

Physiology of vision and the visual system

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Introduction

Vision in all its aspects could arguably be described as the most important physiological function for survival. Vision encompasses detection of luminance (and, we now understand, irradiance), contrast sensitivity (visual acuity), discrimination of texture, colour, depth and motion disparities and integrates them in to what we describe as perception. Most of these functions are located in the higher cortical centres where the retinal ‘sensation’ (image) is converted into our personal view (percept) of the outside world. What is seen (conceived) may not be the same as what is perceived, or even detected, and the latter may be extensively edited through input from other non-visual centres, especially memory and previous visual experience.

Zeki’s notion (1992) of the brain constructing an image of the world by segregating the component parts via cortical regions that are, for instance, directionally selective (motion detectors), orientation selective, hue discriminators (colour) and that assess depth (stereopsis) has now been extended

using functional magnetic resonance imaging (fMRI) to show how the segregated parts are integrated to provide a final but individual-specific image. Indeed fMRI reveals which specific areas of the brain are activated when we visually register different ‘objects’ (Fig. 5-1). At face value it might be thought that spatial resolution would be most important to survival but in fact it has been shown that colour is what we see best.

There are further subtleties to the business of seeing. For instance the manner in which we detect shape/form depends on more than activation of orientation-selective neurones. Remarkably, the recognition of faces and the recognition of the expression on a face are processed separately, as has been demonstrated in patients with damage to highly selective regions of the brain (Fig. 5-1). The recognition of texture is akin to a form of visual ‘touch’. This chapter provides a rather simplified and brief overview of aspects of the complex sensory and psychophysical responses to visual stimuli.

DO I HAVE GOOD VISION?

A certain level of good vision is required for many daily activities, some of which may have a legal requirement, such as driving. However, ‘good vision’ is a variable measure and depends on the set standard. Perhaps it is more valuable to have a concept of the limits of our visual capabilities. Vision can be considered in two ways: the optical requirements to achieve an image (i.e. refraction of light by the eye to focus the image on the retina, also known as physiological optics) and the neural processing of visual stimuli by the retina and the brain. The visual process is initiated by the detection of a light signal by photoreceptor cells in the outer retina. Photoreceptor cells convert light energy to an electric stimulus, which is then

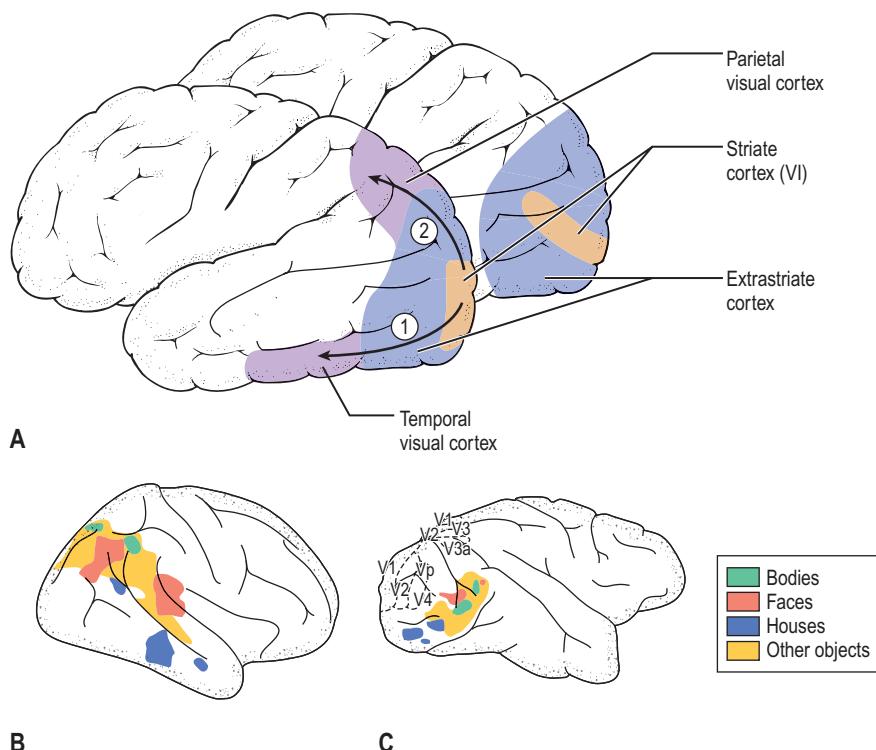


FIGURE 5-1 Typical locations of category-selective regions in the human ventral visual cortex. **(A)** The location of visual regions in the human cortex, including the primary visual cortex (area V1 in the striate cortex) and the extrastriate cortex in the occipital lobe, and the traditional distinction into two visual cortical pathways that start in area V1 and extend into the temporal lobe (the ventral ‘what’ or ‘object-vision’ pathway (1)) or into the parietal lobe (the dorsal ‘where’ pathway (2)). **(B,C)** Ventral pathway regions in one individual that were activated significantly for selectivity of bodies, faces, houses or other objects. In addition, the yellow areas represent the regions that, in a group of people ($n = 9$), activated significantly in the contrast: intact objects > scrambled objects. All data were processed using SPM5 (Wellcome Department of Cognitive Neurology, London). (From Op de Beeck et al., 2008.)

transmitted to the bipolar cells and onwards to the ganglion cells in the retina (see Ch. 1, p. 46). The information is further transmitted in the axons of these cells (the optic nerves which, after 50% crossover in the optic chiasma, become the optic tracts) to the visual thalamic organ, the lateral geniculate nucleus (LGN). Synaptic contact with neurones in the LGN that project to the cerebral cortex permits onward transmission of the signals via optic radiation to the visual or striate cortex (V1), where they interact with many other neuronal connections from visual cortical cells in the prestriate cortex (V3–V5), and where parcelling out and processing of the signals takes place to build up the final perceived visual image. Input is also received by the visual cortex from many other areas, particularly those controlling general motor function and eye movement, cerebellar and spatial

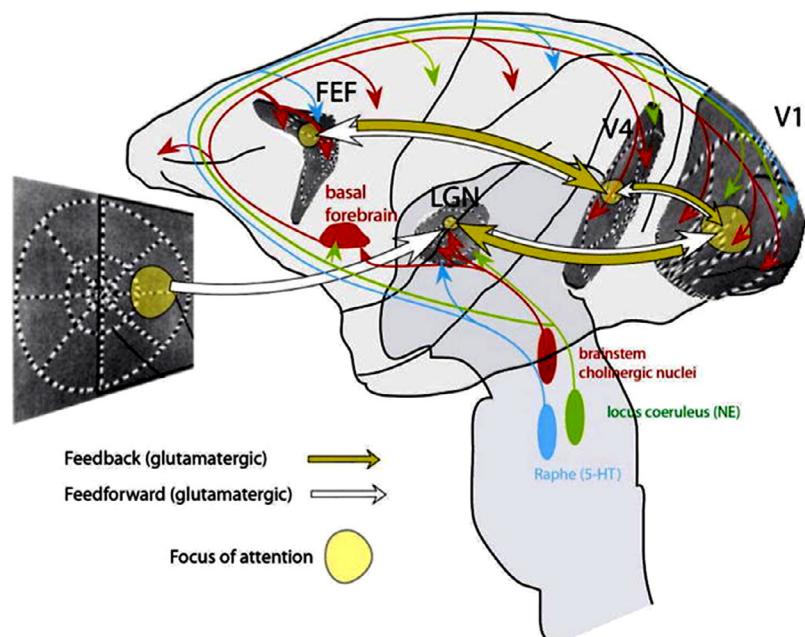
sense, memory and many other functions located in prefrontal cortex. This produces some of what is known as ‘top down’ modulation of visual responses whereby signals received and interpreted in the visual cortex can be influenced by input to the final image (the perceived image) from other areas, such as visual area 4 (V4) which combines elements of object recognition with visual attention (see eFigs 5-1 and 5-8).

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In biophysical terms a photoreceptor is capable of detecting a single photon of light (see Ch. 4, p. 261), but in practice what are the limits of detection of a visual stimulus? This depends on the nature of the stimulus and the nature of the ambient conditions in which it is presented. Sensing light is a function of all regions of the retina but the foveal region is

The brain is constantly shifting its position to meet the requirements of changes in behaviour. It continuously adapts its processing machinery to behavioural demands. Information is therefore transformed, modulated and rechannelled through different neural cortical wiring circuits which have been revealed in series of novel experiments in various animal models which can assess small changes in activity occurring at low frequency. Harris and Thiele suggest that processes involved in selective attention are similar to those involved in state changes; these are summarized in eFig. 5-1 (Harris and Thiele, 2011). They include increased activity of cortical neuromodulatory afferents (red (cholinergic), blue (serotonergic) and green (noradrenergic) arrows) which causes a general

desynchronization and reduction in spontaneous fluctuation, but may lack the spatial selectivity to desynchronize the patch of cortex representing the attended stimulus. Focused glutamatergic inputs arising from feedback connections could provide this specificity (yellow arrows), causing enhanced desynchronization and sensory responses in the regions of cortex activated by the object of attention. The yellow circle in the visual display indicates the focus of attention, which affects processing in thalamic and cortical areas at specific locations (indicated by the yellow patches). The distorted replication of the visual world in the different areas illustrates (approximately) the known retinotopic organization of these different areas.



eFIGURE 5-1 Processes involved in attention are thought to be similar to changes occurring in state changes in cortical activity for specific functions. Neuromodulatory effects are identified by the red, blue and green arrows and are explained in the text. (From Harris and Thiele, 2011.)

specialized for high spatial resolution (visual acuity) and colour detection, served by the small 'midget', slow-transmitting ganglion cells (the parvocellular or P system). In contrast, luminance and motion detection are served by the large, fast-transmitting ganglion cells (the magnocellular or M system) that dominate the remaining retina and thus incorporate the entire visual field. According to Barlow's single neurone doctrine, it should take only one neurone to detect a visual stimulus (Barlow, 1972); however, the question is whether the signal received from the one rod in a thousand stimulated in the dark is sufficient to activate this neurone. Psychophysical studies have shown that both the luminance and colour thresholds for vision are different by orders of magnitude for P neurones between monkeys and humans, suggesting that more than one neurone is involved in detecting a light stimulus. In fact, continuous pooling of information occurs both in the excitatory and inhibitory neuronal activity that is present at all times and that, after a visual stimulus, the changes in the response rate of many neurones are 'sampled' by the brain until they reach a certain threshold level, at which point they register and the stimulus is 'recognized' (Hurlbert and Derrington, 1993). This perhaps explains how we can sometimes look at an object and yet not 'see' it; furthermore, these psychophysical considerations are highly relevant to methods for testing vision, for instance with regard to setting luminance thresholds for studies of visual fields using small transient targets.

Whether or not we have good vision at any moment in time depends on our level of awareness, consciousness and attention to visual stimuli which have many properties such as depth, shape, form, colour texture and more besides, each with its own rate of detection/discrimination.

Flicker can be used to determine limits of vision

Detection of a stationary target or spot depends on the size and brightness of the spot relative to the background. The limits of detectability of the target are therefore determined by the spatial resolution and the anatomical relationships between stimulated receptors (see below). Spatial resolution is highest at the fovea and declines sharply towards the peripheral retina; this is clearly demonstrated by the detection threshold at different eccentricities in the visual field.

The threshold for spatial resolution is, however, considerably higher than that for detecting light; this latter parameter can be measured by flicker detection, which is the ability to detect two stimuli separated in time. This function is normally subserved by rod photoreceptors, while spatial resolution is subserved by cones, with some input from rods.

The critical flicker fusion (CFF) frequency test may be a useful predictor of cataract surgery outcome in cases of co-morbidity of lens opacity and macular disease because the CFF (see below) is relatively unaffected by image degradation due to cataract but would be affected by foveal disease. In addition, as a neurophysiological test, it has been used in the early detection of hepatic encephalopathy.

Motion detection is also a feature of rod vision

It is clear, therefore, that the ability to detect a standard small bright spot in specified regions of the visual field is in fact a much more complex task than would at first appear. Not only does it depend on the absolute brightness of the stimulus but also on the background on which the stimulus is presented and thus on contrast. It also depends on whether the target is moving or stationary and, if stationary, for how long the target is presented. Its detection depends on the density of photoreceptors and thus the region of retina stimulated. If it is a moving target it will stimulate different cortical neurones depending on which direction it is moving. This functional segregation of visual input is retained at several levels within the cortex before construction of the final visual image.

SENSING COLOUR

Cone photoreceptors are built to sense colour, which they do through cone opsin proteins. There are three types in humans: long (L, red), medium (M, green) and short (S, blue) wavelength cones, each with its own specific opsin (see p. 302). Early colour matching experiments in which the colour of a test stimulus is matched by adding together stimuli composed of the three primary colours verified that three colours were all that was required to detect the full spectrum of white light (see below, Colorimetry, p. 302). This is known as the trichromatic theory of colour vision. Each colour has properties such as hue and chromaticity.

There are many hues but only three primary colours

Hue is an idealized term for the colour produced by light of a single wavelength. In spite of having only three cone photoreceptors, we are able to distinguish many hues of colour, e.g. lilac and violet. It is therefore clear that any single colour is recognized by a mixture of the three primaries and that there must be overlap in the spectral sensitivity for each primary colour (see below). Theoretically it should be possible to produce light of a single wavelength using a narrow slit on a device such as a monochrometer, but photoreceptor sensitivity is also subject to the intensity of the light, and narrow wavebands of this degree of selectivity are not sufficiently intense to produce a stimulus.

The hue-discrimination curve (Fig. 5-2) describes the physiological limits at which a shift in wavelength can be discriminated as a change in colour. It was derived empirically by using fixed amplitude selective wavelength stimuli (1.5 cycles/300 nm), which found that there were two peaks of discrimination, one in the yellow/orange and a second in the blue/violet range. Monochromatic light therefore is not a practical reality; most colours are in fact tints, i.e. they are unsaturated hues, the degree of unsaturation being determined by the amount of additional white light they require to match them to a hue.

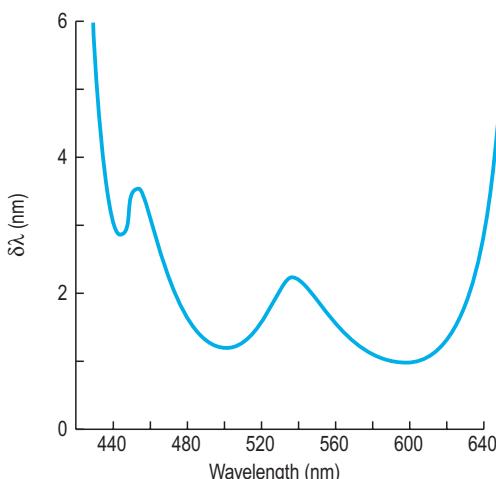


FIGURE 5-2 Hue-discrimination curve comparing wavelength discrimination (y-axis) with changing wavelength (x-axis). Discrimination of hues varies for any given wavelength, being best at 455 and 535 nm.

Chromaticity is semiquantified ‘colouredness’

Chromaticity refers to ‘colouredness’ and depends on hue, saturation and intensity of light (luminosity). Indeed, hue itself is not independent of the luminosity of the stimulus and chromatic shifts occur as the intensity increases until all hues appear yellow–white (the Bezold–Brücke phenomenon) or as the intensity decreases, when all hues appear achromatic (the Purkinje shift; see below). Any colour can thus be matched by a mixture of the three primary colours plus or minus a proportion of white light to account for unsaturation; these are formally described in the chromaticity chart and can be determined at different levels of lower or higher colour metrics (discrimination) (Fig. 5-3). The International Commission on Illumination (CIE) has developed standard colour ‘observers’ (colorimeters) which have proved valuable in defining ‘true’ colours but do not fully take into account the minimally perceptible differences in

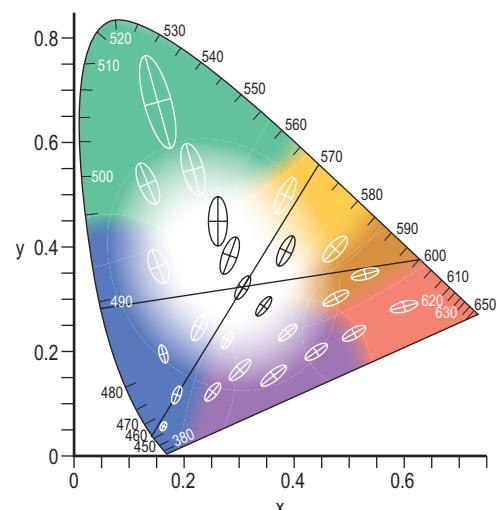


FIGURE 5-3 Lower versus higher colour metrics. The chromaticity diagram is long established in the field of colour discrimination. It represents the laws of colour mixing in terms of (x,y). This is the domain of lower colour metrics. The straight lines through $x = 0.305$, $y = 0.323$ indicate that this white colour can be obtained, for instance, by mixing, in suitable quantities, light of wavelengths 570 and 465 nm or of wavelengths 600 and 489 nm. The ellipses, drawn here at 10 times their true size, are contours of just noticeably different colours from their central colour. The description of the differences in size, shape and orientation of these ‘JND’ ellipses is the domain of higher colour metrics. (From Vos, 2006.)

colour discrimination (just noticeable differences, JND) based on aspects of photoreception affected by 'background noise'.

However, the chromaticity chart has true practical value, for instance in colour-mixing techniques used routinely in computer programs for producing different colours digitally for image creation and other purposes, and have been developed into a computerized colour vision test. Clinically, colour vision can be tested using hue-discrimination techniques (e.g. the Farnsworth–Munsell 100 hue test) and normal values vary with age (affected by JND effects), peak ability occurring around the age of 19 years. Some effect by rods on cone vision has also been shown by rod function studies ('background noise').

SHAPE, FORM AND DEPTH PERCEPTION (AND MORE) HELP TO 'SHAPE' VISION

The discrimination of shape and form is highly developed in primate vision and the cortical localizations which define these functions are now well established. The appreciation of the complexity and sophistication of this aspect of visual perception has in part developed from the realization that the brain recognizes and can categorize objects according to shape irrespective of the angle or distance from which they are viewed, the ambient lighting conditions, or other factors.

Shape processing is achieved by specialized orientation-sensitive cells in the visual cortex, but the extra dimension of form recognition, as in recognition of facial features, requires additional processing. Studies of patients with specific visual defects such as prosopagnosia (inability to recognize familiar faces), however, are powerful indicators of the localization of visual functional sites. Even this apparently specific defect can be subdivided into a perceptual form and an associative form, the latter arising when the patient can perceive the image but cannot draw on visual memory sufficient to 'remember' the face. These separate functions have been ascribed to different regions of the brain, although associative face recognition may also involve other senses such as voice recognition (Fig. 5-4).

Much is also known about depth perception. For instance it has been shown that there are specific cortical cells responsive only to disparate but simultaneous orientations of an object, presented

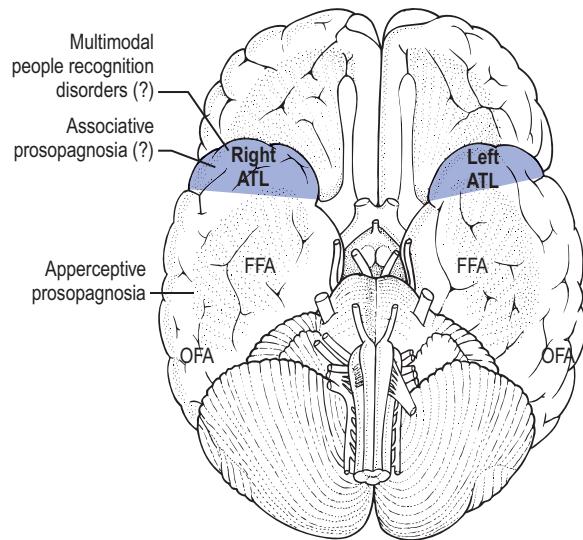


FIGURE 5-4 Processing information for features (of the face) involves a specific neural cortical network, the occipital face area (OFA), the face fusiform area (FFA) and the anterior temporal lobe (ATL), which have a right hemisphere dominance. This region underlies neurological perceptual defects such as prosopagnosia (lesion in the posterior region) as well as person recognition disorders (lesions in the anterior temporal lobe). (From Gainotti, 2013.)

to non-corresponding regions of the retina. In addition, clues on the nature of 3D structures can be obtained from motion detection (structure-from-motion). However, although no specific 'depth appreciation' cortical region has been identified, the lateral occipital cortex is a favoured area showing much activity. The appreciation of depth is more than simply stereopsis and is built up from many other cues (see below). An understanding of how these modify perception can only come after a description and appreciation of the different types of visual stimuli that separately induce discrete responses in the brain.

Light detection and dark adaptation

WHAT ARE THE LIMITS OF DETECTABLE LIGHT?

As in all biological systems, there is no precise answer to the above question. Light energy comes in quanta (small packets) and it has been estimated that between 50 and 150 quanta of light are required to strike the cornea for a discrete signal to be detected. Of these

quanta, only about 10% actually reach the photoreceptors. The detection of this stimulus is not simply a function of photoreceptor stimulation but is subject to 'dark light' (effectively background noise in rhodopsin photoisomerization) and is also dependent on higher neural function, and the concept of a visual threshold is more or less a statistical function dependent on how large the stimulus has to be to reach a level of recognition. This is well recognized by anyone who performs a visual field test using an automated visual field analyser.

Thresholds and the frequency of seeing

A distinction must be made between the theoretical estimate of the number of quanta required to produce an electric stimulus in a patch-clamped photoreceptor cell and the psychophysical conversion of the light stimulus to a perceived sensation. The latter depends on a defined measure, termed the 'frequency of seeing', which is the number of times a repetitively presented minimal stimulus is detected, and is a probability function that varies between and within individual observers.

The former is theoretically a single photon of light. However, there is considerable 'noise' in the system owing, for instance, to random opening and closing of ion channels as a result of thermal isomerization of rhodopsin, or to scatter from background and/or stray light energy from the stimulus itself. These effects can account for up to 1000 quanta/degree, which is well above the absolute threshold for light stimulation. It is thought that some of this is 'smoothed' by coupling between photoreceptors.

What is the minimal stimulus for vision?

Even when theoretical biophysical considerations such as signal-to-noise ratio are taken into account, this deceptively simple question depends on many factors such as background illumination, spatial frequency, summation, wavelength, dark adaptation and optical qualities of the image-gathering system. The specific conditions have to be stated, therefore, before this quantity can be expressed.

In addition, consideration of whether a single rod can detect a single photon of light *in vivo* has to take into account the different routes that a rod can take to stimulate a ganglion cell and convert this into a

behavioural response (see pp. 258–262). Furthermore, the minimal stimulus size for a cone is also an important measure to define with physiological and clinical relevance.

DARK ADAPTATION CURVE AND RETINAL SENSITIVITY

The minimum visual stimulus varies depending on ambient light conditions, i.e. whether the stimulus is viewed in the dark or under normal/bright light conditions. In the dark, the eye becomes progressively more sensitive to light stimulation until the light threshold reaches a minimum after about 30 minutes. This is demonstrated in the dark adaptation curve (Box 5-1), which has two components: an early one resulting from increases in the cone sensitivity and a second

BOX 5-1 DARK ADAPTATION

The normal dark adaptation curve (a) varies if the conditions are varied: with a very small central white target, rods fail to become stimulated at all and the curve flattens out (b). If the cones are first light adapted by weakly stimulating them to maximum sensitivity or by adapting subjects to red light before placing them in the dark, the cone component can be 'lost' (c); subjects without cone vision also have no cone component (rod monochromats).

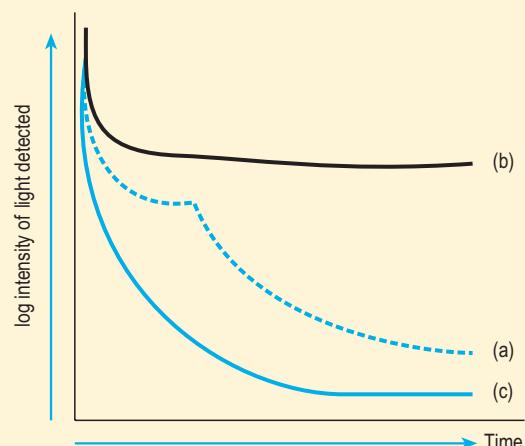


Figure outlining dark/light adaptation responses: (a) mixed rod and cone response of physiological dark adaptation, (b) pure cone response, (c) pure rod response.
(Figure courtesy of H. Dawson.)

produced by increases in rod sensitivity. There is also a light adaptation curve for cones in which the sensitivity to light varies as the luminosity increases or decreases within a wide range of high ambient illumination (see below). Thus the shape of the curve can be varied by altering the conditions.

Light and dark adaptation are the psychophysical correlates of visual pigment bleaching and regeneration, and can be measured by reflection densitometry. This technique is based on the assumption that light reflected from the unbleached retina will contain lower amounts of 500 nm (peak sensitivity for rods) light than that reflected from the bleached retina, since there will be considerable absorption of 500 nm light by the dark-adapted retina. Reflection densitometry studies permit an evaluation of the photosensitivity of the retina, i.e. the rate at which bleaching takes place for a given intensity of illumination. It has been estimated that the normal retina absorbs 50% of the quanta of light striking the retina but, as discussed above, this is not necessarily associated with a perceived visual stimulus because the absorption by a single rod of a photon of light can have at least three outcomes.

Regeneration of rhodopsin after dark adaptation is slow, taking 30 minutes for completion, with a half-time in humans of 5 minutes. This varies significantly between species. Clearly, the sensitivity of the retina in any individual will depend on the total amount of rhodopsin, and this relationship has been delineated in the Dowling–Rushton equation:

$$\log(z)/A = aB$$

where A is the threshold in complete dark adaptation, B is the fraction of bleached rhodopsin and a is a constant of proportionality. This sort of mathematical relationship has been used to estimate the rhodopsin content of the retinas of patients with certain forms of retinal disease, such as Oguchi's disease, fundus albi-punctatus and especially vitamin A deficiency. However, it is important to realize that receptor sensitivity and rhodopsin content are not equivalent and that sensitivity to light is markedly reduced after partial bleaching, long before there is a reduction in rhodopsin content. This is clear in the isolated retina where photosensitivity is permanently reduced even after full recovery in the dark. These changes reflect

the level of rhodopsin intermediates (metarhodopsin I and II) in the retina, which remain after bleaching (see Fig. 4-70, p. 259).

These effects are important in the determination of photosensitivity of discrete regions of the retina where it has been shown that reduced sensitivity can be detected in regions of the retina not exposed to point sources of light. Although this has been attributed to light scatter, there are probably other mechanisms operative here, particularly related to convergence of neural input (see below).

What does adaptation mean at a molecular level? There is considerable evidence to show that dark adaptation and regeneration of rhodopsin are dependent on the local concentration of 11-cis retinal, and the limiting factor for recovery after a large bleach is the rate at which 11-cis retinal is delivered to opsin in the bleached photoreceptors (Fig. 5-5) despite some more recent evidence that some of the retinoid conversion steps occur in the Müller cells also (see Ch. 4, Fig. 4-69). Thus, because a healthy retinal pigment epithelium is central to this process, age-related decline in dark adaptation can be explained on this basis. It is also dependent on termination of the

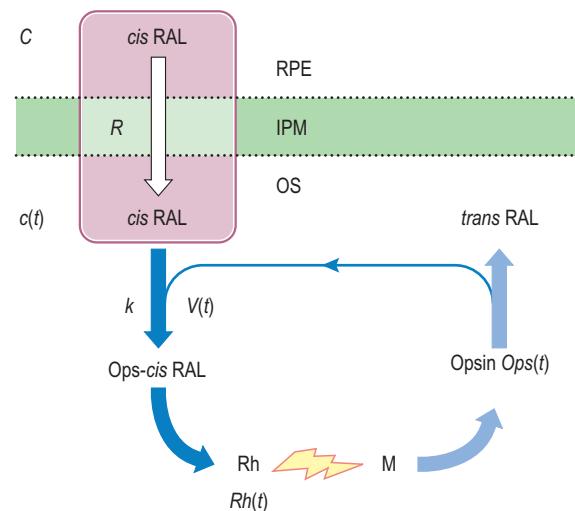


FIGURE 5-5 Schematic of the MLP rate-limited model. Removal of photoproduct and regeneration of visual pigment is rate-limited by the delivery of 11-cis retinal (*cis* RAL) from the retinal pigmented epithelium (RPE) to opsin in the outer segment (OS). IPM, interphotoreceptor matrix; Rh, rhodopsin; M, metarhodopsin. (From Lamb and Pugh, 2004, with permission from Elsevier.)

photon-induced signal brought about by efficient phosphorylation of the enzyme rhodopsin (Ch. 4, p. 262) via rhodopsin kinase, with the subsequent docking of arrestin to the complex, so that free opsin can be made available to bind more 11-cis retinal and respond to a new photon. Absence of rhodopsin kinase (also known as G protein-coupled receptor kinase 1, Grk1) or of arrestin, underlies the pathology of stationary night blindness (Oguchi's disease) while absence of the equivalent cone opsin kinase (Grk7) causes enhanced S cone syndrome.

Psychophysical evaluation of rhodopsin bleaching has been experimentally tested in humans by comparing a range of dark adaptation curves to different background light levels with the amplitude of the a wave of the electroretinogram, also known as the rod current (see p. 288) since both are desensitized to varying degrees by the amount of ambient light. It appears that rhodopsin regeneration and a-wave recovery rates match well.

Cones also regulate their sensitivity in photopic conditions, but it is much more difficult to saturate this response, i.e. cones still adapt at high intensities of steady illumination and the recovery time is very short (100 ms compared to 20–30 minutes for rods). This is probably furnished by Müller cell-derived 11-cis retinal, also under the control of RPE 65 in the Müller cell (see Ch. 4, Fig. 4-69).

In summary, adaptation is exactly what it means: that the retina rapidly adapts to changes in background illumination such that it can respond to increasingly strong or weak stimuli. However, the dynamic range of responses (normally a range from zero to a few hundred impulses per second) over which it functions at any specific level of illumination remains the same and the intensity of the response when it makes one is also the same. Put simply, the retina adapts rapidly to new lighting conditions when there is plenty of light about but slowly when light levels are low.

Melatonin and circadian rhythms

The circadian clock is a process whereby genes regulating various functions such as the sleep–wake cycle, body temperature, immune cell function and behaviour are expressed in a rhythmical manner. At least 11 core clock genes have been discovered, including a set

of period genes (*PER 1,2,3*) and clock genes (*CLOCK*). These genes have multiple downstream effects on other important regulatory transcription factors such as $\text{POPO}\alpha/\beta/\gamma$ important in immune cell function and genes involved in the synthesis of melatonin in the synthesis of melatonin. The light/dark (sleep/wake) cycle, generated by pacemaker cells in the suprachiasmatic nuclei, drives the production of the pineal gland secretory product, melatonin. Melatonin may also be produced at other sites, including the retina and bone marrow. It is synthesized from tryptophan via serotonin in two steps involving the enzymes serotonin-N-acetyltransferase (NAT) and hydroxyindole-O-methyltransferase (HIOMT) (see Ch. 4, p. 248). Melatonin provides information to the organisms to permit organization of various physiological functions and, because it can adapt to night length, it can promote a seasonal (photoperiod) as well as a diurnal rhythmicity (Fig. 5-6). Apart from its obvious physiological functions, such as sleep–wake patterns, melatonin influences immune diurnal variations in innate immune defence functions such as antioxidation, glucose regulation, blood coagulation enzyme systems and ocular functions such as control of aqueous secretion.

Melatonin is a methoxyindole, synthesized and secreted principally by the pineal gland at night under normal environmental conditions and binds to two receptors (M1 and 2). The endogenous rhythm of secretion is generated by the suprachiasmatic nuclei and entrained to the light/dark cycle. Light is able to either suppress or synchronize melatonin production according to the light schedule. The nyctohemeral rhythm of this hormone can be determined by repeated measurement of plasma or saliva melatonin or urine sulphatoxymelatonin, the main hepatic metabolite.

The primary physiological function of melatonin, whose secretion adjusts to night length, is to convey information concerning the daily cycle of light and darkness to body physiology. This information is used for the organization of functions, which respond to changes in the photoperiod (seasons). There is still, however, only limited evidence for seasonal rhythmicity of physiological functions in humans related to possible alteration of the melatonin message in temperate areas under field conditions, although there is

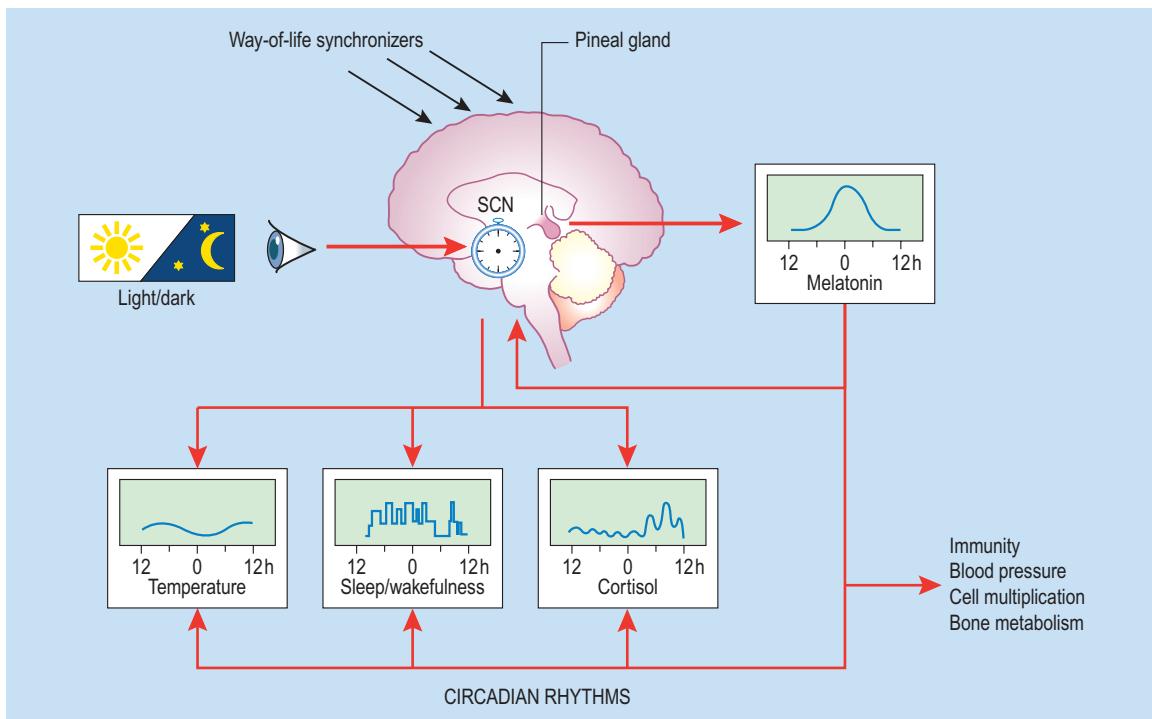


FIGURE 5-6 Melatonin acts as an endogenous synchronizer. (From Claustre et al., 2005, with permission from Elsevier.)

a reported link between seasonal affective disorder, clinical depression and its control with novel antidepressant drugs based on melatonin receptor stimulation, such as agomelatine. Major clinical depressive illness has also been linked to markedly reduced function of the core clock genes in the brain in a recently reported post-mortem microarray analysis.

The daily melatonin secretion, which is a very robust biochemical signal of night, can be used for the organization of circadian rhythms. Although functions of this hormone in humans are mainly based on correlative observations, there is some evidence that melatonin stabilizes and strengthens the coupling of circadian rhythms, especially of core temperature and sleep-wake rhythms. As the regulating system of melatonin secretion is complex, following central and autonomic pathways, there are many pathophysiological situations where the melatonin secretion can be disturbed. The resulting alteration could increase predisposition to disease, add to the severity of symptoms or modify the course and outcome of the disorder.

