Perspectives in neuro-ophthalmology

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Contributed by request and dedicated to Sir Stewart Duke-Elder

Of the 3 million or so fibres that enter the primate brain, two-thirds originate within the eyes (Weiskrantz, 1972), and of the twelve cranial nerves half are necessary for the optimum performance of the eye as a visual organ. Interpretation and diagnosis of visual dysfunction therefore depends on the close clinical harmony established between ophthalmologists and neurologists. This close link, though established before the advent of the ophthalmoscope (von Helmholtz, 1851), was enhanced by this innovation, and recent advances have further propagated this liaison. The clinical challenge of neuro-ophthalmology was particularly accepted by ophthalmologists (Kestenbaum, 1946; Cogan, 1948; Walsh, 1947; Walsh and Hoyt, 1969), but necessitated some understanding of the commensurate advances in neuro-anatomy, neuro-pharmacology, visual physiology, and biomedical engineering. This review will attempt to align some of the information and concepts established by these basic disciplines and harness them for use by the clinical ophthalmologist. The first part will be confined to the visual sensory system and the second to the oculo-motor system.

Sensory system

The visual process commences at a retinal level, where 130 million light-sensitive receptors in each eye initiate a neural process terminating in the brain, where intricate analysis produces a three-dimensional picture which is related to past experience and includes colour, form, and rate of movement. Understanding of this organization began when Kuffler (1953) at the Johns Hopkins Hospital discovered that some analysis of visual information occurred in the retina of cats. The area of receptor mosaic in the retina feeding into a single visual cell is the receptive field of the cell. This fundamental concept was established by Hartline (1940) and utilized in the visual system pre-eminently by two distinguished workers from Harvard University, H. Hubel and T. N. Wiesel. The method depends on a microelectrode recording from a solitary visual cell, which can record from the cell for prolonged periods without impairing function.

RETINAL ORGANIZATION

The receptive fields of ganglion cells are made up of a circular central region concentric with a larger circular surround region which is antagonistic to the central area. The cell is classed as an "on centre" cell when a light projected on the central area produces a response, but if the light is shone on the antagonistic surround the response is inhibited and the surround is termed an "off surround". The other class of ganglion cell has an "off centre" with an "on surround". This organization tends to enhance contours and the "on" and "off" areas tend reciprocally to reinforce their respective actions (Bishop, 1964). Extensive

anatomical investigation of the retina (Dowling and Boycott, 1966) has shown numerous different types of ganglion cells, and also synaptic connections between ganglion cells, amacrine cells, bipolar cells, and horizontal cells. Neurophysiological study has shown further functional subdivision of ganglion cells into "X" and "Y" cells depending on the linearity of response to spatial summation (Enroth-Cugell and Robson, 1966), and these cells may also be either "transient" or "sustained" (Ikeda and Wright, 1972). There is evidence that some information for motion in lower animals may be processed at a retinal level (Grüsser, Grüsser-Cornehls, and Licker, 1968). The afferent neurons are of varying sizes and conduction velocities depending on their ganglion cells of origin; the small axons arise from the "midget ganglion" cells in the macular area and the larger axons from the periphery. Red-free fundus photography (Hoyt, Frisén, and Newman 1973) has been applied to the correlation of visual field defects with neuronal loss in humans.

LATERAL GENICULATE ORGANIZATION

The afferent fibres pass through the optic nerves to hemi-decussate at the chiasm before synapse at the lateral geniculate bodies. This structure has six laminae and two ventral magno-cellular layers with a multiplicity of cell types (Szentagothai, 1973). Though each lamina receives an essentially monocular input, there is modification of the visual information by other intrageniculate layers, or by extrageniculate sources such as the visual cortex or the brain stem reticular formation (Freund, 1973). Though no major changes are produced by the lateral geniculate bodies, they serve to enhance the information obtained in the retina and to prepare it for presentation to the cortex. They may also correct visual information for changes in the orientation of the eyes with respect to the head (Bishop, 1964).

