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Loss of visual cortex and its consequences for residual vision

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Humans rely heavily on their sense of vision to navigate around the world, and this reliance is reflected in the large proportion of the cerebral cortex dedicated to processing visual information. If visual cortex is damaged by a stroke or trauma, the person may be left unable to see half of the visual world. Nonetheless, many people are still able to determine some information about visual stimuli presented within this 'blind' region ('blindsight'), an ability that it may be possible to boost through rehabilitation. This review considers the different types of residual vision that have been identified, and the pathways able to take information from the eyes to the brain avoiding affected areas. While current rehabilitation approaches lead to some improvement in visual performance, it is nowhere near the level of healthy vision. I conclude that the way forward is an individualised approach using visual stimulation that activates intact pathways.

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Why is visual cortex so important?

While light information is detected by the eye and converted into electrical activity in multiple processing stages of the retina, in primates it is the visual cortex that produces the ability to perceive the world in detail. As shown in the upper row of Figure 1, the majority of visual information is projected from the eyes via the lateral geniculate nucleus (LGN) to the primary visual cortex (V1). From there, processing of visual information becomes more specialised, with different visual cortical areas selective for different types of visual content. Damage to – particular parts of the visual cortex leads to a loss of visual perception, reflecting the specific role of the affected region. Specifically, where restricted regions in higher visual cortex are damaged, such as the fusiform face area [1] or lateral occipital cortex [2,3], patients can no longer perceive particular aspects of vision (faces or objects respectively in these examples). However, in order for cortical damage to result in such deficits, the damage usually needs to be bilateral, which is fortunately rare. In contrast, unilateral damage to V1 has a devastating effect on conscious visual perception, as it results in a loss of visual field representation on the opposite side of the visual field, as illustrated in Figure 1c.

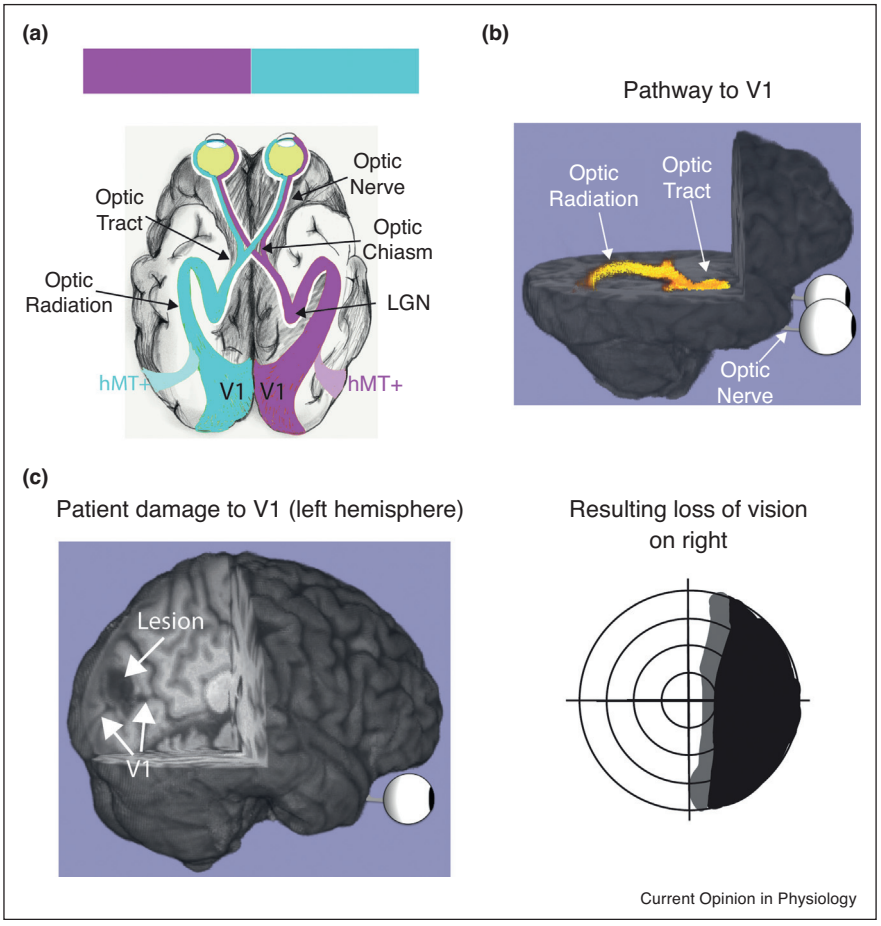
Although damage to V1 leads to a loss of conscious perception in a region of the visual field, it is clear that a reasonable number of people with V1 retain the ability to detect or discriminate stimuli that are presented in the blind region — an ability termed 'blindsight' by Weiskrantz [4]. The potential benefits of using this residual vision as the basis for visual rehabilitation after stroke have led to renewed interest in understanding the neural underpinnings of blindsight.

