochromats). In this case, there are deviations from the conventional visual field map that extend a centimetre or so beyond the conventional organization. But even developmental reorganization is not completely general. For example, no significant developmental reorganization occurs after eye rotation or strabismus.

V1 responses in adults with macular degeneration. In subjects with binocular macular degeneration, a region of V1 is deprived of normal retinogeniculate input. The first fMRI data from a human subject with age-related macular degeneration (AMD) were obtained from a 60-year-old woman[108]. In this subject, bilateral lesions surrounded the spared central fovea, depriving a region of V1 of its normal input, resulting in complete blindness (absolute scotoma) in this part of the visual field. This subject had a large unresponsive zone in the V1 LPZ that, unlike in the congenital rod monochromats, remained unresponsive.

Baker and colleagues[109,110] examined subjects with extensive binocular macular lesions. The subjects had to identify whether targets (faces or objects) presented in the unaffected part of their peripheral visual field occurred twice in a row. These authors found a substantial fMRI response (1.2%) in the LPZ. Most of the subjects had a silent V1 zone, 1–3 cm in width, separating the responses from preserved retina in the periphery from responses in the LPZ, near the occipital pole. The cortical responses in these subjects differed from the single-unit measurements summarized above; the single-unit measurements suggest an expansion of cortical activation adjacent to the LPZ rather than the development of a new active zone several centimetres away from the LPZ. In one or possibly two of the macular degeneration subjects, however, there was a continuous spread of activity from V1 responses in the anterior calcarine (initiated in the preserved peripheral retina) extending to the occipital pole. This activation might reflect the same process as that underlying the activation shown in the single-unit studies, although the spread in the human fMRI activity is measured in centimetres, whereas the maximal spread of activity reported in single-unit studies is <5 mm. We discuss this issue in more detail in Supplementary information S1 (box)).

V1 task-dependent modulations in macular degeneration. Masuda *et al.*[111] set out to understand the difference between the results in REFS 108–110. Using a passive viewing condition (as in REF. 108) and a stimulus-related judgment task (as in REF. 109), they asked whether there was a much smaller LPZ in juvenile macular degeneration (JMD) subjects than in controls with a simulated scotoma. In the passive viewing condition, fMRI in the JMD subjects revealed a large, silent LPZ, the size and location of which were consistent with the size expected from the retinotopic projection of the retinal lesion (confirming the findings of REF. 108). These data cannot reveal whether the LPZ is slightly smaller, by around 2–5mm, than it was before the onset of the JMD, and so these measurements do not test the prediction from the single-unit measurements reviewed above.

In control subjects the V1 response did not differ between the passive and stimulus-related judgment tasks. But in several JMD subjects cortical activity expanded into the LPZ during the stimulus-related judgment (similar to one of the subjects in REF. 109) (FIG. 4). The authors proposed that the spread of the V1 response into the LPZ is caused by cortical signals initiated by the task demands, and not by reorganization of the feedforward pathways carrying the retinal stimulation[111].