Melatonin is also produced by photoreceptors where it can act on melatonin receptors (MRs) in an autocrine manner, as well as on MR+ ganglion cells and other retinal neural cells in a paracrine manner. Thus it regulates the activity of photoreceptors, it acts on horizontal cells stimulated by cones to reduce their responsiveness, but heightens ON-bipolar cells and ganglion cells in some species. In this way melatonin is thought to fine-tune visual function, especially in cone cells under varying ambient light conditions (see eFig. 5-2).

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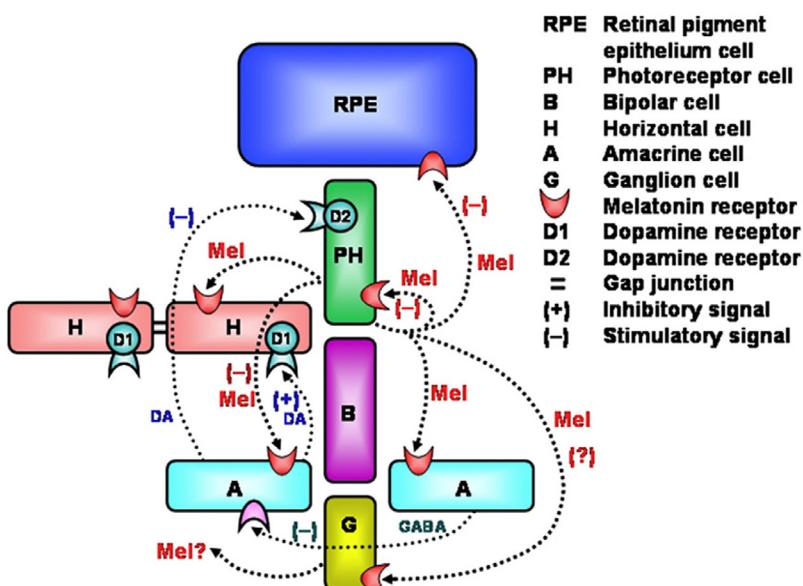
Interestingly MRs are present on many other ocular tissue cells such as ciliary epithelium, RPE cells, lens cells, corneal endothelium and keratocytes, and stromal cells in the sclera and choroid.

ARE TWO SMALL STIMULI EQUIVALENT TO ONE LARGE ONE (SUMMATION)?

The threshold for light detection can be measured arbitrarily by setting certain conditions of stimulus

This occurs via activation of specific receptors on amacrine, horizontal and photoreceptor cells. Wiechman has proposed a working hypothesis for melatonin paracrine signalling in the retina (eFig. 5-2). Melatonin is normally produced by photoreceptors at night, and diffuses to target cells within the retina that have specific receptors on cells such as GABA-ergic and/or dopaminergic amacrine cells which work in a reciprocal manner to some degree since GABA inhibits dopamine release from amacrine cells. A lower rate of dopamine release from amacrine cells results in lower stimulation of D1 receptors on

horizontal cells, which in turn leads to increased coupling of horizontal cells. This would result in an increase in receptive field size and increased sensitivity to light. Lower levels of binding of dopamine to D2 receptors on photoreceptor cells induces an increase in melatonin synthesis. Meanwhile melatonin may bind to horizontal cells to directly inhibit the cellular response to D1 receptor binding. Melatonin may also bind to receptors located on the photoreceptor membrane, which could directly increase rod sensitivity to light, and/or regulate synthesis of melatonin.



eFIGURE 5-2 Diagram outlining mechanism of how melatonin fine-tunes visual function (see text for details). (From Wiechmann et al., 2008.)

size, brightness, pupil size and level of background illumination, and recording how often a subject detects the stimulus. An empirically set level of 'hits' or positive detection responses (e.g. 55%) can then be set and expressed in trolands (Box 5-2). Experimentally it has been estimated that at the limit of light detection in the fully dark-adapted eye, the retina is illuminated to a level of 4.4×10^{-5} trolands, which is equivalent to the stimulation of only 1/5000 rods per second. However, if the light is concentrated on one area it will more readily elicit a response and it therefore becomes less practical to think of light energy in terms of area of retinal illumination; instead the minimum flux in light energy required to induce a detectable response is commonly accepted as the threshold and is around 120 quanta per second or, if the stimulus is instantaneous, between 5 and 15 quanta of light.

From this it is clear that stimulation of a single rod is insufficient to produce a visual sensation (even though an electrical response may occur in terms of a change in hyperpolarization of the cell membrane). Approximately 10–15 rods must be stimulated and the

BOX 5-2 LIGHT ENERGY

Light energy is measured subjectively by its 'brightness', and luminance can be measured in:

- trolands
- candelas
- luxes.

Specific measures of brightness are as follows:

- (a) Intensity of illumination of a surface (L) = intensity of the light source/square of the distance between the source and the surface.

$$L = I/r^2$$

- (b) Unit of L = foot-candela or metre-candela
- 1 lux = 1 metre-candela
 - 1 phot = 1 cm-candela
 - 1 lambert = 1 candela at 1 cm distance for a perfectly diffusing light source on a surface at 1 cm
 - 1 troland = a unit of retinal illumination that results when a surface luminance of 1 candela/m² is viewed through a pupil area of 1 mm²
 - 1 lumen = one unit of flux C , the spherical illumination from a point source of light of intensity of 1 metre-candela or 1 foot-candela.

summed response must be collected either at the bipolar cell level or within the ganglion cells to induce a visual sensation. These determinations are approximate as fluctuations occur at all levels from the stimulus itself to the responses in each of the different cell types, and the final analysis is based on probabilities of a response taking place.

Spatial summation

As indicated above, the empirical determination of the absolute threshold of light detection depends on the stimulus size; therefore, spatial summation must be important in setting this threshold. Each ganglion cell has a receptive field in which a light stimulus falling on a point within that field will produce a response. Receptive fields are the result of convergence of several photoreceptors to synapse with one bipolar cell and of several bipolar cells to synapse with a single ganglion cell (see next section).

Some limited general rules have therefore emerged concerning summation. Ricco's law states that the threshold intensity of a stimulus is inversely proportional to the area of the stimulus, provided the total stimulus area is sufficiently small to fit within the receptive field of a single ganglion cell. In terms of quanta, however, the amount of energy is independent of the area. As the receptive field size increases at greater distances from the fovea, Ricco's law also varies in the area in which it can be applied. In overlapping receptive fields, Ricco's law applies only partially in that larger stimuli require more quanta to reach the absolute threshold. This has led to further attempts to formulate equations that would provide a general solution for these phenomena, but in practice no simple solution covers all possibilities and summation is best explained by probability theory (see above).

Temporal summation

When the retina is stimulated in rapid succession by a target, the level of response is the same as when the target is presented continuously for the same total period of time. This is known as temporal summation and is formulated by Bloch's law, which states: the intensity of the threshold stimulus is inversely proportional to the duration of the stimulus. To a degree this is a difficult psychophysical measurement since at very short intervals it is difficult to distinguish different

contrast and duration. Bloch's law holds true only for a defined period of time as, if the interval between the stimuli were long, the effect would be rapidly lost. Bloch and others found that, in fact, a 'plateau' effect was observed. However, Broca and Sulzer found that there was a peak in perception and then there was a decay before a plateau effect (see eFig. 5-3).

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In practice the peak described by Broca and Sulzer occurred at about 50–100 ms, and beyond this time there is still some degree of summation, known as partial summation, which decays exponentially.

Recently, the question of temporal summation has been revisited in the context of artificial light (which accounts for about 20% of our energy consumption). Using an experimental design in which intrinsic bias from previous learned experience was omitted, Broca's peak was detected and was attributed to a differentiation in duration versus contrast which is eliminated probably by higher neural mechanisms ensuring that the same rapid stimulus is identified with short flashes of light. Bloch's law therefore represents a smoothed-out perception in which the peak of detection/contrast is eliminated by prior learned experience at a subconscious level. If artificial lighting systems were optimally tuned to these temporal summation effects in human vision, for instance by using DC light-emitting diodes, a 20% saving in energy consumption has been estimated, which is not insubstantial.

Detection of minimum stimulus for motion displacement

An extension of these concepts has been developed to evaluate the minimum detectable motion stimulus test, since motion detection is a major function of the magnocellular ganglion cell, i.e. rod-dominated pathway (see below). The test (motion displacement test, MDT) is based on the minimum positional displacement of a standard line stimulus, which is detected as a sensation of motion. Since it is based on a square wave stimulus which oscillates back and forth between two points, it is considered to be the summation of the ON-OFF receptive field responses of the stimulated M cells. The threshold for detection varies with the square root of the stimulus energy and has been described as a new law: namely, the threshold energy displacement law (TED).

Binocular summation

Summation may occur in visual stimuli received by corresponding retinal regions when using both eyes. In practice, mostly because of optical aberrations (see below), the effect is not considered significant. However, it can be demonstrated using wavefront technologies to remove aberrations and indeed it has been shown that such aberrations account for between 5% and 15% of loss in visual discrimination. In a recent study, binocular summation and inhibition, defined as seeing five or more or fewer than five letters on the ETDRS visual acuity chart with both eyes compared with best visual acuity with each eye individually, occurred at a prevalence rate of 21% and 2%, respectively, which has considerable relevance to driving vision. In addition, the effect of amblyopia may be such that the loss of binocular summation has a distinct effect on overall visual acuity.

Visual acuity and contrast sensitivity

VISUAL ACUITY IS NOT SIMPLY A FUNCTION OF CONE ACTIVITY

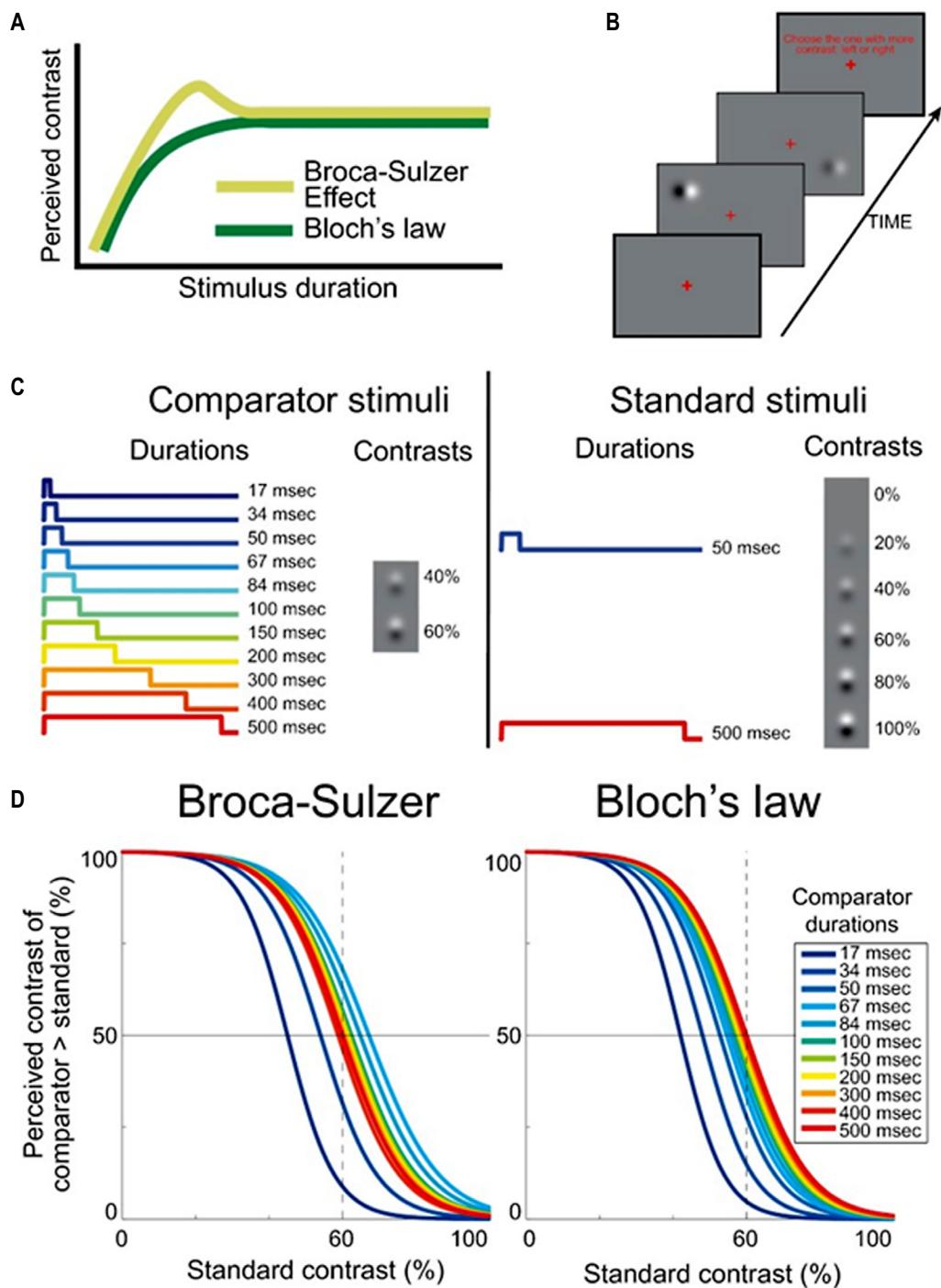
Vision varies for each individual because of refractive errors and visual physiologists have therefore restricted discussion of normal visual physiology to the emmetropic idealized eye (see eFig. 5-4).

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Visual acuity is a measure of the ability to discriminate two stimuli separated in space. Clinically, this is determined by discriminating letters on a chart, but this task also requires recognition of the form and shape of the letters, processes that involve higher centres of visual perception. Discrimination at a retinal level may therefore be determined by less complex stimuli such as contrast sensitivity gratings. The visual processes that allow discrimination between letters and gratings are fundamentally the same, with finer resolution contrast discrimination at lower luminance levels being provided by some newer test charts, such as the Mars contrast sensitivity charts which are graded in log 0.04 units. Charts that have been customized to test visual acuity in different groups of people, such as the SKILL test (Smith-Kettlewell Institute Low Luminance test), may be a good predictor of eventual development of macular degeneration in older people.

Investigation of potential different effects can be modelled experimentally. For instance the following experiments reported recently by Rieiro and colleagues demonstrate the actual effects of the different stimuli as varying potential outcomes (Rieiro et al., 2012). In eFig. 5-3, (A) represents two competing models of temporal vision. Bloch's law postulates a monotonic increase in perceived contrast with increased duration, whereas the Broca–Sulzer effect postulates a peak in perceived contrast with increased duration. In (B) subjects fixated on a central cross, and two Gabor patches flashed in succession on opposite sides of the screen. Following stimulus presentation, subjects reported which Gabor had higher contrast. Part (C) shows the physical contrasts and stimulus durations used for the

comparator and standard stimuli. In the unblocked experiment, all possible combinations were randomized. In the blocked experiment, the different conditions were grouped into four sequential sets of trials or blocks, each with a constant comparator contrast and standard duration and an internally randomized trial sequence. Finally, (D) shows the psychometric curve models of the two possible experimental outcomes, colour-coded for different comparator durations. If contrast perception has a peak, as in the Broca–Sulzer effect, the curves will first shift right and then left as stimulus duration increases. If contrast perception follows Bloch's law, the curves will shift monotonically to the right.



eFIGURE 5-3 Studies of the potential different effects which may occur in temporal summation (see text for details). (From Rieiro et al., 2012.)

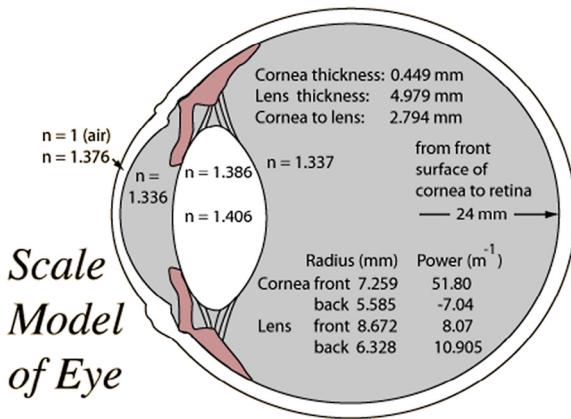
The eye has the power to refract (bend) light waves and, as for any lens, this is measured in dioptres. A dioptr^e (D) is a unit of measurement that describes the strength, or ‘power’, of a lens to bend (refract) light a set amount (degree); the optical power of a lens or curved mirror is equal to the reciprocal of the focal length measured in metres (that is, 1/metres). It is thus a unit of reciprocal length. Thus, a three-dioptr^e lens brings parallel rays of light to focus at 1/3 metre. The overall refractive power of the eye is around 60D for the normal healthy emmetropic eye and much of its refractive power is attributed to the lens-like (focusing) properties of the cornea (which amount to about 40D), with the remaining 20D due to the ocular lens (eFig. 5-4). The effect of this refractive property of the ocular media (i.e. the tissues through which the light passes) is to focus light rays on the retina, and specifically the fovea, when visual acuity is being measured. Many refractive errors occur in the healthy population, including myopia (short-sightedness), hyperopia (long-sightedness) and astigmatism (non-spherical aberrations of the eye’s refractive power).

The scientific discipline dealing with the optics of the eye is known as optometry. Many textbooks are available which deal with physiological optics as well as optical devices such as spectacle correction, contact lenses and the optics of intraocular lenses, including large treatises dealing with many aspects of physiological optics as well as shorter text books summarizing refraction and refractive errors for those not intending a career in optometry.

The reader is referred to the following texts as examples of (1) a short comprehensive text and (2) a three-volume in-depth treatise:

- (1) Hunter DG, West MD. *Last-minute optics: a concise review of optics, refraction, and contact lenses*. 2010.
- (2) von Helmholtz H. *Treatise on physiological optics*, vols I, II and III. Dover Phoenix Editions; 2005

In addition, several texts are available which deal with the optics of the pseudophakic eye (i.e. the eye with a prosthetic intraocular lens), including official publications of professional bodies such as the American Academy of Optometry and the British College of Optometry.



eFIGURE 5-4 Standard dimensions of the eye as related to the model eye. (From Hecht, 1987.)

Theoretically, the resolving power of the eye can be derived from an estimate of the angle subtended by a single photoreceptor (about $1.5\text{ }\mu$ or 20 minutes ($20'$) of arc in the case of cones), as this represents the smallest unit distance separating two individually stimulated photoreceptors. This corresponds to about a pixel on a computer screen when viewed at half a metre. However, it is well recognized that the resolving power of the eye can be as great as $0.5'$ of arc, for instance when looking for the gap in a Landolt C target, or $4''$ of arc when viewing a thin line on an illuminated background. This hyperacuity, or Vernier acuity, is achieved by the complexities of retinal neuronal synaptic organization and is $5\text{--}10\times$ greater than 'standard' visual acuity, but the limits of acuity are still determined to some extent by the retinal photoreceptor mosaic or 'grain'.

The highest discriminatory capacity is subserved by cones, although a certain degree of resolution can be achieved by rods. The level of acuity, however, falls off rapidly the greater the distance from the fovea, such that at 5° from the central fovea visual acuity is only one-quarter of foveal acuity. As rod and cone longitudinal dimensions are not sufficiently different to explain the marked difference in acuity, and as the resolving power of the eye is greater than the theoretical limits based on cell size, other mechanisms must underpin acuity. Visual acuity is affected by the luminance of the test object and the degree of adaptation of the observer; dark adaptation increases both rod

and cone acuity and therefore is not affected by the sensitivity of cones *per se*. In contrast, light adaptation increases sensitivity of cones but not rods (see p. 274).

Vernier acuity is used in everyday life, for instance in measuring distance with a ruler or detecting the time on a mechanical clock. Vernier acuity is not present in infancy but reaches its highest level of function around the age of 14. It is absent in strabismic amblyopia but may be present in patients with anisometropic amblyopia. Vernier acuity is different from the recently recognized state of supervision, which has been revealed by the use of adaptive optics. Adaptive optics were developed for use in astronomy to minimize optical aberrations and correct higher-order dynamic aberrations caused by such aspects as angle of viewing and accommodation, as compared with correction of static aberrations such as astigmatism and defocus (see below). In essence, by using a wave form sensor, adaptive optics measures phase aberrations in reflected light produced by the imaging light source. When applied to the eye, for instance in the use of wavefront aberrometers and wavefront-guided vision correction in refractive corneal surgery, adaptive optics can theoretically increase acuity to 'supervision' levels.

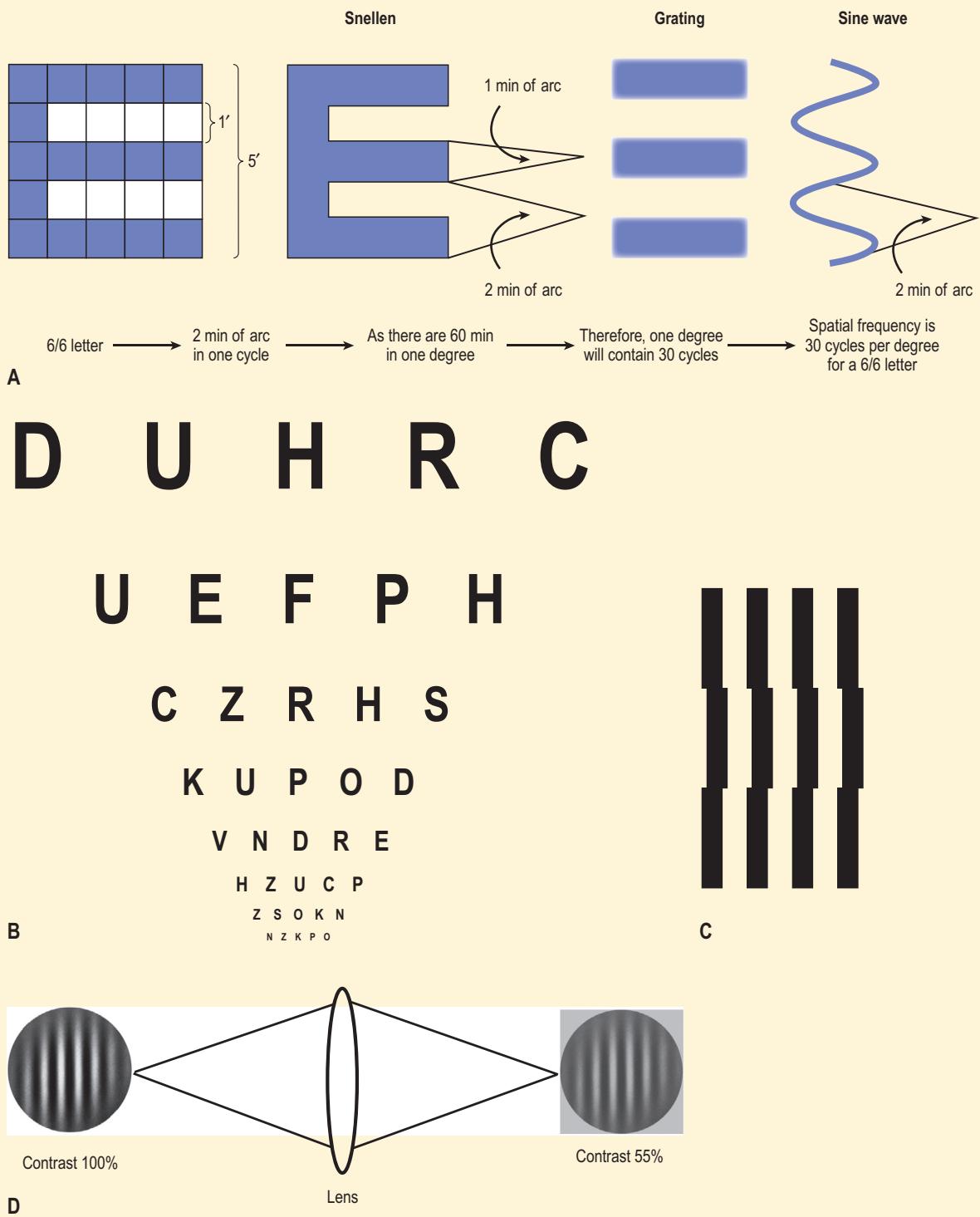
LIMITS OF AND LIMITATIONS ON ACUITY

The letters on reading charts such as the Snellen's test type and the ETDRS chart (Box 5-3) have been constructed on the assumption that the average person

BOX 5-3 ASSESSMENT OF VISUAL ACUITY USING STANDARD LETTER CHARTS

Visual acuity in clinical practice is determined as an empirical value based on the assumption that the cone photoreceptor has the ability to discriminate two objects in space subtended by an angle of 1 minute of arc at the nodal point of the eye (**A**). This is measured using a set of charts (optotypes) and standard normal visual acuity equates to the vision of 6/6 or 20/20 (i.e. 1.0 or 100%) when viewing a predetermined standard target (size of optotype letter) at 6 m (UK) or 20 feet (USA). Test conditions describing the ambient illumination, and the illumination of the letters on the chart to provide contrast are also arbitrarily set. The Snellen chart is based on the concept that the smallest spatial target that can be resolved subtends 1 minute of arc at the nodal point of the eye (see above) and although theoretically inaccurate, it serves as a useful parameter. The Snellen chart has rows of letters of decreasing

size and is arbitrarily set to produce the standard test at 6 m, although other charts with proportionally smaller letters can be used at shorter distances. The LOGMAR (LOGarithm of the Minimal Angle of Resolution (**B**) is more precisely designed with definitive sizing and spacing of the letters and can provide a more quantitative evaluation of visual acuity. It therefore tends to be the standard for use in clinical trials. As indicated in the text, spatial acuity better than 100% can be achieved, for instance when discriminating the 'offset' of a line or edge (**C**). This is termed Vernier acuity. In addition, visual acuity is modified by such factors as glare and contrast, and indeed can be measured as in the contrast sensitivity test using a sine wave grating as shown in (**D**), where diffraction and aberrations have degraded the contrast of a sinusoidal grating pattern.

BOX 5-3 ASSESSMENT OF VISUAL ACUITY USING STANDARD LETTER CHARTS—cont'd

(From Schweigerling, 2000, with permission from Elsevier.)

can resolve two points separated by $1'$ of arc. If the limit on acuity is in part determined by the single photoreceptor theory (above) then a one-to-one relationship between the photoreceptor and the nerve cell must exist if there is to be no downstream loss of acuity. For foveal cones such a relationship exists between cone cells, midget bipolar cells and midget ganglion cells (see section on [retinal connections](#), pp. 291–296), but even midget cells have some interconnections with diffuse bipolar and ganglion cells. In spite of these connections, summation of information should not occur for cells subserving the highest levels of acuity and, indeed, is absent from foveal cone cells but is characteristic of rod cells; furthermore, it has been suggested that the improved visual acuity that occurs under conditions of light adaptation is the result of inhibition of these subsidiary connections.

Visual acuity is also limited by the physical behaviour of light, such as diffraction and chromatic/spheric aberration. A single point of light small enough to stimulate a single cone will produce diffraction rings in its traverse through the pupil sufficient to stimulate more than one cone. Similarly, the prismatic separation of white light into its constituent wavelengths will lead to the stimulation of several cones of different types. It is clear therefore that resolution of images must be achieved at a post-receptor level and is in fact a function of the receptive field of each ganglion cell unit. Where there is minimal convergence of information from each receptor, i.e. where the one-to-one relationship between receptor and bipolar cell is maintained, then resolution is at its highest and this occurs at the fovea. However, where there is increasing convergence of information, such as with several parafoveal cones synapsing with one bipolar cell, resolution obviously decreases.

The one-to-one relationship, however, does not adequately explain hyperacuity or Vernier acuity. Diffraction and spheric/chromatic aberrations have ruled out the concept of single unstimulated cones occurring between neighbouring stimulated cells; however, it is likely that discrimination is more a matter of degree than absolute responses, i.e. that resolution is achieved by certain receptors being *less stimulated* than their neighbouring receptors on either side. This is likely to occur with diffraction, where alternating light and dark rings emanate from a point source of

light, and with chromatic aberration, where different wavelengths of light are likely to stimulate their respective neighbouring cones to different degrees ([Box 5-4](#)). In fact, this fits with the nature of the hyperpolarization response being a graded one in retinal neural cells: as indicated in Chapter 4 (see p. 261), only ganglion cells fire ‘classic’ depolarizing action potentials, while other retinal cells have a graded analogue-type ‘tunable’ electrical response. This differential stimulation from cones is registered with the respective bipolar and ganglion cells and, if combined with a minimal degree of receptor convergence, can explain high levels of discrimination. In this way diffraction could explain, at least partly, the ability to resolve a break in a line subtending an angle of less than $10'$ of arc, since partial diffraction lines deriving from the edge of the break would ensure differential stimulation of cone receptors over a very small area. Stimulation of any particular cone is also likely to induce local inhibition (via receptive field mechanisms; see below) in neighbouring cones, thus enhancing resolution and ‘sharpening the image’ further.

These concepts are embedded in the canon of knowledge going back to the time of Rayleigh in the late nineteenth century. However, Rayleigh’s law does not fully explain the real condition where diffraction spreading from a double line is slightly greater than that from a single line for the same total amount of light energy. Information theory, adaptive optics and modern electro-optical devices for generating discrete stimuli might help to explain this anomaly.

These considerations also have a number of implications. In particular, the resolving power of the eye is limited by the distance between two images such that a single cone or set of cones is appreciably less stimulated than the rest; the limit of resolution is therefore not an absolute determinant, but depends on conditions such as light and dark adaptation, background illumination and other factors. Most importantly, it depends on the degree of dendritic connections that occur between the affected cones and the neural cells.

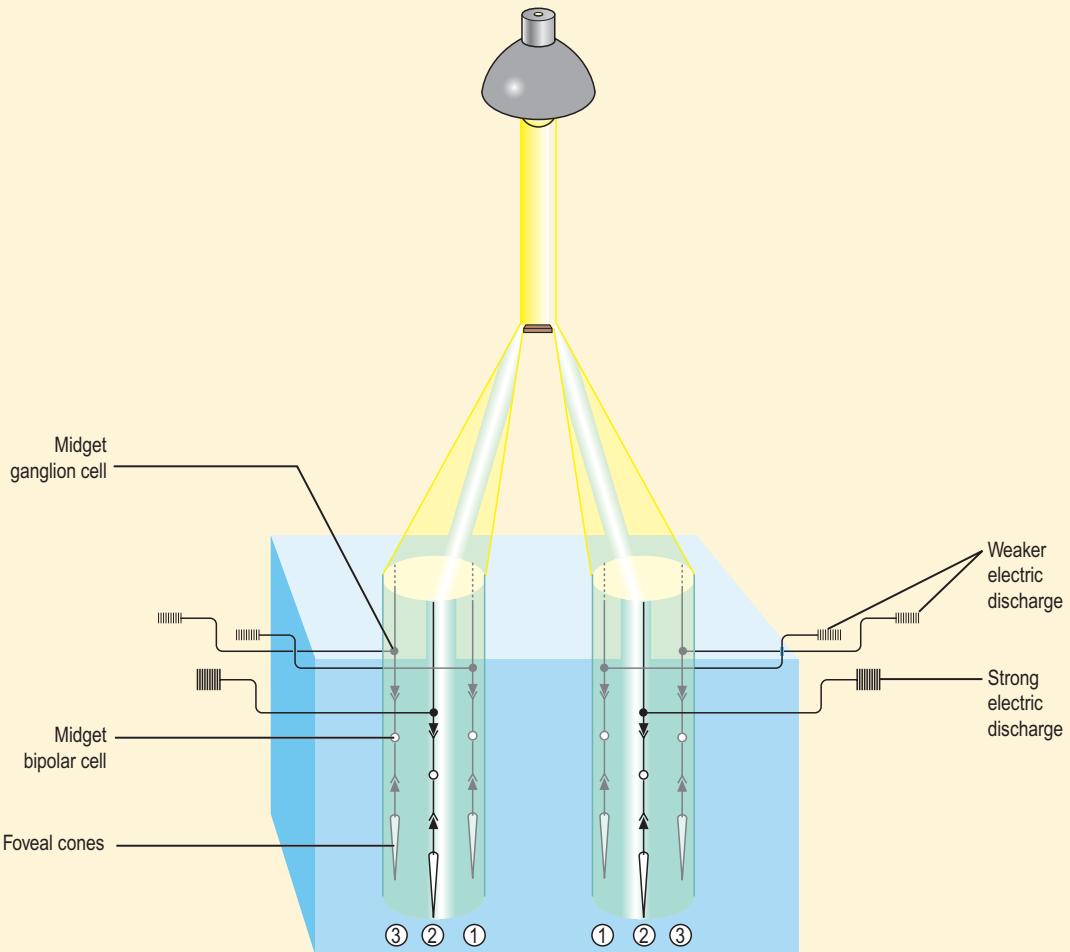
The resolving power of the eye therefore depends on:

- the distance between two objects
- the degree of light and dark adaptation

BOX 5-4 DIFFERENTIAL ACTIVATION OF NEIGHBOURING CONES DETERMINES THE LIMITS OF VISUAL ACUITY

A beam of light interrupted by a small target will produce diffraction rings at its edges – the central rays in each ring will stimulate one cone (2) more than the weaker peripheral rings will stimulate its neighbours (1) and (3). Our ability to detect the break in the light beam is determined by

comparing the differential responses in all the cones in the illuminated region and finding two that produce a similar response to correspond to the edges of the target. Visual acuity is therefore a measure of the retina's ability to produce different graded responses and not absolute responses.



- the background illumination
- the extent of the dendritic connections between the cone and neurones.

CONTRAST SENSITIVITY

Visual acuity is also affected by contrast (sharpness). The finest limits of resolution have been determined

by the ability to discriminate a thin white line against a uniform background illumination ($0.5'$ of arc). The effects of diffraction are such that detection of this line depends on the liminal brightness increment (l.b.i.). This increment represents the endpoint at which the differential in brightness between the individual dark/bright oval diffraction rings produced at the edge of

the line can be detected; if they are not sufficiently different from the background luminosity, then the line will not be detected. The l.b.i. is determined by the contrast between the light and dark lines, and can be measured quantitatively with a sinusoidal grating (see Box 5-3): a spatial pattern where the average luminance remains the same but the contrast between the light and shaded areas can differ.

The degree of contrast (C) is relative to the background luminance (L) and is described in terms of the maximum (L_{\max}) and the minimum (L_{\min}) as follows, also known as the Michelson contrast:

$$C = (L_{\max} - L_{\min}) / (L_{\max} + L_{\min})$$

Alternative measures are the Weber contrast, where the difference between the maximum and the minimum is compared against the background luminance, and RMS contrast, where the mean luminance is a factor of the standard deviation in luminance. The Michelson contrast is used for gratings and a 'threshold' is reached when the target is detected reproducibly. Sensitivity is the inverse of the threshold and thus 'contrast sensitivity' is a measurable quantity, usually described in cycles per degree (the grating frequency) and visual acuity is equivalent to 1/grating frequency. Using this method it has been shown that there is a peak response in the middle range of frequencies (Fig. 5-7).

Contrast sensitivity is therefore set by the limits of the grating frequency and is affected by both the optics of the system and the direction of the grating lines, being most sensitive in vertical or horizontal directions. Remarkably, threshold contrast for many targets sits around 1% independently of target size or brightness, which as Peli observes remains unexplained since originally described by Fechner in 1860 (Peli, 2013).

Contrast sensitivity above threshold is, as for any measure of acuity, affected by luminance. In addition, bar width, length and grating motion all affect sensitivity. In the latter there is likely to be significant cortical processing at this level, as there is for 'line modulation sensitivity', a technique whereby grating bars are composed of wavy lines and the subject is asked to determine whether the line is straight or not. This technique can provide highly sensitive measures of acuity.

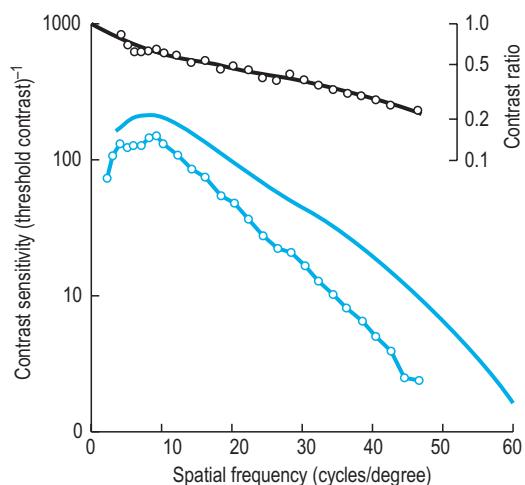


FIGURE 5-7 Contrast sensitivity curve showing peak response at midspatial frequencies.

