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Amblyopia: The Thalamus Is a No-Go Area for Visual Acuity

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When one eye does not function well during development, the visual cortex becomes less responsive to it and visual acuity declines. New research suggests that reduced response strength and deteriorating acuity occur in separate circuits.

You see a rare bird outside at dusk and you quickly make a picture of it using your smartphone. After zooming into the image to identify the bird, you notice it looks like a pixilated blob. All detail is lost in the grainy image. Clearly, resolution and signal strength go hand in hand. But this relationship is not absolute. Increasing the brightness of the image will not improve the resolution, and if you were to reduce the brightness of an image you took on a sunny day, the resolution would remain high. The visual cortex of someone with amblyopia processes the input from the lazy eye like the cheap camera in your smartphone at dusk: both acuity and signal strength are low. A new study by Stephany *et al.* [1], reported in this issue of *Current Biology*, shows that surprisingly, these two issues seem to arise in separate circuitries of the visual system.

In some children the two eyes process visual information differently, because of a large difference in the refractive power between the eyes, a cataract in one eye or strabismus (cross-eyedness). In such cases, the visual system will learn to ignore the eye providing the least reliable information. This condition is known as amblyopia or lazy eye. Before glasses or surgeries to correct eye position were invented, this made sense. Why waste energy on processing unreliable visual information? And when you are attacked by a hungry lion, you do not want to lose time deciding which of the two perceived

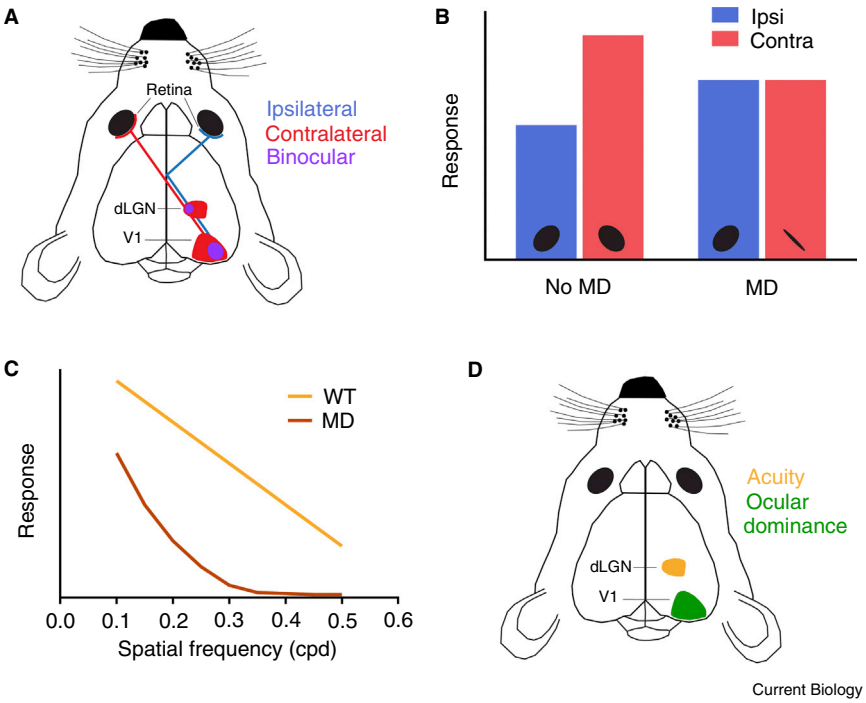

Figure 1. Monocular deprivation as an experimental animal model for amblyopia.
(A) Organization of the mouse primary visual system. dLGN, dorsal lateral geniculate nucleus; V1, primary visual cortex. (B) Monocular deprivation (MD) reduces responses to the deprived eye and increases those to the non-deprived eye. (C) Visual responses to salient stimuli (low spatial frequency) are affected less compared to responses to less salient stimuli (high spatial frequency). cpd, cycles per degree. (D) *Ngr1* in dLGN limits recovery of acuity, while *ngr1* in V1 limits recovery of ocular dominance.

predators you need to fend off with your spear. In modern times, we can often fix the primary eye deficit. When done before the age of 6–8 years, the amblyopia can be treated by temporarily patching the healthy eye in order for the deprived eye to become reconnected. At a later age, however, curing amblyopia is difficult and understanding what is going on under the hood is crucial for the development of new therapies.

The changes in visual processing that underlie amblyopia involve a process known as ocular dominance plasticity [2]. This can be induced experimentally by suturing one eyelid closed for several days to weeks in animals during a critical period of development (Figure. 1A,B). Electrophysiological or imaging methods show that, as a result of this treatment, responses in the primary visual cortex (V1) to the deprived eye become weaker; responses to stimuli that are less salient, such as images with fine detail or low contrasts, are particularly affected, resulting in low grade vision (Figure 1C). These functional changes are matched by a decrease in the extent of projections from the dorsal lateral geniculate nucleus (dLGN) of the thalamus serving the deprived eye and rearrangements within V1 favoring the non-deprived eye.