THE VISUAL CORTEX

Axons of geniculate cells pass in the optic radiation to terminate in layer IV of the striate cortex, and further organization occurs upwards and downwards to produce vertically orientated columns. The cortex is the first site in the visual system with binocular integration, where convergence and analysis of the visual information occurs in an hierarchical pattern. The complexity and capacity of the cortex is emphasized by its size—20 sq. ft by $\frac{1}{10}$ " if flattened out. Cells of increasing complexity have been defined, the simplest ("simple cells") responding to lines and edges, "complex cells" responding to specific line orientation, shapes, and motions, and "hypercomplex cells" responding selectively to a great variety of complicated angular forms (Hubel and Wiesel, 1965b). Simple and complex cells predominate in area 17, and a topographic mirror-image representation occurs in areas 18 and 19, where hypercomplex cells of varying types predominate.

The major part of the striate cortex is concerned with central vision and a cortical magnification factor was established by Daniel and Whitteridge (1961) in monkeys in which 1° of foveal vision represented 6 mm. linearly at the cortex. The organization of the visual system in man, with the left field being represented in the right occipital cortex and *vice versa*, necessitates a concentration of fibres related to the central vertical meridian of each hemifield. The corpus callosum plays a crucial role in binding the two visual hemifields to form a continuous visual world. This binding is effected by neurones of cortical cells representing the vertical meridian which cross in the corpus callosum and include simple, complex, and hypercomplex cells (Hubel and Wiesel, 1967). Representation of the ipsilateral field in the ipsilateral cortex over a small 2° strip in the vertical meridian has also been shown (Stone, 1966; Leicester, 1968). These mechanisms provide an explanation

for macular sparing in homonymous hemianopia. The corpus callosum is also involved in binocular depth perception in the area of fixation (Blakemore, 1970), though specific binocular depth detecting neurones have been isolated in area 18 (Hubel and Wiesel, 1970).

THE "DUAL CONCEPT" OF VISION

Interesting proposals have recently been made for two functionally separate visual systems subserving "ambient" and "focal" vision (Trevarthen 1968), distinction between "where" and "what" (Schneider, 1967, 1969); "orientation" and "evaluation" (Ingle, 1967), "noticing" and "examining" (Weiskrantz, 1972). These support the suggestion made by William James "that the main function of the peripheral part of the retina is that of sentinels which when beams of light move over them cry 'who goes there' and call the fovea to the spot" (James, 1892). The "noticing" aspect detects movements and achieves spatial orientation through rods in the peripheral retina with large ganglion cells ("Y" and "transient") and large nerve fibres, which may be connected not only with the cortex but also with the superior colliculus where a retinotopic map is also situated. This neglected retino-collicular pathway is surprisingly about ten times the size of the auditory nerve (Weiskrantz, 1972). The "examining" system, in contrast, is devoted to detailed visual analysis through foveal mechanisms with small ganglion cells and neurones ("X" and "sustained") referred to the striate cortex. Intensive study of the role of the superior colliculus in primates and subprimates is now being undertaken (Schiller and Koerner, 1971; Goldberg and Wurtz, 1972; Wurtz and Goldberg, 1972). The clinical applications of the progress in the understanding of the organization of the visual system will evolve over the years and only the important implications in regard to strabismus and neurophysiological tests will be discussed in this review.

VISUAL DEPRIVATION AND ITS RELATION TO SQUINT

Neuronal receptive field organization is probably present at birth but, for satisfactory development, binocular and synchronous use of the eyes must be maintained over a certain critical period of ontogenetic development.

In kittens, uniocular occlusion at birth by lid suturing (Wiesel and Hubel, 1963b) and subsequent cortical recording showed that none of the cortical neurones received an input from the occluded eye.

In contrast, bilateral occlusion in kittens disclosed a pattern of ocular dominance within the normal range. From these experiments induction of strabismus in kittens was produced closely simulating the human model. The medial rectus was incised, or the eyes were occluded on alternate days, and cortical recordings in these animals showed that a majority (up to 90 per cent.) of cells received an input from only one eye (Hubel and Wiesel, 1965a). It is interesting that the visual cortex remained anatomically normal, though there were marked morphological changes in the lateral geniculate cells (Wiesel and Hubel, 1963a). A further series of experiments performed on monkeys confirmed this work (von Noorden and Dowling, 1970; von Noorden, Dowling, and Ferguson, 1970) and showed that amblyopia was produced in animals made esotropic at 1 week, but not when esotropia was induced at 1½ years. These experiments do not satisfactorily explain the reduced visual acuity which may be related to inadequate stimulus of the "sustained" (X) cells (Ikeda and Wright, 1974). These experiments have therefore demonstrated that, for normal development of the visual system, an adequate binocular and synchronous sensory stimulus is necessary

over a critical period. The time sequence and duration of this period in humans, however, remains a matter of conjecture.