Contrast sensitivity measurements, while an excellent measure of acuity, are sensitive to phase shifts and grating orientation and for absolute measures of object detection, object contrast is critical. In this context, mesopic low-contrast letter acuity is the most sensitive method for revealing small differences in retinal image 'quality', which influences 'recognition' as opposed to 'detection' of an object. The contrast sensitivity function (CSF) has been arbitrarily measured using a set of five spatial frequencies and has been found to be relatively robust. Age and decreased luminance cause a shift to larger frequencies in the CSF. Glare, which is often a side-effect of refractive surgery, affects the CSF at low rather than high spatial frequencies. For clinical purposes, measurement of the CSF (as opposed to measuring the threshold as in most contrast sensitivity charts) is very time consuming and impractical, but recent developments using customized and selective spatial frequencies and contrasts are allowing tailored CSF tests to be applied to specific conditions, e.g. macular degeneration.

Wavelength also affects contrast sensitivity such that at high spatial frequencies the gratings appear to be of the same colour, whereas at low frequencies (i.e. with coarse gratings), colour differences can be detected. Discrimination is poorest with red-green, however, suggesting that for low frequencies rod-cone

interactions are important in achieving best visual acuity. Interestingly, contrast sensitivity appears to induce more electrical signal responses in M cells, generally thought to subserve rod function, than in P cells, which are linked to cone function (see below).

Does the retinotopic arrangement of fibres in the cortex have a bearing on acuity?

The representation of retinal ganglion cells in the LGN and cortex is disproportionately larger for foveal midget cells than for ganglion cells elsewhere in the retina. This produces a 'cortical magnification factor' for foveal cones over other cones. However, the

magnification factor is not related solely to the reduced convergence of foveal cones on ganglion cells (see below), but also to a disproportionate LGN and cortical representation of neurones served by foveal cones. Current use of fMRI has revealed the retinotopic map of the human visual cortex and demonstrated this magnification factor in technicolour (Fig. 5-8).

BEST-CORRECTED VISUAL ACUITY: EFFECTS OF EXTERNAL FACTORS

Visual acuity is, of course, affected by factors that do not relate directly to the retinal stimulus. These include pupil size, eye movements and binocular viewing.

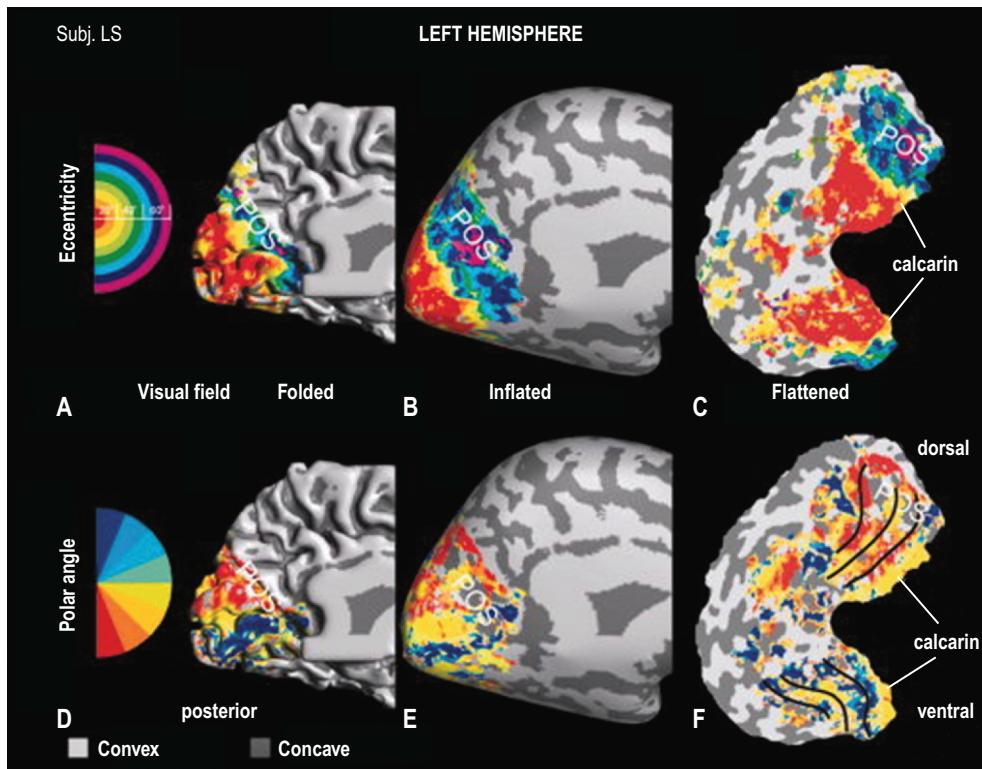


FIGURE 5-8 Dipolar map and isopolar angle maps of human visual areas. These images were prepared using fMRI technology and computer modelling to 'flatten out' the visual cortex (**C** and **F**). The top row shows a map of the occipital cortex indicating the retinotopic location of the stimulus as its eccentricity increases from the fovea; the dipole is coded by colour (brown (fovea) → orange → blue → cyan (periphery)) displayed on the original cortical surface (**A**), the unfolded cortical surface (**B**), and the cut and flattened cortical surface (**C**). The bottom row shows the polar angle of the stimulus (blue (upper vertical meridian) → green (horizontal meridian) → red (lower vertical meridian)) plotted on the same three surfaces (**D–F**). (From Wu et al., 2012.)

Pupil size and visual acuity testing in infants

The size of the pupil affects the level of visual acuity in that a reduction in pupil size reduces aberrations but increases the effects of diffraction. Below 3 mm, these effects tend to cancel each other out, and visual acuity is independent of pupil size, although wavefront aberrometry reveals that a pupil size of 2.5–3.0 mm produces the best image quality.

The level of visual acuity attained may also have the reverse effect on the size of the pupil. Luminance affects the level of acuity and the size of the pupil is affected by the light level via well-characterized pupil reflexes (Box 5-5). The size of the pupil also indirectly affects the visual acuity by reducing the amount of light entering the eye when the light stimulus is intense, and conversely increasing light capture under dim lighting conditions. This three-way relationship has been used to develop an objective measure of visual acuity, which may be useful in assessing vision in infants and others who are not able to cooperate in standard visual acuity testing. The test uses a high-resolution infrared pupillometry device to show changes in the amplitude of constriction in response to sine-wave gratings presented on a uniformly illuminated test background. As for contrast sensitivity, there is a peak response in the middle range of frequencies and the threshold for response correlates well with contrast sensitivity estimates of acuity. This pupil response is governed by higher visual pathways, being altered in patients with hemianopia but normal pupil light reflexes; indeed, the phenomenon is well recognized by clinical neuro-ophthalmologists. Infrared pupillometry has been shown to be valuable in studies of delayed visual maturation and to be significantly more reliable than the Rosenbaum card method in which subjective comparisons of pupil size are made.

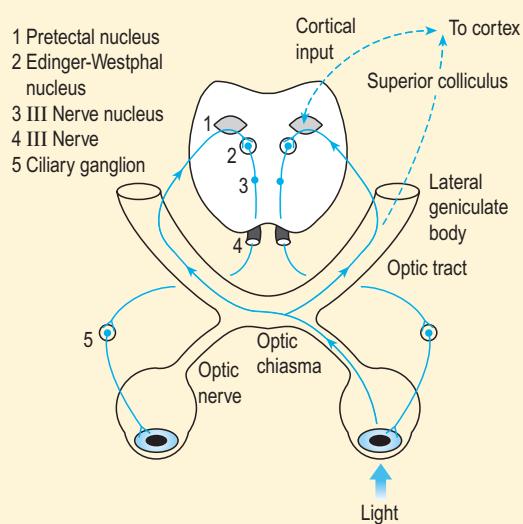
The pupillary response also receives input from the intrinsically photosensitive retinal ganglion cells (ipRGCs) through melanopsin (see Ch. 4, p. 249) and it is possible using chromatic pupillometry (stimulation of pupil responses at different wavelengths) to separate the contributions from rods, cones and ipRGCs. There are diverse types of ipRGCs with several different functions. For instance the sleep/wake circadian rhythm responders connect with the suprachiasmatic nucleus, while the pupillary responsive neurones synapse in the pretectal (olivary) nucleus. In

terms of response to light, ipRGCs are considered to register irradiance or radiating light. They may also be responsible for photoallodynia (the photophobia/light aversion response to very bright light).

Eye movements

The concept that the continuous fine eye movements that occur as part of normal viewing are important in ensuring constant stimulation of the photoreceptors to maintain image perception remains popular. Indeed, it has been shown that images received by peripheral

BOX 5-5 PUPILLARY LIGHT REFLEXES



- The afferent response commences in photoreceptors, is transmitted to retinal ganglion cells, enters the optic nerve, decussates at the chiasm, traverses the optic tract and terminates in the pretectal nucleus (bypassing the lateral geniculate nucleus).
- Both crossed (via posterior commissure) and uncrossed fibres pass from pretectal nucleus to Edinger-Westphal nucleus (parasympathetic).
- Parasympathetic fibres pass to the III nerve nucleus and leave the brainstem via the III nerve. Fibres synapse in the ciliary ganglion before supplying sphincter pupillae of iris (constriction) via short ciliary nerves.
- Unicocular light stimulus therefore gives rises to bilateral and symmetrical pupillary constriction.
- Melanopsin signals through ipRGCs (see text) to the suprachiasmatic nucleus (circadian response) and the pretectal nucleus (irradiance response).

receptors fade rapidly if fixation is deliberately maintained in one position – the Troxler phenomenon. Although this was originally considered to be a mechanism for enhancing the central image by inhibiting peripheral images, use of a ‘stabilized retinal image’ has shown that elimination of these fine movements does not necessarily lead to a reduction in visual acuity. However, these findings were obtained using high-frequency gratings and it is possible that fine eye movements may be important at lower spatial frequencies in improving contrast.

Fine eye movements occur during different visual tasks: for instance, during reading, the fixation time on the target letter is around 200–250 ms and the average saccade is about 8–9 letters. This increases in skim reading but the level of cognition (the perceptual span) is reduced. Useful information is gathered from a region about 3–4 letters to the left of foveal fixation and 8–9 letters to the right.

Binocular viewing and the probability theory of visual perception

Perception is a relative occurrence and depends on many factors to achieve optimal levels (there is a significant element of chance in achieving this optimum which can be expressed as a linear transformation of log odds of frequency and/or probability). Interestingly, determination of some stimuli such as negative (concave) contours versus positive (convex) contours has a greater chance of detection.

It follows therefore that two eyes are better than one, at least in increasing the chances of the highest level of visual processing of the same image.

Electrophysiology of the visual system

The transmission of nerve impulses in retinal receptors and neurones is mediated, as might be expected, by recordable changes in electric potential across the cell membrane (see Ch. 4, p. 161) and is accompanied by electric discharge. The action potential is usually an all-or-nothing event and, in muscle tissue, does not occur in the resting state. However, in neural tissue continuous discharge may be taking place and information is relayed by changes in the frequency or rate of electric discharge in the nerve, an increase in frequency usually representing stimulation and a decrease

representing inhibition, thus emphasizing the essential binary nature of biological information systems similar to computers. This applies for all nerves in any system: the character of the received sensation is determined not by the type of nerve but by the site of information relay in the cortex and its subsequent processing in the brain.

In the retina, these general principles hold true for retinal ganglion cells, but in bipolar, horizontal, amacrine and photoreceptor cells the electrical response is more of a tonic or graded response, and the direction of the response can be positive or negative. For instance, it is this graded response that permits spatial discrimination via differential responses to diffraction rings, as described above (see p. 280). However, the graded response in the bipolar cell becomes an ON/OFF response in the ganglion cell. As Ikeda has put it, retinal information is converted from an analogue signal to a digital signal at the final stage of retinal processing, i.e. at the connection between ganglion and bipolar cells (Ikeda, 1993).

THE ELECTRICAL RESPONSE IS INITIATED BY PHOTOTRANSDUCTION

As we have seen (see Ch. 4, when a photon of light strikes the photoreceptor outer segment, conversion of rhodopsin to the activated molecule induces a series of molecular events culminating in an electrical response. Cells, and particularly neurones, normally exist in a ‘charged’ state in that the inside of the cell is ‘negative’ with respect to the extracellular environment, creating an electrical potential difference across the cell membrane. This condition is maintained by differential distribution of Na^+ and K^+ ions on either side of the cell membrane. When a neurone is stimulated, there is an initial period of gradually increasing positivity (the generator potential), which culminates in a spike discharge characterized by a rapid depolarization response of the cell. This is achieved by the rapid influx of Na^+ through ion channels that are ‘opened’.

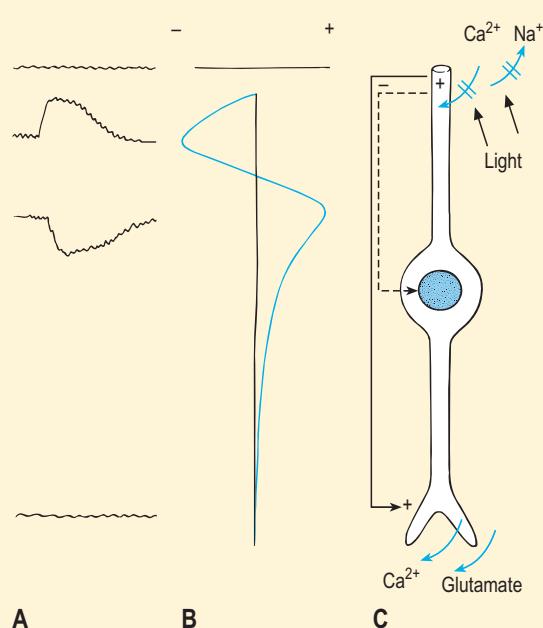
In the photoreceptor the reverse situation occurs. Under resting conditions in the dark, the outer segment is maintained in a depolarized state through open (‘leaky’) Na^+ channels, which permit the influx of sodium ions from the extracellular space. When light stimulates the outer segment, the sodium

channels are abruptly closed, stopping the influx of sodium and thereby leading to a reduced level of depolarization, i.e. a relative hyperpolarization (Box 5-6). This is a direct result of rhodopsin isomerization and is mediated by amplification mechanisms involving cyclic guanosine monophosphate (cGMP) (see Ch. 4, p. 262).

The hyperpolarization response is transmitted by a flux in calcium ions along the length of the photoreceptor to the synapse with the bipolar cell (the Ca^{2+} wave), which is then induced to release its transmitter (glutamate). Bipolar cells may then adapt to one of two responses to glutamate, depending on which type of

BOX 5-6 DARK CURRENTS

Dark currents occur in the resting state (dark adapted eye) owing to ' Na^+ -leaking' outer segments.



The conversion of light energy to an electric response is dependent on specialized ion channels that tightly control the permeability of the cell membrane to Na^+ and Ca^{2+} . Light stimulation reverses the dark current by closing Na^+ channels in outer segments and releasing Ca^{2+} (and glutamate) at synapses. The cGMP-gated Ca^{2+} channel and the $\text{Na}^+/\text{Ca}^{2+}$, K^+ exchanger are located in the plasma membrane of the photoreceptor, not in the disk stack, but are complexed together with peripherin/rds-rom-1, an integral protein of the disk rim.

receptor is induced: an ON response, which is a hyperpolarized state, and an OFF response, which is a depolarization response (see below). Indeed, the hyperpolarized state conferred on the bipolar cell is also transmitted to the horizontal cells in the same region. However, the hyperpolarization response of the bipolar cell is not as steep as that of the photoreceptor in the excited state.

It will be obvious, therefore, that not only is there a resting potential difference across the photoreceptor cell membrane but there is also a potential difference along the length of the photoreceptor in the dark between the relatively depolarized outer segment tip and the hyperpolarized synaptic region of the cell at its interaction with the bipolar cell. This generates the 'dark currents' in the eye, which are reversed by the photic current on light stimulation when the photoreceptor tip becomes hyperpolarized (see Box 5-6).

ELECTROPHYSIOLOGY OF SINGLE RETINAL CELLS

Early studies in this field concentrated on the large single neurones that could be obtained from invertebrate eyes and showed that typical action potentials could be obtained, usually preceded by a generator potential (Box 5-7). Surrounding neurones were usually inhibited when action potentials occurred in a single nerve.

Later studies of electrode-impaled optic nerves in vertebrates showed that the rate of discharge in certain nerve fibres increased (ON response) when a light stimulus was presented to the eye, while it decreased in other fibres (OFF response). Yet others produced an ON/OFF response. As it was known that there were 150×10^6 photoreceptors but only 1×10^6 optic nerve fibres, it followed that many receptors must feed information into a single neurone, i.e. there must be convergence of signals and some of these must be inhibitory while others are stimulatory. On this basis, the concept of receptive fields was developed and confirmed by direct experimental testing on isolated optic nerve fibres using discrete spots of light to stimulate the retina (Box 5-8). Several phenomena, such as summation, which could previously be inferred only from psychophysical experiments, were directly confirmed. Indeed, summation effects could be compared with the effects of generator potentials in other systems that, in ganglion cells, are called synaptic potentials.

BOX 5-7 GENERATOR POTENTIALS

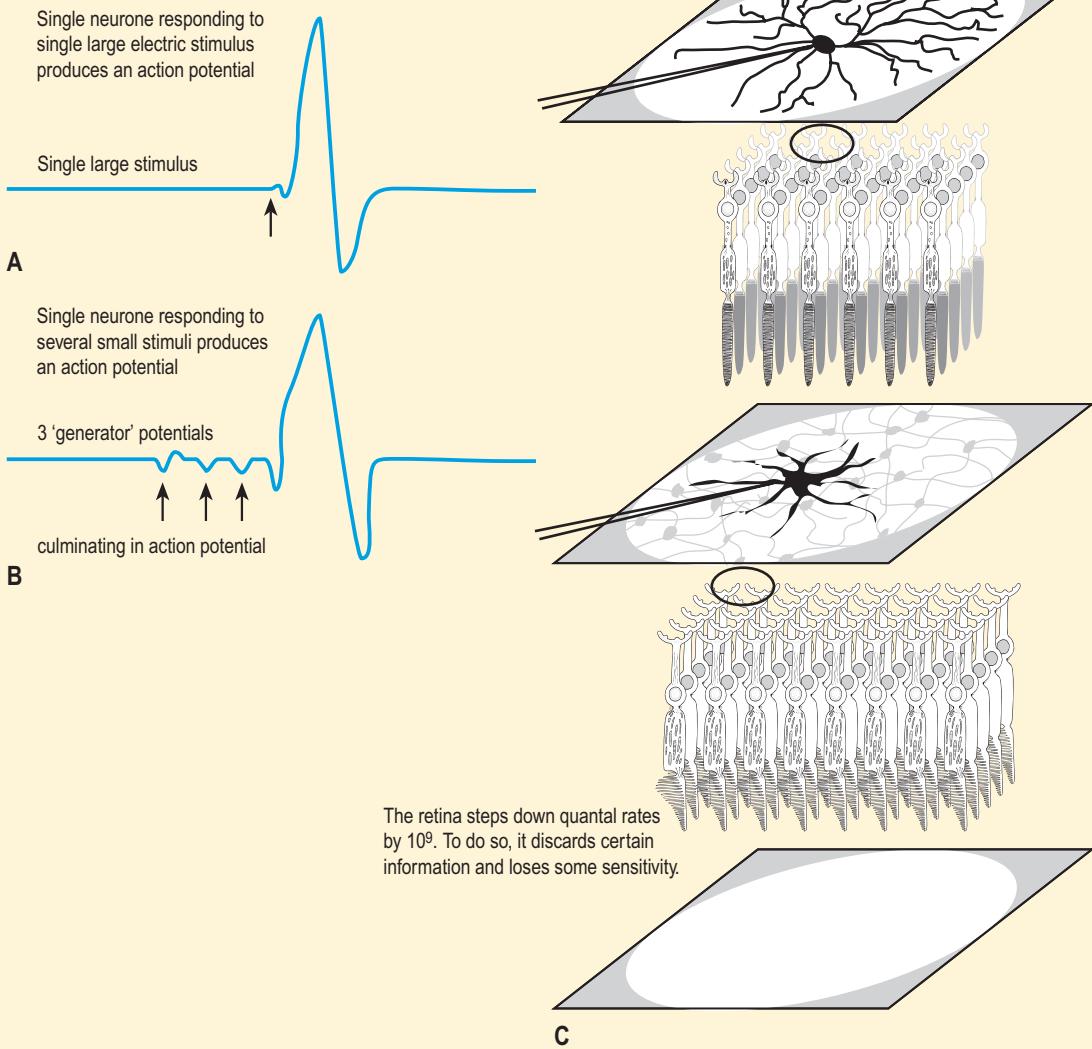
GENERATOR POTENTIALS

- (A) Single neurone responding to single large electric stimulus produces an action potential.
- (B) Single neurone responding to several small stimuli produces an action potential.

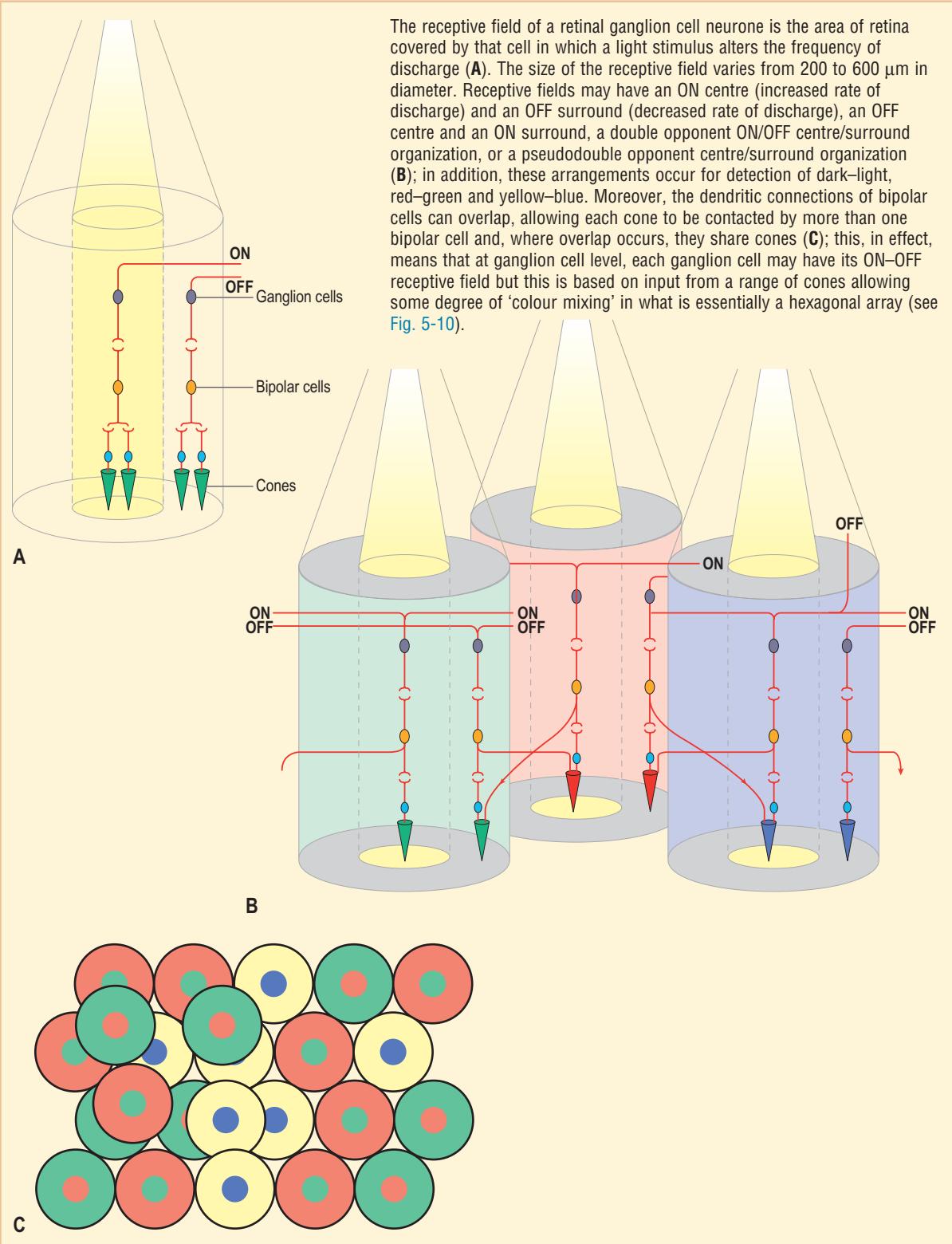
(C) The retinal photoreceptor-bipolar cell electrical response steps down in quantal rates in a graded fashion.

For instance, three 'summed' small light responses produce a typical ON response in ganglion cell neurone

Generator potentials



BOX 5-8 ORGANIZATION OF VISUAL INFORMATION INTO DISCRETE RECEPTIVE FIELDS



The ON/OFF response in the optic nerve fibres has been shown to correlate with the centre/surround organization of the receptive field and is based on interneuronal interactions causing inhibition in surround cells.

ON/OFF receptive fields apply to cone–bipolar–ganglion cell circuitry while rod cells synapse directly into cone–cone circuits (see below). ON/OFF receptive field organization applies to several different types of signal, including light–dark, blue–yellow and red–green (see below). Amacrine cells and horizontal cells considerably modify the ON/OFF microcircuitry organization and, variably so far, each type of circuit. In addition, the receptive fields of retinal neurones depend on the size of the cell: big ganglion cells (magnocells, M cells) have large receptive fields and small ganglion cells (parvocells, P cells) have small ones. M cells receive information from many amacrine and bipolar cells, producing a high degree of convergence. P cells have small receptive fields receiving information directly from single or only a few bipolar cells (see below).

How does the photochemical change in the receptor produce the spike discharge in the retinal neurone?

Horizontal cells at the receptor–bipolar cell interface and amacrine cells at the bipolar–ganglion cell interface are integrally involved in the organization of the retinal neuronal response to light. Single-cell recordings have shown that the hyperpolarization response at the receptor level is a graded response (see above, discussion of visual acuity), not an ON/OFF response. Similarly, the hyperpolarizing horizontal cell response is a graded response, but in the horizontal cell there is a longer latency and the potential for summation over a wide range. The bipolar cell response is also graded but with a centre/surround effect where the centre hyperpolarizes and the surround depolarizes. In the amacrine cell transient spikes can be observed, especially if correlated with the ON/OFF response, but only in the ganglion cell is a sustained spike discharge observed with a true depolarization occurring for ON, OFF and ON/OFF responses, depending on which type of ganglion cell is studied. This all-or-none response is graded only in the sense that the frequency or rate of discharge that occurs in the ganglion cell varies with the degree of depolarization.

RETINAL CONNECTIONS, CIRCUITRY AND NEUROTRANSMITTERS

Retinal connections

What is the basis of receptive field organization in the retina? As detailed above, detection and processing of the light stimuli by the retina is founded on the retinal receptor/neuronal network comprising the photoreceptors (rods and cones) and the neurones (bipolar cells and ganglion cells). The information finally transmitted to the lateral geniculate nucleus in the brain by the ganglion cells (ON, OFF and ON/OFF cells) is received directly from the bipolar cells but is modulated by horizontal cells and amacrine cells in the plexiform layers in the retina. This is canonically described in a simple arrangement of direct bipolar cell activity and lateral inhibition by horizontal cells and amacrine cells (see Ch. 1 for details). In reality, retinal microcircuitry is more complex than this, underpinned by the fact that each retinal cell comes in several different varieties (Fig. 5-9). For instance, only one type of bipolar cell connects with rod photoreceptors but each of the 12 different types of cone bipolar cells connects with each cone photoreceptor in an integrated manner. In addition, the general arrangements found in most mammalian retinas are complicated by the presence of the fovea in primates, which is characterized by a single type of ganglion cell. A series of excellent reviews of this field has been published by Masland (2011, 2012a,b,c).

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There are several retinal microcircuits emanating from the photoreceptors and acting in parallel. As indicated above, each bipolar cell connects all the cones within its branching territory and because of overlap, each cone connects with each of the 12 types of bipolar cells, each of which is transmitting different types of information to the next layer of cells (amacrine, horizontal and ganglion cells) (Fig. 5-10).

Thus, cones from several different types of microcircuits with a range of bipolar cells while rod microcircuitry is minimal. In evolutionary terms, cones developed first, even though there are 20 times more rods than cones in the retina. Cone–bipolar cells synapse in the inner plexiform layer in a highly ordered set of stacks, each with a different number of

Masland's work has shown that the more than 60 different cell types in the retina are functionally organized into three sets which (1) sift the information from photoreceptors into roughly 12 separate channels or streams running alongside each other simultaneously; (2) transfer this information to specific types of ganglion cell; and (3) integrate information from bipolar cells and amacrine cells with ganglion cell output into approximately 20 different coded messages concerning the nature of the visual image which are transmitted to the brain via the ganglion cells (Masland 2011, 2012a,b,c). The very large numbers of amacrine cells are especially interesting and appear to subserve many functions, many of which remain to be discovered but some of which are inferred simply from their positioning and architecture within the retina. For example, most recently, an 'interneurone' which in essence sends a blue OFF signal to the brain has been discovered, further underlying the complexity of neuronal cell integration within the retina.

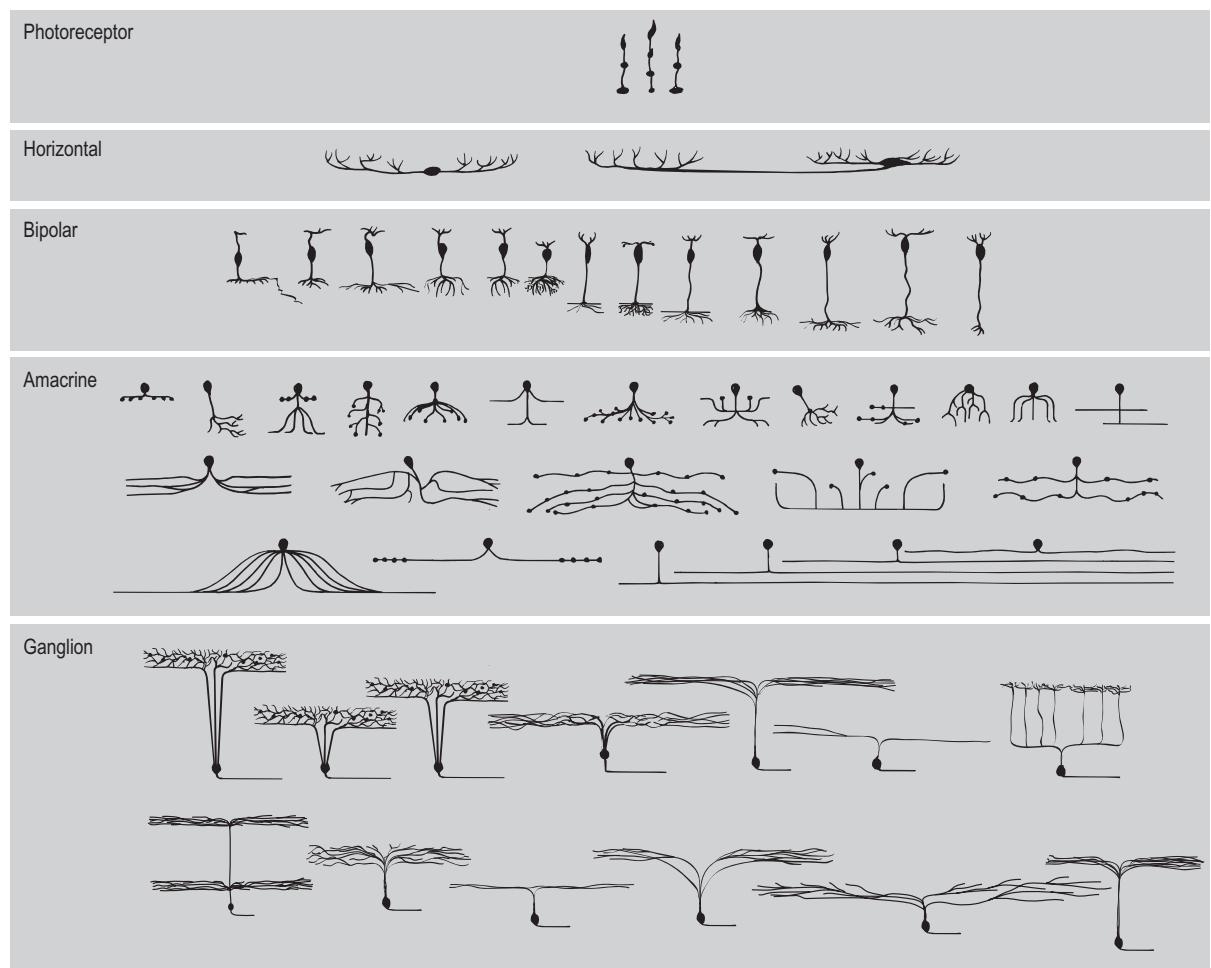


FIGURE 5-9 The major cell types of a typical mammalian retina. (From Masland, 2012.)

connections and with its unique set of ionotropic, metabotropic (mGluR6), glycinergic and GABAergic receptors and calcium-binding proteins reflecting their inhibitory or excitatory output (translated into ON or OFF responses in the ganglion cell (see Box 5-7, Figs 5-9 and 5-10, video 5-1, and additional content online concerning Masland).

There are several different types of ON/OFF bipolar cells, in part determined by the duration of the response (transient versus sustained); in addition, a single bipolar cell for these types of responses (non-chromatic ON/OFF) takes information from more than one cone (Fig. 5-10).

The organization of colour detection is somewhat different. A basic centre surround organization

pertains here also. However, wavelength discrimination (see below) requires output from at least two cones to have something to compare against. 'Blue' (short-wavelength) cones make synapses with a single specialized type of cone-bipolar, while the remainder of the cones (long-wavelength red-green cones, comprising around 85%) connect with the several different types of bipolar cells described above (Figs 5-9 and 5-10). The blue bipolar cell registers ON stimuli but until recently it was unclear how blue OFF responses were generated since there is only a single type of blue bipolar cell. It appears that amacrine cells (see below) can convert a blue bipolar ON signal to an OFF signal through its role as an inhibitory interneurone (Fig. 5-11).

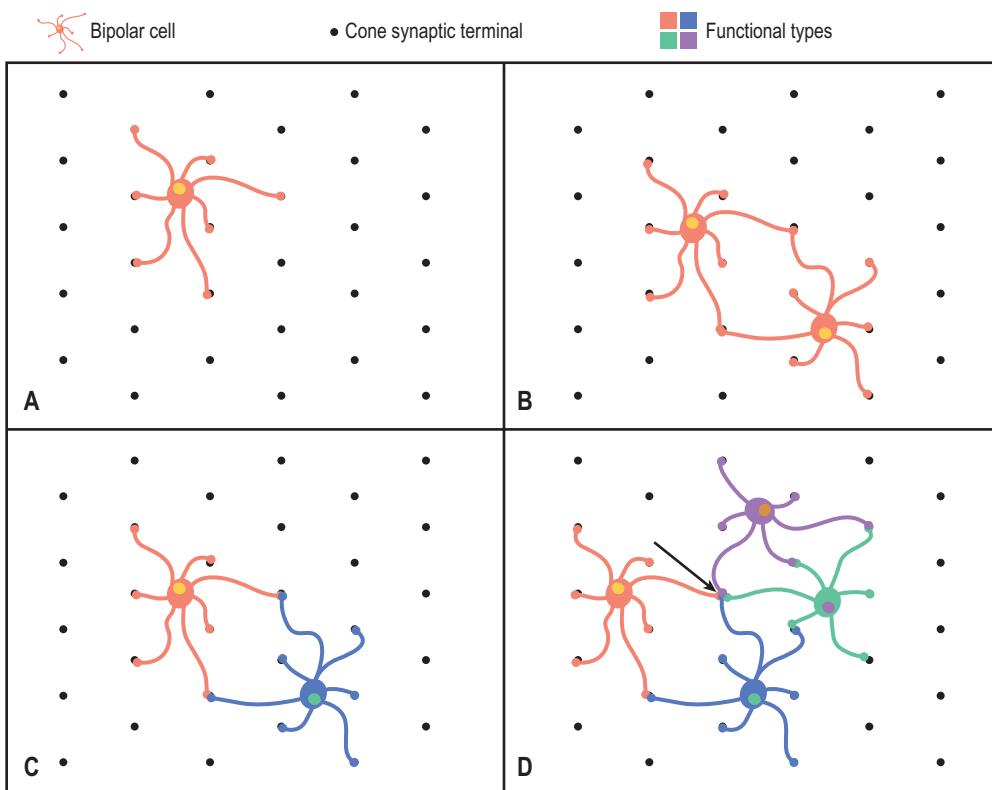


FIGURE 5-10 (A–D) Each bipolar cell (represented by the different colours) connects all the cones within the area of its dendritic tree. The retina is organized such that each bipolar cell makes contact with all of the cones within the spread of its dendritic extensions, with the exception of the ‘blue cone bipolar’ which only connects with blue cones. They are numerically small and the principle remains that each of the different types of bipolar cell that connects with a single cone sends a unique message from that cone to the ganglion (or other) cell in the inner retina. (From Masland, 2012.)