Ocular dominance plasticity has become an extremely popular experimental model for studying plasticity-related structure–function relationships and the molecular and cellular mechanisms that regulate the onset and closure of critical periods [3–5]. These fundamental issues are part of a research scope far beyond the treatment of amblyopia, and are relevant for understanding neurodevelopmental disorders, treating degenerative disorders of the brain, and so forth.

One of the interesting molecules identified in these studies is the Nogo-66 receptor 1 (NgR1), a protein originally identified as an axon guidance molecule [6]. Earlier work by McGee *et al.* [7] showed that inactivating the *ngr1* gene kept the critical period for ocular dominance plasticity open. They then went on to inactivate the gene in different cell types in the visual system to separate out how different functional aspects of ocular dominance plasticity are regulated by different circuitries [8]. The new study by Stephany *et al.* [1] utilized this approach to identify how the shift in ocular dominance and loss of visual acuity are related.

It is generally thought that the loss of visual acuity and reduced response strength to the deprived eye are one and the same process. When V1 neurons respond less strongly to inputs from the deprived eye, responses to high spatial frequency stimuli will disappear in the noise, just like the smartphone photograph of the bird in the dusk. However, to complicate matters, V1 has strong gain control mechanisms [9]: this basically means that V1 increases its 'ISO settings' — settings that control the sensitivity of a digital camera — in order to use most of its dynamic range when responding to weaker inputs. This mechanism will compensate for and partially mask the weakening of visual inputs from the deprived eye caused by ocular dominance plasticity. This results in an apparent discrepancy between loss of visual acuity and measured ocular dominance, even when the two events occur in the same cortical circuitry involving the same synaptic mechanism (Figure 1C). Several mouse models, in which synaptic strength in the visual cortex is reduced, illustrate this phenomenon clearly [10,11]: their V1 responds normally when stimuli are salient, but not when they are of low-contrast or high-spatial frequency.

This apparent discrepancy between acuity and visual response strength could well underlie the outcome of a previous study by Stephany *et al.* [8]. The authors found that the critical period for ocular dominance plasticity remained open in mice lacking *ngr1* in a subset of cortical inhibitory neurons. But when these mutant mice underwent long-term monocular deprivation during the critical period, visual acuity did not fully recover after the eye was reopened despite the increased plasticity levels. A similar result was obtained in wild-type mice housed in an enriched environment [12]. The slightly boring explanation would be that recovery of acuity is harder to achieve than induction of an ocular dominance shift. The more exciting explanation is that acuity and ocular dominance are regulated separately, in different circuits.

In the new study, Stephany *et al.* [1] show that this is indeed the case. The authors removed *ngr1* either in cortical excitatory neurons or in thalamic relay neurons. They discovered that in mice lacking cortical *ngr1*, reopening the deprived eye after prolonged deprivation resulted in the recovery of ocular dominance but not of visual acuity, while in mice lacking thalamic *ngr1*, acuity recovered while the ocular dominance shift remained (Figure 1D).

How can thalamic neurons selectively cause deterioration (and recovery) of acuity? Weakening of thalamocortical synapses could reduce signal strength, and thus acuity (Figure 2A,B). Alternatively, thalamocortical projections may lose precision, causing an enlargement of the receptive fields of postsynaptic V1 neurons (Figure 2C). Very recently, it was discovered that, at least in mice, ocular dominance plasticity can also occur in dLGN in contrast to what has always been assumed [13,14]. Most likely this involves reorganization of projections from retinal ganglion cells to the thalamic relay neurons. This means that the same acuity-reducing mechanisms described for the thalamocortical projection may also occur at retinothalamic connections (Figure 2). Because NgR1 can have pre- and postsynaptic effects [15], its inactivation in thalamic relay neurons could potentially stimulate the recovery of acuity at both sites. Future experiments measuring the responses of single neurons in the dLGN and V1 may determine in which of these structures acuity is reduced and whether this involves reduced response strength or increased receptive field sizes.

It is harder to understand why the remaining ocular dominance shift in V1 does not interfere with recovery of acuity. After all, weaker V1 responses to the deprived eye are expected to reduce responsiveness to less salient stimuli. Before addressing this question, we need to explain that Stephany *et al.* [1] used a behavioral paradigm to measure visual acuity. In this task, mice were forced to choose between two sides of a water tank of which one showed a visual grating and the other an equiluminant grey screen, in order to find a hidden platform. Visual acuity was determined by testing to what extent increasing the spatial frequency of the grating reduced behavioral

