Neuro-ophthalmology of degenerative neurological disorders

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A number of degenerative disorders of the nervous system are associated with visual or ocular motor disturbances. Over recent years, these problems have attracted a great deal of interest because they may aid diagnosis and also improve our understanding of pathophysiology. In this review, we discuss both of these aspects of the study of degenerative conditions and attempt to demonstrate the clinical significance of a number of new findings.

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The study of visual perception and ocular motor control in degenerative conditions of the brain offers not only important insights into the nature of these diseases but also the potential to differentiate between some of them. The advances that have occurred over recent years owe much to investigations of the mechanisms and structures normally involved in these processes in monkey. In this review, we attempt to place observations on degenerative conditions in the context of current views of the normal primate brain. However, it will be clear to the reader that the links between the two are often tenuous. This is due either to limitations of the techniques used to study human brains, or to the nature of some conditions that are associated with pathological change in large areas of the brain. It is likely, therefore, that some of the interpretations of observations offered here will need to be revised but it is important, the authors believe, to offer a theoretical background for the many and diverse findings that have been reported.

Alzheimer's disease

A number of investigators have reported disorders in various modalities of vision in patients believed to have senile dementia of the Alzheimer type (SDAT). Reduced contrast sensitivity has been reported to occur either across the range of spatial frequencies tested; or more often at low frequencies; or at all frequencies except low ones [1–3]. However, two studies failed to find any deficiency in contrast sensitivity [4,5]. Thresholds for stereoacuity measured using the Randot Stereo Acuity Test have been found to be elevated in SDAT but, again, the prevalence is very variable [2]. Similarly, although as a group patients presumed to have SDAT made more errors on a test of hue comparison, many individuals were within the normal range. Interestingly, the distribution of errors revealed a disproportionate number of tritan (blue) errors but the significance of this is unclear [2].

This range of findings may reflect the extent of pathological processes affecting the visual pathways. Degeneration of the retinal ganglion cells, optic nerve, striate and, more prominently, extrastriate visual cortices have all been reported in SDAT [6–8] but morphological changes and dysfunction of these regions may be highly variable. For example, one recent study failed to find any difference in retinal ganglion cell loss between patients with SDAT and elderly control subjects [9].

On the other hand, some investigators claim that there is preferential disruption of the broad-band motion-sensitive magnocellular visual pathway because there appears to be a selective loss of large-diameter optic nerve fibers [7] and cortical cells that receive information from them [10]. In support of this hypothesis, thresholds for detecting coherent motion have consistently been found to be elevated in patients likely to have SDAT [11,12,13•]. Kurylo *et al.* [14••] demonstrated that patients have deficits in flicker (another test of magnocellular pathway function) as well as motion perception. However, their subjects also demonstrated

Abbreviations

ALS—amyotrophic lateral sclerosis; **LP**—levator palpebrae superioris; **MSA**—multisystem atrophy; **OO**—orbicularis oculi; **OPCA**—olivopontocerebellar atrophy; **PD**—Parkinson's disease; **PSP**—progressive supranuclear palsy; **SDAT**—senile dementia of the Alzheimer type; **VEP**—visual evoked potential.

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poor performance on tests used to assess the parvocellular pathway such as texture and blue-violet discrimination [14••].

Although the magnocellular and parvocellular channels may be highly segregated before they reach the striate cortex, their further progress within cortical pathways is more complex, with interactions occurring between the two at many different stages. Kurylo *et al.* [14••] argue that their findings are consistent with the widespread changes that occur in the visual association cortices in SDAT and that disruption of retinocalcarine pathways need not be invoked. This claim is supported by the group's findings that both pattern visual evoked potentials (VEPs) and flash electroretinograms are normal in individuals considered to have SDAT [15]. However, although most previous studies have not found abnormalities of the pattern VEP, one recent investigation demonstrated prolonged latencies of both early and late components of the response [16]. Furthermore, the amplitude of pattern electroretinograms is reported to be reduced in SDAT [17].