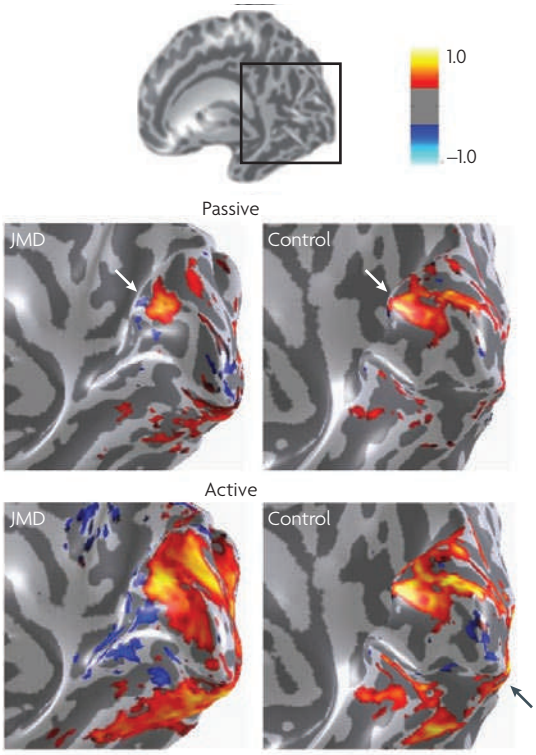

Figure 4 | **Primary visual cortex (V1) responses in humans with central retinal lesions.** The four main images show an expanded posterior view of the calcarine sulcus (the area marked by the box on the upper inset). The colour overlays compare functional MRI responses in a subject with juvenile macular degeneration (JMD) (left) and a control (right). The JMD subject has a large central scotoma and spared vision in the lower peripheral field; the responses from the control subject were measured with a similar 'artificial' scotoma. In the passive condition subjects passively viewed a visual stimulus presented in the peripheral visual field near the lower vertical meridian. In both subjects this produced a modest response in the anterior calcarine at the location corresponding to the position of the stimulus in the peripheral visual field (upper images; arrows). In the active condition subjects were asked to remember the visual stimulus from trial to trial (lower images). In this condition, responses in the calcarine sulcus of the JMD subject spread significantly towards the occipital pole, and responses increased in other regions, such as the ventral surface. But in the control subject there was no significant expansion of the blood oxygen level-dependent signal towards the posterior calcarine sulcus. In both the JMD and the control subject, the active task increased responses broadly, including near the occipital pole (arrow). The location of this activation with respect to V1 has not been defined with any certainty. The colour bar indicates the amplitude of the blood oxygen level-dependent response (percent modulation), either in synchrony (red) or out of synchrony (blue) with the stimulus. Only modulations exceeding 0.3% coherence are shown. Figure is reproduced, with permission, from REF. 111 © 2008 Oxford Journals.

Macular degeneration
A loss of vision due to disease in the central (macular) portion of the retina.

Masuda *et al.* also observed a small modulation of activity near the occipital pole in both JMD subjects and controls during the judgment task (see figures 4 and 5 in REF. 111) (FIG. 4). The nature of this activation is an interesting topic that is currently being investigated[112]. If occipital pole and V1 activation is present in controls, the argument that the occipital response represents V1 plasticity in JMD subjects is weakened. The location of occipital pole activation with respect to the V1 map is not firmly established and will be particularly difficult to determine in JMD subjects in whom foveal cortex cannot be mapped; it might be possible to localize it from anatomical measurements of the stria of Gennari[113–116].

A dispute: V1 LPZ responses and the PRL. Subjects deprived of foveal vision often develop an alternative preferred retinal locus (PRL) that lies in the intact peripheral part of the retina. Schumacher *et al.*[117] measured fMRI responses in six subjects with macular degeneration and a PRL. They too found that stimuli presented in the PRL cause a response in the LPZ near the occipital pole, several centimetres from the projection zone of the intact parts of the retina. By contrast, stimuli presented outside the PRL did not produce an LPZ response. Dilks *et al.*[118] performed the same experiment but found the opposite result: an occipital pole response to peripheral stimuli presented inside or outside of the PRL.

The results in REF. 117 suggest a specific colonization of signals from the cortical representation of the PRL to cortex in the occipital pole, whereas the results in REF. 118 suggest that any relationship between peripheral signals and the occipital pole is general, lacking cortical specificity.

Summary of fMRI studies in humans. Human brain imaging provides a great deal of valuable information regarding cortical plasticity. An advantage of human studies is that they allow the acquisition of information about perception (see Supplementary information S1 (box)) and provide structural and functional information over the entire brain that enables comparisons of major structural features, such as grey matter thickness[119]. But there are also important limitations. For example, because retinal histology cannot be obtained in living subjects, we cannot exclude the possibility that retinal pathology is incomplete or fuzzy, or has changing borders[83]. Also, neuroimaging data are not informative about mechanisms of plasticity; in fact, the data permit a number of explanations that one would be hard pressed to call plasticity. For example, it is widely agreed that task-related demands influence the BOLD responses in human V1 (REFS 120–122). The task-dependent V1 responses in the JMD subjects could arise from activation of normal circuitry, via extrastriate cortex or sub-cortical structures[111]. The removal of the retinogeniculate signal in JMD subjects could expose these responses in V1, even though the circuitry itself does not differ from that in control subjects. More research is needed to establish whether JMD and control response differences are explained by the development of new circuitry or increased response amplitude on existing pathways.

Conclusions

The extent and nature of adult V1 plasticity remains uncertain. The assertion that "Plasticity in adult V1 has been demonstrated by multiple independent lines of evidence from more than twenty studies in three species"[123] masks the many inconsistencies in the experimental literature. There are numerous unanswered questions. What proportion of neurons are visually responsive inside the LPZ? Are receptive field sizes enlarged post-lesion and, if so, by how much? Does orientation tuning follow predictions from models of deafferentation? Does reorganization occur only after binocular lesions or also after monocular lesions? What is the time course of reorganization and what does it depend on? Is there recovery within the retina at the margin of the lesion? What are the specific neural circuits that reorganize, and which stay fixed?

Modelling the effects of lesions. What we know about plasticity is limited by current experimental paradigms. A particular problem is the approach of considering deviations from a poorly specified model of V1 receptive field structure as evidence of plasticity. This is like flattening a car tire and then claiming that changes in the steering properties, which may become more severe over time, are evidence of steering plasticity.

