Learning to see in 3D with two eyes: the role of experience, plasticity and neurochemistry

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Humans, along with other predators, have forward-facing eyes which restrict the area of the world that can be seen when compared to animals with eyes on the side of the head. Why would we sacrifice this panoramic vision? The answer is the very precise ability that having two eyes with overlapping and slightly different viewpoints provides to determine fine differences in depth. While interpreting this type of 'binocular depth' appears effortless, the precise calculations necessary for perceiving binocular depth require significant computational power in the cerebral cortex and the fine tuning of neurochemical interactions. This processing occurs in the visual regions of the brain and must be honed through early experience for accurate performance. By considering each stage of binocular processing and the neurochemical interactions required for integrating signals from the two eyes, we can begin to understand how the inherent ability of the brain to learn might help us when binocular vision goes wrong.

Our visual system is excellent at perceiving depth. With the combined power of our two eyes, we can detect differences in depth as fine as a single human hair. Modern technology increasingly exploits this fundamental ability to see the world in precise and immersive 'binocular depth'. This is evident in the growing popularity of commercial virtual reality systems using 3D and the excitement that accompanies movies screened in 3D. Scientists and medical doctors benefit from the incredible advantage of being able to visualize the structure of a chemical compound in 3D or learn to perform intricate brain surgery in a virtual world.

How does the brain compute depth?

While this ability to determine depth using two eyes appears effortless to us, reconstructing the 3D world is actually a complex computational problem: the third dimension needs to be created from two flat images. Photons of light form the input to our visual system and are absorbed by the retina – a sheet of light-sensitive cells at the back of the eye, arranged such that light from adjacent objects fall onto adjacent cells. The two eyes have different viewpoints that are approximately 6 cm apart in adults. When both eyes are looking at the same point, such as a tennis ball, light from this point will fall on corresponding points on the retinae (Figure 1a). Points that are in front of or behind this fixation point, such as the bug, will generate small, systematic differences on the two retinae. The comparison between the eyes thus generates a difference cue called 'binocular disparity'. The disparity of the images is calculated as the difference in angles **α** and **β**. It is this difference that is exploited to allow us to see depth using two eyes.

Visual information from the two eyes then projects along the optic nerve and optic tract to the brain as shown in Figure 1b. Importantly, projections from the two eyes remain separate until reaching the primary visual cortex (V1). In V1, there are brain cells, neurons, that respond to the binocular disparity between the images in the two eyes. While a large number of neurons in V1 can detect disparity, in order to actually perceive depth, significantly more processing in other visual areas of the brain is required. This is partly because disparity helps us perform many important actions in our visual world, for example, object recognition, navigation and making precise manual movements in space.

How do we study the binocular visual system?

To test binocular vision in the laboratory, slightly different images are presented separately to the left and right eyes. This display method simulates the separation of the two eyes and allows the experimenter to control how different the images are from each other. One such separation can be achieved by placing red and green filters over the two eyes and viewing an image drawn