Irrespective of whether the functional disruption is precortical, cortical, or both, it is tempting to conclude from these studies that there are deficits within the afferent visual pathway in SDAT. There remains a concern, however, that some of the reported sensory deficits are due to a disorder of directing attention. Posner [18] demonstrated in normal individuals that manual reaction times to the onset of a stimulus at a peripheral cued location is reduced compared to uncued areas, even when subjects maintain steady central fixation. It has been suggested that this reflects the covert shift of a "spotlight" of attention to engage the cued location, allowing subjects to process the onset of the stimulus more swiftly. However, if on occasion the cue is invalid so the stimulus appears at a location other than the cued one, reaction times increase presumably because it takes time for attention to disengage and move from the invalidly cued zone to the location of the stimulus. In normal subjects there is evidence to suggest the size of the attentional spotlight can narrow or widen like a zoom lens.

Patients presumed to have SDAT appear to experience difficulty in disengaging attention and either shifting it away from invalidly cued zones [19,20,21•] or changing the size of the focus of attention [22]. Even when the likelihood of a target appearing at the cued location is only 20%, they continue to shift attention to that locus. It has, therefore, been proposed that these patients manifest an "attentional grasp reflex" and are unable to direct attention away from salient visual stimuli [21•]. This would account for their poor performance when asked to make antisaccades, *ie*, saccadic eye movements to a location symmetrically opposite that of a flashed stimulus. In such paradigms, individuals considered to have SDAT experience difficulty in suppressing reflexive saccades to visual stimuli [23,24]. Even when they are required simply to make reflexive saccades to a visual target, patients make errors in directing gaze suggesting they have substantial difficulty in shifting attention [25•]. This may also account for apparent peripheral visual field loss [26] or deficits on form discrimination tasks in which subjects are required to scrutinize closely the shapes of a number of stimuli [27].

There is little argument that difficulties in directing attention are most likely due to disruption of cortical mechanisms. Interestingly, there appears to be a correlation between hypometabolism of the right superior parietal lobule and prolonged disengagement of attention [19]. But neurofibrillary tangles in SDAT are also present in high density within visual areas of the temporal cortex and dysfunction of these regions is likely significantly to affect visual perception. Over recent years, a number of patients with atrophy confined to parietooccipital regions of the brain have been reported, although not all are examples of SDAT [28•]. Detailed psychophysical and neuropsychological study of these cases promises to be a particularly instructive avenue of research.

Parkinson's disease and other movement disorders

Visual dysfunction

Although Parkinson's disease (PD) is generally considered a disorder of movement, in recent years there has been increasing evidence for additional perceptual dysfunction, in particular of vision. It is not uncommon for a PD patient to comment on some form of visual disturbance such as visual blurring or distortion. All too often this is dismissed in the face of normal visual acuity and fundoscopy. However, dopamine, the neurotransmitter which is primarily deficient in the basal ganglia in PD, is also a neurotransmitter found in retinal interplexiform and amacrine cells and in the human visual cortex. It has been proposed that dopamine has a modulatory role in establishing center-surround properties of individual retinal ganglion cells [29], and decreased levels of retinal dopamine have been found in PD [30]. It is possible, therefore, that visual symptoms in PD may have a valid pathophysiological basis.

Clinical evidence for retinal dysfunction in PD comes from psychophysical and electrophysiological studies. Several studies of both spatial and temporal contrast sensitivity measurements in PD have been reported, although with rather inconsistent results. In some studies loss of sensitivity in detection of spatially modulated, temporally static patterns was observed at all frequencies [31], medium and high frequencies [32], or at a notch at 1 to 2 cycles/deg^{-1} [33]. When tested on temporally modulated patterns PD patients showed a loss of sensitivity in the frequency range 4 to 8 cycles/deg^{-1} [34]. Support for the role of dopamine deficiency in these visual defects comes from studies in which lev-

odopa administration has corrected the spatial contrast abnormality [35].

Electrophysiological studies in PD have found levodopa reversible prolongations of the major positive component (P100) latency of the VEP and the latency of the pattern electroretinogram [36].