A specific problem is that the most widely used receptive field model is based on the assumption that V1 neurons all have small, classical receptive fields. But we know that at each cortical location the receptive field sizes vary, are dynamic and depend on the mapping stimulus. For example, the V1 receptive field centre radius represented on the cortical surface includes many cells with small sizes (2 mm), but 20% of the neurons have a radius greater than or equal to 5 mm (see figure 13 in REF. 124). Also, there are large differences between extrastriate input and thalamic input to V1; for example, the spatial extent of axonal fields and their corresponding influence on the properties of V1 receptive fields differ considerably between thalamic and extrastriate V1 inputs[44,45,124–126]. Quantitative models that incorporate these properties, and that enable the prediction of responses following retinal lesions, are necessary before we can interpret the population responses following retinal lesions.

Integrating data from multiple methods. It should become possible to use quantitative V1 models to interpret data from a range of experimental methods. Some researchers suggest that data obtained with methods that do not directly measure neuronal spiking should be discounted: "Any analysis of plastic reorganization at a neuronal locus needs a veridical measure of changes in the functional output — that is, spiking responses of the neurons in question. In a study of the effect of retinal lesions on adult V1, Smirnakis *et al.* propose that there is limited, if any, cortical reorganization. Their results

Preferred retinal locus (PRL). When the fovea is damaged people often place the region of interest on a location in the spared peripheral part of the retina, the PRL.

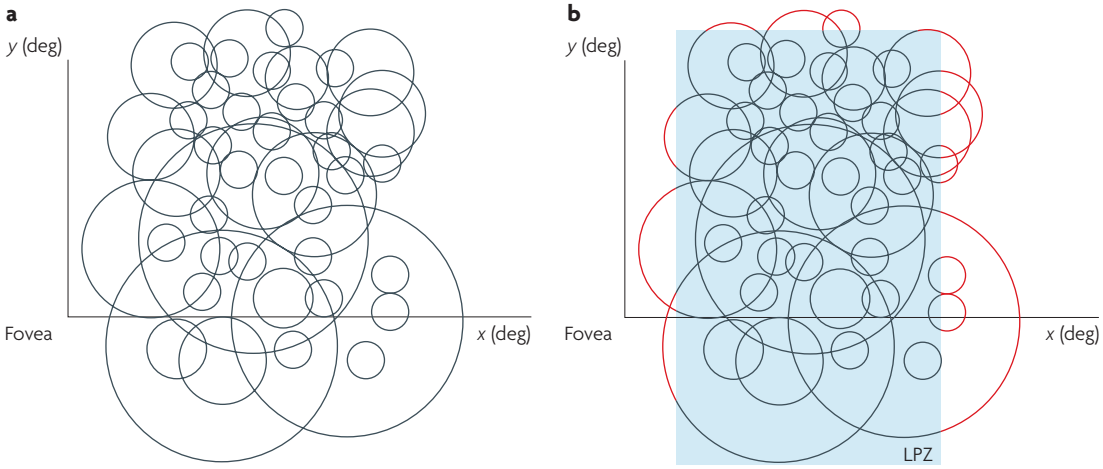

Figure 5 | **The expected effect of retinal lesions on V1 responses. a** | This schematic illustrates the diverse receptive fields of neurons expected to be found within a region of V1. The black circles show the size of the receptive fields of neurons plotted on a representation of the visual field. The receptive field sizes vary and partially overlap. **b** | The same receptive fields are shown with a transparent blue rectangle that indicates the lesion projection zone (LPZ) — the portion of the visual field that is blinded by a simulated retinal lesion. The retinal lesion is located in the centre of the receptive fields that are sampled from this part of the cortex. The effect of the retinal lesion is a reduction in the number of responsive neurons within the LPZ. Assuming that there is no cortical plasticity, we still expect some cells to continue to respond to signals placed on adjacent regions of spared retina (red circles). Such neurons will necessarily have receptive fields that are displaced (ectopic) from their pre-lesion position. There are fewer responsive neurons inside the LPZ post-lesion than pre-lesion[61], presumably because neurons with small receptive fields are silenced. Such data should be construed as supporting adult cortical plasticity only if the reduction in the number of responsive cells, and the change in the properties of the ectopic receptive fields, differs significantly from a model that assumes no plasticity. A complete model should include quantitative specification of the distribution of receptive field sizes, experimental factors (retinal penumbra due to inflammation or swelling) and models of retinal plasticity[83].

are based, however, on BOLD fMRI, which provides an unreliable gauge of spiking activity"[123]. However, it is unwise to dismiss data obtained from the BOLD signal or other non-spiking measures, such as CO activity. Each measurement method provides a new opportunity to understand the full range of cortical responses and should be taken into account in the context of its own limitations.

Interpreting displaced receptive fields. There is one measurement method in the literature that deserves special comment. Electrophysiology studies generally claim that receptive fields that are displaced from their usual position — described as being 'piled up' at the border of the V1 LPZ — are evidence of reorganization[55,58,61–63,65,66,70,71]. This claim is widespread, but we think that it is wrong.