This particular amacrine cell is particularly sensitive to short-wavelength light and uses glycine as its inhibitory neurotransmitter. At the ganglion cell level the blue ON ganglion cells receive input from the blue ON bipolar cell and the red–green OFF bipolar cell and it has been proposed that the blue OFF ganglion cell also receives input from the same amacrine inhibitory cells by sending its dendrites to that stratified layer of the retina. This is less certain, however.

Colour discrimination is therefore made by comparison of light detection by a short-wavelength cone (ON/OFF) with that from a long-wavelength cone (either red or green, ON/OFF), i.e. it is essentially a dichromatic system. In most mammalian retinas, there is no red/green discrimination (i.e. there is true

dichromatism with comparison of only one long-wavelength cone with a short-wavelength cone), while in humans there is also red/green discrimination. However, in 5% of humans this is also true dichromatism (red–green colour blindness). These concepts are dealt with in more detail later in the chapter (p. 302).

So where does rod microcircuitry fit into this neuronal organization? Rods detect dim light, while cones detect bright light. Detection of dim light by rods is not to be confused with the OFF response of cone bipolar OFF cells (i.e. the response to the absence of light) but is a positive response by rod cells to very low levels of light. The majority of rods connect indirectly with ganglion cells through cone bipolar cells; large numbers of rods synapse with a single rod bipolar cell, which then connects via gap junctions

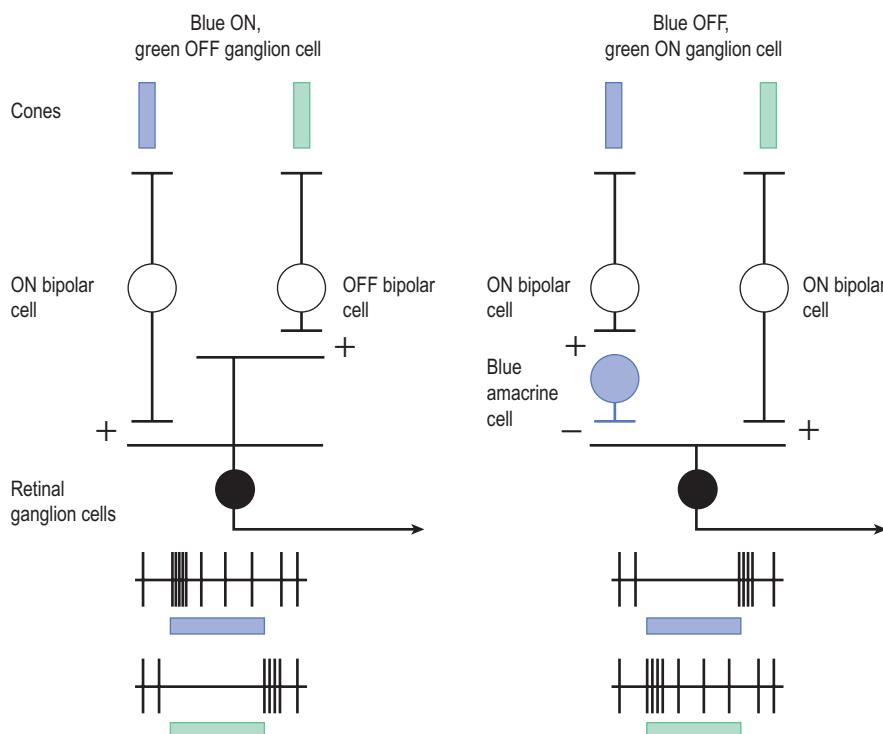


FIGURE 5-11 The physiology of the ON:OFF ganglion cell as shown for the blue ganglion cells. Blue bipolar cells contacting blue-sensitive cones send a signal in response to the brightness of the stimulus (ON stimulus), which synapse directly to a particular ganglion cell (diagram on left of figure). In contrast, if the bipolar cell receives a signal from the amacrine cell, this inhibitory signal generates a response from an OFF bipolar cell. In both cases the signal is complemented by input from an inversely corresponding green cone. The stream of action potentials as the final output to the brain is shown in the lower section of the figure. (From Masland, 2012.)

with a cone bipolar cell through a further particular type of amacrine cell, the AII cell.

In primates, there is further specialization at the ganglion cell level related to the fovea and derived from the system of midget cells: midget ganglion cells connect directly with one cone bipolar cell and through this cell with one cone photoreceptor. Thus there are a huge number of small bipolar cells and midget ganglion cells at the fovea, limited only by the packing of cones in this rod-free area. For instance, midget cells comprise about 70% of the ganglion cells in the monkey fovea. Moreover, in the primate fovea each cone cell connects with an OFF bipolar and an ON bipolar, leading to a greater density of bipolar cells at the fovea than cone photoreceptors. Each midget ganglion cells has a simple centre/surround organization underpinning the excellent spatial resolution of ‘supervision’; in addition, it is believed that the midget

cell system underpins the dual circuits required for red/green differentiation added to the existing blue cone system (see Box 5-8 and Figs 5-9 and 5-10). At the fovea, the colour opponency theory may not be as strict as suggested above, but is modified by input from horizontal cells: thus short-, middle- and long-wavelength cones may compete against all the cones that contribute to the surround area after modulation by the horizontal cells.

Horizontal cells (Fig. 5-9) in the outer plexiform layer thus provide important feedback for both rod and cone outputs. For cones, this is classically believed to be in the form of contrast and mostly via generating inhibitory information to ganglion cells surrounding the activated cell (similar to the inhibitory effect of an action potential in a bundle of peripheral neurones on the neighbouring unstimulated neurones). This produces the centre/surround

H^+ negative feedback onto cone terminals induced by HC polarization

Surround light	HC	V-ATPase at HC	Synaptic cleft $[H^+]$	Cone I_{Ca}	Transmitter release	OFF-BC	ON-BC
OFF	depolarize	↑	↑	↓	↓	hyperpolarize	depolarize
ON	hyperpolarize	↓	↓	↑	↑	depolarize	hyperpolarize

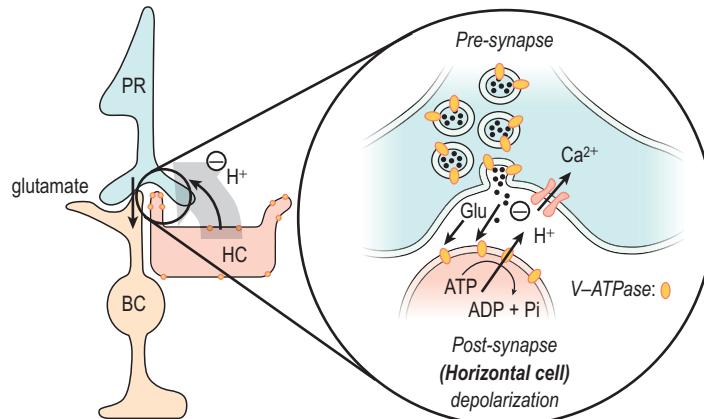
A**B**

FIGURE 5-12 Release of H^+ ions exert negative feedback onto the bipolar cells: this is achieved by changing the H^+ concentration at the cone photoreceptor:bipolar cell (PR:BC) synapse and is induced by horizontal cell (HC) polarization of BCs via change in H^+ concentration change at synaptic clefts of cone terminals induced by HC polarization. (A) Shows the direction of change in the various parameters exerted by HC depolarization and hyperpolarization. (B) Shows a schematic drawing of H^+ negative feedback onto BCs via release of H^+ from depolarized HCs illustrating the 'OFF' case in (A). H^+ release occurs via V-ATPase (a proton pump, turquoise circles in the inset figure) resulting in suppression of glutamate release from cones. V-ATPase is in synaptic vesicles at the cone terminals. (From Hirasawa et al., 2012.)

organization of ganglion cells (see Box 5-8). Some also believe that horizontal cells may mediate their effects based on subtracting the information on the average illumination of the entire retina from that stimulating a restricted set of cones, thus underpinning the mechanism of light adaptation. Rods are separately modified by horizontal cells because of the anatomical location which separates the contact point with the rod far from the rod's contact with the cone bipolar cell.

One biochemical mechanism whereby horizontal cells direct the nature of the ON or OFF response appears to be mediated by acidification at the photoreceptor:bipolar cell synapse, mediated by a membrane-bound proton pump, and suppressing the effects of the glutamate neurotransmitter (Fig. 5-12). In contrast, amacrine cells are much more numerous than horizontal cells (Fig. 5-9) and have a wide range of functions. There are around 30 types of amacrine cells, some modifying ganglion cell response over a wide

area while others are much more restricted. In addition, they inhibit, enhance, entrain and refine through the large range of neurotransmitters and receptors discussed above (e.g. dopamine, acetylcholine, glutamate, GABA, glycine, etc.). They thus affect many functions such as centre/surround organization, orientation selectivity, light-dark effects and colour discrimination. Some amacrine cells may have very small arborizations and function entirely within the receptive fields of a wide-field ganglion cell. For instance, starburst amacrine cells have been identified as being ON-OFF direction sensitive, a feature that may involve only a section of the branching arborization in signalling (Fig. 5-13). In addition, other amacrine cells are sensitive to saccade-induced suppression which allows differentiation of true object motion from motion of the entire visual field induced by fine eye movements. Amacrine cells may have paracrine and multiple neurotransmitter secretory functions as well as release nitric oxide.

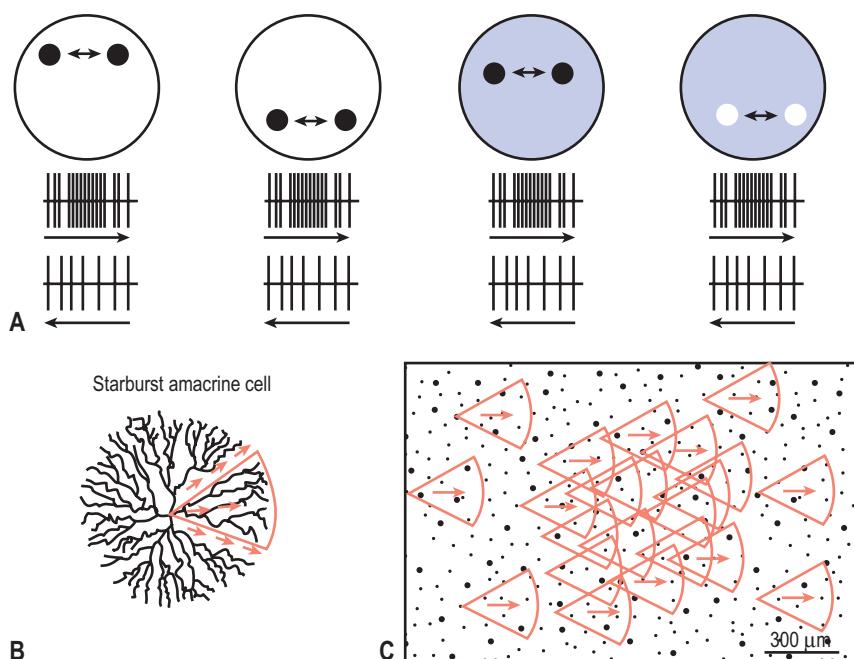


FIGURE 5-13 The ON-OFF direction selectivity of the starburst amacrine cell is the same within all regions of its receptive field (**A**) and can be detected even within a sector of the field (**B**) as shown for small moving targets (**C**). Because the sectors served by each dendrite (represented by the black dots) are smaller than the receptive field, small OFF movements can be detected. (From Masland, 2012.)

Thus some degree of information processing may occur at the inner plexiform/ganglion cell level (e.g. in contrast gain control) before it reaches the visual cortex.

Finally there are about 20 different types of ganglion cell (Fig. 5-10). Originally described as X (slow, tonic) and Y (fast, transient) cells in the cat, and P (parvocellular, midget) and M (magnocellular, parasol) cells in the monkey, several others are now known to be responsible for centre/surround organization and direction/orientation selectivity. Each of the 20 different ganglion cells ‘tiles’ the retina in its dendritic field so that the specific function of that ganglion cell is represented at that point in the retina (Fig. 5-14).

In addition, a separate rare population of ipRGCs (see Ch. 4, p. 249) connects with neurones in the pretectal and suprachiasmatic nuclei and responds to the level of ‘irradiance’ and controls pupil light responses as well as sleep/wake cycles (see Box 5-5).

It is now known that there are several types of ipRGCs (see eFig. 5-2) which regulate the production of

melatonin by the pineal gland and are thus involved in entrainment of circadian rhythms (see p. 277).

From all of the above it is clear that there is considerable diversity in the retinal microcircuitry in which significant information processing occurs before its transmission to the higher centres in the brain.

CLINICAL VISUAL ELECTROPHYSIOLOGY

The electrical potentials which exist in the eye, by virtue of factors such as the dark currents in the retina and the transcorneal epithelial potential difference, can be altered by stimulation with bright flashes of light, producing mass responses of the tissue. These responses represent the resultants of many cellular potentials and the source of the discharges can only be inferred. However, extensive studies have located the source of retinal electric responses at different levels in the retina (Fig. 5-15). There are established internationally agreed standards describing normal responses set by the International Society for Clinical Electrophysiology of Vision (ISCEV).

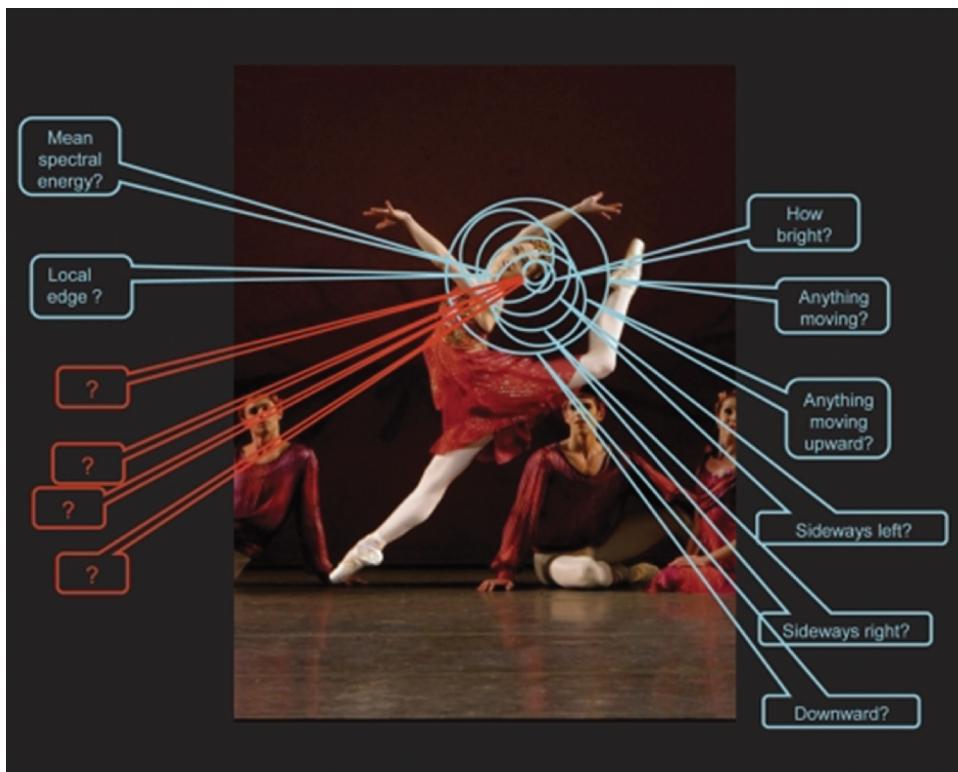


FIGURE 5-14 The numerous components that contribute to an image are managed by the retina on a point-by-point basis. Twenty types of ganglion cells provide a unique inner retinal surface mosaic so that each is represented at any point in the retina corresponding to a point in space which is the object being viewed. In the above image, a small area on the dancer's head is assessed for various features, e.g. motion, direction, tilt, spectral composition (colour), tone, texture and more. (From Masland, 2011.)

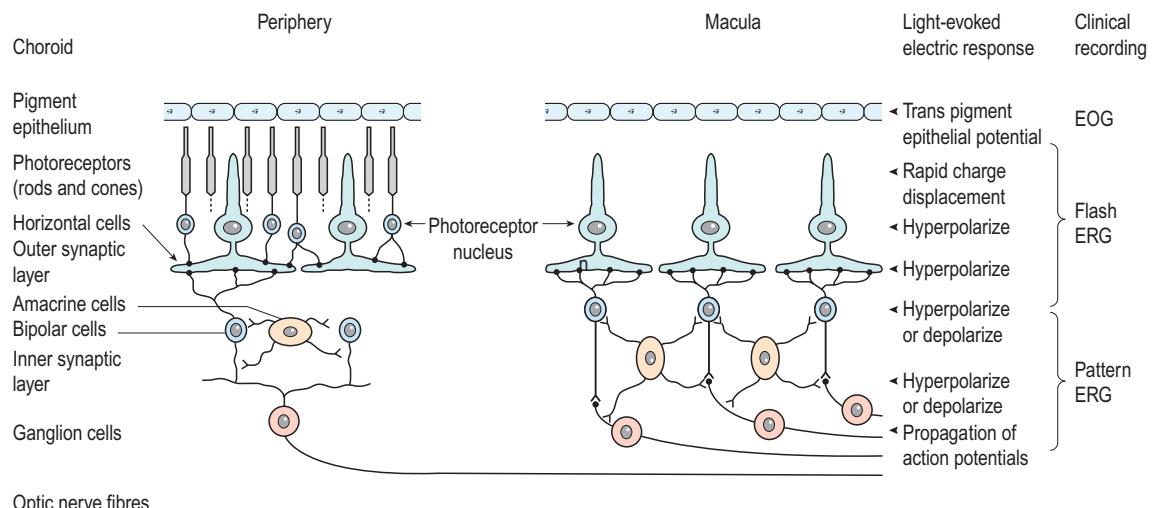


FIGURE 5-15 Source of electrophysiological 'traces' from retinal layers. The electro-oculogram lies at the RPE layer, while the ERG is retinal. The pattern ERG represents the response after processing in the bipolar cell layer. (Courtesy of A.M. Halliday.)

Resting potential and the electro-oculogram

Since the eye acts as a dipole, it possesses a measurable resting potential, which is generated at the interface between the retinal pigment epithelium (RPE) and the photoreceptors (the resting retinal potential) and is about 60 mV in height. At a molecular level, the electro-oculogram is representative of the transretinal pigment epithelial potential differences generated by separation of ionic gradients across the RPE by genes such as the bestrophin gene (see Ch. 4, p. 254), and maintained by tight junctions. Similar transepithelial potential differences occur across all non-leaking epithelial layers. As the eye becomes light adapted there is a steady rise in this potential, which is recordable as a reversible potential on horizontal eye movement and is known as the light rise (Box 5-9). Ratios less than 1.5 are abnormal, while a ratio >2.0 is regarded as normal. This effect is the result of an extracellular flow of current caused by changes in the potassium concentration in the interphotoreceptor matrix. The EOG is measured as a ratio of the light peak (i.e. peak amplitude when light adapted) to dark trough (i.e. lowest amplitude measured in the dark). The electro-oculogram (EOG) is lost in conditions that disrupt the RPE–photoreceptor relationship, such as retinal detachment.

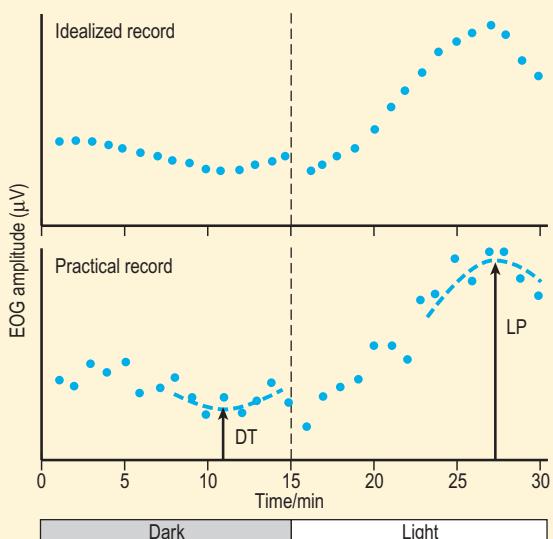
The electroretinogram

The electroretinogram (ERG) is superimposed on the electro-oculogram and is the cumulative electrical response to a light stimulus from all the retinal elements. It is affected not only by the intensity and duration of the stimulus but also by the stimulus wavelength and pattern, and the level of light–dark adaptation of the retina as for the sensory response itself.

The ERG has several components (Fig. 5-16). Under mesopic conditions, the early receptor potential is barely detectable and becomes apparent only with an extremely high-intensity flash stimulus in a deeply dark-adapted eye. It originates from the photochemical reactions in the rod outer segments on stimulation by light and is dependent on the density of rods and high levels of unbleached rhodopsin. The early receptor potential may therefore be detectable in eyes where the inner retina has been destroyed but the outer retina is substantially intact, e.g. central retinal artery

BOX 5-9 THE ELECTRO-OELOGRAM

The electro-oculogram (EOG) is a record of the electrical dipole occurring between the front and the back of the eye and reversing in current direction when the eye moves from side to side. The height of the potential difference increases in conditions of bright illumination.



An EOG recording – vertical lines represent the alternating dipole as eyes are moved from left (L) to right (R). The ‘light rise’ is seen as an increase in the height of the vertical lines as the light is switched ‘on’. The electro-oculogram (EOG) is measured in microvolts as a ‘light rise’, i.e. an increase in amplitude as the light stimulus is increased. The standard curve is shown in the upper two boxes on the left at low light levels and on the right as the light is increased. Actual EOG values are shown in the bottom two boxes. Idealized (*upper*) and practical (*lower*) EOG amplitude versus time curves for a healthy subject. The actual EOG is estimated from the points measured as in the dashed line. DT, dark trough; LP, light peak.

occlusion. However, it is not normally recorded because of the above physiological constraints.

The negative ‘a’ wave is generated by hyperpolarization in the photoreceptors’ inner segments (Granit’s PIII component), the a1 component coming from the cones and the a2 from the rods. In contrast, the ‘b’ wave (Granit’s PII component) is believed to come from the bipolar cells either directly or indirectly via signal spread to the Müller cells; b1 is generated by

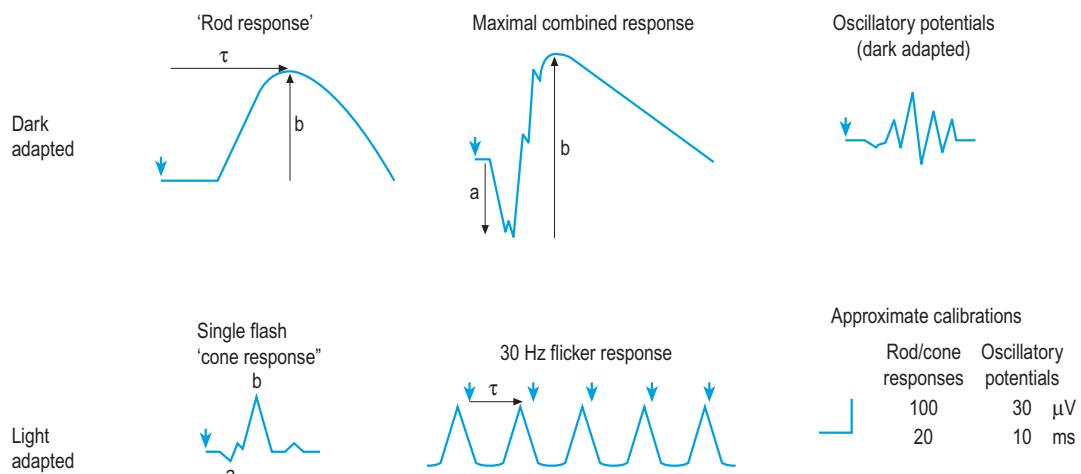


FIGURE 5-16 Diagram of the five basic ERG responses defined by the standard. These waveforms are exemplary only and are not intended to indicate minimum, maximum or even average values. Large arrowheads indicate the stimulus flash. Dotted arrows exemplify how to measure time to peak (τ , implicit time), a-wave amplitude and b-wave amplitude.

cone-dominated and b2 by rod-dominated bipolar cells. The b wave is lost in certain retinal vascular conditions, such as central retinal vein occlusion.

Oscillatory potentials are thought to be generated by amacrine cells, while the slow rising 'c' wave (Granit's PI) depends on an intact pigment epithelium. However, the electro-oculogram provides a more effective estimate of the integrity of the pigment epithelium. Oscillatory potentials are lost in patients with diabetes.

The ERG as described above is in essence a response to luminous intense stimuli. However, the pattern ERG (PERG), which is the ERG response to a reversing checkerboard of black and white squares of equivalent luminance, is thought to represent the electric response to spatial contrast, probably from ON-centre ganglion cells.

The multifocal ERG

The multifocal ERG records discrete electrophysiological responses from specified regions of the retina. An array of hexagonal elements in a changing frame is used to stimulate the retina rather than a full field flash of light and each element has a 50% chance of stimulating the defined retinal area (Fig. 5-17). Each stimulus is randomly illuminated over time, producing a continuous ERG response which is correlated

with the ON and OFF phases of each patch and so the final result is not truly an ERG response from a discrete retinal region: instead, the response is interpreted as a statistical/mathematical resolved factor and produces a typical waveform (see eFig. 5-5).

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The multifocal ERG can be evaluated in conjunction with complementary function and imaging techniques which assess the visual field: for instance, microperimetry is a technique in which the visual sensitivity to discrete stimuli of a specific area of the retina, identified by scanning laser ophthalmoscopy, is correlated with optical coherence tomographic imaging of the corresponding retinal region.

The visual evoked potential

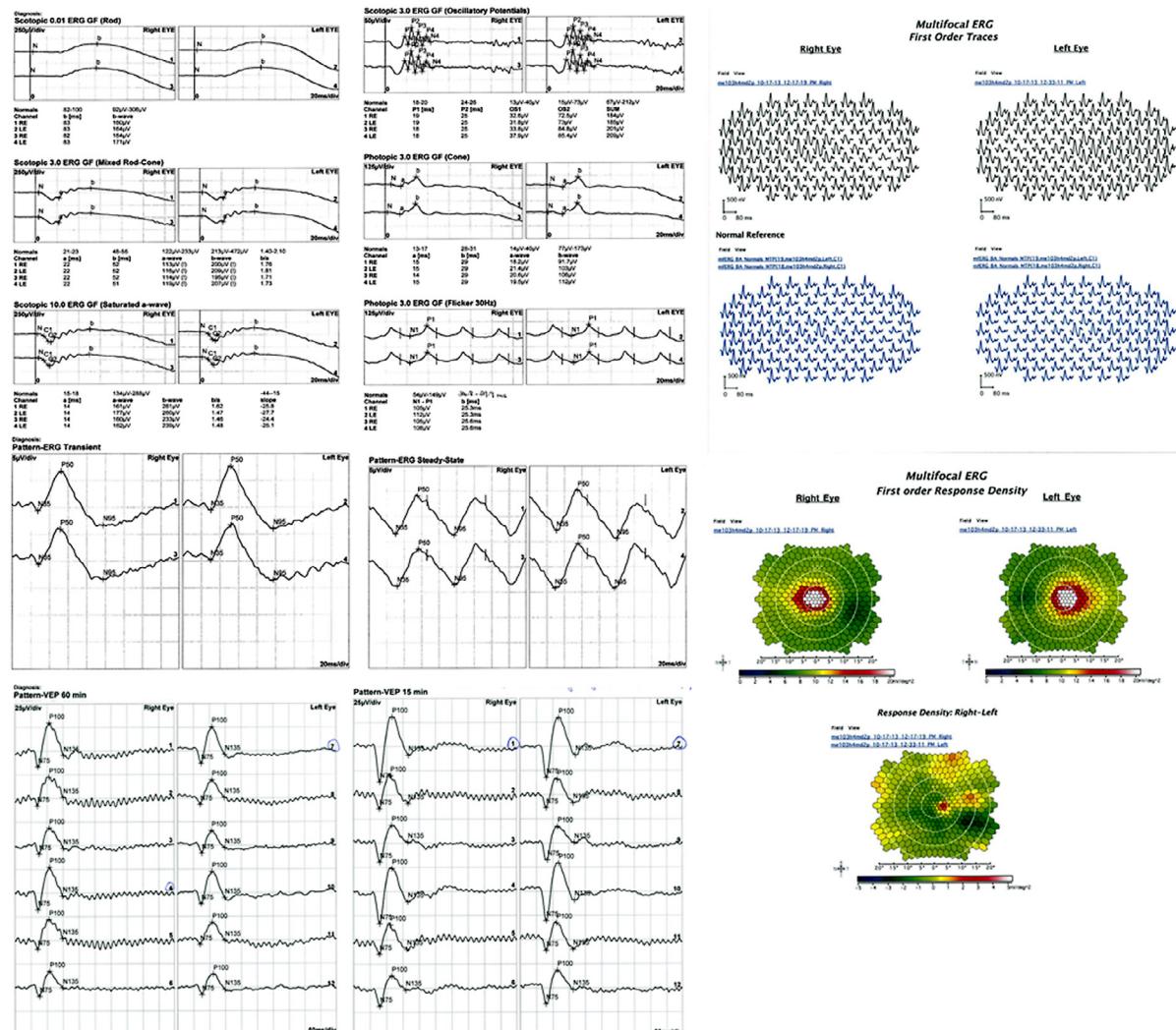
The visual evoked potential (VEP) records electric activity from the occipital cortex following presentation of a light stimulus to the retina and represents a limited electroencephalogram (EEG). Recordings are taken from a set of six electrodes placed around both left and right occipital cortices, each producing a discrete wave pattern of different amplitudes (Fig. 5-18).

Several types of VEP can be induced, including flash, flash-pattern, pattern-onset, pattern-offset and

The multifocal ERG has greatly improved the detection of functional abnormalities in the retina as well as precise localization of such abnormalities to specific regions of the retina. In a standard examination protocol several data sets are taken, including: an ISCEV standard ERG (scotopic and photopic), the multifocal ERG, a pattern ERG (both transient and steady state) as well as the

visual evoked potential using a large check and a small check stimulus (see eFig. 5-5). In addition, visual acuity and contrast sensitivity measurements are taken. Using this battery of tests, differentiation between generalized retinal dysfunction, disorders of the macula, optic nerve dysfunction and 'non-organic' disorders can be reliably made.

(Courtesy, Dr. Fred Chen, Lions Eye, University of Western Australia.)



eFIGURE 5-5 Typical set of information obtained from electrophysiological evaluation of retinal and optic nerve function.

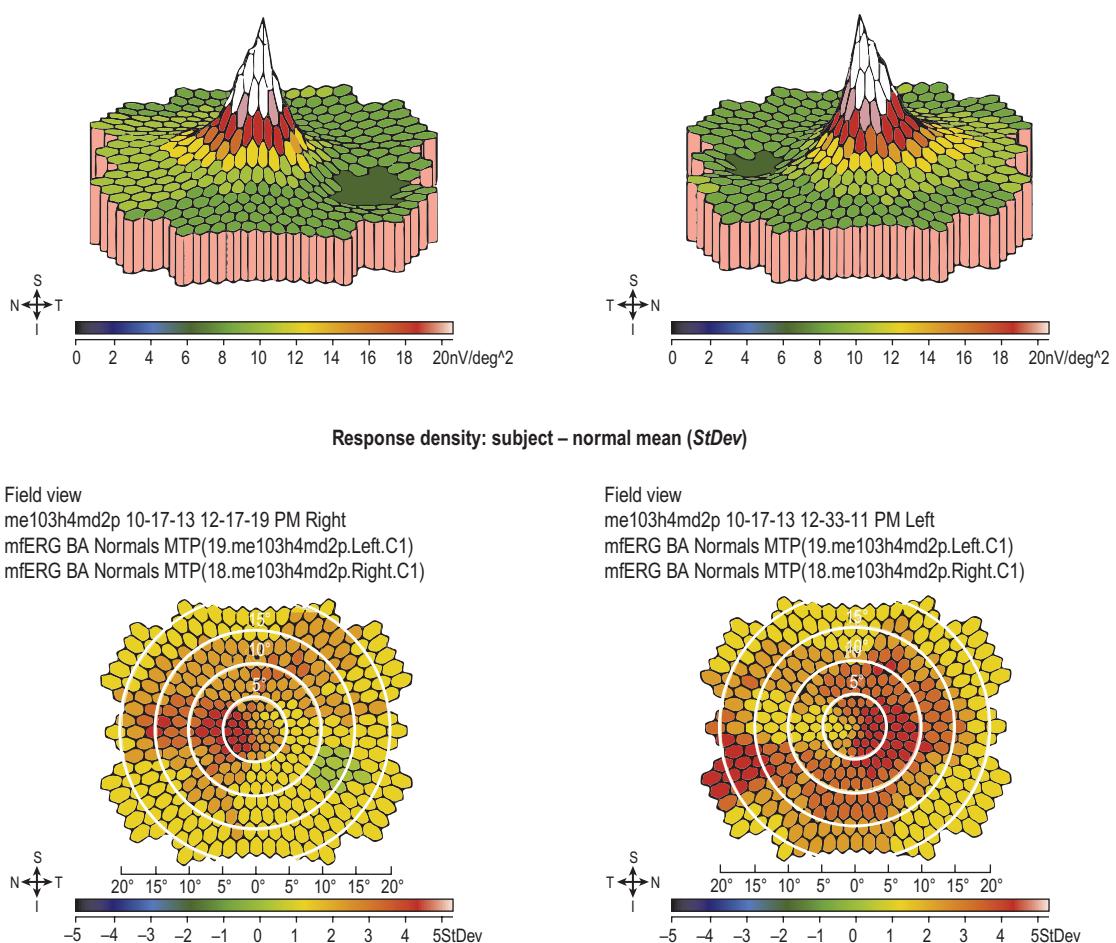


FIGURE 5-17 Normal multifocal ERG record showing the characteristic ‘hill of vision’ and the hexagonal arrays representing each retinal region analysed. (Courtesy Dr. Fred Chen, Lions Eye Institute, University of Western Australia.)

pattern-reversal. Considerable individual variability in the wave pattern is seen with the flash VEP, which is composed of two phases: the evoked potential and the after discharge.

Variations also occur in the amplitude of response, depending on the level of dark adaptation. A pattern-flash VEP is evoked when a black-and-white checkerboard stimulus is presented (Fig. 5-19). The amplitude of this response is considerably better correlated with the visual acuity. However, a significant electric interference in this response is caused by switching the stimulus on and off (the onset/offset response). The flash-evoked potential has three components – N1, P1; N2, P2;

and N3, P3 – while the pattern-evoked potential is essentially monophasic (see Figs 5-18 and 5-19). The flash VEP is considered to arise from area V2 of the cortex with its retinal origins arising in the entire papillomacular bundle, while the pattern response is considered to arise in V1 plus ganglion cell receptive fields corresponding to large checks (M cells) and small checks (P cells).

