A pathophysiological approach to saccadic eye movements in neurological and psychiatric disease

Normal vision represents a complex sensorimotor act in which eye movements provide two essential components. One is the ability to shift gaze rapidly to bring the image of an object of interest on to regions of the retina containing the highest density of photoreceptors, the fovea, and the other is to stabilise the new image on this area despite movement of the object (smooth pursuit) or of the head and body (vestibulo-ocular and optokinetic reflexes). It is the rapid gaze shifts, saccades, which enable mammalian predators to identify possible prey in the visual scene, in response to the sudden appearance of its image on the peripheral retina. These saccades are termed reflexive because they are made in response to the appearance of a novel visual target in the peripheral visual field (visually guided reflexive saccade), or to an auditory stimulus (auditory reflexive saccade). Intentional (voluntary) saccades are internally triggered, and are made to foveate a goal in a variety of different circumstances. In a visual search mode a series of saccades (the scanpath) may be made to locate a target of interest in the environment or to identify an object. If this target of interest is expected at a known location a predictive saccade may be generated, or, if it has previously been present but then disappears, a memory guided (remembered) saccade will be made. In addition to these ecologically valid situations are other paradigms such as the antisaccade task which will be discussed later, devised by experimenters to test aspects of the functional integrity of the saccadic neural circuitry. All these saccades are internally generated, along with the spontaneous saccades which occur at rest or during other activities such as speech.

Brainstem control of saccades

The final common pathway for horizontal saccades is the abducens nucleus which contains motor neurons innervating the ipsilateral lateral rectus muscle, intermingled with interneurons which, after decussating in the lower pons, project via the medial longitudinal fasciculus to the contralateral medial rectus subnucleus of the oculomotor nucleus.1 A total ipsilateral gaze palsy occurs with a lesion of the abducens nucleus, and a complete lesion of the medial longitudinal fasciculus gives rise to total failure of ipsilateral adduction associated with nystagmus in the abducting eye, an internuclear ophthalmoplegia.2 The saccadic motor command received in the abducens nucleus is prepared in specialised areas of the reticular formation of the brainstem, which receive supranuclear inputs from a number of different areas. The main premotor region for horizontal saccades is the paramedian pontine reticular formation, located on either side of the midline in the nuclei reticularis pontis just ventral to and extending rostrally from the abducens nucleus3 (figure). The equivalent premotor area for vertical saccades is the rostral interstitial nucleus of the medial longitudinal fasciculus located rostral to the oculomotor nucleus at the level of the upper pole of the red nucleus.5 The paramedian pontine reticular formation of the rostral interstitial medial longitudinal fasciculus nucleus contain various groups of cells with different functions and properties. These include the excitatory burst neurons which discharge at a high frequency just before and during saccades,5 providing the eye velocity commands, known as the “pulse”. Discrete lesions of the paramedian pontine reticular formation only produce a loss of saccades and quick phases of nystagmus to the side ipsilateral to the lesion,7 whereas a lesion of the abducens nucleus results in a complete ipsilateral gaze palsy, involving all types of eye movement.8 Another type of neuron, the omnipause neuron, located in a midline caudal pontine area, the nucleus raphe interpositus, discharges tonically except just before and during saccades.9 These neurons appear to exert an inhibitory influence on the burst neurons during fixation, and slowed saccades may result from omnipause cell dysfunction in some conditions.10 Following a laterally directed saccade, viscoelastic forces in the orbit tend to drag the eye back to the primary position. Maintenance of the eccentric position of the eye, therefore, requires tonic change in the innervation level of the abducens motor neurons, called the “step”. This is provided by a third set of neurons known as integrator neurons because they produce the equivalent of a mathematical integration of the burst neuron activity. The integrator neurons are located in the perihypoglossal complex (especially the nucleus prepositus hypoglossi) and the medial vestibular nuclei.11 Dysfunction of the integrator neurons or their inputs, particularly from the flocculus, results in an exponential drift of the eye towards the primary position due to a poorly maintained step innervation.12 A saccade (fast phase) returns the eye to refixate the target, resulting in the development of gaze evoked nystagmus. Disturbances of saccades, therefore, can be considered in terms of the pulse-step innervation pattern of the motor neuron,
Saccadic oscillations can be considered repetitive bursts of intrusions and may be distinguished by the presence or absence of an intersaccadic interval, which usually has to be determined by oculographic recordings. Macrosaccadic oscillations are horizontal salvos of saccades which straddle the intended fixation point with an intersaccadic interval of about 200 ms. They are mainly associated with cerebellar lesions especially of the deep cerebellar nuclei.\(^{23}\) Opsoclonus and ocular flutter consist of back to back saccades, that is, no intersaccadic interval, which are multidirectional in the former, and only horizontal in the latter. Although it has been hypothesised that dysfunction of the omnipause neurons may produce opsoclonus,\(^ {24}\) pathological examination of the nucleus raphe interpositus in patients with opsoclonus failed to reveal any abnormalities.\(^ {25}\) Instead opsoclonus may result from abnormal inputs to either the burst or pause neurons. Opsoclonus most frequently occurs in relation to a viral encephalitis or as a paraneoplastic manifestation in children usually due to an occult neuroblastoma, or in adults due to a carcinoma of the lung, breast, or uterus.\(^ {26}\)