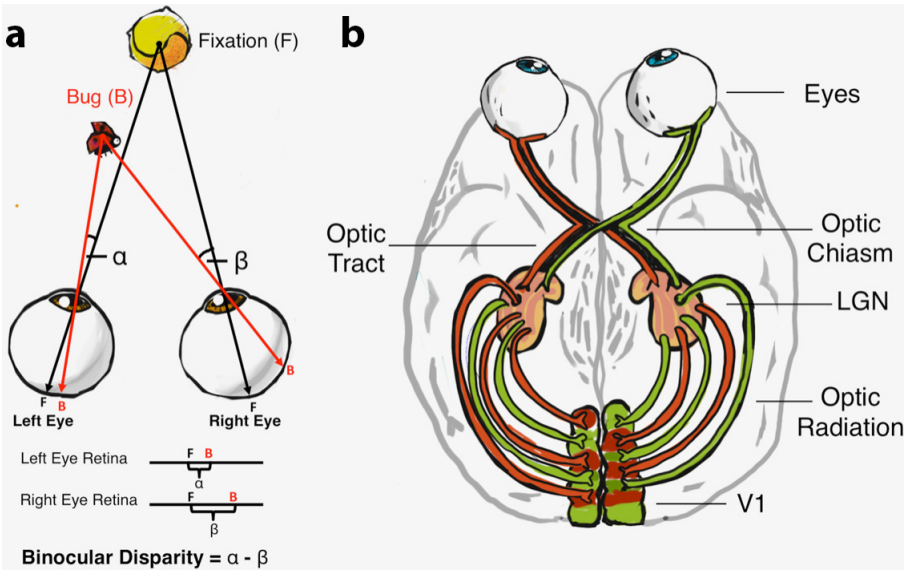

Figure 1. **(a)** The tennis ball at fixation (F) falls onto the fovea at the centre of the retina, in both eyes. These points are described as 'corresponding points'. A bug (B) that is closer to the observer will fall on non-corresponding points. The angular difference in **α** and **β** creates the cue for binocular depth called 'binocular disparity'. **(b)** Visual information from the two eyes crosses at the optic chiasm, so that in the optic tract, there is information from both eyes, although it remains in separate anatomical compartments in the lateral geniculate nucleus (LGN) and optic radiation. It is only once the projections reach the primary visual cortex 'V1' that neurons receive input from both eyes and those that are sensitive to binocular disparity help to reconstruct the third dimension from two flat images.

only in red and green. Without glasses, you may see that there are slight shifts in the cacti that are coded in red or green (Figure 2a). However, once you put the glasses on, one eye will only see red and the other eye see only green parts. The brain will combine them and perceive the slight shift as depth. This is an approach that was commonly used in early 3D films.

To isolate binocular depth perception, it is necessary to remove any other cues about depth that can be seen with only one eye, such as the relative size of objects.

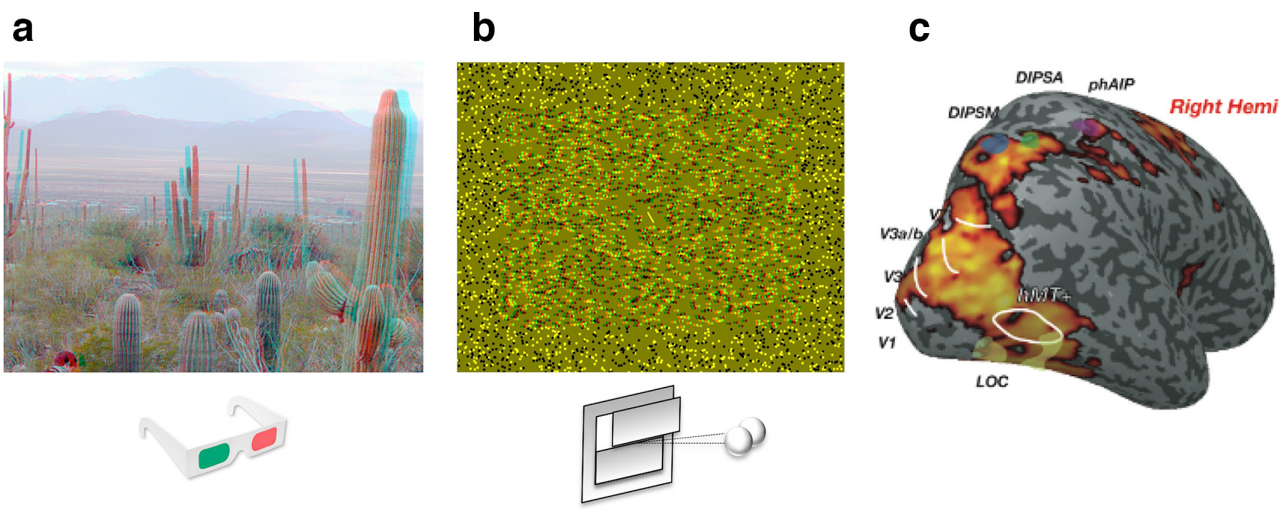

Figure 2. **(a)** The view from two eyes can be simulated in the laboratory using red-green glasses. Here, small differences in the red and green aspects of the picture appear as binocular depth, together with other cues for depth, such as relative size (image licensed under Creative Commons). In contrast, any depth coded in random dot stereograms (RDSs) cannot be seen without the use of binocular vision. For example, when viewed through red-green glasses, the RDS in **(b)** contains the surface shown below. RDS stimuli can be shown to people in an MRI brain scanner to illustrate the areas of the brain that are sensitive to binocular depth, shown in **(c)**, adapted from Ip et al., 2014.

Experimentally, this is often accomplished by using a stimulus known as a random dot stereogram (RDS). When viewed without red-green glasses, the red and green elements look the same because all monocular information about depth is removed. However, when the RDS image is viewed with glasses, the brain combines these differences and allows us to perceive a surface made of two planes, one near and one far relative to fixation (Figure 2b).