Presentation of a pattern-reversed black-and-white equiluminant checkerboard can overcome the onset–offset problem if the pattern is reversed at an appropriately short interval, as the effects tend to cancel each other out. Indeed the stimulus can be set to produce pattern-onset, pattern-offset and pattern-reversal

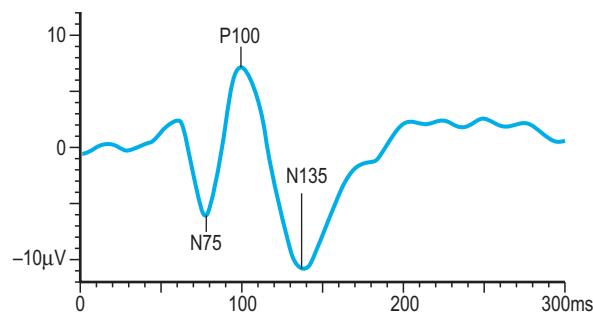


FIGURE 5-18 Diagram demonstrating the visual evoked response showing the potential map for the location of the electrical output from the scalp electrodes. (From Kevin Whittingstall: <http://fizz.phys.dal.ca/~medbiophys/kevinp.htm>.)

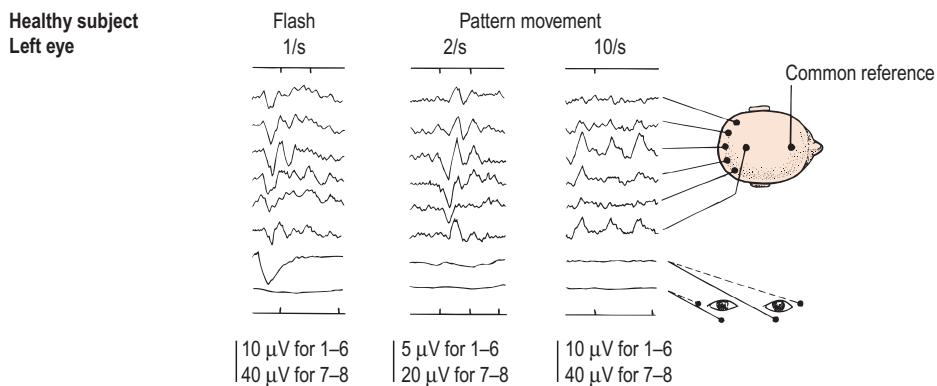


FIGURE 5-19 Flash and pattern-averaged VEP responses from each of six electrodes placed over the occipital region of the skull. Pattern reversals were performed at two different rates (middle and right panels). The two lower tracings represent simultaneous ERG recordings. (Courtesy of Dr Ikeda.)

VEPs, each of which has a characteristic set of wave patterns depending on the conditions (Fig. 5-19). Considerable ingenuity has been developed in techniques for studying half-field stimulation, macular vision and the effects of age, right versus left eye, etc. However, clinically, this test has greatest applicability in assessing the function of the optic nerve by measuring the latency of the response, and in assessing the integrity of foveal vision by evaluation of the pattern and amplitude of the wave forms.

FLICKER

A spoor or beam of light can flicker so fast that the sensation of flicker is lost. The point at which this happens is known as the critical fusion frequency (CFF) and the brightness of the steady-state light is the same as the mean brightness of the flickering light midway through its cycle. Brighter stimuli have a higher CFF and rods have less ability to achieve fusion than cones (see below).

The fact that fusion occurs at all indicates that there must be some degree of persistence of sensation after the stimulus has ceased, but clearly this is more effective at lower levels of illumination than at higher ones. Fusion is thought to be the result of an after-effect, so that a succeeding stimulus can fall on the retina while it is still responding to the first stimulus. However, it is more probably related to light adaptation in which the response to light is accelerated at higher intensities. In terms of flicker measured by an ERG response, the CFF is seen as a smoothing out of the electric response, which is set at a higher level in millivolts. Presumably it would be possible to induce a second ERG response by presenting a superimposed flash on this new level of illumination.

Subjectively, fusion occurs at 60 cycles/s, but the ERG CFF occurs at 25 cycles/s. Therefore, by setting the flicker cycle at 25 cycles/s, one can obtain, through the flicker ERG, a measure of cone function in isolation (see below). Interestingly, direct electrophysiological studies on optic nerve fibres have shown that ganglion cells with a high spike discharge rate also have a high threshold for CFF and vice versa.

Colour vision

COLORIMETRY AND COLOUR DISCRIMINATION

Colorimetry is a measure of visual function at the photoreceptor level. In contrast, colour discrimination is a cortical function related to perception and the later stages of visual processing. Colorimetry or the measurement of colour is based on techniques of colour matching, which have a long history going back to the days of Newton, Helmholtz and particularly Maxwell in the mid-nineteenth century.

For further information on Maxwell, see additional content available at <https://expertconsult.inkling.com/>.

Maxwell is credited with asserting that all vision is colour vision; in a sense, as will be seen later, this is probably a valid perspective. Standards for measuring colour have been established for certain reference conditions of illumination based on the assumption that only a small area of the central fovea is illuminated by the test stimulus; a standard V (λ) or visible wavelength curve was adopted by the Commission Internationale de l'Eclairage (CIE) in 1964. A colour (C) is specified in terms of the three primary colours by the equation:

$$C = r \cdot (R) + g \cdot (G) + b \cdot (B)$$

and is measured with colour-matching instruments such as the flicker photometer or with spectrophotometers fitted, for instance, with arrays of wavelength-selective photodiode detectors.

DIFFERENT COLOURS HAVE DIFFERENT LUMINOSITY

Spectral sensitivity curves

In the dark-adapted state, light of different wavelengths appears variably bright with a peak luminosity at about 500 nm in the blue-green region, i.e. for lights of equal energy, blue-green appears brightest in the dark (Fig. 5-20). Under photopic conditions, however, peak brightness occurs around 555 nm in the yellow-green. Brightness curves of different wavelengths like this are determined under photopic conditions by flicker photometry. This phenomenon, in which short wavelengths become brighter compared with long wavelengths as luminance is reduced, is known as the Purkinje shift, and begins under mesopic conditions when cone function is still active. Experimentally, the flicker ERG is useful in studying the Purkinje shift because rod and cone responses can be distinguished by setting the flicker rate above 25 cycles/s, which rod photoreceptors cannot detect (see

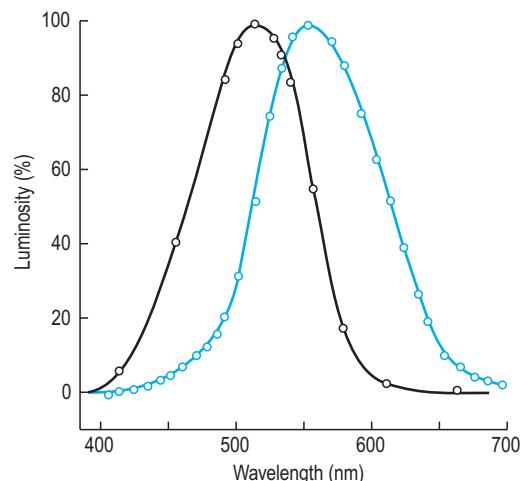


FIGURE 5-20 The Purkinje shift showing differences in luminosity observed at different wavelengths.

Described as ‘the man who changed the world’, James Clerk Maxwell is known as the most influential physicist of the nineteenth century, ranking with Isaac Newton and Albert Einstein. He developed one of the major unifying theories of physics, namely that of electromagnetism, demonstrating that light energy was one component of this unifying theory of electricity, magnetism and optics. Maxwell was born in Edinburgh and studied at Edinburgh University and after further training at Cambridge became professor of Natural Philosophy at University of Aberdeen, before moving to University College London where he developed most of his seminal work. It was while in London that he completed much of his work on colour and produced the first ‘light-fast’ colour photograph. He also completed his work on electromagnetism.

above). Purkinje shifts are therefore not detectable in guinea-pigs (pure rod) or squirrels (pure cone), but can be detected in cats, which are rod-dominated.

Although cone and rod responses can be differentiated using the flicker ERG, it is also possible to differentiate long (L) and middle (M) wavelength responses using appropriate flicker frequencies. In addition, using mixed luminance (rod) and chromatic (cone) flicker frequencies around 12 Hz and appropriate colour backgrounds for the stimuli, it has been possible to separate out the luminance and colour electrophysiological responses detectable at a retinal (ERG) level rather than at a post-signal processing (cortical /perceptual) level.

Photochromatic interval

The Purkinje shift underlies the photochromatic interval, which is a measure of the difference in 'brightness' between the absolute threshold at which light of any wavelength is just detected and the brightness at which it appears coloured. Clearly, this interval is vanishingly small at the red end of the visible spectrum and is maximal at about 570 nm.

Cone thresholds

As we have seen above, thresholds are an artificial concept that depend on a critical number of 'hits' on photoreceptors by quanta of light. In practice, under defined conditions, light thresholds are measurable and have been well characterized for rods. Cone thresholds can also be measured, for instance by using only the early part of the dark adaptation curve or by using very small bright flash stimuli, which only impinge on the central fovea. By choosing suitable conditions of light adaptation (e.g. by adapting with blue light to desensitize the rods), it is possible to measure cone thresholds with different wavelengths of light. Using wavefront adaptive optics technology which minimizes chromatic and other aberrations, the absolute threshold for cone vision has been determined at 203 ± 38 photons at the cornea and is considerably greater than previous estimates. Using these methods cone-specific spectral curves can be produced.

COLOUR DETECTION REQUIRES MORE THAN ONE TYPE OF PHOTORECEPTOR

Photoreceptors respond to stimuli by changes in the frequency of electric discharge. Indeed, this is true for

all neuronal impulses. Since photoreceptors respond to both luminosity and wavelength, a retina that has a single type of photoreceptor (such as a rod) will not be able to distinguish one stimulus from the other under different circumstances. Wavelength discrimination therefore requires a panel of photoreceptors (minimum of two) with peak responsiveness at specific wavelengths independent of their responses to changing luminosity. In theory, the more variety in receptor type with specific spectral sensitivities, the greater the ability to discriminate wavelength, as for any single wavelength stimulus it is the pattern of discharges from the entire panel of receptors that determines this discriminatory ability. Probably through evolutionary constraints, two types of cone photoreceptor provide sufficient discriminatory ability for survival of the species and the red–green medium (M) to long (L) wavelength separation is an additional component restricted to primates (see above under *Retinal connections*).

Trichromatic theory of colour vision

A specific colour or hue is therefore detected by the summation of responses from a mixture of receptors, and the contribution from each of the three primary photoreceptor types can be deduced from spectral mixing curves (*Box 5-10*). Indeed, such colour mixing phenomena are the result of 'confusion', i.e. our inability to differentiate sufficiently narrow wavelengths. This is a reflection of the physiological limits on wavelength discrimination set by our having only three cone photoreceptors. (Certain species of fish have four cone photoreceptors.)

However, hue discrimination is more than a retinal-processing phenomenon. Experiments testing the ability of humans to detect the four unique hues (red, green, yellow and blue) using three chromatic mechanisms in P cells tuned to detect L/M and S-L/M show that hue discrimination requires higher-order colour perceptual mechanisms.

Psychophysical evidence for three cone photoreceptors

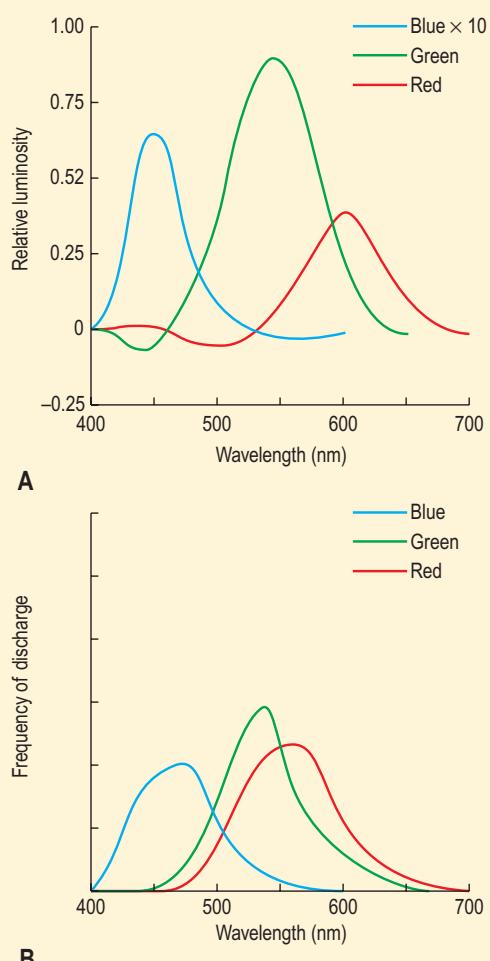
An intrinsic property of sensory receptors is to adapt and this is well demonstrated by rod (dark adaptation) and cones (light adaptation). Experiments using cone thresholds and light adaptation techniques have confirmed that there are three types of cone that respond differently to the same wavelength of light. These are

BOX 5-10 SPECTRAL MIXING CURVES

Mixing the three primary colours will produce any secondary colour or hue. However, a specific quantity of the primary colour is required to produce each hue, and this amount is determined by spectral mixing curves.

(A) Graph showing relative amount of each primary colour required to match any specific wavelength.

(B) Actual frequency of discharge in retinal neurones for each primary colour at any specific wavelength.



reflected in the spectral sensitivity curves for the three photoreceptors, which form the basis of the chromaticity chart (see pp. 272 and 275). Light adaptation is accompanied by several molecular events: (1) changes in intracellular calcium level regulating guanylate

cyclase activity in some species, duration of opsin activation and channel opening; (2) phosphodiesterase activity; and (3) a slower mechanism, possibly involving interaction between dopamine release and melatonin (see Ch. 4, pp. 247–248). Studies of colour-blind individuals have also provided confirmatory evidence of the trichromatic theory.

Similar results can be obtained using a technique known as the liminal brightness increment (l.b.i.), in which the amount of additional light required to produce a detectable difference in the brightness of a target against a changing background luminance is determined. The technique can be highly discriminatory by measuring, for instance, the liminal brightness increment in a blue central target against a green background. The studies confirmed that there are indeed single receptors that peak in the red and green regions, but the blue spectral sensitivity curve is more complex and there are probably three components for the blue mechanism. Whether the influence of rod mechanisms on these tests can be completely eliminated is not clear. Techniques combining spectral reflectance densitometry and adaptive optics in healthy volunteers have demonstrated the unique arrangement of S, M and L photoreceptors. Interestingly, despite normal colour vision, the variation in density of L and M cones, in particular, varies considerably between individuals (Fig. 5-21). It has been suggested that this may represent a compromise between the competing requirements for spatial versus colour vision, and this is reflected in the patchy distribution of the L/M cones at the fovea and their different distribution in the peripheral retina.

Molecular evidence for three receptors

Just as rhodopsin represents the molecular receptor for light energy at the level of the photon, so there are cone pigments that are sensitive to photons of light generated within specific wavebands. The amino acid sequences of these proteins are known and there are surprisingly few differences in the three cone opsins, especially in the transmembrane regions of the proteins that are important for retinal binding (see Ch. 4, eBox 4-5) (Nathans et al., 1986). These differences must, however, account for peak wavelength sensitivity of each of the three opsins, thus revealing the extraordinarily fine spectral tuning that occurs at

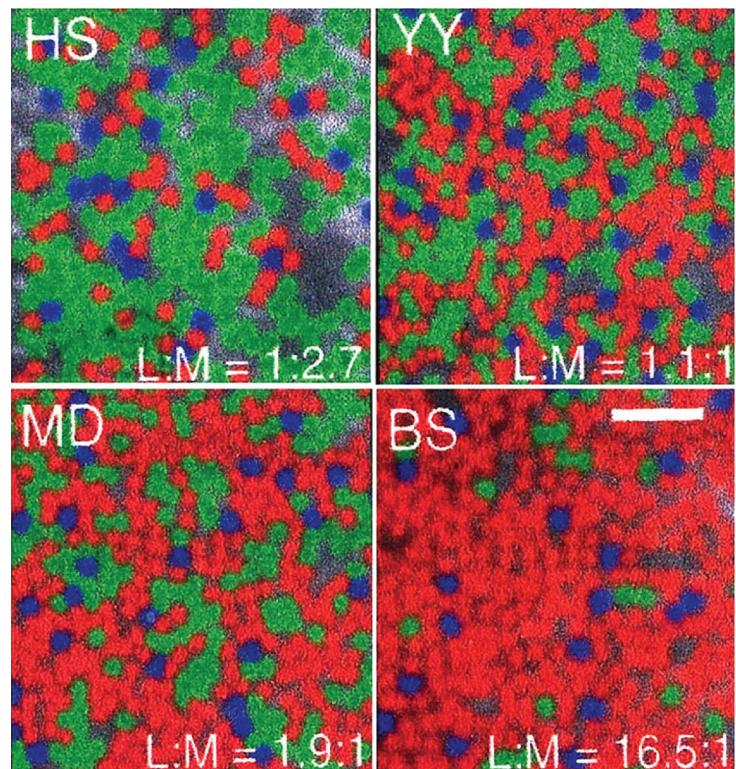


FIGURE 5-21 Images of long-wavelength (L, red), medium-wavelength (M, green) and short-wavelength (S, blue) cones as seen using adaptive optics in three healthy individuals. There is a constant ratio of blue to red and green cones but considerable variation exists between red and green cones between individuals. (From Webvision: Color vision, by Peter Gouras: <http://retina.umh.es/webvision/color.html>.)

a molecular level. For instance, a threonine at position 65 correlates with the ‘red’ opsin, while isoleucine is present at the same position in the ‘green’ opsin. Although the mechanism of light-induced activation of rhodopsin and cone opsins is in principle similarly based on the conversion of 11-cis retinal to all-trans retinal (see Ch. 4, p. 256), the differences in detail are highly physiologically significant. For instance, although the light response by cones is 100 times less sensitive, the cone opsin responses are several-fold faster, capturing something in the order of 500 photons of light per second. This is related to the availability of Ca^{2+} ions, regulated by a guanylate cyclase-activating protein. In addition, about 10% of cone opsin may be in the apo-state (i.e. lacking any binding to retinol), but still retains a sufficient level of activity to weakly activate transducin, in what is termed ‘dark’ noise (see Box 5-6).

Studies using microspectrophotometric techniques and infrared photography have shown that the distribution of the photopigments in the short-wave,

middle-wave, and long-wave sensitive cones (Fig. 5-21) is not interdependent as might have been expected on the basis of receptive field analyses (see below), but is random or clumped at least for the long- and middle-wavelength receptors. In the case of short-wave receptors, some degree of organization has been observed from immunohistochemistry data, which shows that there are different P ganglion cells for spatial, chromatic and other functions (see section on **Retinal connections**). In the foveal region, blue-sensitive cones are by far the most infrequent while, in humans at least, psychophysical studies suggest that long- to middle-waveband cones exist in a ratio of 2 : 1 (Fig. 5-21).

CONVERGENCE, YOUNG–HELMHOLTZ AND HERING Responses between photoreceptors and neural cells

Considerable processing of information occurs in the retina between the photoreceptor and the ganglion cell. In the magnocellular pathway, which deals with

light and motion detection, M ganglion cells have large receptive fields and many rod photoreceptors feed information indirectly onto a single ganglion cell (see above). In contrast, the parvocellular pathway deals with spatial and colour vision, P cells have small receptive fields, and a single cone cell may have sole input to a single bipolar cell (see Ch. 1, pp. 45–47). At a retinal level, convergence in the case of colour vision is non-existent (although there is convergence for colour in the cortex).

In spite of this, sensory perception of colour does not correlate directly with stimulation of a wavelength-specific cone. As we have seen, a red-specific bipolar cell responds simply by producing a change in the firing rate in its nerve terminal, which of itself cannot be distinguished from a similar change in a green-specific bipolar cell, i.e. the bipolar cell cannot distinguish wavelengths although its receptor can. In addition, as there is considerable overlap in the spectral sensitivity of the receptors (see Fig. 5-20 and Box 5-10), some degree of confusion must exist in the initial response, which is smoothed out during processing.

Ganglion cell responses and opponent colour theory

Smoothing out this confusion is achieved by the colour-opponent mechanism based on the receptive field organization of the ganglion cells (see Ch. 4, p. 264). In this scheme, there are three colour-opponent arrangements: a reciprocal ON-centre red/OFF-centre green, in which the bipolar cell receives stimulatory or inhibitory input from a single red or green cone; a similar ON-centre blue/OFF-centre yellow; and a third ON-centre white/OFF-centre black in which the bipolar cell receives input from all three cones and in which colour mixing occurs. This has the effect of greatly refining the spectral sensitivity of the ganglion cell responses; it allows the perception of hues and ‘unsaturated’ colours and accommodates the Young–Helmholtz trichromatic theory of colour vision with Hering’s colour-opponent scheme. It also goes some way towards explaining the various colour anomalies found in humans.

Studies have shown that blue-ON/yellow-OFF responses arise from a distinctive bistratified ganglion cell type derived from a dual excitatory cone bipolar cell input: an ON-bipolar cell receiving input only

from S cones and an OFF-bipolar cell contacting L and M cone inputs. The mechanism of red–green opponency is still unknown. However, a recently proposed theory that incorporates a contribution of ‘white’ from rods stimulated under light conditions to the cone input allows a unified concept of how vision is integrated through simultaneous rod and cone input to allow subtle visual perception, such as hue discrimination, motion detection, orientation selectivity and others.

This last concept has been further modified with the discovery of the melanopsin-containing ganglion cells. Although these light-sensitive cells are considered to sense ‘irradiance’ (see Ch. 4, p. 249), it has been shown that they also can sense colour if the threshold is set sufficiently high. Thus while the trichromatic theory still holds true at the fovea, with three sets of cones detecting L+ (L+M), (L-M)+M, and (S-(L+M)) ON-OFF colour opponent receptive fields, in the periphery there is a fourth receptor, generating a tetrachromatic mode of colour vision detection, but whether this modifies perception of colours as tested in colour matching experiments is not known and the most accepted notion at present is that this fourth receptor influences visibility rather than specific wavelength detection (Fig. 5-22).

Colour constancy

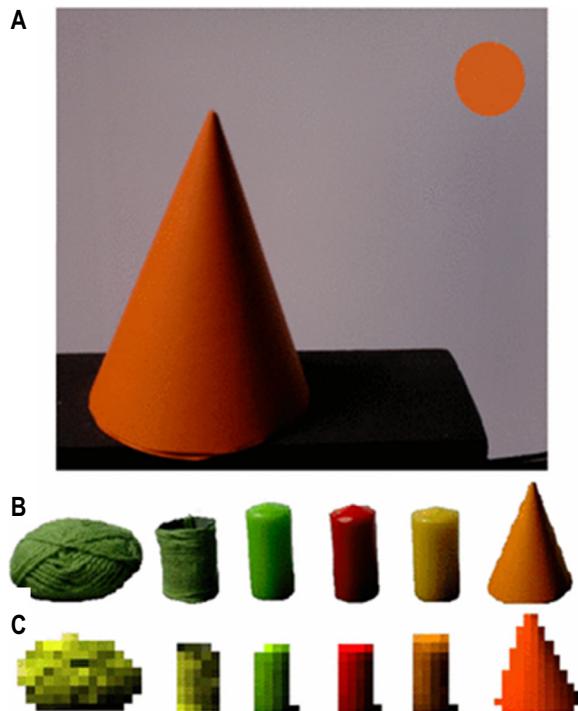
We use colour to detect and recognize objects. Most of the light we detect is light reflected from objects, and their colour depends mainly on the surface properties of the object and not on the illuminating light. The wavelength of the reflected light clearly varies with the lighting conditions. In spite of this, the colour of an object remains the same, a phenomenon known as colour constancy, which is a function of higher visual processing in the cortex.

Factors determining the perception of colour (colour sensitivity) as well as other perceptions (lightness of an object, contrast sensitivity, sensitivity of depth perception) are influenced by several factors including attention, fixation and eye movement. It has been shown that we tend to take the brighter parts of an object much more into account when we make colour or brightness matches.

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Both the illumination and the light reflecting from an object, as well as the composition of the scene, determine the amount of light reaching the eye. However, only the reflectance is constant and is therefore the most important factor for vision. When we look at an object we interrogate the scene both with eye movements and attention and where we look strongly influences our judgement of object properties such as lightness and texture. Our natural tendency is to fixate objects which are brightest and we fix even more closely on the brightest parts of an object and use this level of lightness to determine its colour (as in colour matching tests; [eFig. 5-6](#)). For instance in the figure shown opposite, Toscani and colleagues tested an individual's colour matching abilities using the set-up shown: the orange paper cone (**A**) is variably 'bright' from one side to the other and was one of a series of real objects used to match spectroradiometrically with a corresponding image on a cathode ray tube monitor ([Toscani et al., 2013](#)). Several real objects were used, such as a green wool ball, a green wool cylinder (same wool), green candle, red candle, yellow candle, and orange paper cone as shown in (**B**), while (**C**) shows the spectroradiometric data transformed to RGB (red–green–blue) values. The reason for this is that the brightest or 'lightest', i.e. most immunodominant, part of an object gives us the greatest information regarding the object's reflectance and, because it is constant, we rely more heavily on this for visual judgements. A recent review of colour vision, perception and colour constancy has been published by [Conway \(2009\)](#).



eFIGURE 5-6 Matching set-up for generating visual information (see text for explanation). (From [Toscani et al., 2013](#).)

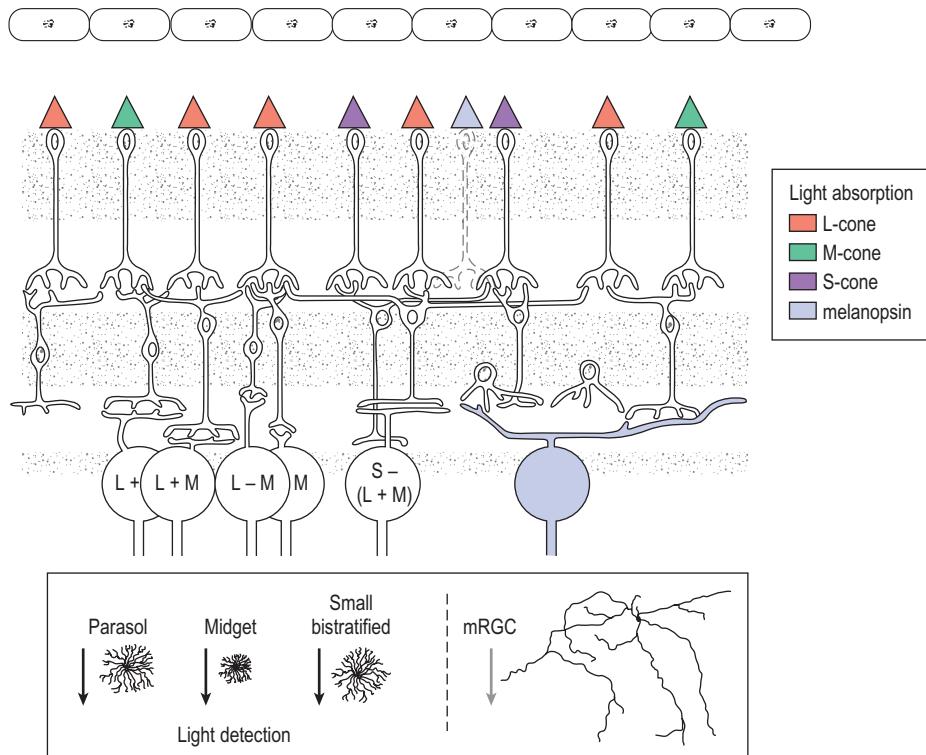


FIGURE 5-22 Schematic diagram of the retina showing the three light-sensing cones: in photopic conditions, rod vision is minimal (as Maxwell claimed: ‘most vision is colour vision’). Detection of light is mediated by multiple types of ganglion cell serving the three main channels of composite light ($L+M$, $L-M$, and $S-(L+M)$). In addition, there is a small population of newly discovered ganglion cells containing a fourth photopigment, melanopsin, and most recently melanopsin-containing cones have also been discovered, but the nature of their contribution to vision is as yet unknown. (From Horiguchi et al., 2013.)

Remarkably, colour constancy remains stable during a normal life span despite changes in peripheral vision and lens transparency to yellow light. Cortical compensatory mechanisms are considered to allow this.

COLOUR BLINDNESS

Some of the defined colour vision defects can be explained in simple terms of loss of one or other specific type of receptor. However, in practice the situation is often more complex, involving not the loss of one particular receptor but the production of combination genes as the result, for instance, of aberrant crossing over in meiosis (see Ch. 3, p. 131); these produce proteins that are intermediate in their spectral sensitivities, thus reducing the range of responsiveness of the protein.

Monochromatism

Rod monochromatism occurs in about 1 in 30 000 of the population; such individuals have true achromatic vision, low visual acuity (0.1–0.3), find high-intensity lights uncomfortable, display nystagmus, and may have some signs of macular dystrophy. These patients have morphologically normal cones in their outer retina but their functional status is unclear. It has been suggested that they have a single type of blue cone.

Cone monochromatism is very rare (1 in 100 000). These individuals have normal visual acuity but cannot discriminate coloured lights of equal luminosity. Apparently, cone monochromats possess all three types of cones, indicating that the defect occurs in cortical processing, probably in area V4.

Dichromatism

Dichromatism occurs when the affected individual matches all colours with mixtures of two primaries. Therefore, the range of secondary colours is restricted. Protanopes are missing the red wavelength, deutanopes the green, and tritanopes the blue. Mixing of the two colours will produce a sensation of white at certain specificities, which for protanopes is 495 nm and for deutanopes is 500 nm. The dichromat cannot distinguish the large range of non-spectral hues from spectral hues as the trichromat can, leading to a much narrower range of colour detection by the isocolour charts.

Anomalous trichromatism

Red-green colour deficiency occurs in around 10% of males and is X-linked (see Ch. 3, p. 137). Due to their close relationship on the chromosome, unequal recombination events can readily occur, thus removing the green (deutanopia) or the red (protanopia) genes. Defects in S cone opsin are much less frequent.

Red-green colour deficiency is rarely absolute and in effect such individuals are 'anomalous trichromats' in that they use different proportions of the three primaries to match colour. This is due to the fact that with one single L gene and several M isogenes (mostly single gene polymorphism at Ser180Ala on the red opsin gene), all of which have considerable homology, there is considerable scope for generation of hybrid genes. Thus, protans use more red, deutans more green and tritans more blue. The colour-anomalous individual differs from the trichromat and the dichromat in that he or she will not accept those matches that the other two agree on. This is the common form of 'colour blindness', occurring in 10% of the male population.

Achromatopsia

Colour blindness may also be the result of defects in cortical processing (area V4). Congenital (rare) or acquired lesions in the lingual or fusiform gyrus are associated with cerebral achromatopsia (also accompanied by prosopagnosia – a failure to recognize familiar faces, i.e. from memory). Similarly, cortical lesions in the superior temporal sulcus (V5) can produce defects in the ability to detect motion (motion blindness or akinetopsia; see p. 319). Isolated

defects in form vision have not so far been detected, possibly because they involve more than one cortical area, e.g. V3 and V4, plus connections to other cortical regions involved in psychophysical attributes, and texture analysis.

Visual perception

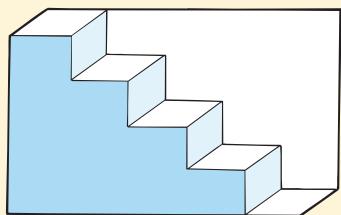
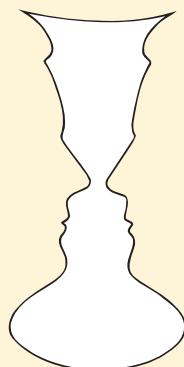
Visual perception is the end product of the processing or reinterpretation by the cortex of sensory responses made by the retina to visual stimuli. However, a strict separation of cortical and retinal events does not occur as some degree of processing takes place in the retina and, conversely, certain processes such as instantaneous parallax (see below) occur so quickly that it is difficult to believe they occur exclusively at a cortical level. In addition, perception should not be considered solely as the end product of the processing of sensory information. Instead, it is part of the 'action–perception cycle', in which perception modifies activity, which then modifies perception in a continuous cyclic pattern, the boundaries of which become indistinct (Wexler and Boxtel, 2005). Motor activity (head and eye positioning, etc.), therefore, is central to perception such as stereopsis (see below) and colour (see above).

As shown above, there are many different types of visual stimuli, each of which may produce one or more different psychophysical perceptual responses. Sensory perception occurring at an elemental level encompasses visual stimuli such as luminosity, flicker, colour and form, because it involves simple processing of features such as points and lines or wavelengths, but even such an apparently fundamental function as visual acuity determination involves higher levels of processing because it is more than simply a point-to-point projection of the retina on the cortex.

Evidence for higher integrative activity at the cortical level comes from illusions such as the Schrödinger staircase and Rubin's vase as well as more specific illusions that involve both space and time such as the tilt illusions (Box 5-11). A clear example of the role of cortical function in visual perception is the phenomenon of colour constancy in which large variations in the chromaticity of an object, induced for instance by changing the wavelength of the illuminating light of the object, do not alter the perceived

BOX 5-11 VISUAL ILLUSIONS

Visual illusions such as the Schrödinger staircase (**A**) and Rubin's vase (**B**) occur in a cyclical manner in which each of the perceptions regularly alternates. Such illusions have a periodicity and are in this sense time-dependent. In addition they can be modified spatially, as in the tilt illusion (**C**) in which a vertically oriented tilted image occupying a surround region of vertical stripes will generate the illusion that the orthogonally vertical surround stripes are tilted in the opposite direction. This illusion can be overcome by adaptation using an image after-effect induced by gazing for 30 seconds or more at stripes tilted anti-parallel to the original image and then quickly fixating on the tilted image once more. The periodicity of the fluctuations is also alterable with drugs.

**A****B****C** Tilt illusion

(**A**) Schrödinger's staircase; (**B**) Rubin's vase; (**C**) the tilt illusion.

colour of the object: a yellow banana remains yellow even when illuminated by a green light (see above).

Our understanding of these processes has been greatly advanced by the careful analysis of both the stimuli and the responses, and has allowed specific functions to be attributed to discrete regions of the cortex.

MONOCULAR VERSUS BINOCULAR VISION

Positioning objects in space

Most of the primary visual sensory responses are monocular and are not changed by binocular viewing. Images of objects are projected onto definite positions in space (spatial perception) and each retina has its own delimited visual field. However, the position of an object in space is not an absolute entity but is related to the position of the observer and of other objects. The relative position of objects can be determined only if the retinal sensors are composed of discrete units that have precise 'markers' for localization. This, indeed, is the basis of the visual field.

In spite of this, objects appear fixed in position even when the observer changes position; simple ray diagrams demonstrate that a new set of retinal receptors must be stimulated every time the relative position of the object to the observer changes, but the observer does not experience the sensation of motion. This 'image stabilization' is achieved by compensatory psychophysical events at the cortical level. Recently, however, it has been shown that a proportion of this neural processing takes place at the retinal level through selective inhibition of ganglion cell firing (see above).

The existence of such mechanisms can be deduced in part from experiments showing that accurate localization of objects does not occur with all forms of eye or head movement. For instance, if the eye of an alert individual is forcibly moved using a surgical instrument such as a squint hook, the image is falsely projected to an incorrect position as if the eye has not moved. Spatial perception on normal eye movement must therefore be integrated with, if not controlled by, higher centres within the brain, such as the frontal cortical eye fields, which influence motor discharge in the ocular muscles. The corollary, of course, is that the proprioceptive stretch receptors in the ocular muscles

do not have a role in determining eye position as was previously thought, but that their probable role is simply to coordinate muscle tension in opposing muscles at a local ‘axon reflex’ level. This, however, may not hold true for all situations.

For instance, a problem arises in analysis of images that are perceived during slow visual tracking of a moving object. Despite the fact that no compensation is made for movements of the eyes during tracking, the changing position of the object is accurately observed and followed. This indicates that the higher centres are receiving a continuous flow of information from centres controlling ocular muscle movement, which is assimilated into the total information concerning object positioning; the actual adjustment of speed of eye movement to permit accurate tracking is achieved through visual input, which is ignored by the perceptual process. This means that having initiated a tracking movement, sequential images are interpreted on angular velocity assumptions determined by this initial response and ignored by the higher integrative centres. These assumptions may, of course, be inaccurate, especially if the velocity of the moving target changes. Thus, any induced errors require repetitive readjustments of the tracking response.