Further sidelines of this research have led to the rearing of cats in environments where they are exposed only to horizontal or vertical stripes, and cortical testing showed a response only to the line orientations to which they had been exposed (Blakemore and Cooper, 1971). It is also of interest that the genetically determined squint of the Siamese cat shows an abnormal anatomical arrangement of visual fibres and an absence of binocularly driven cells (Guillery, 1969; Hubel and Wiesel, 1971).

NEUROPHYSIOLOGICAL TESTS

The electroretinogram (ERG) and electro-oculogram (EOG) have been established as important indices of retinal and pigment epithelial function respectively. The assessment of cortical evoked responses has developed since Adrian and Matthews (1934) described occipital responses after looking at a flickering light. Dawson (1954) introduced the summation technique utilizing averaging devices (computer of average transients), and latency measurements were made with an averaged visually evoked response (Cobb and Dawson, 1956). Different wave forms have been classified (Cigánek, 1961), though techniques of stimulation and recording vary in different laboratories. A bright light flash lasting a few microseconds produced satisfactory responses, though the fact that inhibition and excitation seemed likely, using analogy with receptive field organization, led to the use of pattern responses as well (Spehlmann, 1965). Widespread use of patterned visually evoked responses (VER) has shown that the response is dependent on the optical definition (White, 1969) and on the size of the pattern element (Spehlmann, 1965). Clinical application of this technique will depend on adequate discrimination in stimulus and recording. Diagnostic value has been established, however, in babies with impaired vision (Harden and Pampiglione, 1970), and in optic nerve lesions where delayed conduction has been a feature of demyelination (Halliday, McDonald, and Mushin, 1972) even in the presence of "normal" vision (Feinsod, Abramsky, and Auerbach, 1973). Studies of amblyopia in strabismus patients have also shown abnormal response to patterned VERs (Lombroso, Duffy, and Robb, 1969; Arden, 1973), and focal areas of retina may be tested (Regan, 1972). The technique is valuable in the diagnosis of hysterical blindness and has been used clinically (Regan and Heron, 1970) and experimentally in monkeys (Vaughan and Gross, 1969) in retrochiasmal disease. It remains increasingly important for the ophthalmologist to use information gained in this expanding field as part of his diagnostic armamentarium.

The oculo-motor system

The oculo-motor system is closely and harmoniously integrated with the visual sensory system for the combined purposes of "looking" and "seeing". Disabilities produced by disorders of the oculo-motor system approximate in severity to those of the visual sensory system and this review, after discussing briefly the organization of ocular movements will consider some of the disorders of diagnostic significance to the ophthalmologist.

CEREBRAL CONTROL OF OCULAR MOVEMENTS

The advent of a belligerent face at the window whilst reading these words will initiate a high velocity saccadic movement (400–600°) to the object of regard, which if inaccurately localized will be followed by smaller compensatory saccadic movements. During this movement vision will be suppressed (saccadic suppression), the room will not rotate in the

opposite direction, though a head movement may occur in conjunction. The reaction time for this movement is 200 m sec., the duration is 45 m sec., for a 10° saccade, and the system in computer terminology behaves as a sampled data system (Robinson, 1968). Examination of the object of fixation then occurs after adjusting the eyes for optimal binocular vision with use of the vergence system (Delisle Burns and Pritchard, 1968), and the object is scanned by micro-saccades for which a pattern or 'scanpath' is established which differs in individuals (Noton and Stark, 1971). During observation slow involuntary eye movements maintain fixation by use of the "pursuit" system, which has a short latency (125 m sec.) and functions as a continuous data sampling system. An efficient oculo-vestibular system retains ocular fixation in regard to head or body movement.