From motion to emotion: an infinite range of residual vision

Historically, residual vision and blindsight were initially described based on experiments with detection of 'simple' stimuli likely to activate early visual areas, such as flashes of light to which participants were required to saccade or point [4,5]. This type of approach led to controversy based on the suggestion that these abilities using such a detection paradigm could be the result of light being scattered into the seeing field [6]. However, since that early work, the types of stimulation used to identify and classify blindsight have been broadened to include motion [7,8], colour [9] and faces [10]. Indeed, Danckert and Rossetti [11], almost 15 years ago suggested that blindsight could be subdivided into three types of residual behaviours: 'Action blindsight' in which patients could make saccades to, and point at, unseen objects, 'Attention blindsight' which included detection and discrimination of motion as well as covert orienting to unseen objects and 'Agnosopsia', or 'Perception blindsight' in which patients maintained wavelength and form detection and discrimination. The term 'Affective blindsight' was introduced around 20 years ago and is used to describe the ability to detect emotional information from unseen stimuli [12].

The specific categories defined by Danckert and Rossetti have not extensively entered the blindsight literature, but there is certainly recognition that individual patients vary in the pattern of blindsight that they exhibit. GY, who is likely the most studied blindsight patient, has been reported to show action [13], attention [7,8] and

Figure 1



(a) Shows the visual pathway in a healthy brain. The right side of the visual field (cyan) is coded in the left side of brain, with the information from the eyes reconfigured at the optic chiasm. The pathway thus runs from the eye, along the optic nerve, and optic tract before synapsing in the lateral geniculate nucleus (LGN). The pathway then continues along the optic radiation to the primary visual cortex (V1). The location of the pathway in a brain image is shown in **(b)**. **(c)** Shows the brain of someone who has suffered a stroke affecting left V1 (marked Lesion), and the resulting visual field deficit affecting the right side. Motion area hMT+, shown in **(a),** continues to respond to visual stimulation after V1 is damaged.

perceptual [8] (agnosopsia) abilities, in addition to affective blindsight [12]. The fact that GY's V1 damage occurred early in life when there was still reasonable capacity for neural reorganisation may account for these extensive blindsight abilities. Nonetheless, even where damage is sustained in adulthood, there are likely to be multiple types of blindsight present. For example, it does not make sense for someone with hemianopia to be able to discriminate the direction of movement (attention blindsight) without being able to indicate the location of the target (action blindsight). In contrast, there may be patients able to indicate location, without any knowledge of the stimulus properties.