Cortical control of saccades

There are two main areas of the cerebral cortex involved in triggering saccades. The frontal eye field which lies at the caudal end of the middle frontal gyrus (Brodmann's area 8) and adjacent precentral gyrus, and the posterior parietal cortex in the region of the superior part of the angular gyrus (Brodmann's area 39). Two other areas have been identified as being involved in saccade generation; the supplementary motor area which lies medially in the first frontal gyrus (Brodmann's area 6), and the dorsolateral prefrontal cortex (Brodmann's area 46).

Although the generation of saccades by the cortex is still incompletely understood, there is converging evidence from animal neurophysiology, and human lesion and neuroimaging studies that enable us to describe the relative roles of these different areas, along with the basal ganglia. This provides a useful basis on which to consider the effect on saccades of a number of different neurological and psychiatric diseases.

It has been known for over a century that electrical stimulation of the frontal eye field in the monkey results in a contralaterally directed saccade,\(^ {27}\) whereas an acute lesion due to infarction in man produces a failure of such saccades. This is often associated with an ipsilaterally directed conjugate deviation of the eyes which is usually only temporary,\(^ {28}\) unless there is preexisting damage to the contralateral frontal eye field.\(^ {29}\) Thereafter contralateral reflexive saccades are usually normal or of slightly prolonged latency,\(^ {30}\) despite neurophysiological evidence for involvement of frontal eye field cells in all types of saccades.\(^ {31}\) Memory guided saccades made to the remembered location of a previously visible target located either contralaterally or ipsilaterally to the lesion show a prolonged latency and reduced accuracy.\(^ {32}\) This suggests that each frontal eye field can control saccades directed bilaterally, and is the probable explanation for the relatively subtle saccadic abnormalities which are found following unilateral lesions.

The supplementary motor area is generally considered to be involved in the preparation and coordination of somatomotor programmes. Recent neurophysiological recordings in monkeys have identified an area in the rostral supplementary motor area containing cells which discharge in relation to saccades, called the supplementary eye field.\(^ {33}\) Focal unilateral lesions of the supplementary motor area in man have failed to reveal abnormalities in visually directed reflexive saccades, single memory
guided saccades or antisaccades, although recent activation studies using PET have shown significant activation of the supplementary motor area in the last two paradigms. Lesions of the supplementary motor area, however, result in saccadic abnormalities when sequences of memory-guided saccades or memory-guided saccades made after a body rotation (i.e. based on vestibular input) were performed.

An important role for the frontal lobes is that of inhibiting routine or automatic behaviour when it is irrelevant to the current action plan, failure of which leads to distractibility and indecisiveness. A good challenge to this system is the antisaccade paradigm in which the subject is instructed to suppress a reflexive saccade on the appearance of a peripheral target, while at the same time generating a voluntary saccade to a mirror image location in the contralateral visual field. Increased distractibility (an abnormally high frequency of reflexive saccades) was initially found in patients with large frontal lobe lesions, that appears to relate more specifically to focal lesions in the region of the dorsolateral prefrontal cortex. These observations, along with PET studies which have shown activation of prefrontal cortex during fixation, suggest that this cortical area may be involved in the inhibition of reflexive saccades. The pathways from these cortical areas to the brainstem have not been clearly identified, but could project to fixation cells in the superior colliculus or omnipause neurons in the nucleus raphe interpositus. Two routes to the superior colliculus are available, one direct and the other via the caudate nucleus and the substantia nigra pars reticulata which tonically inhibits the superior colliculus.

The dorsolateral prefrontal cortex has also been considered to play a role in short term spatial memory since this area contains cells which discharge during the delay period in the memory guided saccade paradigm, and lesions and blockade of D1 dopamine receptors in the area result in hypometric memory guided saccades.