Thus, for clinical purposes, there are four subsystems controlling ocular movements—one producing rapid eye movements and the remainder slow movements:

- (1) Saccadic system
- (2) Pursuit system
- (3) Vergence system
- (4) Vestibular system

(1) The saccadic system is responsible for high velocity movements which may be produced voluntarily with impulses mediated from the frontal cortex (Area 8 of Brodman), or in response to auditory or eccentric visual stimuli, or in the rapid eye movement (REM) phase of sleep, and also in the fast phase of vestibular and optokinetic nystagmus. The anatomical substrate includes a pathway from the frontal cortex, *via* the anterior limb of the internal capsule to the subthalamic region and zona incerta, to terminate in the pretectal region for the control of vertical movements, and in the paramedian pontine reticular formation after decussation in the midbrain for horizontal movements (Brucher, 1966). Evidence for participation of frontal neurones in all saccadic movements is lacking, though Bizzi and Schiller (1968) recorded discharges from frontal neurones during the fast phase of optokinetic and vestibular nystagmus. The polysynaptic nature of this pathway (Robinson and Fuchs, 1969; Astruc, 1971) may have clinical significance. The final common pathway for horizontal conjugate movements lies in the paramedian pontine reticular formation (PPRF) (Cohen and Feldman, 1968), which is situated ventral to the median longitudinal fasciculus at the level of the abducens nucleus. This cellular organization is responsible for all conjugate horizontal movements and functions as a pulse generator (Robinson, 1972).

(2) Smooth pursuit movements probably originate in the visual association areas with a tract passing lateral to the ventricles, but medial to the optic radiation in the internal sagittal stratum to the posterior limb of the internal capsule and terminating in the PPRF and pretectal and superior collicular nuclei. Precise knowledge of the brainstem organization for this system is lacking, though for clinical purposes the occipital cortex controls pursuit movements to the same side. This system maintains visual fixation, and is fundamental in visual stabilization (Collwijn and van der Mark, 1969; Robinson, 1972).

(3) The *vergence system*, which is a phylogenetically recent addition, is unique in that, in contrast to all other subsystems, it produces movement of the eyes in opposite directions. Understanding of the near reflex (accommodation, convergence, and pupillary constriction) is dependent on the neural mechanism of binocular depth perception which is currently under physiological investigation in many centres (Delisle Burns and Pritchard, 1968; Barlow, Blakemore, and Pettigrew, 1967), and specific binocular depth perception

cells have been found in area 18 (Hubel and Weisel, 1970). Stimulation experiments of the pre-occipital cortex (Jampel, 1959) have induced convergence, and Nashold and Gills (1967) have induced convergence by stimulation of the pre-rubral fields of Forel.

(4) The normal functioning of the vestibular system produces ocular stability in relation to head, body, and environmental movement. This is achieved by close integration of vestibular, neck muscle, and cervical afferents, with the pontine and cerebellar complexes.

SUB-CORTICAL ORGANIZATION OF OCULAR MOVEMENTS

For conjugate horizontal gaze, pathways from the paramedian pontine reticular formation convey excitatory impulses to the ipsilateral abducens nucleus and *via* the median longitudinal fasciculus (MLF) to the contralateral mesencephalic medial rectus nucleus which is situated ventrally in the oculo-motor complex (Warwick, 1953). Simultaneously inhibitory impulses pass to the contralateral abducens and ipsilateral medial rectus nuclei. Generation of saccadic movements is dependent on the rate of discharge (Robinson, 1972) and this is related to eye position as well as velocity. There is also evidence that saccadic movements utilize rapid conducting neurones innervating fast twitch fibres situated centrally in ocular muscles, whereas small peripheral "tonic" muscle fibres, with a rich capillary plexus and large numbers of mitochondria, are well served to maintain sustained activity (Bach-y-Rita, 1971). The superior colliculus has been shown not only to have a sensory map (Cynader and Berman, 1972) but also a motor map (Robinson, 1974), and stimulation has produced saccadic movements (Schiller and Koerner, 1971). Integration of ocular movements may be a function of the cerebellum which not only receives stretch afferents (Fuchs and Kornhuber, 1969) but also produces saccades on vermis stimulation (Ron, 1971). Alert unrestrained animal preparations with implanted recording devices are now being used in this important field of research and should answer many of the current problems about sub-cortical organization.

DISORDERS OF OCULAR MOVEMENTS

Major interest in this subject has been shared by neurologists, ophthalmologists, neurophysiologists, psychologists, and biomedical engineers, resulting in several recent comprehensive reviews (Bender, 1964; Bach-y-Rita, Collins, and Hyde, 1971; Dichgans and Bizzi, 1972). Dependent on this has been the ability, using infra-red or DC amplifying techniques, to measure the latency, velocity, and accuracy of ocular movements. This section will serve to highlight certain aspects of this work; examination techniques are described elsewhere (Bird and Sanders, 1970; Sanders and Bird, 1970).