RDSs are so good at isolating the cue for binocular depth that they can be used to rapidly screen children for deficits of binocular vision by asking them to pick out objects only visible with binocular depth perception. Indeed, in the UK, around 2%–5% of children show deficits in binocular vision at screening. Similarly, from a research perspective, use of RDS allows investigation of the regions of the brain that respond to depth, but not the dots themselves. Indeed, when brain activity is measured using functional magnetic resonance imaging (fMRI), large swathes of the visual brain respond to these disparity-defined images (Figure 2c).

What happens when binocular vision goes wrong?

The response of neurons is shaped by experience in a process called 'plasticity' – the ability of the nervous system to adapt. Plasticity is greatest during childhood and involves changes in multiple aspects of neuronal processing, including the structure and connections of individual neurons and networks. Balanced input from the two eyes during childhood is necessary for normal binocular vision. Thus, the images arriving at the retina of the two eyes need to be similar. There are two main ways in which the images at the retina may not match, leading to problems with binocular vision. Firstly, the ability to move our eyes accurately requires the precise function of extraocular muscles. If young children are unable to move their two eyes to look at the same point, then the images at the retina will differ. This is known as strabismus, or 'lazy eye', and can sometimes be corrected with surgery to tighten the extraocular muscles. Secondly, the eyes may have very different refractive power such that one eye can focus perfectly but the other is very short-sighted or far-sighted, resulting in a blurred image (anisometropia). In this case, the blurred image is ignored and only the information from the 'good' eye is processed. Early detection of anisometropia can help improve the condition using a corrective lens to focus the image of the poor eye.

In both strabismus and anisometropia, the result is that information from the weaker, or 'amblyopic' eye, is not as reliable as the stronger eye. Consequently, the connection between the weaker eye and the brain degrades over time. Without the balanced input to V1 and the inability to use the differences in images arriving at the retina, the person is unable to see depth, and importantly, relies predominantly on one eye.

What shapes the function of the binocular visual system during development?

The surface of V1, where input from the two eyes converges for the first time, can be visualized as a pattern of stripes known as 'ocular dominance columns' (Figure 3a). One set of columns represents the left eye (red) and the other the right eye (green). In the normal visual system, the pattern of stripes will be balanced, with equal number of inputs coming from each eye. These ocular dominance columns in the binocular visual system are a model for how experience can shape the brain because their relative distribution can reflect imbalances in visual experience early in development.

For example, if a cat is deprived of one eye's visual input during development, only the non-deprived eye contributes to visual experience (Figure 3a). Under these conditions, the ocular dominance columns are profoundly altered such that the region representing the deprived eye is significantly reduced by losing territory to the viewing eye. Moreover, while V1 cells are usually predominantly binocular in the cortex, after deprivation, most cells respond only to the viewing eye. Importantly, although deprivation *early* during brain development causes extreme effects, deprivation in adulthood has little effect on neural representation (Figure 3b). This highlights the importance of early experience in shaping organization of the visual brain and the existence of a limited time window, or 'critical period', for this plasticity to occur (Figure 3c).

What controls plasticity in the developing binocular visual system?

The ability of the visual system to change its responses with visual experience is related to the emergence of a specific neurochemical in the nervous system called γ-aminobutyric acid (GABA). GABA is the major inhibitory neurotransmitter in the brain and, together with the major excitatory neurotransmitter glutamate, plays a key role in maintaining stable function in the brain. However, early in development, neural activity is dominated by excitation, and it is the appearance of GABAergic signalling that triggers plasticity in the visual cortex.