The posterior parietal cortex has direct connections with the frontal eye field and the superior colliculus, the latter providing a probable route for saccade generation following lesions of the frontal eye field. Unilateral lesions of the posterior parietal cortex result in increased latencies of visually directed reflexive saccades and decreased accuracy of memory guided saccades. The latter may be due to impaired visuospatial integration in the human homologue of area 7a in the monkey. Following right parietal lesions the effects are more marked and affect saccades bilaterally, supporting the concept of the dominance of the right parietal lobe for visuospatial functions in humans. It should be noted that there is no correlation between visual neglect and these saccadic disturbances following a lesion in the posterior parietal cortex, presumably due to a separation of the areas involved in the control of saccades and visual attention.

Disorders of the basal ganglia

A wide variety of saccadic abnormalities have been associated with diseases of the basal ganglia. In Huntington’s disease, where there is degeneration in the caudate nucleus and substantia nigra pars reticulata as well as the frontal lobes, a number of saccadic abnormalities have been identified including difficulty in suppressing reflexive saccades in the antisaccade task, and prolonged latencies of memory guided and predictive saccades. In addition, there are increased numbers of square wave jerks, and a slowing of saccadic velocity which usually affects vertical saccades prior to involvement of horizontal saccades.

Because of the difficulties often encountered in the differential diagnosis of Parkinsonian syndromes a number of saccadic studies have recently been reported aimed at identifying specific patterns of saccadic abnormalities in the different conditions. In idiopathic Parkinson’s disease, reflexive saccades are normal in early stages of the disease. Patients, however, exhibit a reduction in the amplitude of memory guided and predictive saccades. In progressive supranuclear palsy there is often an early reduction in the velocity of downward and later upward saccades leading to a complete supranuclear palsy in which the vestibulo-ocular reflex is usually preserved. These saccadic abnormalities are probably a reflection of the focus of degenerative change in this condition involving midbrain structures such as the superior colliculus, rostral interstitial nucleus of the medial longitudinal fasciculus, as well as the substantia nigra pars compacta. In addition there is also increased distractibility in the antisaccade task, which may be due to a functional deafferentation of the prefrontal cortex from the subcortical areas. Vertical saccades are preserved in other parkinsonian syndromes such as striatogranular degeneration and corticobasal degeneration. Saccades in striatongranular degeneration could not be differentiated from those in idiopathic Parkinson’s disease, whereas in corticobasal degeneration, visually guided reflexive saccades showed markedly prolonged latencies, possibly reflecting degeneration in the parietal lobes.

Saccadic abnormalities in functional psychoses

The literature on eye movements in the psychoses has centred on the analysis of smooth pursuit eye movements in schizophrenia, with the specific intent of identifying an abnormality which could serve as a biological marker for the disorder. Although it was 1908 when Diefendorf and Dodge first reported an analysis of saccades in schizophrenia, it is only recently that there has been renewed interest. A major methodological problem, however, has been the almost universal use of patients treated with neuroleptic medication, which raises doubts about the validity of conclusions relating abnormalities of saccadic latency and amplitude to the underlying disease process. One of the most obvious side effects of neuroleptic medication is an extrapyramidal syndrome due to blockade of the nigrostriatal dopamine pathway, and from the discussion of saccadic abnormalities in Parkinson’s disease it might be expected that some if not all the saccadic abnormalities found in neuroleptically treated schizophrenic patients could be due to this effect. In a recent study this potential drug effect has been clarified by a comparison of groups of patients free from neuroleptic medication with other groups of patients taking medication. In the memory guided and predictive saccadic tasks a reduced saccadic amplitude, as previously reported in Parkinson’s disease, was only found in the neuroleptically treated groups. In obsessive compulsive disorder, there is an abnormal tendency towards hypometria, which is most marked for predictive saccades, consistent with the idea that those frontobasal ganglia pathways that are hyperactive in negative schizophrenia are hyperactive in obsessive compulsive disorder.

One saccadic abnormality found in schizophrenia which was unrelated to neuroleptic medication does, however, appear to relate to the underlying disease pathology. This is an increased distractibility in the antisaccade task, as found in neurological patients with lesions in the prefrontal cortex. Several recent studies have shown this abnormality which was most marked in patients exhibiting tardive dyskinesia, frontal atrophy,
and either pernicious errors in the Wisconsin card sort test, or an abundance of negative signs,77 both of which are associated with frontal lobe dysfunction. These find-
ings, therefore, suggest that the saccadic distractibility
found in schizophrenia represents some general frontal
frontal type dysfunction of strategic control processes in schiz-
ophrenia.63 In line with the view that underlying schizo-
phrenic negative symptoms lies a disorder of uncued, internally generated action,64 the saccades employed in
spontaneous scanning of visual patterns also seem to be
abnormal in negative schizophrenia.65 Prefrontal regions
seem to play a role in the control of these saccades.66