If one could identify with some certainty a V1 neuron that is driven entirely by lesioned photoreceptors, then a post-lesion response in that neuron would be evidence of plasticity. Electrophysiological single-unit recordings, however, do not follow individual neurons from pre- to post-lesion but compare samples from a neuronal population pre- and post-lesion. It is quite likely that some neurons in the V1 LPZ will respond post-lesion to input from photoreceptors at the margin of the damaged retina[83] (FIG. 5). V1 responses might also arise from neurons with large receptive fields, lateral connections intrinsic to V1 or feedback from extrastriate sources (FIG. 2). Consequently, even in the absence of post-lesion reorganization, there might be receptive fields with centres that lie just beyond the margin of the lesion.

Any plausible model of V1 neurons would predict that removing retinal input alters the population responses but does not abolish them. To establish reorganization would require a demonstration that the number and properties of ectopic receptive fields differs from model predictions in which retinal inputs are simply silenced. In the absence of such a model, empiricists demonstrate plasticity by showing that the sampled neuronal population changes over time. This approach is subject to significant sampling bias, as different populations of neurons are sampled at different times following experimental manipulations. For example, in one study the probability of isolating a neuron inside the V1 LPZ is one-sixth the probability of isolating a neuron in control cortex (see figure 2B in REF. 61). Most V1 neurons are thought to survive after V1 deafferentation, so this reduction in sampling probability is probably due to the fact that the majority of deafferented neurons are quiet and therefore harder to isolate. Because there is no way of knowing *a priori* which subset of neurons (~10–20% of units) will be detected post-lesion, we are probably comparing different neuronal populations, and differences between the pre- and post-lesion samples might be misinterpreted as plasticity. Following V1 population responses over time after the lesion does not entirely solve the problem, as the recording bias probably depends on the recovery at the borders of the retinal lesion (the penumbra).

Box 2 | **Restoring vision**

New experimental evidence for the existence of adult cortical plasticity is sometimes used to market behavioural training methods for people suffering from neurological disease or injury. The commercial applications claim that certain behavioural regimens will slow or even reverse neurological disorders such as dementia or blindness caused by stroke. The research papers reviewed in this article are sometimes cited to support these commercial claims.

It is worth noting, therefore, that in our experience the scientists involved in the experiments do not suggest that findings in adult V1 plasticity offer a plausible mechanism for restoring loss of the visual field caused by damage to the retina or optic nerve. This can be deduced from first principles: information that is not present in the retina cannot be extracted by V1 processing. The best one might hope for is that plasticity will improve the processing of signals that originate in the spared retina. But there are no substantiated claims of adult behavioural improvement that can be traced to the development of ectopic V1 receptive fields.

This specific objection does not deny all reports that visual performance in a 'blind' region of the visual field may improve after visual training. But there are many potential sources for improvements in task performance apart from the work reviewed here, and it is important to recognize that the source of the improved visual performance might differ depending on the specific nature of the loss. For example, some authors suggest that visual performance improvements following retinal damage may be explained by learning new eye movement habits[127]. When geniculo-cortical pathways are damaged it might also be possible to help patients by teaching them to interpret the residual sub-cortical signals that arrive through the colliculus and pulvinar[128–131]. Correctly identifying the neural source of behavioural improvements has practical consequences: if we understand the basis for the improvement, rehabilitation strategies can focus on developing the mechanisms that are appropriate for the individual patient.

A more decisive approach for the future will be to apply chronic recording methods. New methods are being developed that isolate and follow the responses of individual neuronal units over time[50–52]. This approach bypasses the need for a general model and may reduce the recording bias in the LPZ (see figure 2B in REF. 61). Until methods and models for this analysis are created, the presence of responsive neurons with ectopic receptive fields should not be considered a decisive measure of plasticity.

Future directions. We hope that this review of the significant contradictions regarding V1 adult plasticity will speed efforts to resolve them. We have described a need for better theoretical models of healthy cortical signals at the cellular and systems scales to interpret experimental measurements following retinal lesion models. We add that such models will be needed at many scales. For example, it is likely that changes at the scale of dendritic and axonal arbors also exist, and models will be essential for understanding the effect of changes at the synaptic level on receptive fields and networks (Supplementary information S1 (box)). Further experiments assessing whether specific cellular and neuroimaging measures of adult cortical plasticity influence perception and behaviour also will be needed before we can establish which neurobiological measurements are meaningful in clinical (BOX 2), educational and policy applications.

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DATABASES
Entrez Gene: http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?db=gene
GAD65

FURTHER INFORMATION
Brian A. Wandell's homepage: http://white.stanford.edu/wandell.html
Stelios M. Smirnakis's homepage: http://www.bcm.edu/neurology/faculty/smirnakis.html

SUPPLEMENTARY INFORMATION
See online article: S1 (box)

ALL LINKS ARE ACTIVE IN THE ONLINE PDF

Supplementary information S1 (box) | Comparing measurements from different modalities

Relating brain measurements across length scales from behavior and neuroimaging to spikes and sub-cellular changes is an important goal. It difficult, however, to demonstrate rigorously that measurements across scales and methods reflect the same phenomena. In the following sections we consider several putative connections between observations at different scales and methods.

