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INVITED REVIEW

Using saccades as a research tool in the clinical neurosciences

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Summary

Saccades are rapid eye movements that move the line of sight between successive points of fixation; they are among the best understood of movements, possessing dynamic properties that are easily measured. Saccades have become a popular means to study motor control, cognition and memory, and are often used in conjunction with techniques such as functional imaging and transcranial magnetic stimulation. It has been possible to identify several, distinct populations of neurons, from brainstem to cerebral cortex, that contribute to behaviours ranging from reflexive glances to memorized sequences of saccades during learned tasks. This progress has led to the development of schemes for the neurobiology of saccades that imply an equivalence of a region of the brain with specific behaviours (e.g. prefrontal cortex with memory-guided saccades). In fact, multiple neuronal populations contribute to each type of saccadic behaviour, be it 'reflexive' or 'complex'. Furthermore, an important difference exists between cortical areas that encode visual stimuli or desired saccades over a population of neurons as 'place maps', and motoneurons in oculomotor, trochlear and abducens nuclei that dictate eye rotations in terms of their discharge rates. This dichotomy implies that a 'spatial-temporal transformation' of saccadic signals must occur between cerebral cortex and ocular motoneurons, to which the superior colliculus and cerebellum contribute. Consideration of such factors may broaden the value of saccades, which can be used to test a range of hypotheses, and provide a simple scheme for understanding clinical disorders of saccades; some illustrative video clips are available as supplementary material at Brain Online.

Keywords: cerebellum; eye fields; functional imaging; basal ganglia

Abbreviations: DLPC = dorsolateral prefrontal cortex; FEF = frontal eye field; LIP = lateral intraparietal area; PEF = parietal eye field; PPRF = paramedian pontine reticular formation; PMT = paramedian tracts; PPC = posterior parietal cortex; PSP = progressive supranuclear palsy; riMLF = rostral interstitial nucleus of the medial longitudinal fasciculus; SEF = supplementary eye field; SMA = supplementary motor area; SNpr = substantia nigra, pars reticulata; TMS = transcranial magnetic stimulation.

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Introduction

Our vision of fine details is best at the foveal (macular) region of the retina, which contains the highest concentration of cone photoreceptors (Carpenter, 1991). Saccades are rapid eye movements by which we shift our line of sight and point the fovea at objects of interest (Fig. 1) (Becker 1989; Leigh and Zee, 1999). Saccades contribute to a variety of ocular motor behaviours that range from reflexive movements towards novel stimuli (e.g. a passing bird) to remembered sequences