Involvement of the "saccadic" system produces an inability to perform an accurate high velocity eye movement (saccadic palsy) (Hoyt and Daroff, 1971). Previous descriptions have concentrated mainly on frontal lesions which, in the acute phase, show ipsilateral deviation of the eyes owing to the inability to execute contralateral saccades, but recently a wide spectrum of basal ganglia disorders have been reported. These include Huntington's chorea (Starr, 1967), Wilson's disease (Kirkham and Kamin, 1974), Parkinson's disease (Walsh and Hoyt, 1969), ataxia telangiectasia (Walsh and Hoyt, 1969), Tay-Sachs disease (Jampel and Quaglio, 1964), and juvenile Gaucher's disease (personal observation). Preferential involvement of vertical saccades may be seen in adults with a progressive degenerative extrapyramidal syndrome (Steele, Richardson, and Olszewski, 1964) and in children with kernicterus (Haymaker, Margoles, Pentschew, Jacob, Lindenburg, Arroyo, Stochdorf, and Stowens, 1961), or an unusual neuropiloidosis resembling Niemann-Pick disease but characterized by "sea blue histiocytes" (Sanders and Wybar, 1969; Neville,

Lake, Stevens, and Sanders, 1973). Ophthalmic examination may be diagnostic in these groups by showing "saccadic palsy" but with intact pursuit and vestibular responses. Concomitant involvement of the pursuit and vestibular movements, however, localizes lesions to the paramedian pontine reticular formation.

CEREBELLAR SYSTEM DISORDERS

The inability accurately to differentiate between cerebellar and brain stem disease necessitates the use of this comprehensive term, and some ocular disorders of this system will be briefly described:

Ocular dysmetria

This manifests as an inability to perform accurate saccadic movements on repeated testing and is characterized by an undershoot followed by a corrective saccade. An overshoot rarely occurs and accurate diagnosis is made by electro-oculographic recording (Higgins and Daroff, 1966).

Ocular flutter

Spontaneous, rapid, intermittent oscillations of the eyes, often in the primary position, characterize this disorder, which has often been associated with brain stem encephalitis (Cogan, 1968; Brumlik and Means, 1969).

Opsoclonus

Rapid, involuntary conjugate saccadic movements of a chaotic nature may occur with encephalitis, postencephalitic syndromes (Cogan, 1968), or remote neoplasms (Ross and Zeman, 1967). First described in children as "myoclonic encephalopathy" (Kinsbourne, 1962), recent publications have stressed the association of this condition with neuroblastoma (Solomon and Chutorian, 1968; Moe and Nellhaus, 1970).

Pendular macro-oscillations

Bursts of large oscillations, often provoked by a saccadic movement, characterize this manifestation of unilateral cerebellar disease (Hoyt and Daroff, 1971).

Ocular myoclonus

Unilateral or bilateral slow pendular vertical movements, often in synchrony with movements of other midline structures, particularly the palate, characterize this anomaly (Daroff and Waldman, 1965).

Rebound nystagmus

Cerebellar disease was implicated in a recent report of 25 patients with an unusual pattern of nystagmus (Hood, Kayan, and Leech, 1973). Nystagmus on lateral conjugate gaze gradually fatigued, and returning the eyes to the primary position produced nystagmus in the opposite direction which also gradually fatigued. This was associated with enhanced caloric responses, but deranged optokinetic and pursuit movements.

Upbeat nystagmus

Large amplitude primary position nystagmus with the fast phase upwards, increasing on elevation but diminishing with down gaze, may be associated with dysfunction of the anterior vermis of the cerebellum (Daroff and Troost, 1973).

Summary

This review has attempted to correlate for the clinical ophthalmologist some of the changing patterns in our understanding of the visual sensory and oculo-motor systems. The complexity is enormous, but functional characteristics are becoming apparent, such as the concept of "fast" and "slow" fibres in both systems, and the realization that previously neglected areas such as the superior colliculus may play an important role. Sophisticated testing will be possible only in specially equipped institutes, but clinical recognition of some of the disorders described may localize disease and facilitate diagnosis.

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