A. Comparing electrophysiology and fMRI measures

A recent review of the literature[1] groups a functional MRI study[2] with an array of single-unit physiology reports:

> "Topographically, V1 becomes remapped, with a shrinkage in the representation of the lesioned part of the retina and an expansion in the representation of the parts of the retina surrounding the lesion (Gilbert *et al*. 1990; Chino *et al*. 1992; Gilbert & Wiesel, 1992; Heinen & Skavenski, 1992; Eysel *et al*. 1999; Calford *et al*. 2000; Baker *et al*. 2005; Giannikopoulos & Eysel, 2006)."

One can find a similar grouping of references in an fMRI study[3]:

> "Extensive topographic reorganization of primary visual cortex (V1) has also been reported in adult cats and monkeys following discrete retinal lesions (Chino, Kaas, Smith, Langston, & Cheng, 1992; Chino, Smith, Kaas, Sasaki, & Cheng, 1995; Gilbert & Wiesel, 1992; Heinen & Skavenski, 1991; Kaas et al., 1990). Neurons in the deprived region of V1 (i.e., the region that previously responded only to stimuli falling on the subsequently lesioned part of the retina) became responsive to stimuli falling on parts of the retina adjacent to the lesioned area. … Here, we used fMRI to test for reorganization of visual processing in five individuals with extensive retinal damage from MD with different etiologies and ages of onset."

The electrophysiological and fMRI measures data are dissimilar in important ways. Perhaps the most glaring is that the electrophysiological reports claim that deafferented cortex responds to stimuli that normally evoke responses in adjacent cortex. The neuroimaging data claim that cortex several centimeters away from preserved cortex is recruited.

To see the difference, consider the images in Figure S1. These images represent fMRI data reported in four macular degeneration subjects. Each has a scotoma spanning more than 10 deg in the central visual field. The authors identify all four subjects as supporting large-scale reorganization in V1. The response from intact retina is labeled as PRL (white arrow). Because of the macular degeneration, these authors believe that these subjects would not ordinarily have a foveal V1 response (but see REF[4]). Hence, data demonstrating reorganization is based on the responses present in the portion of V1 that typically responds to foveal stimulation (white

elliptical ROI). In the first study, the authors write "for both subjects (Fig. 2), visual stimulation, compared with the blank screen baseline, strongly activated the foveal confluence and adjacent cortical regions corresponding to the projection zone of the damaged retina." On the other hand, "The activation of the foveal confluence and adjacent cortex by peripheral stimuli was not observed in matched control subjects."