Conclusions
From this brief survey of saccadic disorders it is apparent
that analysis of saccadic function can be of value in clinical
practice to assist in the differential diagnosis and
anatomical localisation of a wide variety of diseases.
Although oculographic recordings are required in some
situations simple clinical observation will often suffice.
This should include careful inspection for saccadic intru-
sions and oscillations during fixation, and of horizontal
and vertical saccades generated at the bedside reflectively
in response, for example, to the brief flash of a torch or
sudden movement of a finger, and volitionally to a spoken
command. In addition, saccades can be used to serve as
a model system for the analysis of the neural control of
motor performance. In the future, the continuing inter-
action between clinicians and neurophysiologists will help
to refine more precisely the role of the many different
neural centres in saccade generation, a task which will be
increasingly aided by the use of functional imaging with
PET.34 35 66 One area of study which has received little
attention is the neuropharmacology of saccades.67 Initial
studies, for example, correlating saccadic function with the
pharmacokinetics of benzodiazepines,68 or analysing the
effects of neuroleptic drugs in schizophrenia69 70 or of
catecholamine drugs,71 suggest that this could prove
to be of considerable interest.

C KENNARD, T J CRAWFORD, L HENDERSON

Academic Unit of Neuroscience, 
Charing Cross and Westminster Medical School, 
St Dunstan’s Road, London W6 8RF, UK

Correspondence to: Professor C Kennard.

Baillière’s clinical neuroscience, 1992:1.
3 Büttner-Ennever JA, Büttner U. The reticulotomy. In: Büttner-
Ennever JA, ed. Neuroanatomy of the ocular motor system. Amsterdam:
6 Strassman A, Hightstein SM, McRea RA. Anatomy and physiology of saccadic burst neurons in the alert squirrel monkey. I. Excitatory burst
7 Henn V, Lang W, Hepp K, Reintie H. Experimental gaze palsy in mon-
8 Bronstein AM, Morris J, Du Boulay G, Gresty MA, Rudge P. Abnormalities of horizontal gaze. Clinical, oculographic and magnetic
reverberation imaging findings. I. Abducens palsy. J Neurol Neurosurg
9 Büttner-Ennever JA, Cohen B, Pause M, Friew W. A raphe nucleus
of the pons containing saccadic burst neurons of the oculomotor system in the
10 Büttner-Ennever JA, Uemura T, Ariy A, Mehraein P. A possible cause
11 Cannon SC, Robinson DA. Loss of the neural integrator of the oculomo-
tor system from brain stem lesions in monkeys. J Neurol Neurosurg
12 Strasburg AM, Robinson U. Differential effects of bicuculline and
cuscimul microinjections into the vestibular nuclei on saccade
13 Selhorst JB, Stark L, Ochs AL, Hoyt WF. Disorders in cerebellar
ocular motor control. I. Saccadic overshoot dysmetria, an ocularographic,
control analysis of frontal lobe dysfunction. These findings, therefore,
suggest that the saccadic distractibility found in schizophrenia represents
some general frontal type dysfunction of strategic control processes in
schizophrenia. In line with the view that underlying schizophrenic negative
symptoms lies a disorder of uncued, internally generated action, the
saccades employed in spontaneous scanning of visual patterns also seem
to be abnormal in negative schizophrenia. Prefrontal regions seem to play
a role in the control of these saccades.

14 Baloh RW, Yee RD, Honrubia V. Eye movements in patients in
15 Heywood S, Ratcliff G, Lawton G. The relationship between oculomoto-
nuclear disconnection and horizontal saccadic inco-
NEUROLOGICAL STAMP

Alexander Ypsilante (1792–1832)

In 1933, Dr J E Caughey described a 54 year old woman with advanced myotonic dystrophy. The patient was one of eight children, five of whom had the disorder. The family lived in quite poor circumstances in Brixton, London. Her father’s generation were men of a professional class. Her grandfather was a professor of Greek at a northern university and her great grandmother was a “princess” of Greece whose brother was a “prince” and prominent statesman of a century previously. Dr Caughey found a historical document recording that the “prince” talked with a nasal voice and by age 20 was bald. This was Prince Alexander Ypsilante who was honoured on a Greek stamp in 1930. (Stanley Gibbons 435, Scott 354). The baldness is clearly shown but other features of the disorder cannot be clearly seen. The sternomastoids are covered by the tall collar. Dr Caughey’s report is almost certainly the first contribution to neurological phily.

L F HAAS