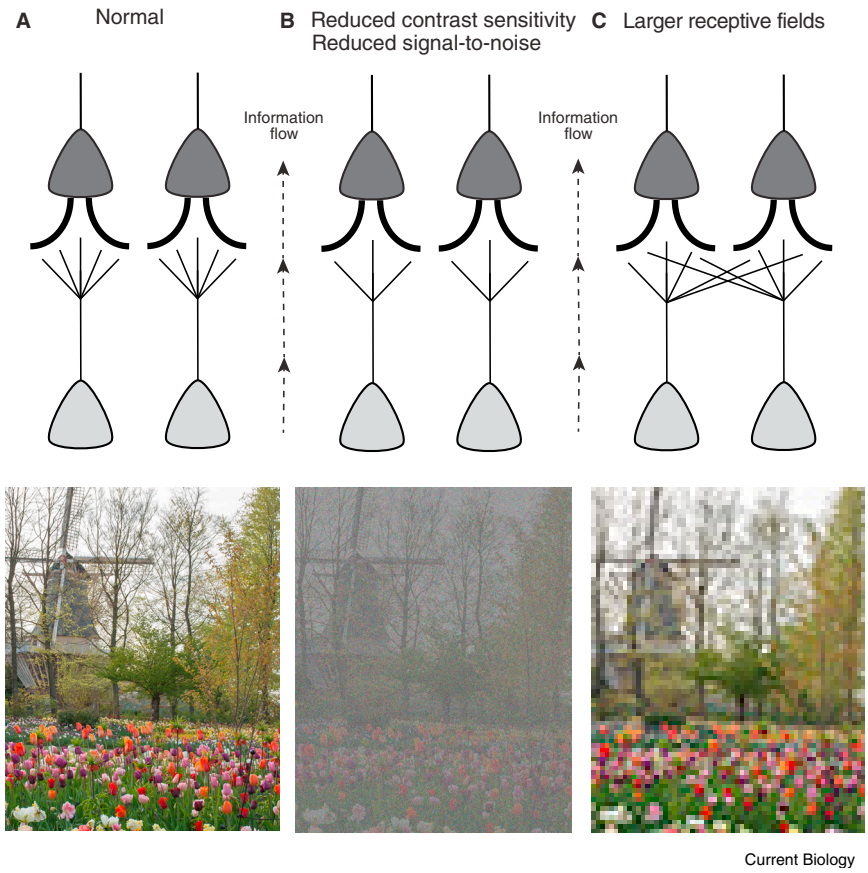

Figure 2. Mechanisms of reduced acuity.
(A) Highly simplified model of retinogeniculate/thalamocortical connectivity (top) and perceived image (bottom) under normal conditions. (B) Weakening of inputs lowers contrast sensitivity and signal strength (signal-to-noise), thereby reducing acuity. (C) Less precise connectivity increases receptive field size, thereby reducing acuity.

performance of the mice. This is a great way to determine acuity, as it tests what the mice can actually perceive. A disadvantage, however, is that we do not know *how* the mice perceive the stimulus. Perhaps mice only require a low number of V1 neurons to respond to high spatial frequencies to successfully execute the task. Alternatively, they may execute the task by using monocular V1, in which response strength is much less affected by monocular deprivation [16]. Future electrophysiological recordings or two-photon microscopy of calcium signals in V1 combined with the behavioral data can address these issues.

The new observations may lead to new entry points for the treatment of amblyopia. In this respect it is important that the authors found that deleting *ngr1* in adult mice also allowed the recovery of acuity. But are we ready to alter NgR1-signaling in people with amblyopia to improve vision in their lazy eye? Not quite. One important hurdle is that specifically targeting NgR1-signaling pharmacologically is not yet possible. We also need to understand whether the acuity improvement involves the central, binocular visual field or only monocular V1, and whether it occurs at the retinogeniculate or the thalamocortical synapse. A hint supporting the latter conclusion comes from previous studies in rats and mice showing that acuity (measured electrophysiologically) can recover in adulthood by altering signaling pathways within the cortex that may affect its thalamic inputs [17,18].

It is also not certain that the results of Stephany *et al.* [1] can be translated to humans. The stronger retraction of thalamocortical projections in carnivores than in rodents [19] may cause amblyopia to be more permanent [20]. The most important question, however, is whether

we dare to reintroduce substantial plasticity levels in the adult thalamus or cortex in order to cure amblyopia. The human visual system is far more complex than that of the rodent, and we have no clue yet how enhancement of thalamic or cortical plasticity may affect visual perception.

Although therapeutic applications will have to wait, this new study by Stephany *et al.* [1] makes an important contribution to the amblyopia research field by forcing us to rethink how visual acuity and ocular dominance are related. The study also illustrates that we have been left in the dark for too long about the role of the thalamus in ocular dominance plasticity. Let's put the thalamus in the spotlight to get a better picture of its function!

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Microsporidia: A Single Horizontal Gene Transfer Drives a Great Leap Forward

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Horizontal gene transfer from bacteria to eukaryotes is the subject of much debate. A recent study reveals the instrumental role that the acquisition of bacterial nucleotide transporters played in the evolution of the ubiquitous, intracellular eukaryotic parasites, the microsporidia.

Since their discovery ~150 years ago [1], microsporidia have retained a unique position among unicellular (that is, protist) parasites, mostly due to their dissimilarity to other eukaryotes. Their developmental stages lack some key features, such as mitochondrial cristae and a stacked Golgi apparatus. Instead, they developed unusual morphological structures, such as a long extrusive polar tube and a membranous polaroplast (Figure 1A), which together allow the injection of the sporoplasm into the host cytoplasm, an unusual yet highly efficient mechanism of cell infection (Figure 1B). No wonder microsporidia were considered the most