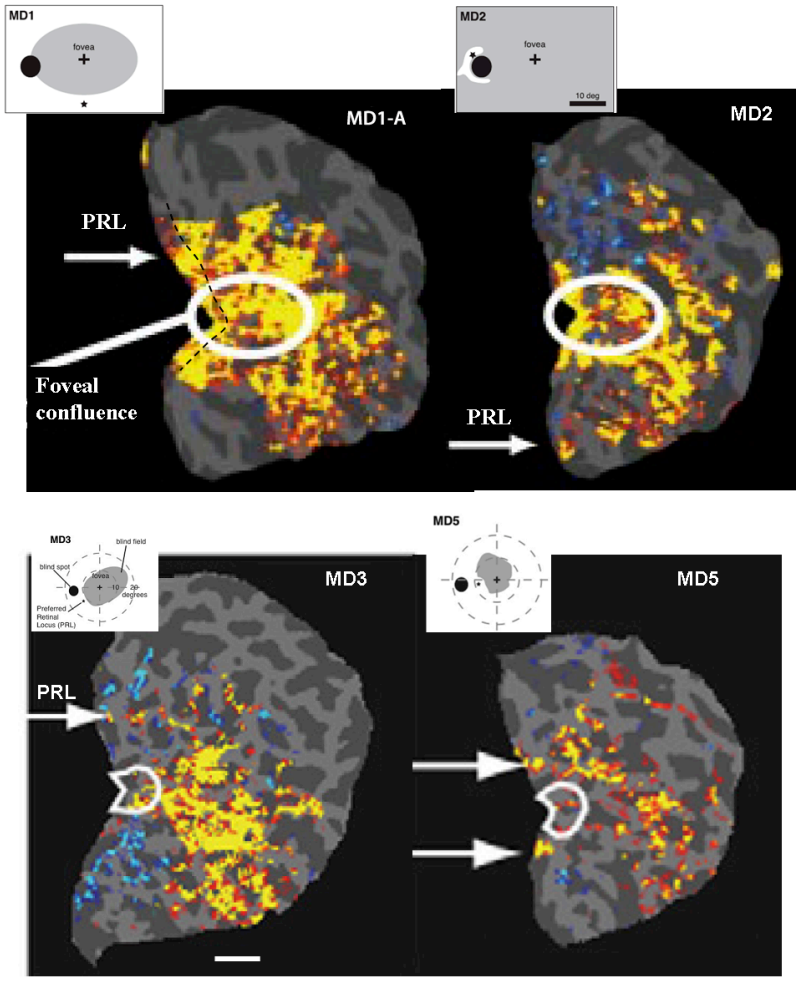

Figure S1. Responses in the visual cortex of subjects with macular degeneration. The images are flattened representations near calcarine cortex (V1). To create the flattened images, a cut is made along the calcarine sulcus so that the dorsal and ventral portions of V1 fall along the left margin (black dashed line, upper left image). The foveal representation is near the middle-left of the image (white outline); peripheral representations are in anterior calcarine, both above and below the middle-left (white arrows). Warm colors indicate a positive BOLD response; cool colors a negative response. Subjects MD1-A and MD2 were reported in REF[2]; subjects MD3 and MD5 were reported in REF[3]. The authors present these examples as supporting adult V1 plasticity (see text). PRL: preferred retinal locus, bottom arrows indicate activity expected based on the location of the stimulus in the periphery. White outline indicates the foveal confluence. White scale bar: ~1 cm.

In three of the subjects the fMRI responses in regions normally corresponding to the PRL (white arrows) are separated by several centimeters from the putatively recruited responses in the foveal representations within the LPZ (white ellipses). This

contrasts with electrophysiology measurements; in that case cortical activation spreads at most a few millimeters from adjacent cortex into the LPZ. In addition to the very large difference in scale, there is a large silent zone in V1 separating between responsive cortex of the PRL and the putative reorganized activity. This type of reorganization, a response several centimeters away from the intact response, has not been described with conventional electrophysiological methods. Additional evidence should be provided before we accept that these two measurements reflect a common phenomenon.

One fMRI data set (MD1-A) is more consistent with the electrophysiological measures. In this subject the spatial scale of fMRI response is much larger than the electrophysiological spread, but there is no silent zone: the response extends continuously from the PRL to the foveal representation. Data from this subject have been reported in the literature using very similar methods on two occasions, and we show the second set of measurements in Figure S2. These differ from the first in that there is a large silent zone separating the PRL responses from the foveal responses, similar to the data from MD2, MD3 and MD5. Hence, further measurements should be undertaken to demonstrate whether or not this subject has a large silent zone.

In summary, much work remains to show whether or not the neuroimaging responses in these studies measure the same phenomenon as the electrophysiological studies. The current weight of the evidence is that they do not.

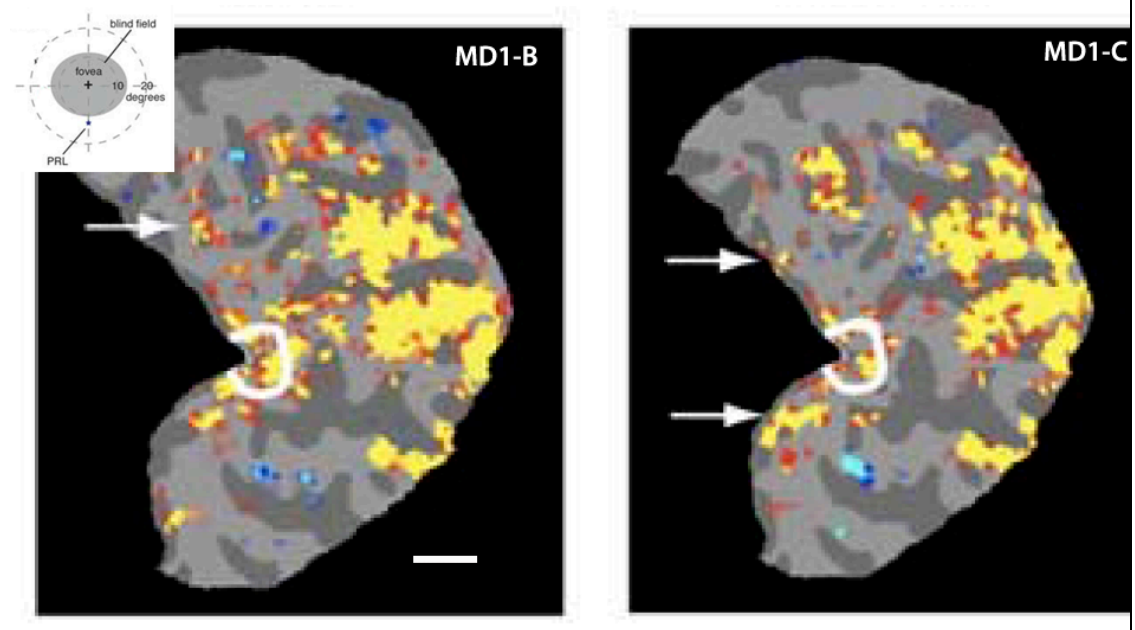

Figure S2. A second set of measurements in subject MD1. Methods and stimuli are very similar to the original report[2]. In the two data sets shown here the peripheral stimuli were presented at different locations and produced slightly different responses (white arrows). In both cases there is a response in foveal V1. In these measurements there is a large silent zone in V1 separating the peripheral (PRL) and foveal responses, in contrast to MD1-A where the activity appears to be confluent for several centimeters. The large intra-subject variability of statistical maps in this subject underscores the need of performing additional measurements in order to understand this phenomenon. Data from REF[5, Figure 2].