Conclusions derived from experiments such as these are greatly influenced by the design of the experiment. It has been observed that the perception of heading (i.e. the direction taken by the observer under conditions of radial retinal image flow, or optic flow) in a situation where a moving target is also fixated can be achieved accurately only if extraretinal information concerning the position of the eyes is available, i.e. via proprioceptors from extraocular and head and neck muscles. Under special circumstances, such information, termed structure from motion (SFM) information, can be integrated with purely retinal image information. In addition, the resultant perception can vary significantly depending on whether the object or the observer is moving, even if the relative disparity in motion between them is the same. This sort of information has direct relevance to clinical problems, as in the condition of oscillopsia, where image stabilization is lost and the patient experiences ‘retinal slip’ (see next section). In such patients it is not clear whether the defect lies in the well-established vestibulo-ocular reflexes or whether loss of a putative

cervico-ocular reflex, via neck proprioceptors, is contributory.

Thus spatial constancy, i.e. maintaining a ‘stationary’ percept of moving objects despite their repeated and sudden changes in retinal stimulation, is a fundamental visual perception. Spatial constancy also has a memory component. When an illuminated object is viewed in the dark, the eyes will, after an initial ‘searching’ response, adopt a position close to fixation (approximately within 2° of the target) when the illumination is switched off (Fig. 5-23). This has been attributed to some element of positional sense from an extraretinal source, such as head–eye position in space and locomotion (egocentric versus allocentric signals). Similarly, the constant drift of the eyes towards fixation in the dark has been attributed to a similar mechanism (see next section). ‘Place’ cells occur in the hypothalamus and thalamus of the brain and correct visual input to active locomotor and possibly navigational (optic flow, see below) input.

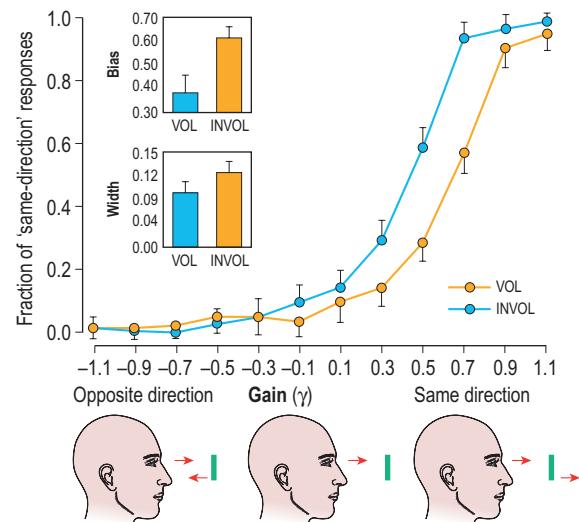


FIGURE 5-23 Results of the voluntary (VOL) and involuntary (INVOL) eye movement studies. The curves show responses averaged over subjects, and over all simulated distances (there was no significant effect of distance). Mean bias and width were calculated by fitting the data of individual subjects with the logistic curves and averaging the parameters thus obtained. Bars indicate between-subjects standard errors. (From Wexler, 2003, with permission from Blackwell Publishing.)

Measuring by eye

We frequently use our vision to measure things by eye, e.g. to line up objects in a row or to determine the distance between two points. Simplistically, it might be thought that, for example, the distance between two objects should correlate with a defined distance between stimulated receptors in the retina, or that the length of a line will be determined by stimulation of a fixed number of retinal receptors. However, the psychophysical basis of these abilities is not as simple as it might appear. For instance, two lines of the same length running in different directions may stimulate a different number of receptors as the direction of lines will be distorted by the curvature of the eye and its position on eye movement. In addition, errors will be introduced on head movement since the head rolls further than the eye in the socket (some of this disparity is compensated for by input from the

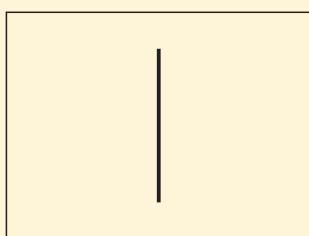
semicircular canals). Attempts have been made to adjust for image distortion due to eye curvature and movement using after-images, which obviously must reflect closely the actual retinal stimulation versus the 'real' direction of the object, but even this is not sufficient to account for the fact that we perceive the object in its true position and not in its distorted position. This is nicely demonstrated by Aubert's phenomenon (Box 5-12) in which the speed of a moving object appears slower when the object is tracked by eye movements than when its motion is detected with the eyes remaining in one position, i.e. the object is not visually tracked.

A compensatory mechanism based in the higher centres must therefore be in place; it must be highly developed because the accuracy of measuring by eye is extremely high: for detecting the orientation of horizontal lines the error rate is 0.2% and for vertical lines

BOX 5-12 AUBERT'S PHENOMENON

A vertical bright light viewed in a completely dark room will tilt to the left if the head is slowly tilted to the right (**B**). If the head is tilted suddenly or if the line is viewed in the light, the line appears upright in its normal position

(**C**). Thus information on retinal position is fed via the semicircular canals to the object-positioning centre; (**A**) resting position.



A



B



C

(**A**) Resting position; (**B**) slow head tilt to right, object appears to move to left; (**C**) fast head tilt to right, object stays upright.

it is 1.0%, as determined with a perceived direction test. The greater accuracy for estimating vertical and horizontal lines over oblique lines is not the result of preferred direction of eye movements or of the numbers of retinal receptors stimulated but is a function of cortical activity.

Considerable evidence has now accrued to show that the visual cortex contains specific cells that are responsive to the orientation of lines. Indeed, the ability to 'parse visual scenes for the orientation of purely spatial cues' has been shown to be a fundamental property of even the simple insect brain. Vertical and horizontal orientation detectors occur as simple cortical cells (see below) and are distinct from motion detectors. Orientation detectors are considered essential to the analysis of form.

The patterns of objects also greatly influence our ability to make visual measurements. For instance, two angles can be accurately compared if we can fixate each of them directly and if the sides are parallel. In addition there are numerous examples of optical illusions where objects to be compared appear to be different in length or area/size if one of them has been altered by the addition of other visual cues that are interpreted by the higher visual centres in one particular direction (see [Box 5-11](#)).

Therefore, both patterns and directions are important in visually estimating object dimensions: the retina uses the horizontal and vertical meridians as x and y axes to provide coordinates and thereby to pinpoint objects in space. As these axes are subject to displacement by, for instance, eye movement, it is important that a psychophysical compensatory mechanism exists that will reinterpret the position of the co-ordinates to project the real position and direction of the object in space.

Are two eyes better than one?

As most 'objects' are three-dimensional, it is clearly important that depth perception is achievable by the visual system. The major advantage obtained by binocular viewing is that it permits depth perception or stereopsis. This occurs in the cortex and depends on the fusion of images from each eye. However, depth perception is a complex event and information from many sources is used to achieve it.

One mechanism for depth perception could be related to the convergence of the eyes. Fixation of an object with both eyes requires a variable degree of convergence depending on the distance of the object, and information derived from this can be utilized to determine object distance. Indeed it has been suggested that variations in convergence can lead to three-dimensional illusions, although these may be caused by other mechanisms.

Is it possible to perceive depth with one eye only? Determination of object position using x and y axes as described above provides two-dimensional information only. Geometrically, it should not be possible to obtain three-dimensional information using one eye. However, certain cues, mostly built upon previous experience, indicate that some sense of depth is possible, e.g. by comparing the relative size of objects (for example, a person and a house), the blue colour of distant mountains (although they should be yellow – they are darker blue in comparison with the background light blue of the sky), overlapping edges of objects, effects of light and dark shading, effects of texture, and parallax on movement of the observer's head. It has also been suggested that the sensory feedback from the ciliary muscles on accommodation might provide some information centrally regarding depth (similar to the effects of convergence when both eyes are used), but this is unlikely.

When both eyes are used to observe an object in the straight ahead (primary) position, the image is still perceived as one, even though the image of that object must appear positionally but symmetrically different to each eye individually – indeed the image can be treated as if it were projected from a single centrally placed eye (the 'cyclopean' eye). When a second object is presented in the primary position, but closer to the observer than the original object, the second object is seen double when the original object is fixated ([Fig. 5-24](#)). Diplopia in this position is described as heteronymous; when the second object is distant from the first, the induced diplopia is described as homonymous. However, this form of diplopia is rarely appreciated because we normally do not attempt to fixate more than one object in the primary position when viewing with both eyes. When we aim at a target using a second object to line up fixation, as with the sights

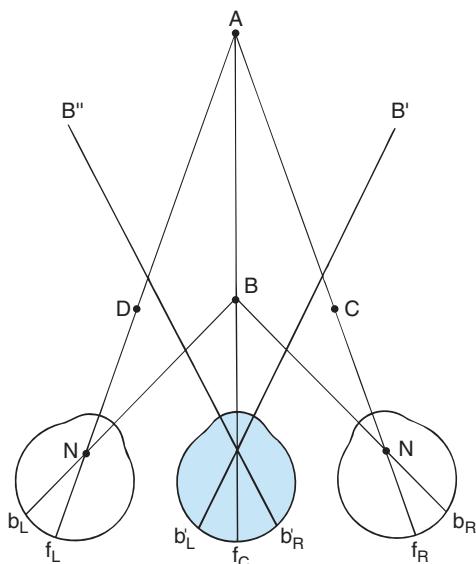


FIGURE 5-24 The ‘cyclopean eye’ (shaded) is the abstract notion representing fusion of the two images from left and right. Image A is fused ($f_L + f_R$ at f_C) but image B cannot be simultaneously viewed without diplopia (heteronymous) ($b_L + b_R$ at b'_L and b'_R) due to the projected images at B' and B'' , respectively. Homonymous diplopia would occur if B was distant from A. Using either eye alone for alignment of the object would entail point C aligning with A (right eye) and point D aligning with A for the left eye. N, nodal point. (Courtesy of H. Dawson.)

of a rifle, we normally do so with one eye only (see Fig. 5-24).

A similar form of diplopia can be induced by a divergent squint, or by placing a base-out prism in front of one eye; both of these conditions have the effect of re-siting the projection of the image to a ‘false’ position from its normal cyclopean position. False projection in a squinting eye can lead to the development of a ‘false’ macula, which in fact is a cortical event because the anatomy of the retina remains the same. The development of a false macula reflects the plasticity of the cortex and indicates that projection of the eye through the nodal point is an innate mechanism. A similar ‘pseudofovea’ may develop in the presence of hemianopia.

The fact that we rarely experience double vision, even when rapidly and simultaneously fixating many objects in a scene, indicates that the images from both eyes are merged or fused; this is not simply a reduplication of information from both eyes but an actual

psychophysical event that is used to provide depth information or stereopsis.

STEREOPSIS AND DEPTH PERCEPTION

The fusion of images to create the perception of depth requires certain conditions: first, the images from each eye must have corresponding points on both retinas. If all points on a sizeable object were exactly corresponding, however, this would merely lead to a reduplication of information and it is likely that only one of these points would register (this would be analogous to allelic dominance in chromosomal gene duplication in which only one gene is expressed transcriptionally while its partner is not; see Ch. 3, p. 137). Single-cell measurements have shown, however, that impulses from both retinas induce electrical activity in cortical neurones.

The second requirement for image fusion is that a certain proportion of points are non-corresponding, and represent the differences between the two images on the retina, which may be smaller than the width of a single cone, and are known as binocular disparities.

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It is the integration of information from corresponding and disparate points that induces the perception of depth. Both position and phase disparity in the corresponding receptive fields are important in the detection of depth cues (Fig. 5-25).

The horopter

Psychophysical and theoretical investigation of the projected points in space where an object is seen as a single image have a long history going back to the ancient studies of Ptolemy and the work of Ibn al-Haytham in the eleventh century. The corresponding regions in the retina include both the horizontal and vertical meridia and equidistant points from each of these meridia. Single vision can be achieved only when the images of the object are projected from each eye to the same point in space.

Corresponding points can be charted as a ‘horopter’, in which specific points on the retina project to definite single points in space – within the field of binocular single vision (Box 5-13). The vertical horopter has a backwards tilt that passes through the fixation point and a point near the feet of the observer

The images registered through each eye are different (see open access link to <http://www.vision3d.com/stereo.html>) and the brain processes these images, making note particularly of the differences (disparities). Simultaneous registration of the images is thought to be necessary for the images to be fused, although there is evidence that each image is registered differently in time, i.e. each eye takes a 'shot' of the image with a very brief time interval between the registrations. Stereopsis can be measured with a variety of devices, one of the oldest being the stereoscope, which is essentially an instrument constructed from a pair of base-out prisms, whose position can be manipulated. The stereoscope has a long history but continues to be modernized, one of the latest being the View-Master® which is now fully within the digital age and includes a video-based version (see <http://gajitz.com/view-master-grows-up-modern-stereoscope-video-viewer/>).

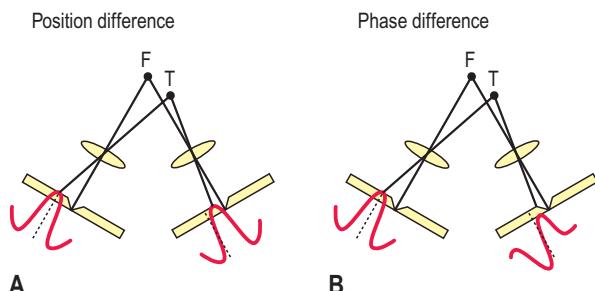


FIGURE 5-25 Depth perception based on binocular disparities. The fovea of each eye fixates point F; because object T is closer than F, the image of T falls at a different retinal location in the two eyes. The dotted line marks the equivalent retinal location in the two eyes. Neurones with receptive fields in both eyes could detect this disparity in two ways. (A) Position difference: the right eye receptive field is an exact copy of the left eye receptive field, but in a different retinal location. (B) Phase difference: the envelope enclosing the right receptive field profile sits in the same position as for the left receptive field but, within the envelope, the right receptive field has a different structure, responding best to white light on the right-hand side. When tested with a bright bar, both of these mechanisms produce a maximal response to a stimulus with a disparity equal to that of T. (From Cumming, 1997, with permission from Elsevier.)

and is the result of a shear in binocular retinal correspondence. Thus the vertical horopter takes the form of a cylinder which may be reversed (see Box 5-13). The true (empirical/actual) horopter is strictly limited to an area of about 3° from fixation, as determined experimentally. A special form of horopter is one based solely on corresponding points, defined as a circle of projected points in space passing through the fixation point and the nodal point of the eye (theoretical horopter). This is truly applicable only in the horizontal meridian, as the vertical meridians are not exactly parallel. Horizontally placed horopters can form a 'stack of slices', producing a longitudinal horopter named so as to reflect the vertical lines of longitude on the globe of the earth. In practical terms the longitudinal horopter is not a circle but has a well-defined shape, approximately representing the field of binocular single vision (BSV) (see Box 5-13).

The field of BSV is an important parameter, not simply from a physiological standpoint but also for socioeconomic reasons. The normal visual field of each eye is approximately elliptical, with a considerable degree of overlap (Fig. 5-26), and the overlapping fields of each eye represent the field of BSV in which

full stereopsis is assumed to occur in the context of horopter-related corresponding points on the retina. In the UK, a certain minimum field of BSV is required to qualify for a driver's licence and is defined as a BSV field of 20° above and below the horizontal meridian and 60° to either side of the vertical meridian (Fig. 5-26). Measurement of visual fields can be performed by many techniques: currently, static automated visual fields are the normal practice, although kinetic and flicker-based fields are also highly informative. In addition, microperimetry is a development of visual field testing, which, when combined with scanning-laser ophthalmoscopy, permits fine retinal mapping and analysis of discrete regions of retinal function or dysfunction.

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Thus it has considerable value for detecting retina-derived as opposed to visual pathway associated field defects (see Ch. 1, p. 92). In clinical practice, quite different visual field tests are performed when assessing either of these central causes of visual field defects.

The horizontal horopter is also defined for specific fixation points and therefore certain degrees of convergence; clearly this will change with the distance from the observer. At about 2 m from the observer the horopter is approximately a straight line, while it is concave to the face within this distance and convex beyond (see Box 5-13).

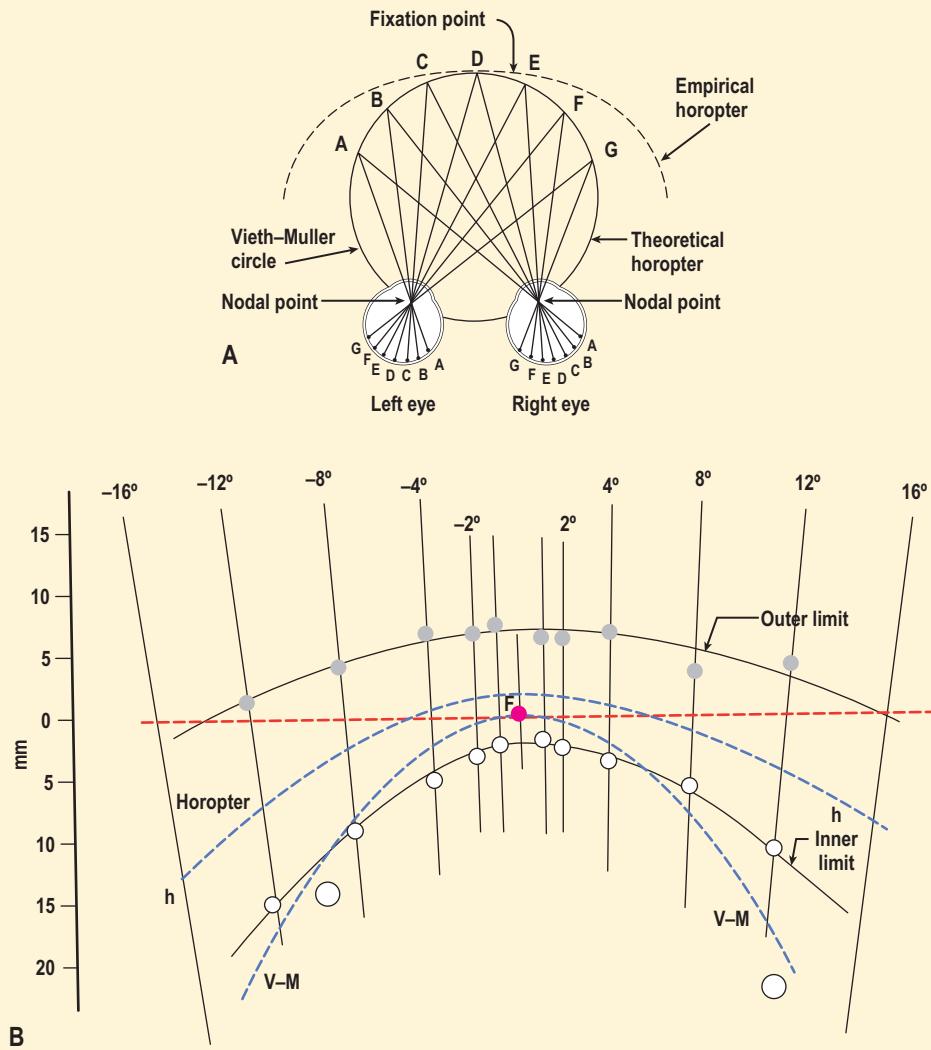
Measuring stereopsis

The measurement of stereopsis involves at least two parameters: the degree of convergence required to fuse images from two slightly dissimilar objects, and the limits of dissimilarity between two objects at which the two images can be fused (stereoacuity). The former is relatively easy to measure with an instrument incorporating two base-out prisms, known as a stereoscope. In the stereoscope, two slightly dissimilar but symmetrical images are presented to each eye and the angle of convergence at which the sensation of depth is achieved is recorded. In practice, true stereopsis is not measured by this method because light and shade (i.e. monocular cues) provide considerable amounts of image disparity to the same object viewed by each eye in turn. Other tests that remove the monocular cues but use a camouflaged object include the

BOX 5-13 CORRESPONDING POINTS OF FIXATION ON THE RETINA CONSTITUTE THE 'HOROPTER' FIELD OF VISION

(A) The horopter circle. The theoretical horopter circle is shown as the dark inner sphere, while the actual horopter for an emmetropic individual is shown by the dashed line. The horopter has been known for centuries. However, in 1818 Vieth-Muller calculated that the horizontal line of binocular fixation was a circle which passed through the centre (nodal point) of the lenses.

(B) The binocular single vision horopter field. In practice the 'empirical' horopter is larger than the theoretical horopter since there are many more areas both forward and rear of the circle where single vision can be obtained: these are the inner and outer limits of binocular single vision and correspond to Panum's area.



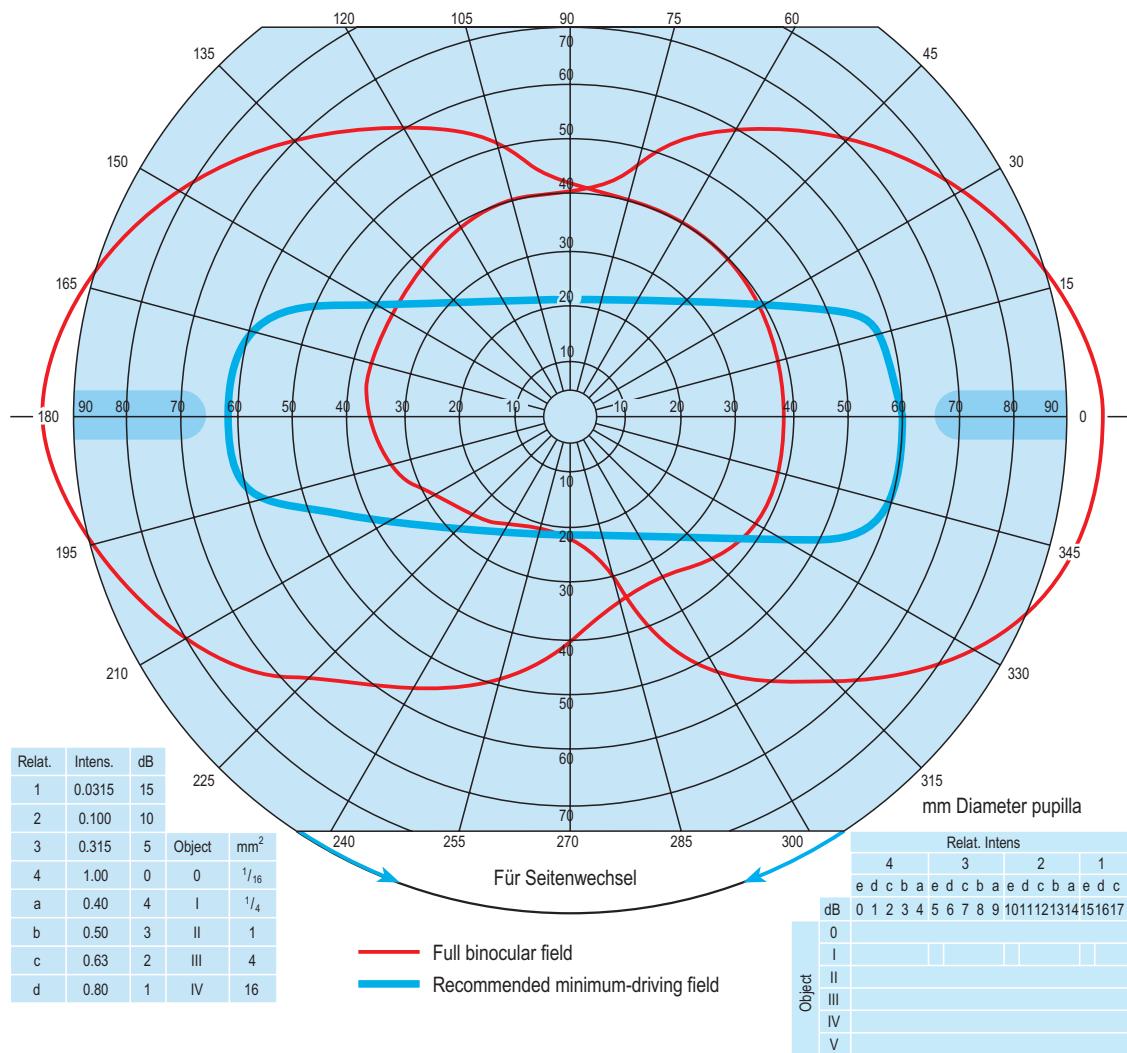


FIGURE 5-26 The field of vision for each eye separately, the field of binocular vision (BSV) and the minimum visual field required for driving licence purposes in the UK are shown. (Courtesy of H. Dawson.)

random-dot stereogram, the random-dot E-test and the Frisby test, in which elements that are non-resolvable monocularly are presented in a random pattern at different disparities and the ability to perceive depth and form in the objects is assessed.

Stereoacuity can be measured as instantaneous parallax, which is the difference in binocular parallax of both objects (Fig. 5-27). The limits of stereoacuity are in the region of 4' of arc (range 1.6–24'), which is equivalent to an image disparity less than the diameter of a cone. Instantaneous parallax is lost at a distance

of about 450 m but varies with the measurement technique. Conversely, within a certain range of distances, stereoacuity is improved the further away the object is from the observer, although theoretically this should not be so. In this case, the improvement is attributed to greater differences in monocular cues such as relative object size, to which the eye is more sensitive, than instantaneous parallax. Stereopsis also improves with duration of the stimulus, which is not the result of small searching or ‘image-refreshing’ movements of the eye but reflects the minimum time required for

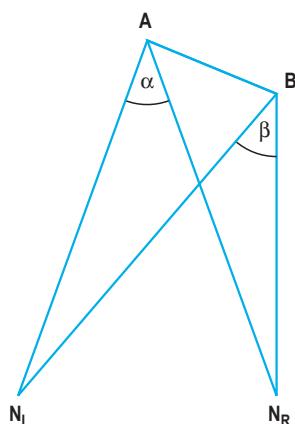


FIGURE 5-27 Images A and B cannot be fused; instead they induce 'instantaneous parallax'.

neural processing of the stimuli. Indeed, similar but disparate images can be perceived in three dimensions if they are presented to each eye in sequence, but the time interval has to be small (less than 5' of arc).

Image disparity and stereopsis

True stereopsis is dependent on disparities between the two images received by each eye, and therefore a certain number of points must fall on disparate points on the retina. It is also essential that these disparate points are fused like the corresponding points. The position of corresponding versus disparate points can be assessed by determining the actual differences in the stereoscopic projection of a point in space from the separate projections of the point made by each eye (Nouin's technique).

There is a limit to the fusional capacity of projected images, which is a circumscribed area known as Panum's area (see Box 5-13). It has been shown that it is possible to fuse greater disparities in the horizontal meridian than in the vertical, and therefore Panum's area forms an ellipse. The size of this area varies between individuals, while the threshold disparity that can be fused is greatest at the horopter. The extent of Panum's area is reduced by small 'normal' disjunctive eye movements, which can be compensated for by using stabilized retinal images. Double images can be induced outside Panum's area and can be used effectively to estimate depth.

Fusion of disparate images to produce stereopsis tends to invalidate the notion of the cyclopean eye in which single vision is produced by fusion of corresponding points. However, the cyclopean eye is of value in providing a baseline on which an estimate of the degree of neural processing involved in the fusion of disparate images can be made. Studies of neural circuitry in stereopsis have thus shown that it is possible to perceive depth without monocular cues, for instance by using random-dot stereograms and other more novel tests.

In these tests, 9 × 10 picture elements composed of dots, some of which correspond while others are symmetrically disparate, are presented in duplicate to each eye. These studies also reveal that discrete contours or edges are not essential for three-dimensional vision, although the contribution from 'texture analysis' is not clear (see below). Random-dot stereograms are also not quantitative.

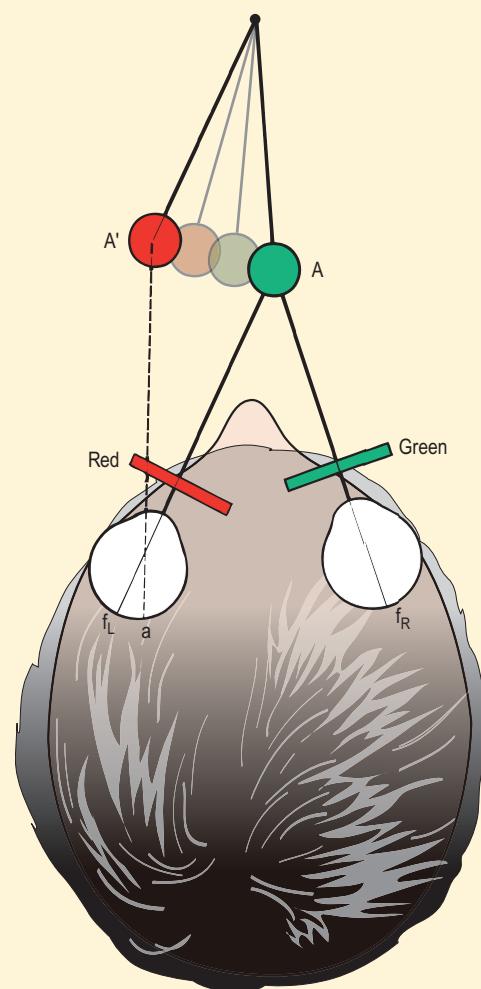
The level at which processing for stereopsis occurs has been questioned on many occasions because it is such an instantaneous response and is difficult to separate from a retinal 'sensation'. Stereopsis is also sensitive to certain optical effects such as aniseikonia; horizontally it is affected by as little as a 0.25% change in image size, while vertical magnification disparities are simply transferred to the horizontal meridian of the fellow eye. The Pulfrich phenomenon is an optical illusion based on similar processing events (Box 5-14). However, true disparity selective cortical neurones have been detected in V1, although the extent to which these neurones are simply 'rivalrous' (see next section) or stereopsis-inducing may depend on the degree of further cortical processing which appears to take place in the middle temporal (MT, V5) area of the visual cortex, an area associated with motion detection (see below). Furthermore, disparity matching appears to be a two-dimensional and not merely a one-dimensional process, involving fusion of images in a vertical as well as horizontal disparity.

RETINAL RIVALRY AND OCULAR DOMINANCE

Retinal rivalry is in essence a term that describes simultaneous perception by each eye individually without fusion of the images. This can be demonstrated as, for instance, when the letters F and L are viewed by each

BOX 5-14 THE PULFRICH PHENOMENON

The illusion of depth can be demonstrated by viewing a swinging, luminous pendulum through both eyes, one of which is covered by a red filter and the other by a green filter. It is thought to be the result of disparate images occurring during the movement of the pendulum stimulating corresponding points at fractionally different times.



eye separately to produce the letter E. This phenomenon also has a periodicity to it, which is involuntary. It is related to but different from binocular rivalry as illustrated by the Schrödinger staircase or Rubin's vase (see Box 5-11). Both are described as 'bistable phenomena' and are processed at retinal and cortical

levels, respectively. Recent fMRI studies confirm that activation of the sensation of monocular rivalry involves recruitment of whole-brain networks as well as visual area V3 (see below), particularly for complex objects such as faces and houses (Fig. 5-28). Retinal rivalry can also be affected by saccades and extraretinal eye movement signals.

Ocular dominance refers to the preferential use of one eye when performing monocular activities. This can be demonstrated electrophysiologically and is not necessarily related to handedness. However, whether there is evidence for true 'cortical' dominance for preferential use of one eye has not been established. In a perfectly equally sighted individual, input from one retina will mirror exactly that from the other retina.

Certain involuntary events take place that bear on retinal rivalry and ocular dominance. For instance, if the same image is presented to each eye at different levels of brightness, then the image in one eye may be suppressed (ocular dominance). Or the binocular image may appear less bright than the same image when viewed monocularly (e.g. with a uniocular cataract).

COLOUR PROCESSING

The perception of colour is a complex cortical event that is dependent on input from several sources. The use of mondrians (coloured patterns produced with variably illuminated narrow-waveband light) has shown that the predominance of a given waveband reflected from a surface does not alone determine its colour, but that its colour also depends on the wavelength composition of the light reflected from its surround. Mondrians have been used to demonstrate the phenomenon of colour constancy but their relative artificiality has been challenged: for instance, demonstration of other phenomena, such as the AMBE-GUJAS phenomenon, in which perceived colours can change dramatically depending on the three-dimensional surface of wavelength reflectance. Instead, well-defined real colour scenes have been devised that contain cues for the intrinsic surface colours and the recovery of the light source. These studies show that colour constancy is a real phenomenon but is not as absolute as previously thought and depends on input from local and global contrast. This depends on several factors, including spatial

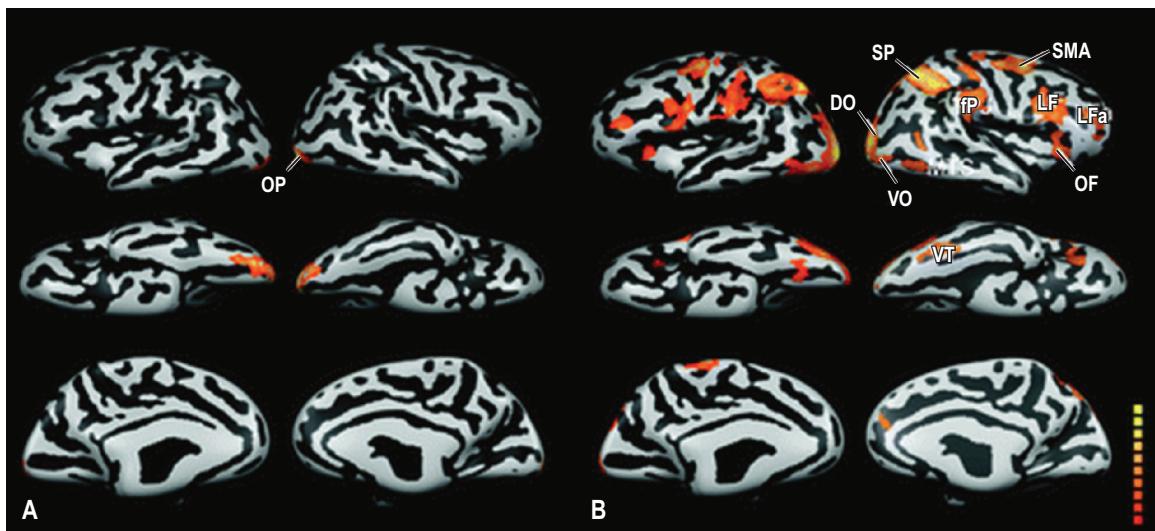


FIGURE 5-28 Monocular rivalry as demonstrated by fMRI using a ‘passive’ stimulation protocol and complex objects such as faces and houses. (A) Shows cortical activation for the non-rivalrous control stimulus as a limited region of activation in the occipital pole and includes areas V1 and V2. The lateral, ventral and medial views of the inflated brain are shown (left and right hemisphere). (B) Shows cortical activation for passive viewing of monocular rivalry with grating stimuli. Cortical sites included dorso-occipital (DO), ventral-occipital (VO), ventro-temporal (VT), medial temporal sulcus (MTS), superior parietal (SP), temporal-parietal junction (TPJ), supplementary motor area (SMA), lateral prefrontal (LF) and anterior lateral prefrontal (LFa) and orbital frontal (OF). (From Mendola and Buckthout, 2013.)

configuration and scale, and context. Texture, as in the AMBEGUJAS phenomenon, appears to the most important (Fig. 5-29).

It is clear, therefore, that the reflectance of light is central to the perception of colour. Although the amount of light reflected from a surface may vary, the brain constructs an image that fits the reflectance, which is a constant physical attribute of the object. The brain assesses the ‘lightness’ or ‘darkness’ of a surface compared with the surround, for each of the three predominant wavelengths in turn, and this permits it to assign a colour to the surface.

Colour is achieved, therefore, by a comparison of the reflected intensities of lights from one surface with those of surrounding surfaces for lights of different wavebands, followed by a comparison of the comparisons.