Several recent studies have focused on abnormalities of color vision in PD. Using the Farnsworth-Munsell 100-hue test of color discrimination, Büttner *et al.* [37] found an elevated total error score positively correlated with the duration and severity of the disease, was also present in untreated patients, and improved with levodopa medication [38,39]. In a more detailed psychophysical study abnormalities of the tritan (blue) contrast threshold only were found in both static and dynamic test conditions when luminance contrast was kept constant [40••]. Difficulties in achieving this may explain why in a study of color VEPs similar abnormalities were found for monochromatic red, green, and blue gratings [41]. One possible explanation for this preferential involvement of the blue cone system is the relative sparseness of these cones, requiring interactions over greater distances, thereby involving processing in the interplexiform and amacrine cells both of which are dopaminergic neurons.

Although most studies have suggested abnormalities at a retinal level in PD, possible disturbances at a cortical level require consideration. An intriguing observation by Regan and Maxner [42] and Bulens *et al.* [43] of an orientation deficit specific for horizontally oriented patterns has recently been confirmed [44]. The observations point to visual cortical dysfunction, because orientation sensitivity is observed only at cortical levels in primates.

Oculomotor dysfunction

The association of disturbances of eye movements in basal ganglia disease has been recognized for over a century. In some conditions an oculomotor abnormality is a defining feature of the condition, for example, the supranuclear vertical gaze disorder in progressive supranuclear palsy (PSP) (Steele-Richardson-Olszewski disease). In others, more subtle abnormalities may require oculographic recordings in the laboratory for their recognition, but may still be of value in diagnosis. In addition to their clinical value oculomotor abnormalities in basal ganglia disease can provide important insights into the normal neural control of different types of eye movement.

To the clinician a patient presenting with a parkinsonian syndrome of rigidity and bradykinesia (akinetic-rigid syndrome) poses a difficult diagnostic problem. Although idiopathic PD is the most likely diagnosis, postmortem examination of such patients has shown that up to 15% to 20% have some other condition [45]. These include PSP, multisystem atrophy (MSA), striatonigral degeneration, and a relatively newly described condition, corticobasal degeneration. Saccadic eye movements may serve as a useful guide to differentiate between some of these conditions. In PSP, in which there is degeneration in the midbrain and cerebellum in addition to the basal ganglia, the characteristic oculomotor disorder of a supranuclear vertical gaze palsy is usually preceded by slowing of vertical saccades, downward before upward [46]. However, in a retrospective analysis of pathologically confirmed cases of PSP 50% had no gaze paresis at initial clinical examination, and in 20% downgaze paresis was never detected [47]. MSA is a clinical pathological term encompassing striatonigral degeneration, OPCA, and some entities of autonomic failure with or without added neurological signs. Early in the course of the disease, patients can be separated in subgroups; however, as the disease progresses, considerable overlap occurs [48]. In a pathologically proven group of patients with MSA who presented with a parkinsonian syndrome a mild vertical gaze palsy was detected in only one of 16 patients [49].

Corticobasal degeneration is characterized by progressive asymmetric idiomotor apraxia and extrapyramidal symptoms. In a comprehensive study of 34 patients with the condition the typical oculomotor abnormalities were a delay in the initiation of voluntary saccades, saccadic hypometria and broken-up, jerky (saccadic) pursuit [50]. The saccadic paresis affected both horizontal and vertical gaze. These abnormalities were evident in about one third of the patients in the early stages of the disease, but had developed in 90% on follow-up. Further confirmation of this impairment in voluntary saccade initiation in corticobasal degeneration, which differentiated them from patients with PD, PSP, and strionigral degeneration, was found in an oculographic comparison of horizontal eye movements in these groups [51••].

The antisaccade paradigm has proved to be popular in studies of saccadic eye movements because it not only tests voluntary saccade generation, but also the ability to suppress saccades. The subject is instructed to suppress a reflexive saccade on the appearance of a peripheral target, while at the same time generating a volitional saccade to a minor image location in the contralateral visual field. In PSP an increased percentage of errors, *ie*, misdirected saccades made toward the target, was found at an early stage [52]. However, increased antisaccade errors may be found in corticobasal degeneration [51••,53], and also in patients with advanced idiopathic PD [54].