The presence or absence of any particular type of blindsight is likely to depend on the quality of pathways remaining between different visual areas. The introduction of high-resolution diffusion tractography to measure connections between brain areas *in vivo* [14] has permitted the investigation of tracts in the visual system of people with hemianopia. This diffusion imaging permits the measurements of tract microstructure by quantifying the diffusion of water molecules. It is easier for water molecules to move along (parallel to) a white matter tract than perpendicular to it due to the axon membrane and myelination. This can be quantified using a metric termed 'fractional anisotropy (FA)' that varies between zero for free diffusion and one for diffusion in a single direction. The FA metric provides a measure of white matter microstructure because damaged white matter fibre tracts will constrain diffusion less, and therefore have reduced FA. Ajina *et al.* [15] divided a group of participants with hemianopia into those with and without

blindsight and demonstrated that the FA of the tract between LGN and hMT+ was comparable to healthy participants in those with blindsight, but significantly lower in those without. This suggests that the pathway may provide the anatomical basis for blindsight. A case study in GY using tractography indicated the presence of a tract between superior colliculus, pulvinar and amygdala that might underlie affective blindsight [10]. Interestingly, recent work in healthy subjects has shown that the microstructure of this tract correlates with bias in orienting towards a threatening stimulus [16] and, using human connectome project data, McFadyen *et al.* [17] showed across a large sample that this tract also correlated with recognition of fearful faces. Thus, combining data from healthy visual systems and those with hemianopia can provide insight into the pathways critical for blindsight.

Big data studies of brain imaging and genetic data are now permitting the investigation of brain structures and pathways across large samples of healthy volunteers, for example [18,19]. To understand the relationship between blindsight abilities and brain neuroanatomy and function, common approaches across both behavioural testing and neuroimaging data, or meta-analyses across datasets are required. With a few exceptions [15,20–24], the majority of studies investigating hemianopia have five or fewer participants [25–27], which means generalisation is challenging.

The effects of cortical loss in the macaque

Since damage to the visual cortex occurs most often as a result of stroke or trauma, the location and extent of damage are highly variable, and therefore determining the specific pathways that underlie residual vision is challenging. Thus, using animal models may be informative since lesions and reversible inactivation can be employed in a systematic manner. Early reports of the effects of primary visual cortex damage suggested that the visual consequences were less severe than in humans with comparable damage. The narrative of Humphrey [28] describes the case of macaque monkey 'Helen', who had V1 removed bilaterally. After initial deficits, her visually guided behaviour appeared relatively normal, and she was able to locate food throughout the visual field. On psychophysical testing, stimulus detection was close to normal, while discrimination was only possible when stimuli differed in salience, suggesting that detailed vision was significantly affected by the V1 loss. Indeed, elegant work by Stoerig and Cowey [29] showed that macaque monkeys with unilateral damage to V1 behaved in a similar way to humans with blindsight in that they did not report seeing a stimulus presented in the blind field unless forced to make a choice.

These early studies of monkeys with V1 damage indicated the extent of residual vision evident in the macaque, but did not investigate the visual areas likely to underlie these abilities. More recent attempts have used experimental lesions to investigate the visual areas that can support visual function in the absence of V1. Schmid *et al.* lesioned V1 in two monkeys and, using fMRI, found that responses in V2 and V3 persisted in a retinotopic organisation, although the signal amplitudes were reduced by around 70% [30]. Their subsequent study found that these responses were abolished by the inactivation of LGN, along with any residual visual function, implying that the input to V2 and V3 or other extrastriate visual areas may be relayed by this subcortical nucleus [31]. The critical role for the LGN has been questioned by a more recent study by Kinoshita *et al.* [32] who selectively blocked the superior colliculus to ventral pulvinar pathway by combining two viral vectors. Blockage of this pathway and inactivation of the ventral pulvinar using GABA antagonist muscimol in two animals with V1 lesions significantly impaired visually guided saccades to targets within the blind field. However, given the role of the superior colliculus in saccadic eye movements, it is not clear whether the impairment is due to a loss of blindsight or inability to generate saccades.