SHAPE DETECTION

The detection of form and shape also presents a problem when we consider exactly what we mean by shape. As described above, specialized cells exist that act as edge detectors for vertical and horizontal lines.

However, the shapes we perceive are much more complex than can be simply broken down to a series of discrete lines on x and y axes. For example, most shapes in the natural world are curvilinear and solid, and require significant processing in the cortex. This has led psychophysicists to develop mathematical algorithms and a ‘shape index’ to describe these shapes and thus provide insight into how the brain might compute the information. These effects can be demonstrated using specially oriented stimuli and show that global orientation detection is not simply the result of input to the primary visual cortex (V1). Second-order orientation detection may therefore also exist as ‘collector units’ for first-order V1 stimuli. Such collector units may also be affected by brightness and texture.

CONTRIBUTION OF TEXTURE ANALYSIS AND MOTION DETECTION TO DEPTH PERCEPTION

Depth perception is, of course, not only about locating objects in space but also about perceiving solid shapes. In fact, some of the early work on depth perception involved studies of visual function in aircraft pilots,

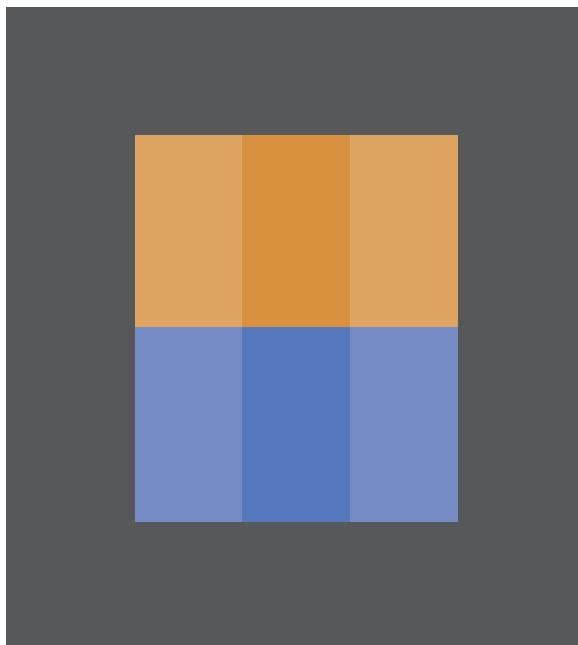


FIGURE 5-29 AMBEGUJAS is a recently described visual perceptual phenomenon in which shapes can be discerned from shading of colours. In this image a 3D illusion is created by the darker-shaded colour strip passing through the centre of the blue and orange rectangles, giving the impression of a box. It is, however, ambiguous as to both shape and colour and frequently returns to a flat surface with a grey central strip. (Bergstrom SS, 2011. The AMBEGUJAS phenomenon and colour constancy. Perception 40: 30–38. <http://www.ncbi.nlm.nih.gov/pubmed/15460510>, Fig 4, Pion Ltd, London. <http://www.pion.co.uk>; <http://www.perceptionweb.com>.)

particularly on take-off and landing. They revealed that motion detection and texture analysis were more relevant for the detection of solid structures, probably the most important aspect of visual perception (Figs 5-30 and 5-31). Many other sources of information combine to produce this effect, including binocular viewing, parallax, illumination and shading, and edge detection. For instance, a random set of dots may assume shape if a group of dots within the set ‘moved’ in relation to the remaining dots – an image would thus ‘pop out’ of the page. Similarly, texture and lustre are attributes of an object that relate to discontinuities in colour and/or luminance coming from the edges of the object, and significantly affect perception of its shape.

Most recently it has also been shown that the detection of a shape also depends on previous experience/

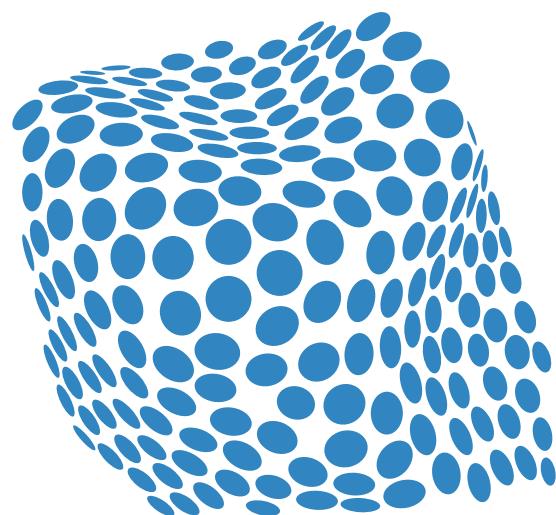


FIGURE 5-30 A pattern of optical texture that is perceptually interpreted as a smoothly curved three-dimensional surface. (From Todd et al., 2005, with permission from Elsevier.)

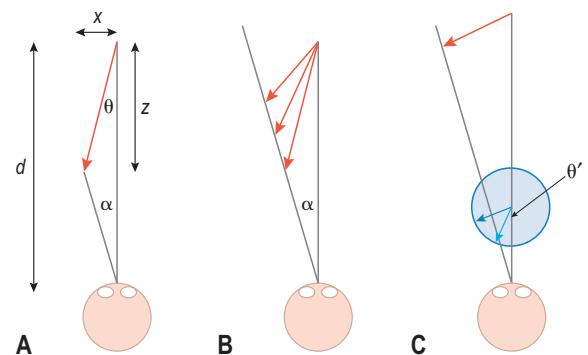


FIGURE 5-31 Schematic of stimulus geometry. (A) Observer and typical target trajectory (solid arrow) at an angle θ to straight ahead are illustrated. Visual direction of the moving target at the end of its motion is given by angle α . (B) Many different trajectories correspond to a single visual direction. (C) Location of the pointer (grey circle). If observers used θ to set the pointer, they would respond as shown by the black arrow. The grey arrow shows a typical response if observers used α . (From Harris and Drga, 2005.)

memory and whether the observer is ‘expecting’ to see the shape. It is clear therefore that this complex response is built up from multiple inputs and that the search for a shape-detecting centre may prove elusive.

Division of labour in the visual system: parcellation and the human connectome

Topographic mapping of brain function has advanced considerably in the last 5 years and this applies particularly to vision, specific visual functions and the connections between visual areas and other areas which influence visual perception. Zeki's early conceptual framework for what he describes as the division of labour in the visual cortex has now been elaborated to reveal the numerous interconnections between different regions of the brain and how both bottom-up and top-down processing occur almost continuously (Fig. 5-32). In this context, it is now well recognized that the dorsal (occipito-parietal) and ventral (occipito-ventral) parcel out bottom-up and top-down processing, respectively. Studies like this are contributing to a major project under construction at the present time aimed at mapping the human neuronal connections in what is termed the 'human connectome' (<http://www.humanconnectomeproject.org/>).

According to current ideas concerning construction of the visual image, anatomically discrete areas of cortex subserving different functions are reconstituted through their extensive connections to produce the perception of a final integrated image, for instance during complex psychophysical process such as those involved in ocular dominance (see Fig. 5-28). Thus an image should not be regarded as being 'impressed' on the retina like the film in a camera, which is then

codified to make it 'understood' by the cortex; rather we should appreciate that the processes of sensing (seeing) and cognition (understanding) are not separate but totally integrated. It is likely that, as additional sensory information is added to the image, a higher level of cognition and thus perception can be achieved.

IMAGING STUDIES

Much of the early information came from work in animals but advances in imaging the human brain have in many ways now taken precedence. 'Parcellation' in the human visual cortex has been shown by positron emission tomography (PET), magnetoencephalography and functional magnetic resonance imaging (fMRI). Several developments in MRI from initial diffusion tensor imaging (DTI) (imaging of molecules as they move) to newer techniques such as diffuse functional MRI, diffusion-weighted imaging and diffusion spectrum imaging have provided the tools for the human connectome project. Importantly, advances in spatial resolution of fMRI images such that active regions in specific gyri can be determined without interference from image signal of irrelevant neighbouring sites has allowed localization of ventral occipito-temporal pathways involved in, for instance, seeing words (Fig. 5-33). Similar fMRI studies of V4 for coloured stimuli and V5 for moving targets have been done.

In humans, therefore, it can be said that there is a 'colour centre' outside the visual cortex; i.e. that there is functional specialization as in the monkey. Another intriguing observation is that the effect of coloured stimuli is lateralized in humans and is not necessarily related to handedness or ocular dominance. Similarly, three different 'types' of motion detection have been located to discrete areas of the visual cortex.

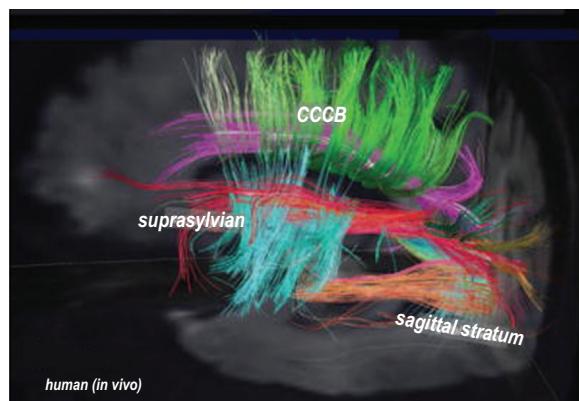


FIGURE 5-32 A cerebral grid structure of the human brain showing the plan of the fibre pathways; image taken using diffusion magnetic resonance imaging. (From Wedeen et al., 2012.)

THE MAGNOCELLULAR AND PARVOCELLULAR PATHWAYS SUBSERVE DIFFERENT FUNCTIONS

The striate cortex (area V1) contains the entire map of the retina in a highly ordered and predictable distribution. It receives this information via the LGN, where the neuronal organization is also highly ordered (see Ch. 1, p. 93–95). At first sight it would seem, therefore, that retinal images should be truly represented in the visual cortex on the basis of a point-to-point topographical representation. In a very limited sense

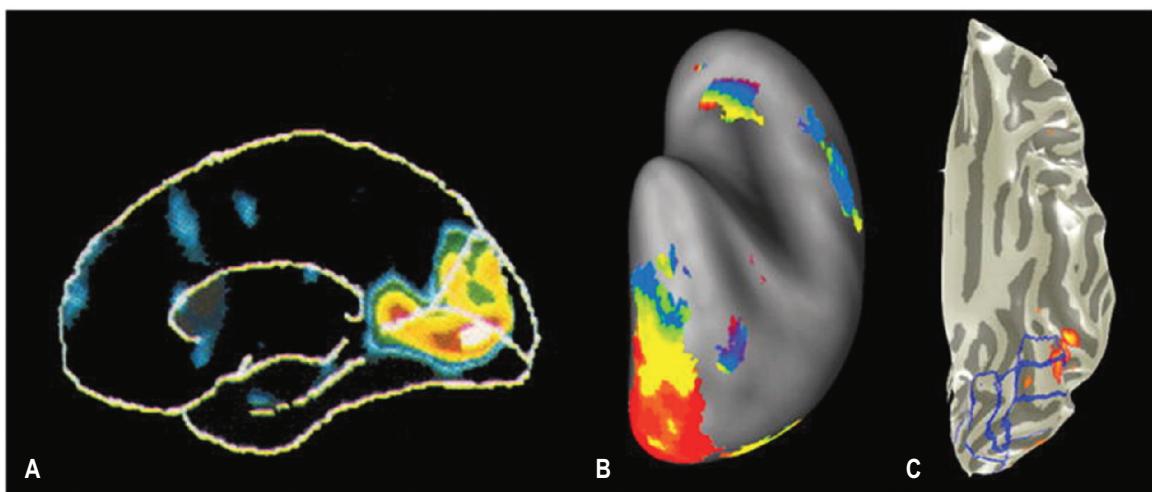


FIGURE 5-33 Neuroimaging technology has greatly improved to allow high levels of spatial resolution from positron emission tomography (PET) (**A**), to fMRI on 3D surfaces (**B**), to fMRI data (**C**) (allowing words to be differentiated from phase-scrambled words) coordinated with visual field maps (shown in the blue outlines) in individual subjects (right, ventral view) using retinotopic mapping procedures. The word-related activation is near the foveal representation of ventral occipital maps (VO-1 and VO-2); V2 and V3 are also outlined. (From Wandell, 2011.)

this is true and may even apply to functional differentiations associated with certain neuronal cell types. Thus, the parvocellular (slow) fibres carry information concerning foveal and parafoveal activity such as spatial discrimination and colour, while the magnocellular (fast) fibres act as transmitters of light detection. This explains in part the high sensitivity that we have for light and motion detection, which are served via the peripheral retina, while contrast and colour detection are slower processes.

However, psychophysical phenomena such as colour and spatial constancy indicate that simple representation of images on the visual cortex in a retinotopic fashion is insufficient to explain the resultant perception. Even the briefest consideration of wavelength discrimination, which is an intrinsically colourless event, despite the fact that there are three discrete receptors, would reveal this truth; thus a pillar box appears red in most conditions of illumination even though the actual wavelength of the reflected light from the pillar box will vary greatly depending on the light source (but see discussion of colour constancy above). The perception of colour, and indeed of any visual stimulus, is the result of input from many other cortical sources in addition to the primary visual cortex. A further unexplained problem in studying

cortical and indeed lower levels of activity is the constant high level of neuronal ‘noise’. It appears that even in the absence of specific stimulation, there is a significant level of endogenous neuronal activity, which is now presumed to modify output (i.e. perception in the case of vision). This is considered to be one form of top-down modulation of output.

THE STRIATE CORTEX AND THE PRESTRIATE CORTEX SHUFFLE INFORMATION BETWEEN THEM IN THE BUILD-UP TO A PERCEIVED IMAGE

The striate cortex (area V1) is connected to the prestriate cortex (areas V3–V8) directly and also via area V2 (Fig. 5-34). Each of these areas has one or more specific functions. For example, all cells in area V5 respond to motion in the visual system, and are directionally selective (i.e. each cell responds to motion in only one direction); none of these cells, however, is specific for colour. This function is subserved by cells in area V4, in which some of the cells act as wavelength discriminators, but some of these cells also respond to orientation of lines and are involved in shape (form) detection. Other studies have, however, shown that contour information can also be derived from motion detection and that this activity takes place in the primary visual cortex. Cells in V3 and V3A

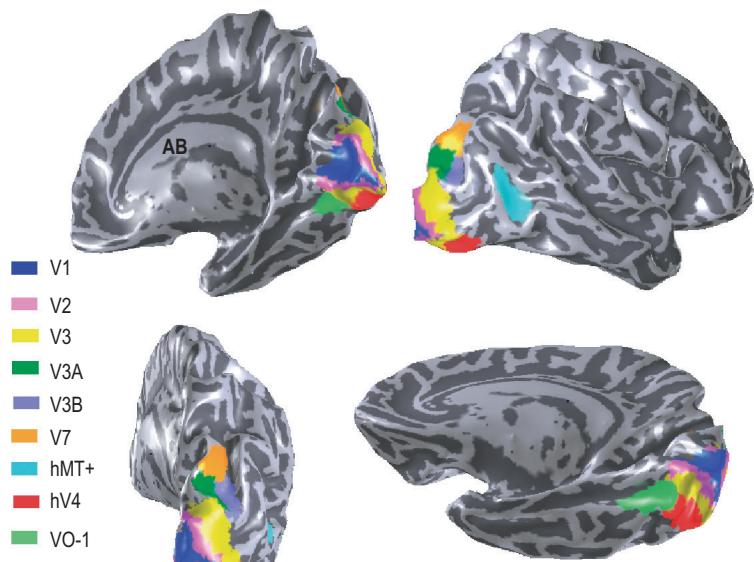


FIGURE 5-34 The locations of nine hemifield maps in the human visual cortex. The maps are shown for one typical subject (AB). (From Wandell et al., 2005, with permission from the Royal Society of London.)

are also selective for form but are indifferent to changes in wavelength.

It is clear, therefore, that colour, orientation, motion, stereoacuity, texture, etc., are all processed separately in areas V3–V8. As areas V3–V8 receive their information from V1, V1 (and V2) must also be functionally specialized. It has been suggested that there may be a population of cells that respond to more than one stimulus, such as texture and motion, when these are tested separately. However, this is not the common response.

V2 is likewise organized into areas with thin stripes (for colour detection) and thick stripes (for motion detection) separated by interstripes. Form-selective detectors are present in both the thick and the thin stripes. This form of organization of the visual, and indeed the entire, grey matter into discrete columns of cells responding to specific stimuli has long been known (>50 years) but its functional significance is not clear.

PARCELLING OUT THE PROCESSING IN V1

The concept of functional/anatomical segregation of visual stimuli into components such as colour, motion and orientation detection, depth perception, and other features is now well established (but see below). The

cortical sites of other visual tasks, such as texture analysis and shape recognition, are not so easily located. Still others, such as face recognition, involve regions outside the visual and prestriate cortex, including sites that store memory.

Despite our lack of knowledge, it is still remarkable that such a level of segregation occurs from the retinal ganglion cell input, through the LGN to V1, V2 and V3–V8 in the cortex. Segregation may have developed as a result of the different requirements for generating form, colour and motion (e.g. colour compares input from one part of the visual field to another) but topography for colour may be less important. In contrast, precise topographic localization is important for form analysis and motion detection; in the latter, however, this is assessed only transiently.

Our perception of the external environment may therefore depend on a system of circuits rather like combined and serial parallel processing in computers where there is 'multistage integration', as Zeki describes it, with feedforward and feedback control (now described as bottom-up and top-down processing) (Zeki, 1990). In line with this concept, perception and comprehension of the visual world occur simultaneously and continuous processing of information, both past and present, is ongoing.

IS THE VISUAL CORTEX ORGANIZED FOR HIERARCHICAL NEURAL PROCESSING OR FOR FUNCTIONAL SPECIALIZATION?

The above outline of the organization of visual information at the cortical level may be oversimplistic. In reality, organization of information reception and integration has been considered in two ways, both of which are probably contributory: (1) hierarchical processing of information through the different regions (e.g. sequentially from retinal to LGN to V1, then to V2, and then simultaneously or differentially to V3, V4, V5, etc.); (2) functional specialization in the form of precise topographical localization of aspects of vision to discrete areas of the visual cortex. One of the important recent observations from fMRI work is that the concept of precise retinotopic mapping being restricted to V1 (i.e. representation of the fovea and peripheral retinal regions to precise sites on the striate cortex) may not be accurate. Areas previously considered non-retinotopic such as V4 for colour and V5 for motion also have retinotopic representation although less exact than in V1. Not only is there region-specific cortical representation for instance of colour, but eccentricity maps (distance from fovea) and polar angular maps (angle from the horizontal meridian) cross each other in their cortical representations, allowing a form of mapping of 'visual space' on the cortex (Figs 5-35 and 5-36).

It has now become clear that perception of colour, motion, form, texture and stereopsis all have varying levels of the following attributes: (1) functional specialization in discrete cortical areas; (2) retinotopic representation within each of those areas; and (3) processing in 'streams', e.g. in a colour stream where neural processing for wavelength discrimination takes place at several levels from the retina, to the LGN to V1 and onwards to the specific cortical region in V4. Similar organization underpins motion detection but less is known about stereopsis or texture appreciation. Stereopsis and depth perception are particularly interesting since this requires 'binocular neurones' which will merge signals from right and left eyes: while V1 is clearly important, it is now realized that extrastrate input, e.g. from V2 and V4 as well as other areas, is important. Broadly, dorsal visual pathways control cross-correlation between signals while

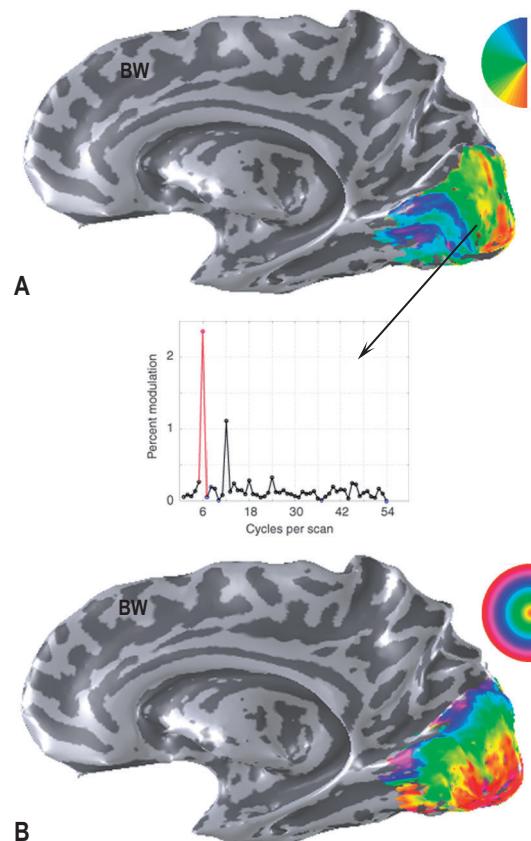


FIGURE 5-35 Angular and eccentricity maps near the calcarine cortex. Maps were measured using (A) rotating wedges and (B) expanding rings comprising contrast-reversing dartboard patterns. The stimuli extended over the central 20° of the visual field and completed six cycles during each experimental scan. The colour overlay indicates the visual field angle (A) or eccentricity (B) that produces the most powerful response at each cortical location. For clarity, only responses near the calcarine cortex are shown. The graph plots the response amplitude as a function of temporal frequency as measured in a 3 mm radius disc located in the calcarine (see arrow). The response is significantly greater at the stimulus repetition frequency (six cycles per scan, shown in red) than other temporal frequencies. The secondary peaks at integer multiples of the stimulus frequency are expected and are also significant. The graph is included in the image to provide the reader with an assessment of the reliability of the responses. The stimulus-driven responses shown here are substantially above the statistical threshold ($P < 0.001$, uncorrected). (From Wandell et al., 2005, with permission from the Royal Society of London.)

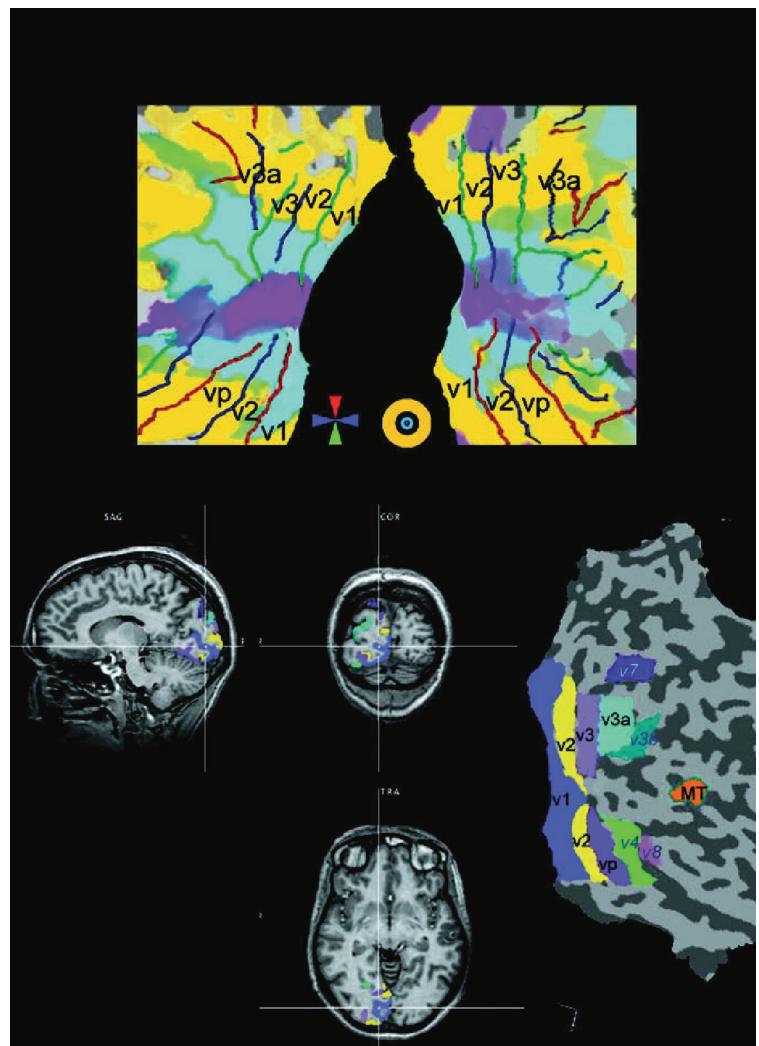


FIGURE 5-36 Early and mid-level visual areas. *Top:* Superposition of eccentricity and polar angle maps. Yellow, blue and pink bands indicate eccentricity maps; lines indicate centres of upper, lower and horizontal representations (see icons). Note that meridian lines cross all eccentricities orthogonally. *Bottom:* Visual areas on a flattened representation and on the brain volume. Visual area names under consensus are denoted in black, and areas under debate are marked in blue italics. (From Grill-Spector and Malach, 2004, with permission from the publisher of Annual Reviews.)

ventral pathways address the problem of making multiple signal matches.

There is further sophistication in perceptual pathways. Regions anterodorsal and anteroventral to the striate cortex are not only specialized to detect aspects of vision such as form or colour but also to detect specific objects such as faces, tools, words and even places (Fig. 5-37). Despite this, there is still a strong hierarchical organization for information processing. For instance the receptive fields for the same stimulus are smallest in V1 and increase progressively through V2, to V3A and V4. To add further complexity to the final percept, there is evidence that top-down processing

occurs, for instance activity induced in visual areas V1 and V2 by increased ‘expectation’ or attention to a region even in the absence of a specific visual object. Even input from emotional stimuli or stereotypical events can modify the visual areas as seen on fMRI.

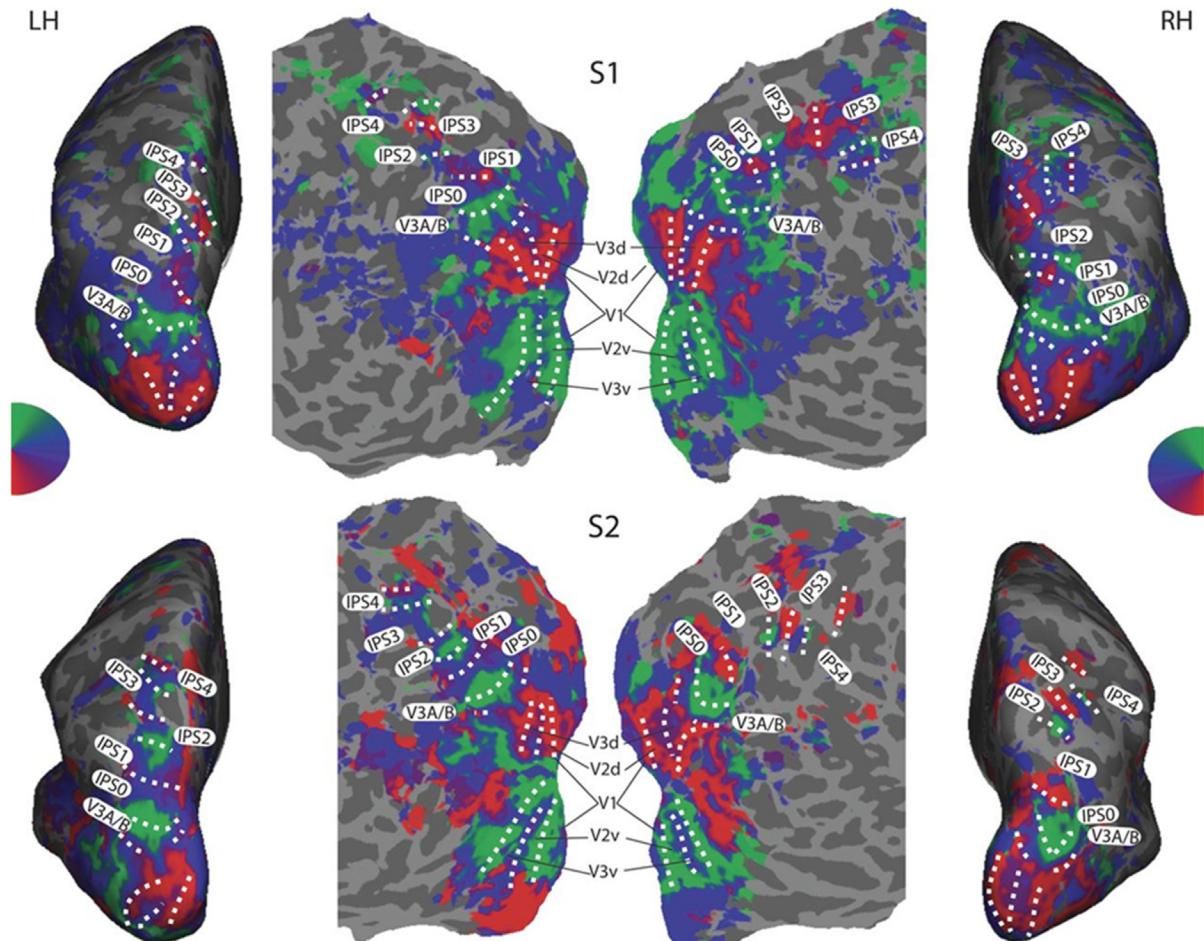
As fMRI advances with ever better technology, including diffusion tensor MRI, detailed information about the organization of areas such as the intraparietal suture (IPS) have been revealed.

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Functional connectivity analyses also showed increased interaction between the IPS and prefrontal

Tasks which involve attention as well as the maintenance and re-configuration of information in working memory (WM) are centred on the IPS (eFig. 5-7). WM tasks are closely integrated with what is termed the ‘contralateral visual space’ (i.e. fMRI mappable areas on the contralateral visual cortex) while both sides of the IPS are used for processing this information. In a recent study, Bray and

colleagues performed visuotopic mapping in a group of volunteers and showed that a briefly flashed target preferentially engaged the contralateral IPS but when the target was ‘mentally’ rotated around a circle (i.e. manipulating spatial information) both IPS were activated, and activation was most marked in region IPS1 in most but not all individuals (Bray et al., 2013).



eFIGURE 5-7 The intraparietal sulcus (IPS) shown in its various regions (IPS0-4) in various views of inflated images of the cortex. Visual cortex areas 1–4 are also shown. Dashed white lines represent borders between adjacent areas. (From Bray et al., 2013.)

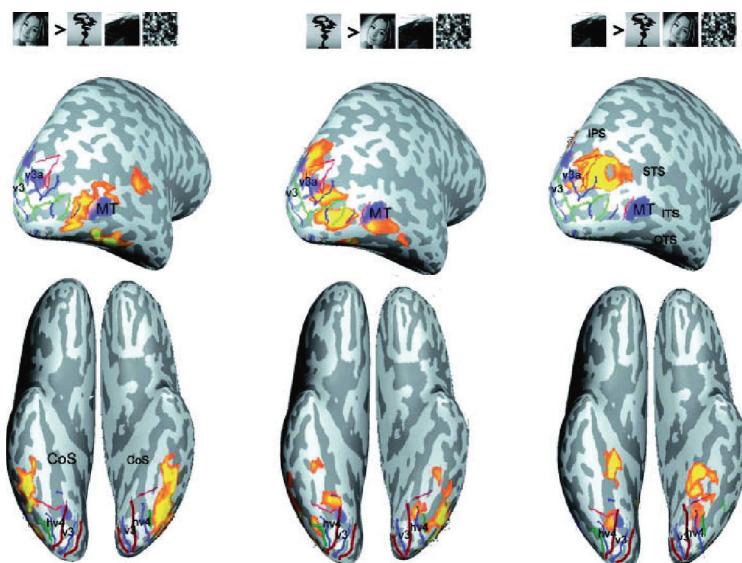


FIGURE 5-37 Face-, object-, and place-selective regions in the human brain displayed on an inflated surface representation of the same subject as in Fig. 5-36. Icons indicate the comparisons done in the statistical tests. *Left:* areas responding more strongly to faces than objects, places, or textures. *Centre:* areas responding more strongly to objects than faces, places, or textures. *Right:* areas responding more strongly to places (scenes) than faces, objects, or textures. Yellow and orange indicate statistical significance: $P < 10^{-12} < P < 10^{-6}$. Coloured lines indicate borders of retinotopic visual areas. Blue indicates area hMT1, defined as a region in the posterior bank of the inferotemporal sulcus that responds more strongly to moving versus stationary low-contrast gratings (with $P < 10^{-6}$). (From Grill-Spector and Malach, 2004, with permission from the publisher of Annual Reviews.)

regions during manipulation, as well as interhemispheric interactions. Two control tasks demonstrated that covert attention shifts and non-spatial manipulation (arithmetic) engaged patterns of IPS activation and connectivity that were distinct from WM manipulation. These findings add to our understanding of the role of IPS in spatial WM maintenance and manipulation. This type of study reveals the visuotopic arrangement of the fibres as they pass through the classically described ‘optic radiation’ (see Ch. 1, p. 95) and will be of considerable value in identifying very specific neurological defects as well as informing us on basic neurophysiology.

Area V4 remains a bit of a puzzle. While many functions have been attributed to it, precisely how this region modulates other visual areas such as colour or feature processing are unclear. It has recently been proposed that the role of V4 is to facilitate neuronal traffic into sets of domain-based networks (such as colour and motion) in two directions, i.e. it probably acts as a hub for the convergence of top-down and bottom-up information (Roe *et al.*, 2012).

Physiology of ocular movement

Many of the aspects of the visual response described above would not be possible without the coordinated

movement of the eyes; indeed, eye motion is a fundamental feature of ocular and visual physiology since eyes in the alert state are never at rest. Eye movements are paired even when they move in different directions, as in convergence responses. Neural control of paired eye movements occurs at several levels, as for any neuromuscular event, i.e. at a reflex/subcortical level and via cortical control. The anatomy of the ocular muscles and the innervations of the ocular muscles via the cranial nerves and brainstem nucleus have been reviewed in Chapter 1 (see pp. 68–77).

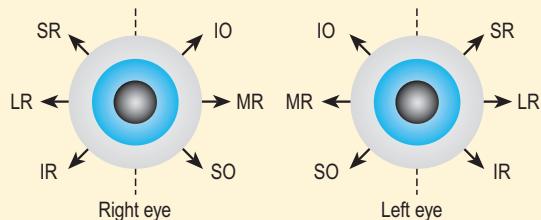
TYPES OF MOVEMENT

Unicocular eye movements

Each eye can be moved in the direction of action of the ocular muscles (Box 5-15), which are usually described around a centre of rotation of the globe placed about 14 mm behind the cornea. Rotation is either in a vertical (*z* axis) or a horizontal (*x* axis) plane, otherwise known as Listing’s plane. Torsional motion of the eye occurs around a median or vertical plane through the midline of the skull; this movement can also be described in most circumstances in reference to the retinal horizon (the *x,y* plane). Rolling movements of the eye occur along an anteroposterior axis, while intermediate movements between any of these axes are possible.

BOX 5-15 EVALUATION OF EXTRAOCULAR MUSCLE FUNCTION

The direction of action of the extraocular muscles is complex and should be considered in three dimensions. The diagram indicates the action of the muscles when they are to be tested clinically for their function, as explained below.



For instance, the action of the SO muscle is to move the eye down (depression) and out (divergence). However, depression of the eye can also be induced by the IR. Therefore, in order to test the depressor (downward) function of the SO, the simplest way is to test this function when the eye is in a position where the other depressor (the IR) cannot act, i.e. when the eye is adducted. Adducting the eye in effect 'shortens' the IR (the other depressor of the eye, thereby compromising its role as a depressor – muscles are less efficient if their muscle belly is shortened). The SO is thus the only depressor in the adducted position and vice versa for IR. IR, inferior rectus; SO, superior oblique; IO, inferior oblique; LR, lateral rectus; MR, medial rectus; SR, superior rectus.

Binocular eye movements

The extent of movement of one eye is equal and symmetric to the other (Hering's rule); in conjugate movements the eyes move in parallel while in dysjunctive movements (convergence and divergence) they move in opposite directions. In the fusion-free or physiological position of rest (not the primary position of gaze, as this requires fixation on a target) the eyes are slightly divergent.

Conjugate movements require reciprocal innervation of the muscles, which can therefore be described as conjugate pairs of muscles for each direction of gaze (see Box 5-15). This is limited in that the excursion of each muscle is usually greater than that of the pair. The effect is to produce a field of binocular single vision, a parameter of great practical significance with respect to standards of normal visual function for the purposes of vehicle license regulations (see Fig. 5-26).