Several studies have found reduced amplitude primary saccades in PD patients performing the remembered saccade paradigm [55], in which the target is briefly presented and after a variable delay of 0.5 to 15 seconds the subject makes a saccade to the remembered location of the target. Levodopa medication was found to have no effect on the hypometria of these single-remembered saccades, but produced improvement in the

chronology of sequences of remembered saccades [56]. Because a similar saccadic abnormality has been observed in patients with a focal lesion of the supplementary motor area [57], Vemersch *et al.* [56] suggested that levodopa had led to a reversal of the decreased activation of the supplementary motor area, and a restoration of this part of the oculomotor circuit. This dependence on vision during the generation of saccades in PD was extended to other sensory modalities, vestibular and cervical proprioceptive, in a comparison of vestibular, cervical, and visual remembered saccades [58].

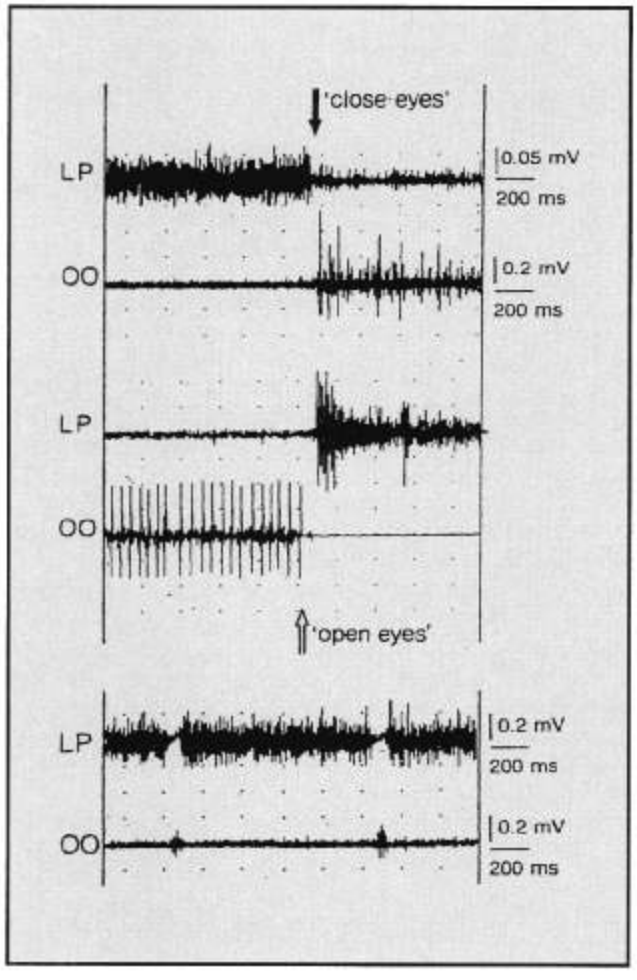

Fig. 1. Electromyographs from levator palpebrae superioris (LP) and orbicularis oculi (OO) muscles in a control subject and a patient with blepharospasm. Note the normal reciprocal inhibition of these muscles in the control subject. The recordings from the patient show different types of dystonic activities of OO. The *top panel* demonstrates tremulous discharges while the eyes are closed; the *middle panel* shows tonic activity causing forceful closing of the eyelids; the *bottom panel* demonstrates phasic discharges followed by postinhibition potentiation of LP. (*From* Aramideh *et al.* [61••]; with permission.)

Further physiological details of the neural circuitry in the basal ganglia related to the generation of saccades were reported in monkeys in whom a deficiency of nigrostriatal dopaminergic innervation has been induced [59,60].

Blepharospasm and related conditions

Interest in disturbances of eyelid movement has increased since the introduction of botulinum toxin for the treatment of blepharospasm. Yet a proportion of patients fail to have a satisfactory response to the toxin, raising the possibility that the clinical disorder, blepharospasm, may contain many different eyelid disorders within its confines.