B. Behavioral assays and V1 plasticity

Just as it is difficult to confidently connect neural measurements spanning length scales, it is also challenging to couple neural and behavioral measures. The peripheral pathways and in particular sensory encoding offer the best target for establishing a relationship between behavior and the nervous system[6]. Connections between cortical signals and behavior are challenging to establish across all fields of neuroscience, though there have been some important achievements[7-9].

One recent report[5] suggests a connection between V1 adult cortical plasticity and a visual shape illusion. Specifically, the shape illusion arises from patching one eye and presenting stimuli near the blind spot in the fellow eye. The illusion can be measured within seconds of applying the patch and disappears within seconds of removing the patch. This report is similar to illusions that have been observed near an artificial scotoma, rather than the natural scotoma of the blind spot[10, 11]. It is proposed that these rapid and reversible visual illusions are explained by the "rapid receptive field expansion within the deprived V1 as reported in electrophysiological studies after retinal lesions (REF[5] Abstract)." As we describe in the main text, there is an unsettled controversy about the effects of an artificial scotoma on V1 receptive fields. Moreover, this type of rapid and reversible phenomenon is generally in the category of sensory adaptation rather than adult cortical plasticity. Even so, it is possible that there could be a connection. How might it be demonstrated?

The most secure methods of demonstrating links between specific neural activity and a behavioral measure use independent quantification of the neural signals and behavior; these measurements are then coupled by a specific model defining how the measures are connected. The classic work on color-matching, in which quantification of the behavior and neural signals come together in perfect agreement is the best example[12, 13].

The quantitative measurements comparing these shape illusions with adult V1 cortical plasticity do not agree well. For example, one study made measurements of filling-in using subjects with macular degeneration[14]. These authors quantified the extent of the filling-in phenomenon and found that it was too large to be explained by measured plasticity in V1 circuitry. Another study[10] found that the dependence of their effect on eccentricity was inconsistent with the V1 cortical magnification function, although they were reluctant to abandon the hypothesis that V1 mechanisms explained the phenomenon.

Related to the shape measurements, there have also been attempts to directly combine measurements of filling-in and plasticity. The Komatsu lab[15-18] carried out a thorough set of studies examining perceptual filling-in responses to artificial and retinal scotomas. They found that "the normal visual system possesses a mechanism that yields filling-in when some part of the retina is damaged, and that such a mechanism requires no topographical reorganization in V1." In the main text we noted other electrophysiological measures of filling-in[19] that failed to support a connection between V1 signals and perceptual filling-in.

The quantitative measures in these experiments do not support a close coupling between the perceptual phenomena of filling-in, shape perception, and adult V1 plasticity. There are quantitative inconsistencies between the data, and there are no compelling models to explain how shape or filling-in could be predicted from the neural responses. To advance this field of inquiry, one must first achieve greater clarity about the neural measurements – the timing, size of the receptive field

changes, and dependency on visual eccentricity. Once the neural measures are secure, we require a model that explains how receptive field size changes predict the visual shape illusion. Quantitative measurements that compare these perceptual and neural measures could then be used to prove – or disprove – the case.

C. Optical imaging

Optical imaging combined with electrophysiological measurements can promote a deeper understanding of the relationship between fMRI data and single unit data. The contrast signal measured by optical imaging is based on the same contrast mechanism as fMRI (blood oxygenation). Because optical imaging is generally invasive, it is possible to make electrophysiological measurements at the imaged cortical locations. Coordinating blood oxygenation and electrophysiological measurements from the same cortical region provides valuable information about the relationship between the two types of data.

Some readers of the main text were no doubt alarmed that we failed to cite an influential paper seeking to do just this in the area of adult cortical reorganization[20]. That paper measured optical imaging and spiking responses in cat cortex and demonstrated that a small (~0.5 degree) stimulus evokes (a) spiking activity across a range of cortex (0.4-1.1mm) and, (b) subthreshold activity over a region extending ~3-5 mm (for similar estimates in primate see REF[21]). The authors then lesioned the retina and concluded that the extent of the subthreshold signal is linked to the degree of cortical reorganization: "In the reorganized cortex the spike PS expanded, approximating the extent of the optical PS seen in normal cortex (abstract)".