Convergence movements require the combined action of both medial recti; the extent of movement is limited by the near point (5–10 cm from the eyes; this is not affected by age unlike the near point of accommodation) and the far point of convergence (determined in the position of rest as the projected intersection). The converging power of the eye is measured by the metre angle, which depends on the interpupillary distance and can be assessed using graded prisms. From this, the amplitude of convergence can be calculated, which is the difference between the converging power of the eye for the near and far points of convergence. The fusional drive can add a component to the converging power of the eye – the fusion supplement. This has practical significance, for instance, when estimating the effects of accommodating intraocular lenses on depth of field (see eFig. 5-4).

Conjugate movements of the eye may be in the form of short sharp movements (saccades) or continuous tracking movements (smooth pursuit). Even when under apparent steady fixation, there are small conjugate movements (microsaccades). Voluntary gaze or 'search' movements (i.e. directed towards non-defined targets) are under higher cortical control (see below). Experimental studies have shown that visual input is required for saccadic movements and is linked to image latency. Tracking movements, however, require visual input plus object speed to be no greater than 30–40° per second and to match that of the eye movement.

Saccades

- Rapid voluntary relocation of fixation
- Under supranuclear contralateral control
- Latency of 100 ms
- Velocity of 800–1000°/s.

Pursuit

- Slower tracking movements
- Under supranuclear ipsilateral cortical control
- Latency of 150 ms
- Velocity of 30–50°/s.

During saccades, there is selective suppression of motion detection over other stimuli, suggesting that saccades suppress only the magnocellular pathway. It is also important to consider the concept of optic flow,

in which an object moving in relation to a static observer generates a pattern of relative motion in the retinal image. The control of eye movements under these conditions may be difficult to analyse, particularly if the observer is tracking a slowly moving object against a faster moving background.

BOX 5-16 THE IMAGE WE SEE IS DESTABILIZED WHEN WE ARE MOVING BECAUSE OF OPTIC FLOW

Optic flow is a form of visual streaming which occurs as we are moving continuously in one direction. It occurs because the image of the same object(s) are constantly changing with regards to which area of the retina they stimulate. An object of interest is fixed by our gaze and is usually tracked as we go forward but the eye movement used for this purpose interferes with the flow of information (optic flow) generated by objects in the background which inform us where we are going and allow us to navigate properly. Accordingly, the object of interest loses 'focus' and becomes blurred (see figure). Both the visuomotor and vestibulomotor systems are at play here and attempt to compensate for the instabilities of retinal images, which typically vary as a function of retinal location and differ for each eye.

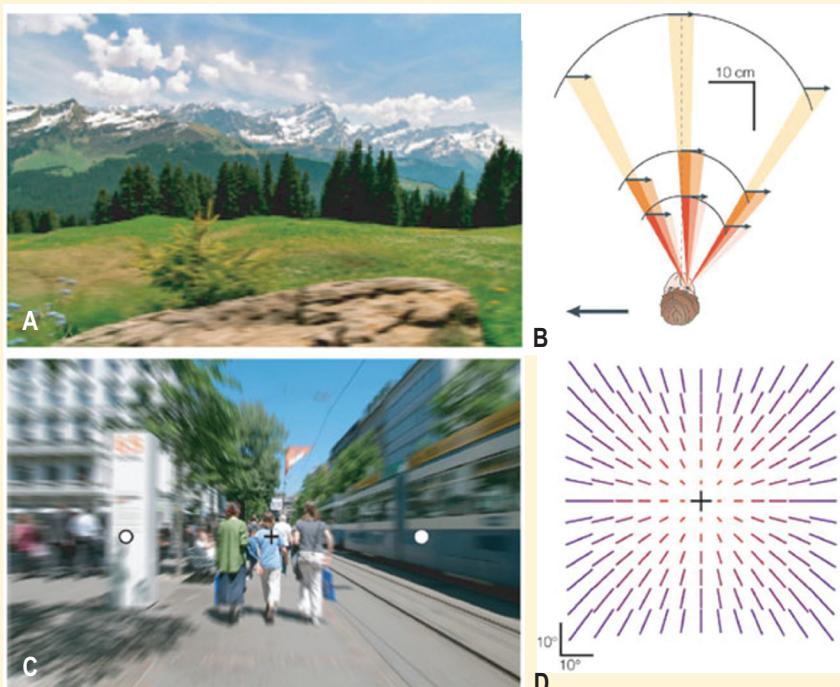
(A) Blurring of a natural scene image on the retina during simulated leftward self-motion. Near objects blur more than far objects. Without a compensatory eye movement, only

The situation becomes even more complex if the observer is also moving. Here the visuomotor and vestibulomotor interact with each other to stabilize the image (Box 5-16).

Optic flow is based on what are described as 'short latency' eye movements generated by the sensation of

objects at optical infinity (for example, mountains on the horizon) remain stable on the retina. (B) Idealized patterns of corresponding planar optic flow (in panel (A)). Small black arrows indicate the relative displacement of three groups of targets, located at different isovergence distances, during the first 100 ms of constant velocity (50 cm s^{-1}) translation to the left (large black arrow). Shaded areas indicate the angular displacements of the targets at different distances and horizontal eccentricities, as seen from the right eye.

(C) White circles indicate two horizontal spatial locations of image blurring on the retina; cross indicates forward movement direction. (D) Idealized patterns of corresponding planar optic flow (in panel (C)). Shades from red to blue illustrate transition from the fovea to the retinal periphery. Note that these components represent the flow velocity perpendicular to the optic axis.



a changing image or scene, experienced by the observer while moving so that correct navigational or directional movement can be made, e.g. 'heading'.

CONTROL OF EYE MOVEMENT

The eye muscles in the primary position of gaze are in a state of tonic activity. Each muscle, however, is activated when the eye moves in its field of action and is inhibited in the opposite direction. The final pathway for neuronal control of eye movement occurs via the cranial nerves (see Ch. 1, p. 69), which are the motor neurone equivalent of the spinal nerves subserving reflex responses. As for any muscle, however, the ocular muscles are under both reflex and 'higher centre' control, with the frontal cortex regulating voluntary activity and the occipital cortex and superior colliculus serving as coordinating centres. In addition, there are numerous interneurones and connections with other pathways at the cortical level, e.g. via the paramedian pontine reticular formation (PPRF), and at the reflex level, e.g. the vestibulo-ocular reflex and the cervico-ocular reflex (see above section in relation to optic flow). The generation of horizontal and vertical saccades (gaze) and the fine-tuning of eye movements involve the integrated supranuclear network within the midbrain (PPRF and rostral interstitial nucleus of medial longitudinal fasciculus (riMLF)) and brainstem (vestibulo-ocular and cervico-ocular reflexes), which will be discussed in more detail below.

The fixation reflex

The ability to fixate a bright light is a basic reflex that is evident within a few days of birth, but the binocular reflex involving conjugate eye movements and a sustained response takes several months to be fully developed. Foveal fixation is the endpoint of the searching movement of the muscles and may be considered the point of peak activity in the nerve/muscle response. The nerve response can therefore be said to be 'tuned' to foveal fixation. In addition, the very small fine eye movements (microsaccades) that occur with sustained foveal fixation are the result of reflex attempts by the oculomotor centre to achieve the best perceived image, as this falls off rapidly unless a new set of cones is stimulated (Box 5-17).

The fixation reflex can be demonstrated easily by testing for optokinetic nystagmus, where either the stationary subject views a moving scene or a moving subject views a stationary scene. The nystagmus has a slow phase when the eyes follow the target and a fast flick when they readjust to the new target position. The optokinetic nystagmus response in humans requires an intact cortex, although there may be a subcortical pathway via the superior colliculus especially for the 'involuntary' searching component of the response (see Box 5-17). Lesions of the cerebral cortex, for example in the temporal lobe, are associated with defects in the optokinetic nystagmus response. The nystagmus is preserved in parietal lobe lesions, and this test is therefore clinically useful in localizing lesions.

Microsaccades are probably as important in achieving a strong fixation reflex as saccades are in searching or exploratory eye movements.

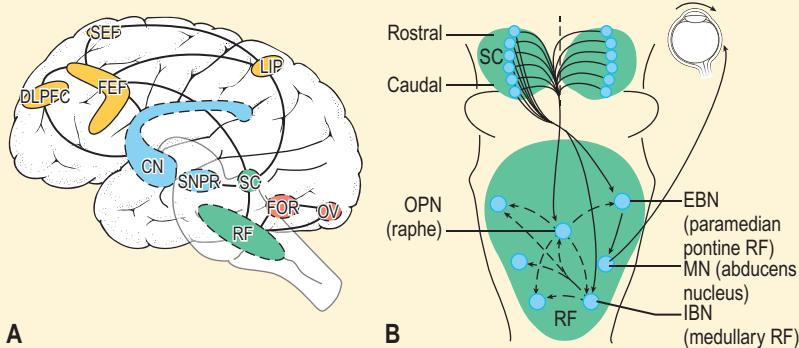
Oculovestibular reflexes are eye movement responses to positional changes in the relationship between the head and the trunk

The vestibular apparatus has structures that convey static head/trunk positional reflex information (i.e. when the subject is not in motion) – the utricle and saccule – and kinetic positional information under conditions of head/trunk acceleration and deceleration – the semicircular canals. In the utricle and saccule, stimulation of the receptor may occur simply on changing position of the head with respect to gravity, but the ampullae in the semicircular canals are stimulated via inertial forces in the endolymph surrounding the hair cells (viscous drag). The semicircular canals are arranged so that they act in synergistic pairs on each side of the head in the x, y and z axes. Vertical and torsional movements involve all four vertical canals. The vestibulo-ocular apparatus is thus of great importance to navigational movements, heading and optic flow (see above section). Three-dimensional analysis of ocular movements allows the possible location of defects to, for instance, a single semicircular canal. The techniques are based on mathematical models containing information on rotation vectors, reference frames, coordinate systems and Listing's law, and use magnetic search coils in preference to video-based systems.

BOX 5-17 SACCADES ARE GENERATED IN DIFFERENT AREAS OF THE BRAIN

Saccades describe a fundamental feature of our eyes, i.e. they are never at rest (even when we are sleeping). Even when we fix our gaze on an object, our eyes still continually make small movements termed microsaccades. There is also a tendency for the eyes to 'drift', especially if we are not fixing strongly on an object, and ocular tremor adds a third intrinsic movement to the eyes. These movements are essential to continued perception of an image since without repeated retinal stimulation the image fades. Saccadic eye movements are generated in several areas of the brain, including the lateral intraparietal area, the frontal eye fields,

the supplementary eye fields and the dorsolateral prefrontal cortex (see figure). The neural connections are integrated with input from the basal ganglia (blue in the figure) while the substantia nigra generate inhibitory impulses which prevent unwanted eye movements as well as control the onset of saccades. The brainstem (shown in green in (A) and in higher magnification in (B)) contains a complex feedback and feedforward circuitry involving 'excitatory burst' and 'omnipause' neurones in the superior colliculus which control the overall regulation of the microsaccades through inhibitory and activating impulses.



Listing's law states that, when the head is fixed, the primary position of the eye is such that there is a restricted degree of orientation that can be reached by a single rotation about an axis in Listing's plane (see above) (nine positions of gaze; Box 5-15 and Figs 5-38 and 5-39). Listing's law applies during fixation, saccades, smooth pursuit and vergence movements but not during sleep or during vestibulo-ocular reflexes.

The oculovestibular reflex can be demonstrated by the ability of a rotating observer to maintain fixation on a stationary target by reflex movement of the eyes at the same angular rotation (up to 300°/s) as the observer in the opposite direction. In this way there is stabilization of the retinal image. The reflex can also occur in the dark but is less accurate in its predicted excursion.

Rolling eye movements are due to oculovestibular and oculocervical reflexes

Compensatory eye movements during tilting of the head towards the shoulders initially involve the semi-circular canals but, if the movement is sustained, static

(utricle and saccule) responses participate. However, this compensatory movement of the eyes also involves information about neck position from proprioceptors in the neck (oculocervical reflex). Lateral movement of the head about a vertical axis will induce predominantly oculocervical reflexes, while movement of the head in the median plane with the eyes fixated produces predominantly oculovestibular reflexes (doll's head movement). Doll's head movements are an important clinical sign to test for intact brainstem reflexes in cases of cortical damage and loss of supranuclear control.

The midbrain is a coordinating centre for reflex eye movement and connects input from multiple sources

Voluntary eye movements (saccades) are initiated in the contralateral motor strip of the frontal cortex (see Ch. 1, p. 72) and pass down to the midbrain via the anterior limb of the internal capsule to synapse in the horizontal gaze centre within the PPRF (see Box 5-17; Fig. 5-40). Neurones then pass to the ipsilateral VI nerve and interneurones cross to the opposite

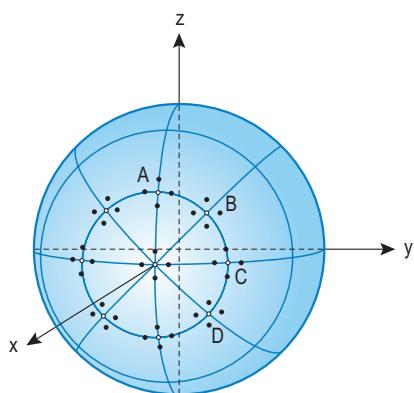


FIGURE 5-38 Primary position and Listing's plane. There is a unique orientation of the eye, called 'primary position' or 'primary gaze direction' (direction parallel to the x -axis), such that pure vertical and pure horizontal movements that move the eye or gaze line from primary to secondary positions do not change ocular torsion (eye rotations along the respective meridians through A or through C). Similarly, any movement that rotates the eye/gaze line from primary to tertiary positions on oblique meridian planes does not change torsion (e.g. movements along the meridians through B to D). The axes of single rotations that move the eye from primary to secondary or tertiary positions lie all in one plane, called Listing's plane (the plane containing the y and z axes). Tertiary positions cannot be reached from secondary positions by any combination of horizontal and vertical ocular rotations (a torsional component is also needed; see half-angle rule). (From Angelaki and Hess, 2004, with permission from Blackwell Publishing.)

medial longitudinal fasciculus to subserve the contralateral III nerve. Within the PPRF are burst cells, which have a high but transient rate of discharge (1000 Hz/s) and, when fired, generate the saccade. Normally the burst cells are continuously inhibited by pause cells, until this inhibition is released by discharge from neurones from the frontal eye fields. Burst-pause cells, and other types of cells such as pacemaking cells, are characteristic of different types of neurones in other areas of the brain such as the cerebellum.

Once the saccade has been generated, eye position and fixation are maintained via the tonic neural integrators, also situated within the PPRF. The PPRF also receives inputs from vestibular nuclei, cerebellum, basal ganglia and cervical proprioceptors, giving rise to fine accurate control of gaze, and their contributions will be discussed below.

The vertical gaze centre is located in the reticular medial longitudinal fasciculus (RMLF), opposite the

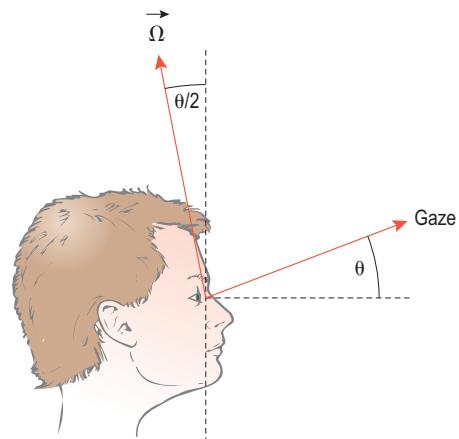


FIGURE 5-39 According to Listing's law, the axis of rotation of the eye (Ω) is neither head-fixed nor eye-fixed, but rotates in the same direction as gaze through half the gaze angle ($\theta/2$; the half-angle rule). Thus, at eccentric eye positions, during a horizontal saccade or pursuit eye movement, the axis of rotation of the eye is not purely horizontal (head-vertical dashed line) but also has a torsional component (head-horizontal dashed line). (From Angelaki and Hess, 2004, with permission from Blackwell Publishing.)

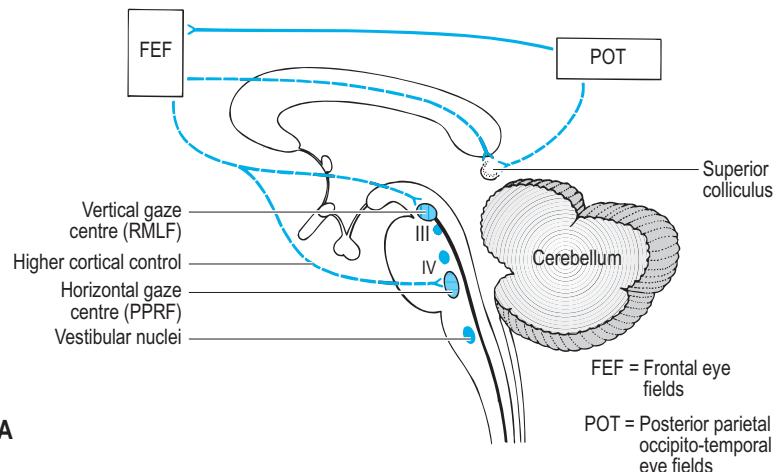
superior colliculus and above the level of the III nerve nucleus. Unlike the horizontal gaze centre, the vertical gaze centre has no identifiable cortical control, neurones from which cross to the III and IV nerves nuclei to subserve vertical gaze. The medial longitudinal fasciculus, as already mentioned, carries fibres of conjugate horizontal eye movement (involving the VI and III nerves) and also signals for holding vertical eye position, vertical smooth pursuit and vertical vestibulo-ocular reflexes.

Loss of supranuclear control by lesions affecting the midbrain and brainstem can give rise to a variety of clinical features, the commonest being involvement of the medial longitudinal fasciculus in multiple sclerosis, giving rise to abnormal horizontal saccades (internuclear ophthalmoplegia) (Box 5-18).

The superior colliculus is involved in both perception and eye movement control

A small number of fast (M) fibres relay from the retina to the superior colliculus, and thence to the pulvinar and finally the cortex. These fibres bypass the LGN and are described as the extrageniculostriate pathway. The fibres have crossed chiasmatic representation, like optic tract fibres, and synapse in the superior

CONTROL OF GAZE/OCULAR MOVEMENT



CONTROL OF HORIZONTAL GAZE

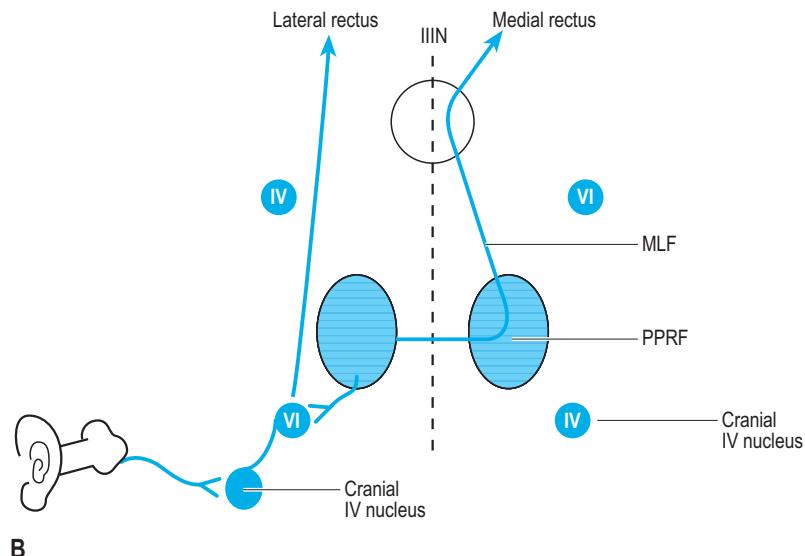


FIGURE 5-40 Outline diagrams for integrated control of ocular movements: (A) 'higher centre' regulation; (B) brainstem, nuclear control. RMLF, reticular medial longitudinal fasciculus; PPRF, paramedian pontine reticular formation; MLF, medial longitudinal fasciculus.

colliculus in retinotopic structured layers, as occurs in fibres to the LGN. The organization, however, is less clearly demarcated, being in broad superficial and deep categories of fibres.

The function of these fibres is not entirely clear. There is evidence for neuronal delay to and from the visual cortex via the posterior pulvinar system of the thalamus and also to the pretectal region where the pupillary fibres relay (Fig. 5-41). The cells also have a receptive field organization and a preference for

motion detection (a 'movement field'), particularly the rapid 'reflex' locking-on eye movement that occurs in the initiation of tracking a moving target or in automatic scanning during reading. In certain patients with occipital cortex lesions, 'blindsight' (the patient can detect motion or adjudge orientation without perceptually 'seeing' the object) may be present through preservation of this extrageniculostriate pathway.

Cells in the superficial layers of the pulvinar respond to visual input, while those in the deeper

BOX 5-18 fMRI IMAGING AND DETECTION OF DISCRETE BRAINSTEM LESIONS

fMRI imaging of patients with gaze palsies and similar oculomotor lesions are revealing discrete lesions in the brainstem. For instance, lesions in the PPRF or the VI nerve nucleus cause lateral gaze palsies, while internuclear ophthalmoplegia is caused by a lesion of the MLF, and the one-and-a-half syndrome is caused by lesions at both sites. Tiny infarcts in the region of the pons correlating with the gaze palsies have been described (reviewed by Bae et al., 2013).

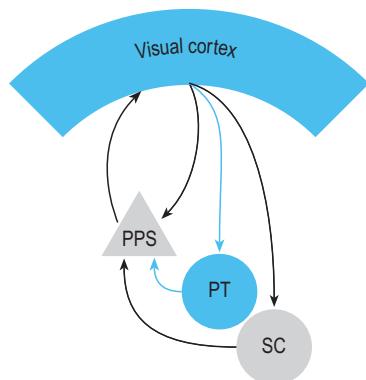


FIGURE 5-41 The extrageniculostriate pathway. Neuronal information to the superior colliculus (SC) is relayed to the posterior pulvinar system (PPS) and on to the visual cortex. From there it relays back to the PPS, the SC and the pretectal nucleus (PT), which completes the reverberating loop with the PPS.

layers respond to motion stimuli, although the cells in both layers are in register with each other. The pulvinar also receives many other subcortical inputs and acts as an 'early processing centre', receiving feedback and feedforward information from the cortex and the retina.

Recent studies in rats as well as fMRI studies in humans have suggested that connections through this pathway also occur with the amygdala and several other regions associated with 'phobic' stimuli and the experience of visually induced 'fear' perceptions induced by danger (Fig. 5-42).

Lesions in the pulvinar may thus affect such diverse functions as pattern recognition, eye movement and cerebellar integration in visual responses (see below). The colliculus–pulvinar–cortex relay system, there-

fore, is a priming system for ocular movement and for reducing errors in the localization response by linking visual and saccadic activity, possibly in response to danger.

Cortical centres regulate complex eye movements

Voluntary saccadic gaze movements are initiated by centres in the frontal cortex. Most of the fibres cross the midline in the anterior limb of the internal capsule to end in the gaze centres for motor neurone control of eye movement, but some pass to the ipsilateral superior colliculus where they inhibit automatic gaze responses (see above). In addition, cortical efferents remove tonic inhibitory impulses from collicular output to the ocular muscles, which are present between saccades, as if to 'free them up' for full-exursion eye movements.

Cortical voluntary saccades are 'tuned' as for automatic saccades, controlled by the superior colliculus; in the cortex, tuning is broad and appears to depend on recruitment of a precise number of neurones rather than a selected number of highly tuned neurones responsive to motion and visual activity. Single-cell recording studies have also shown that there are cells that exhibit presaccadic activity, while others respond only to the visual stimuli. A third group appears to show complex responses and may be involved in the integration of the response through a direct connection with the PPRF. The frontal eye fields also have an oculomotor loop to the substantia nigra in the basal ganglia, which contains high levels of dopamine. Loss of cells in the substantia nigra and a consequent decrease in dopamine concentration is a characteristic feature of Parkinson's disease. This can be tested using the 'anti-saccadic task' test, in which the urge to fix on objects in the peripheral field is voluntarily suppressed through frontal eye field and superior collicular activity. Patients with this disorder characteristically have difficulties with voluntary gaze movements and the anti-saccadic task.

Tracking, smooth pursuit eye movements are under cortical control through relay of object position information from the occipital cortex to the posterior parietal cortex (motor cortex of smooth pursuit, posterior parietal occipito-temporal regions) and thence to the PPRF. Here the information is integrated with retinal information on object velocity via the optic tract and

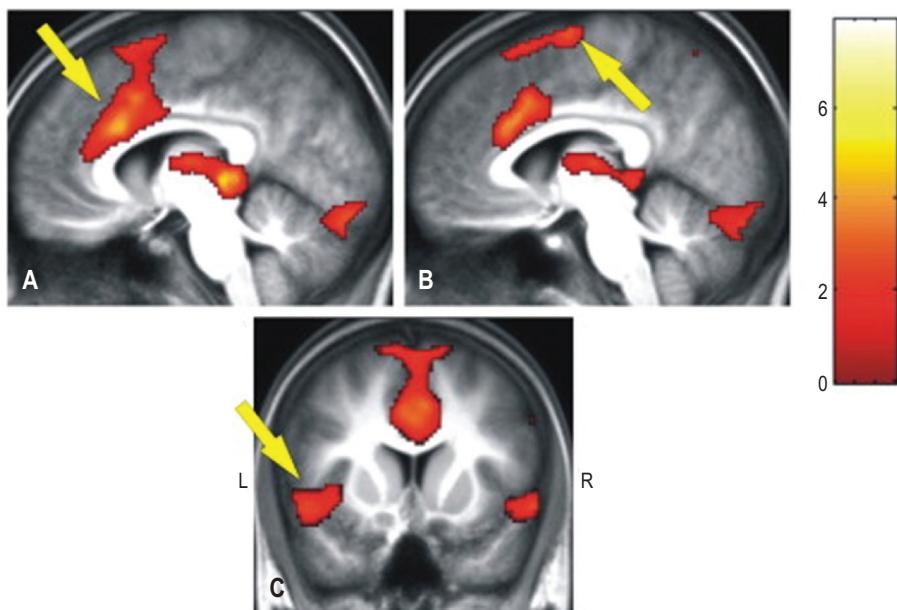


FIGURE 5-42 BOLD MRI activation maps. Patients with arachnophobia show much stronger signals compared with the controls in (A) the anterior cingulate cortex, (B) the supplementary motor cortex and (C) the insula for the contrast 'Spider > Neutral' (colour bar indicates the t-value) (From Goossens et al., 2007.)

with impulses from the head and neck on observer position, before being forwarded to the conjugate gaze centre for horizontal eye movement. In addition, recent studies have revealed that the frontal eye fields have control over pursuits as well as saccades.

The temporal cortex, as a centre for relay of motion detection information (see above), might be expected to be involved in the control of eye movement. Thus, lesions in this area affect saccades to moving targets but not to stationary ones, while smooth pursuit movements are also impaired.

Aside from obvious visual responses to objects and other specific stimuli, the process of entraining visual attention in deciding what is to be seen is extremely important. Clearly, higher cortical centres are at play here. The role of eye movements in initiating visual attention is paramount and requires integration of information from various regions of the brain, particularly the frontal eye fields (Fig. 5-43). Attention can be both overt (rapid fixating, saccadic eye movement) and covert (selective, 'out of the corner of the eye', not involving eye movement) and each can also be voluntary or involuntary (top-down or bottom-up,

respectively). Parieto-frontal and superior collicular pathways are important in determining how attention is directed (see Fig. 5-42).

THE CEREBELLUM

Afferent input from the extraocular muscles (the stretch fibres and proprioceptors) is carried in the trigeminal nerve to synapse with cells in the granular cell layer (the Purkinje cell layer; see Ch. 1). There are two, and in some species three, different types of proprioceptor: muscle spindles, Golgi tendon organs and palisade endings, each restricted to the orbital, global and marginal layers of the ocular muscle, respectively. However, some direct cerebellar afferent input is also visual via slit-like, narrow, vertical receptive fields.

The bulk of information connecting the cerebellum with the visual system is transferred via two-way traffic with brainstem centres. The oculomotor cerebellar centre, located in lobules VI and VII, produces saccade-type movements for which Purkinje cells are essential. Input is derived via the PPRF, the vestibular nucleus and the mesencephalic reticular formation.

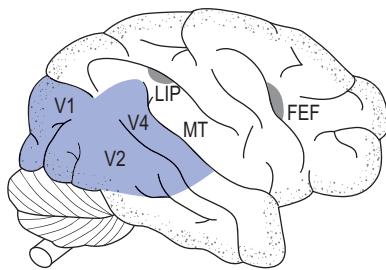


FIGURE 5-43 Schematic diagram of primate brain. Areas of the visual cortex which are activated by visual attention are V1, V2 and V4. The lateral intraparietal areas (LIP) and the frontal eye field (FEF) determine attention responses in conjunction with the control of eye movements, also served by the superior colliculus (not visible from this view). MT, middle temporal area. (From Bisley, 2011.)

The output from the cerebellum predominantly concerns positional sense, and some of it is inhibitory/regulatory. Positional information applies not only to the position of the observer with relation to the object but also to the velocity of the eye movement with relation to the target and the position of the head. Most of this is derived from the vestibular apparatus and not from visual or proprioceptive input.

This combined input also contributes to tracking movements. Experimental data have shown that cells in lobules VI and VII respond with bursts of activity during smooth pursuit movement when the eye is not actually fixating on a target (burst-pause cells).

Compensatory eye movements during movements of the head (e.g. during walking or running) are mediated mostly by the vestibulo-ocular reflex and less so by the cervico-ocular reflex through neck proprioceptors. The effect of these reflexes is to stabilize the retinal image by preventing ‘retinal slip,’ but the control is imperfect. The perceptual system can cope with a certain amount of retinal slip, but if this is too great (more than 5°/s), symptoms of oscillopsia appear. The cerebellum may contribute to control of the vestibulo-ocular reflex via input from the retina to the flocculus. It has been suggested that the cerebellum is the seat of a control mechanism for integration of information on spatial displacement during eye movement.

Currently, it is considered that there are two processes occurring simultaneously in vestibulo-ocular control of posture and ‘body sway’: L namely, a

fast-responding and short-lived response to visual cues such as parallax and a slower developing response to self-motion as it occurs during spontaneous displacement.

Ocular movements during natural activity

Most of the information regarding eye movement has come from studies that were designed to evaluate a particular movement, e.g. saccades or smooth pursuit movements. Investigation of eye movements during normal activities using infrared eye tracking devices have revealed the complex pattern of eye movements involved in performing day-to-day tasks, and has shown how extensively higher cortical information guides eye movements. Most recently, eye tracking devices have been developed which allow differentiation of microsaccades from even finer movements, termed ocular microtremors (OMTs) (Fig. 5-44). This has shown that microsaccades rather than OMTs underpin image persistence (prevent ‘perceptual fade’) during fixation (see p. 329).

Neural versus mechanical control of eye movement?

A continuing issue in studies of gaze control is to understand how much regulation of muscle function is mediated via neural control and how much can be attributed to mechanical effects of the muscles. Gaze control involves rotational three-dimensional movements (which obey Listing’s law when the head is fixed but do not when the head is moving), plus other movements such as optokinetic nystagmus and those generated via the vestibulo-ocular reflex, to achieve image stabilization. Not all movements under control of the vestibulo-ocular reflex fail to obey Listing’s law, such as the rotational movement that occurs in response to head movement, but the majority do. Movements which do not obey Listing’s law, i.e. gaze shifts when the head is not restrained, obey Donder’s law: for each position of gaze there is only one three-dimensional orientation (torsional movement).

Anatomical studies have suggested that the surrounding muscle sheath with the check ligaments can act like a pulley, allowing fine changes in the pulling direction related to the degree of torsional rotation. The data from these studies are also consistent with Listing’s law and have formed the basis of some aspects of management of patients after strabismus surgery

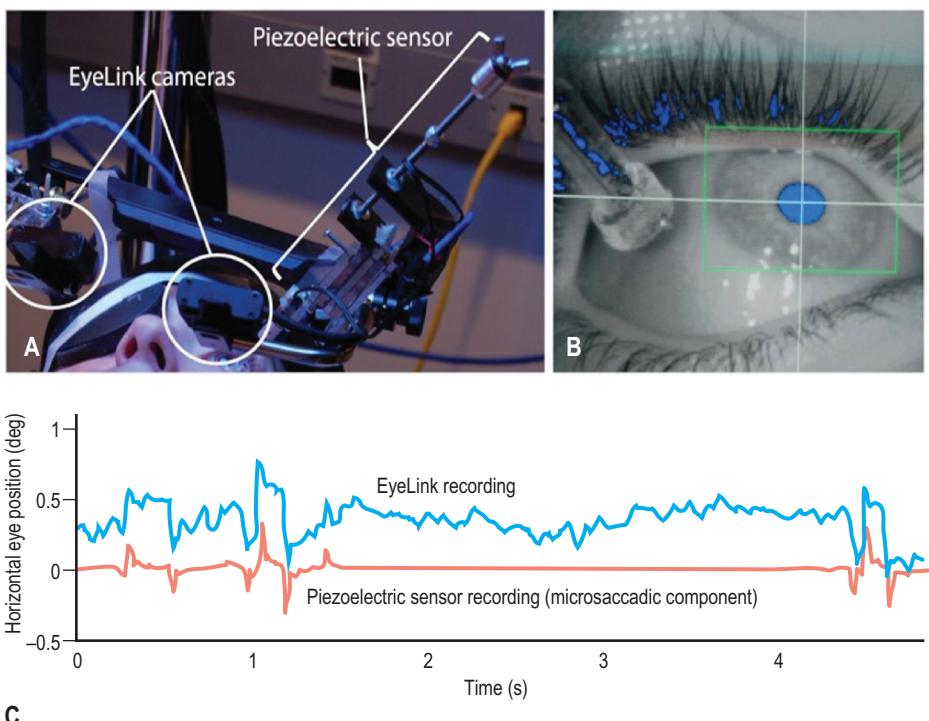


FIGURE 5-44 A custom-built set-up for recording simultaneous eye movement. In (A) a piezoelectric sensor is mounted to the EyeLink II helmet, while the image in (B) is a close-up of the sensor on the eye. The subject's pupil (blue) was tracked easily and data collected (C), showing microsaccade detection as small changes in eye position in degrees. (From McCamy et al., 2013.)

using adjustable sutures. However, the major, if not the sole, control of muscle behaviour rests with neural elements at both nuclear and supranuclear levels, with considerable regulation coming from higher centres such as the frontal eye fields and the cerebro-cerebellar network (see above). Moreover, some of the neurophysiological control would be consistent with a pulley mechanism while others such as saccades, which also obey Listing's law, are not. What is clear is that both mechanical and neural mechanisms regulate motor activity, but what remains to be determined is how the three-dimensional perception of space regulates the final motor command (top-down control) as well as the role of visual attention.

Conclusion

Visual neurophysiology continues to be the cornerstone of psychophysical neurophysiology but it is

under increasing challenge from advances in imaging such as diffusion tensor MRI as well as very recent information on high-resolution mapping of the human brain (The Human Connectome Project <http://www.humanconnectomeproject.org/>). Increasingly, our understanding of what constitutes a visual image becomes more sophisticated. Research in this field is extremely active since there are many areas of uncertainty and, possibly more importantly, many potential applications of this knowledge to clinical medicine.

The primate visual system is a highly complex arrangement for analysing information concerning the external world derived from a wide array of possible signals, all of which are captured by the retinal sensory receptors. It is remarkable to consider that around 30% of all sensory information to the brain comes via the visual system. This information is integrated with input from many other sensory systems and stored information from past experience (memory).

The final image and its interpretation (perception) are extensively edited by the brain to ensure normality and ‘constancy’ wherever possible. However, this image is, of course, unique to each individual, despite the fact that we ascribe common definitions to familiar objects. Continuing research into the psychophysics

of vision will fuel our thirst for knowledge into what makes us tick.

FURTHER READING

A full reading list is available online at <https://expert-consult.inkling.com/>.



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