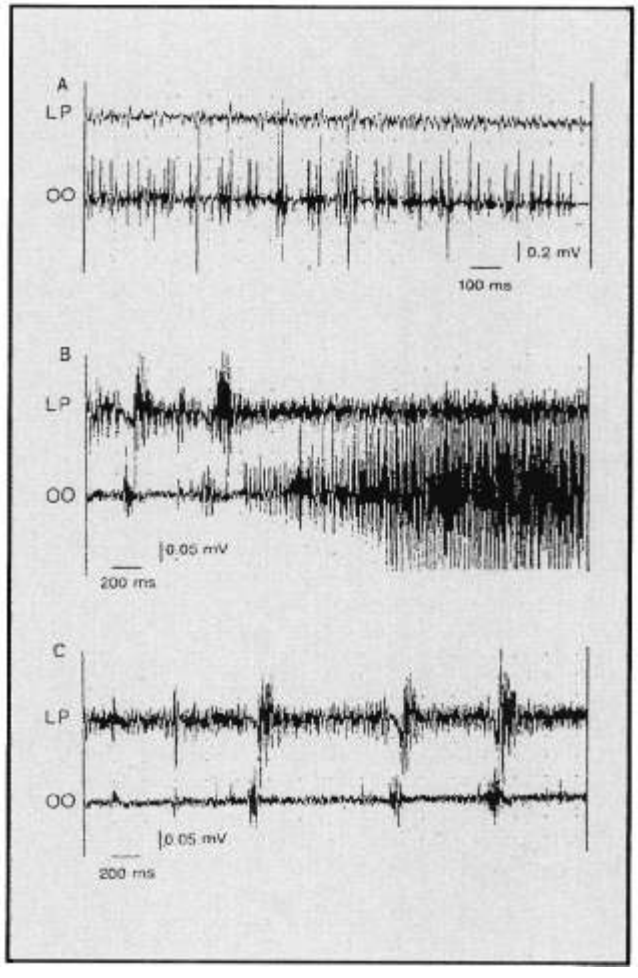

Fig. 2. Electromyographs from levator palpebrae superioris (LP) and orbicularis oculi (OO) muscles in a control subject and a patient with blepharospasm. Note the normal reciprocal inhibition of these muscles in the control subject. The recordings from the patient show different types of dystonic activities of OO. The *top panel* demonstrates tremulous discharges while the eyes are closed; the *middle panel* shows tonic activity causing forceful closing of the eyelids; the *bottom panel* demonstrates phasic discharges followed by postinhibition potentiation of LP. (*From* Aramideh *et al.* [61••]; with permission.)

During a blink there is an antagonistic activity of the levator palpebrae superioris (LP) and the orbicularis oculi (OO) muscles. LP relaxes, followed by contraction of the OO, causing rapid lowering of the eyelid. As soon as the OO activity returns to its quiescent state, the LP resumes its tonic activity thereby raising the eyelid (Figs. 1 and 2). Supranuclear disorders of the eyelid

motility arise from disruption of this novel sequence of neural activation of LP and OO. Blepharospasm, a focal dystonia, arises when there are involuntary variable bursts of activation of OO. In apraxia of eyelid opening there are episodes of total inhibition of LP activity, and the OO remains inactive.