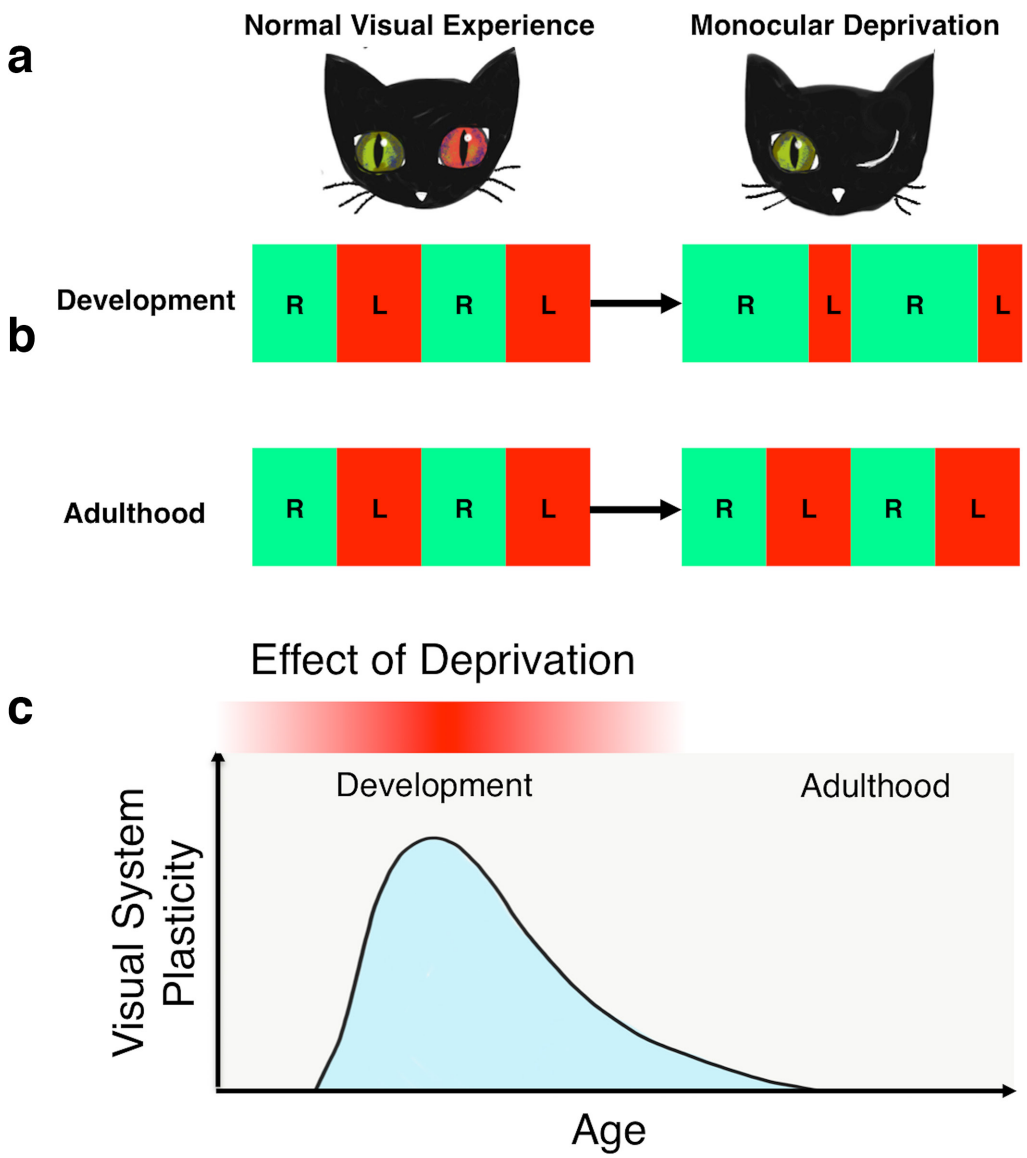

Figure 3. **(a)** Normal binocular visual experience during development provides balanced input into V1, which can be visualized as regular ocular dominance columns. Abnormal visual input, such as due to monocular deprivation, causes abnormal ocular dominance columns, whereby the open eye inputs take over the deprived eye regions. **(b)** If the same deprivation occurs in adulthood, there is little or no change in the ocular dominance columns. **(c)** The effect of monocular deprivation is limited to a 'critical period' of heightened plasticity in early development and decreases with age.

While the onset of GABAergic inhibition is necessary for critical period plasticity in the developing brain, reducing inhibition plays a role in reinstating plasticity in the mature brain. For example, decreasing the level of GABA in the adult rat brain using pharmacology can cause the amblyopic visual system to reflect normal distribution of ocular dominance columns and recover visual functions. Other manipulations that also cause a decrease in GABA, such as exposing rats to highly engaging and stimulating environments, have been linked to an ability to re-engage the physiological mechanisms necessary to shape normal binocular vision.

Can experience improve abnormal binocular vision in humans?