A recent case of congenital bilateral hemianopia in a macaque monkey (Monkey S) has provided the opportunity to investigate the effects of V1 loss on visual pathways, and brain structure. While visual behaviour within the home cage was unremarkable, monkey S was unable to learn to perform a visual psychophysical task. Using multi-modal MRI, Bridge *et al.* [33] found that the LGN responded significantly to checkerboard stimulation of the blind visual field, while the pulvinar responded when moving dot stimuli were used. Motion area MT was structurally normal, and showed a pattern of functional connectivity that was comparable to animals with healthy visual systems. Consistent with these findings, the white matter tracts between LGN and MT and pulvinar and MT were reduced in volume compared to control animals, but the microstructure was intact. Unfortunately, detailed psychophysical tests of blindsight were unavailable due to challenges of training, so it was not possible to determine the critical link between structure, function and behaviour.

The literature in the macaque, therefore, raises the possibility that other structures such as the superior colliculus and pulvinar may also carry residual visual information. Indeed, work in the marmoset has shown that when V1 is lesioned peri-natally, there is an increase in the strength of the connection between the pulvinar and area MT [34]. This connection, however, was not strengthened in animals who received lesions in adulthood. While differences in visual function between the adult and neonatally lesioned animals were not possible to quantify, growing evidence suggests greater capacity for residual vision following early lesions. Indeed, monkey Helen was an adolescent when her visual cortex was damaged, and

the lesion in monkey S was likely pre-natal or peri-natal. Moreover, recent studies of hemianopia acquired in childhood support the idea that lesions arising peri-natally lead to increased residual vision and neural reorganisation [35], and in a recent case study a child had almost normal vision despite extensive bilateral V1 loss [36]. Thus, both the timing of damage and the specific neural structures contributing to residual function are likely to be important in determining the capacity for visual function.

Harnessing residual vision through training

The lack of awareness of residual vision after V1 damage means people are usually unable to exploit these persisting visual functions. Across the brain, it has been shown that repeated practice of a task improves performance; this is true in the healthy visual system for many different types of visual stimulation [37,38]. The past few years have seen increasing efforts to test the extent to which residual (unconscious) vision can be enhanced and reach consciousness. The earlier discussion about different types of residual vision raises the question about whether there are optimal stimulus types to use for training.

Early training regimes which targeted the edge of the blind region were susceptible to small eye movements which moved the stimuli into the sighted field [39–41]. However, more recent training regimes have been less susceptible to this type of artefact, and have led to improvements in visual performance measured with psychophysical testing [42,43]. The crucial test of rehabilitation strategies, however, is whether any improvement can translate to untrained visual tasks, but more importantly to real life functioning. Early work by Chokron used four different training stimuli, consisting of both detection and discrimination tasks, which led to significant improvement across all tasks, and a reduction in visual field loss measured with Humphrey perimetry [44]. A similar type of approach by Huxlin and colleagues over the past decade has significantly advanced the field of visual rehabilitation after visual cortex damage. The use of a motion direction discrimination task for training has shown considerable success in improving performance almost to the level of the intact visual field [45,46]. This is true, not only on the trained task, but also transferring to untrained tasks [45] and improving visual fields measured with Humphrey perimetry [47]. Furthermore, recent data indicate that attention can enhance the effects of training [48]. However, the transfer of visual improvement to 'real world' visual function is challenging to determine, and training regimes are on the order of months rather than weeks, requiring considerable dedication from the participant.

While there has been significant progress in improving residual vision, the extent of recovery appears to be less than is seen in recovery from stroke affecting the motor system. The use of adjunct therapies, such as transcranial direct current stimulation, has been beneficial in the motor system [49,50], although early studies using brain stimulation in hemianopia have shown more ambiguous results [51,52].

Conclusion

Understanding the nature of residual vision following damage to the early visual cortex is likely to drive future rehabilitation approaches. Thus, combining datasets and acquiring data from larger samples is particularly important. Depending on the specific nature of the cortical grey matter and occipital pathways that are affected by the damage, the extent and type of residual vision will be variable. By designing rehabilitation programmes that target the intact or virtually intact areas, those with visual cortical damage have the greatest chance of regaining conscious vision.

Conflict of interest statement

Nothing declared.

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