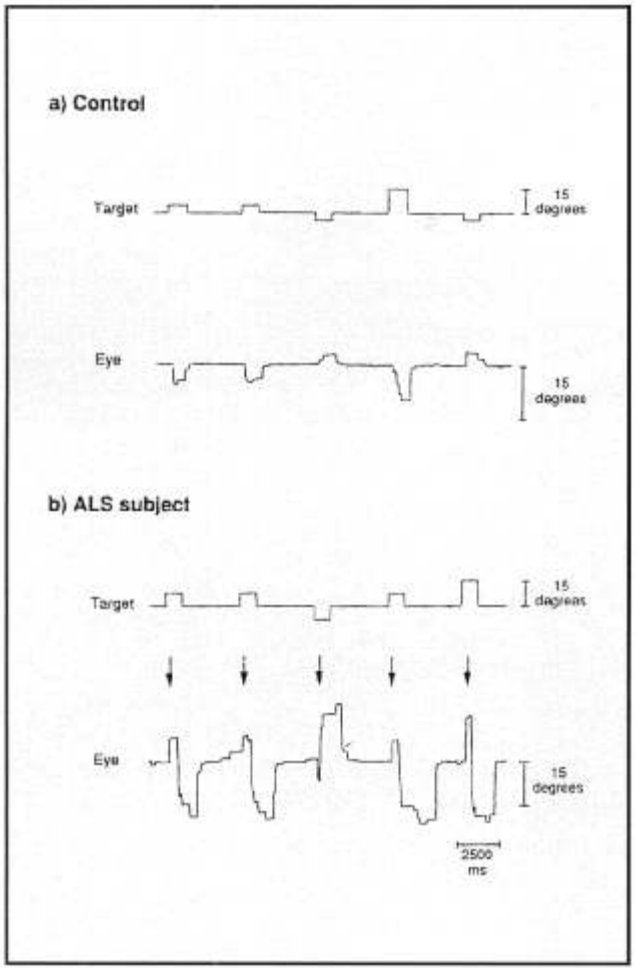

Fig. 3. Performance of a patient with amyotrophic lateral sclerosis compared to a control subject on an antisaccade paradigm. The patient initially makes reflexive saccades (*arrows*) which are subsequently corrected by saccades in the opposite direction. (*From* Shaunak *et al.* [67•]; with permission.)

Electrophysiological recording of the OO and LP reveal, among patients with clinically apparent blepharospasm, abnormal activities in one or both muscles in different combinations (Figs. 1 and 2) [61••]. Groups of patients were found to have combined alternating dystonic activation of both OO and LP (clinically appearing as flickering of the eyelids), a combination of blepharospasm and LP motor impersistence, or of blepharospasm and involuntary LP inhibition. The response to botulinum toxin in these groups is variable. Finally a fifth group showed involuntary LP inhibition causing drooping of the eyelids and an inability to open the eyes as long as the LP inhibition persisted. Clinically the eyes of these patients were closed most of the time, and on attempted eye opening the frontalis muscle was often markedly contracted. This latter group, generally referred to as involuntary LP inhibition [62] responded poorly to botulinum toxin. A newly described type of supranuclear eyelid disorder, clinically indistinguishable from involuntary LP inhibition, results from an inability to inhibit the voluntary discharges in OO on the command to open the eyes after voluntary closure of the eyelids [63]. This is a form of motor persistence.

Amyotrophic lateral sclerosis

One of the intriguing clinical features of amyotrophic lateral sclerosis (ALS) is the apparent sparing of eye movements, often in the face of devastating upper and lower motor neuron limb involvement. Recent reports of electro-oculographic studies have failed to reach a consensus, some studies finding no abnormalities of saccades or smooth pursuit [64] except in patients with associated parkinsonian features, and others finding slow saccades [65] or defects of conjugate gaze [66]. Some clarification of the situation has come from a new study of saccades and pursuit in ALS patients, using high-resolution oculography [67•]. Subjects with ALS had significantly elevated error rates in the antisaccade paradigm and prolonged latency in this and the remembered saccade paradigms (Fig. 3). Reflexive saccades were normal.

This pattern of abnormalities suggests dysfunction in prefrontal centers involved in saccade generation, a view which has support both from pathological and functional positron-emission tomographic studies.

Cerebellar degenerations

A comparison of quantitative oculomotor function in patients with progressive cerebellar disease due to Friedrich's ataxia, OPCA, and cerebello-olivary atrophy, revealed common features such as gaze-evoked nystagmus, saccadic dysmetria, and increased saccadic latency [68•]. In cerebello-olivary atrophy optokinetic nystagmus and smooth pursuit were severely impaired, but the vestibulo-ocular reflex gain was usually normal. In Friedrich's ataxia the opposite was found with, in addition, frequent saccadic intrusions (square wave jerks, flutter). In OPCA there were more variable results. In a series of patients with idiopathic cerebellar ataxia with (mainly OPCA) and without extracerebellar symptoms the oculomotor abnormalities correlated with the amount of atrophy of the flocculus and vermis [69].

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