While research in animal models provides evidence for the neurochemical basis of plasticity, it is now known that vision through the amblyopic eye can also be improved by visual training. The traditional childhood treatment of amblyopia consists of patching the stronger eye, meaning that there is an increased use of the weaker eye at the expense of interaction between the eyes. Conversely, current approaches used in adulthood acknowledge the importance of the eyes working together for normal

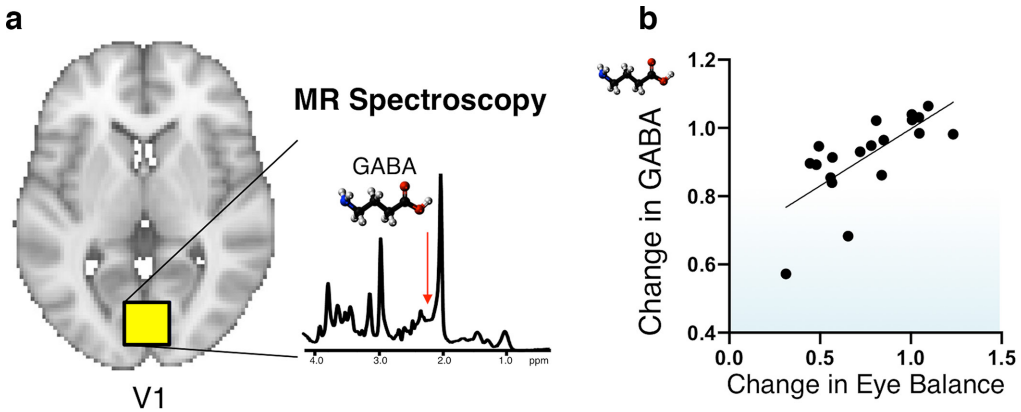

Figure 4. GABA is one of the many neurochemicals that can be measured non-invasively in the human visual cortex using magnetic resonance spectroscopy (MRS). **(a)** The chemical spectrum measured from the yellow box located in V1, with an arrow pointing at one of the GABA peaks. When binocular vision is disrupted through monocular deprivation, the change in the balance of the eyes is correlated with the change in GABA concentration **(b)**Participants who show a large change in their eye balance after the deprivation also show a large reduction in GABA concentration, implicating GABA in determining the balance between the two eyes (adapted with permission from Lunghi et al., 2015).

visual system function. Visual training can improve acuity in the amblyopic eye by around two lines on a standard optician's chart. Some people even develop the ability to see in binocular depth, indicating that amblyopia, the most common childhood vision disorder, may be 'fixable' by neuroscience. More recently, training regimes have been adapted to combine binocular training with video game environments. Such approaches address one of the major hurdles to recovery using visual perceptual training, namely, boredom from performing tedious and repetitive tasks. Better compliance amounts to more exposure to training and therefore enhanced outcomes in a shorter amount of time compared to conventional patching treatment.

What approaches can help us better understand plasticity in the human binocular visual system?

Most of what we know about plasticity in the binocular visual system comes from studies in animals. Thanks to technological advances, GABA can now be measured in the human brain in a non-invasive way using 'magnetic resonance spectroscopy' (MRS), a technique that is sensitive to the biochemical environment within the visual cortex (Figure 4a). Usually, images from the two eyes are fused by the brain to provide a unified view of the world, an equilibrium believed to be reflected in balanced GABA release between eyes. In extreme cases, where the images presented to the two eyes are too different from each other, the result is 'binocular rivalry', in which a unified visual percept is impossible and an alternation between the two images is perceived. The role of GABA can be explored by manipulating the interaction between the eyes using temporary blindfolding of one eye in healthy participants. When the blindfold is removed after 2.5 hours, the amount of time that the deprived eye's image is perceived is increased; a type of short-term binocular plasticity. Importantly, across a group of healthy volunteers, the greater this change in eye dominance, the larger the reduction in GABA concentration (Figure 4b). This suggests that a reduction in GABA concentration is linked to greater plasticity.

This improvement in technology may, therefore, bring us one step closer to obtaining a mechanistic understanding of plasticity in the human binocular visual system and predict interventions that may improve outcome of treatments for binocular dysfunction.

Summary

The fundamental ability to see in depth using two eyes underlies our sensation of 3D vision. The ease with which we navigate through a dynamic world and perceive and respond to objects with great precision relies on this ability. Over the past 60 years, the binocular visual system has become one of the most extensively studied models of neurodevelopmental plasticity in animals. Looking to the future, rapid advances in non-invasive human brain imaging will shed new light on the plasticity of the human binocular visual system. Combined with a strong framework from mechanistic investigations in animals, this will ultimately lead us to a more complete understanding of brain plasticity and the effects of other developmental conditions. ■

Further Reading

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