The key optical images assessing reorganization are reproduced in Figure S3. The three images show orientation-preference estimates in a region of V1. A white line, indicating the upper edge of the estimated cortical scotoma, is shown on all the images. The limits of the scotoma were verified by electrode recordings. The three images (starting at the left) were measured before the binocular lesion, immediately after the lesion, and five months after the lesion. The authors write that "In the 'recovered' cortex, visually driven activity had returned, with the RFs shifted to positions outside the retinal lesion (REF[20], Caption of Figure 4)." The differences between pre-lesion and recovered orientation-preference estimates are shown in the fourth image. The authors conclude that orientation columns measured in deafferented V1 cortex form in the weeks following the retinal lesion and the recovered orientation-preferences "stayed roughly unchanged from the pre-lesion state, despite reorganization of RF input."

Notice that immediately post lesion the signals are highly degraded in both deafferented cortex and control cortex. The reported restoration of orientation column structure in deafferented cortex is commensurate to that seen during the same time in control cortex. Hence, the optical imaging data do not show that deafferented cortex was more influenced by the binocular lesion than control cortex (which should have remained unchanged).

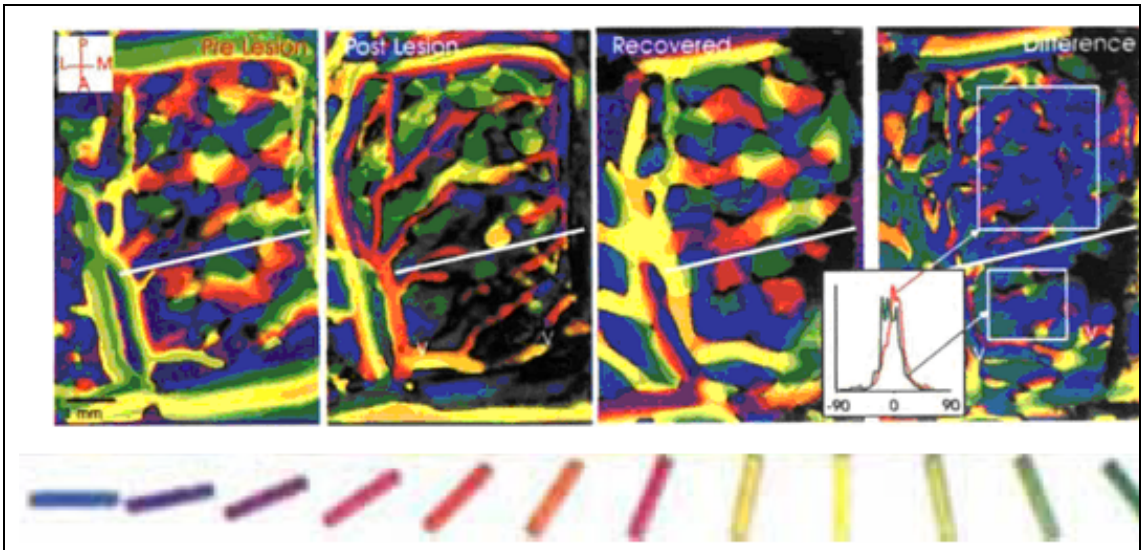

Figure S3. Images representing reorganization measured by optical imaging. The three images on the left are orientation-preference estimates prior to lesion, immediately following binocular lesions, and five months after recovery. The white line separates nominally spared cortex (above) – which is intended to serve as a control – from the lesion projection zone (below). Control cortex shows a marked change in response immediately post-lesion compared to "Pre Lesion" and "Recovered". The responses in control cortex and the lesion projection zone evolve together, making it difficult to argue convincingly that the changes inside the LPZ differ from control cortex. Oriented lines at the bottom indicate the association between color and preferred stimulus orientation. Images are from REF[20, Figure 4].

It is possible the authors are correct; but the data in this brief study need to be made more convincing. Among the issues one might consider in designing a more complete optical imaging study are these: How faithfully does the optical image signal reflect subthreshold activity? Can we compare the signal amplitude between deafferented and control cortex? Can we measure the retinal recovery in the penumbra of the lesions and compare this with the changes at the border of the LPZ? Can we use quantitative methods to measure the receptive field properties in the LPZ and control cortex? Can we interpret the relationship between the two data sets using a model that relates the properties of the single-unit recordings and the optical image data, accounting for sampling bias and cell diversity?

D. Synaptic and molecular dynamics

There is a substantial literature analyzing stability and plasticity of synaptic processes in adult V1[22-30]. The experimental methods for synaptic measurements are evolving at a rapid pace, but there can be little doubt that in several cases there are activity-dependent changes at the scale of the dendritic and axonal arbors. The implication of these synaptic level changes for receptive field properties – or, even more importantly, for visual behavior – should be investigated. Further, there are important open questions about the influence of the invasive experimental methods themselves, which can involve skull removal and penetration of the dura[31]. This literature is well

beyond the scope of our review, but it is a good example of an important field where there are opportunities to explore the relationship across length scales and methods.

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