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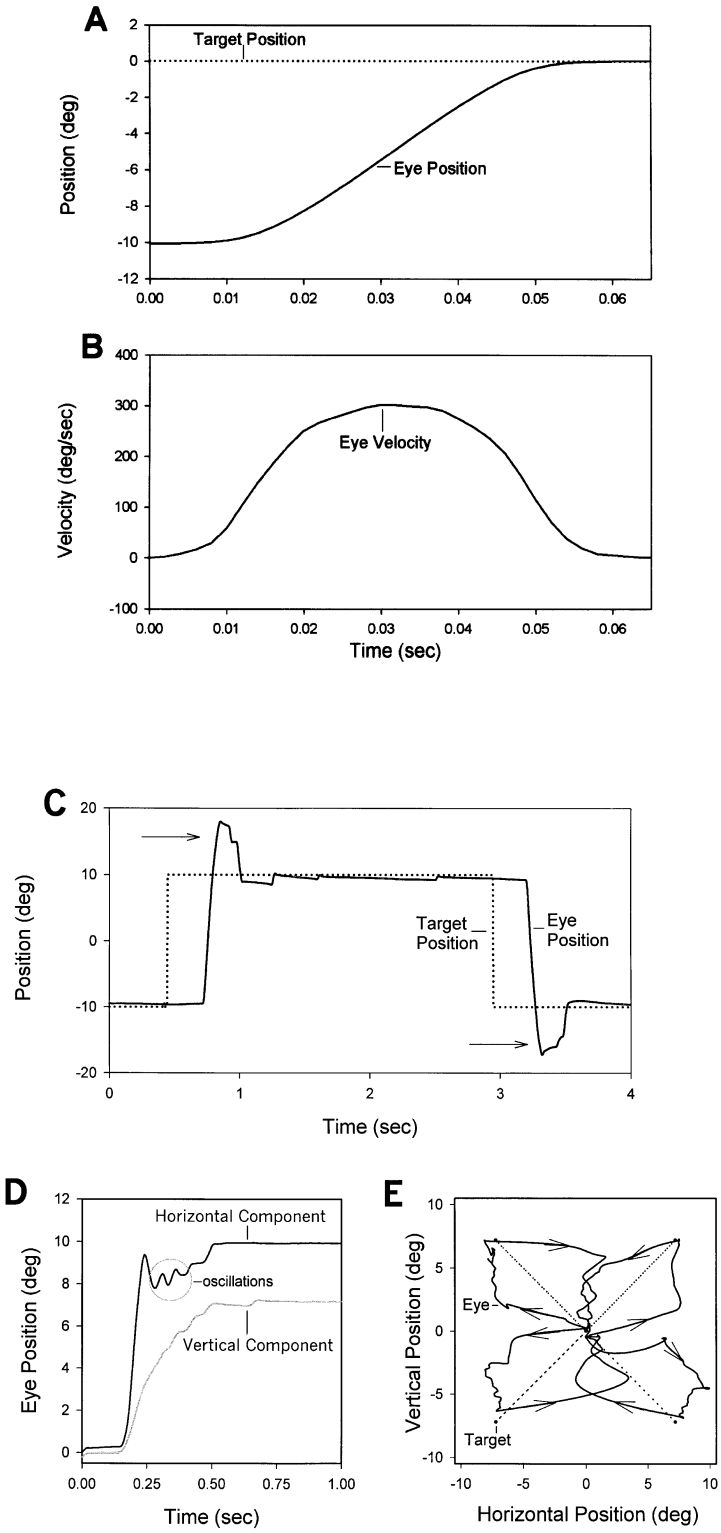

Fig. 1 Examples of normal and abnormal saccades. (**A**) Position and (**B**) velocity plots of an accurate 10 saccade made by a normal subject. Note that the duration of the saccade (evident on the velocity trace) is <65 ms. (**C**) Hypermetric saccade made by a patient with a cerebellar fastigial nucleus lesion; overshoots are indicated by arrows. (**D**) Saccade made by patient with Niemann–Pick type C disease in response to diagonal target jumps. The vertical component is slow, but the horizontal saccade is normal; small horizontal oscillations occur as the vertical component is being completed. (**E**) Similar movements as in (**D**), illustrating the curved trajectory of saccades due to slow vertical components; arrows indicate the direction of the movements.

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Table 1 *Range of saccadic behaviours*

Name	Properties of behaviour
Quick phases	Quick phases of nystagmus generated during vestibular or optokinetic stimulation or as automatic resetting movements in the presence of spontaneous drift of the eyes
Spontaneous	Seemingly random saccades that occur when the subject is not required to perform any specific behavioural task
Reflexive	Saccades generated to novel stimuli (visual, auditory or tactile) that unexpectedly occur within the environment
Express	Short-latency saccades that can be elicited when the novel stimulus is presented after the fixation stimulus has disappeared (gap stimulus)
Voluntary	Elective saccades made as part of purposeful behaviour
Memory-guided	Saccades generated to the location in which a target has been previously present
Predictive, anticipatory	Saccades generated in anticipation of the appearance of a target at a particular location
Antisaccades	Saccades generated voluntarily in the opposite direction to the sudden appearance of a target
Sequences of saccades	Memory-guided saccades made in response to targets presented sequentially at series of locations

Table 2 *Summary of some effects of lesions on saccades**

Anatomical structure or pathway	General effects of lesions
Motoneurons and ocular motor nerves	Slow saccades with limited range of movement
Premotor burst neurons	Slow saccades
PPRF	Horizontally
riMLF	Vertically
Omnipause neurons	Saccadic oscillations (opsoclonus and flutter); Slow horizontal and vertical saccades
Cerebellar dorsal vermis	Saccadic dysmetria
Cerebellar fastigial nucleus	Saccadic hypermetria
Superior colliculus	Loss of short-latency (express) saccades
Thalamus	Inaccurate responses to double-step stimuli
Parietal eye field	Increased latency of visually guided saccades Inaccurate responses to double-step stimuli Impaired visual search
Frontal eye field	Bilaterally increased latency to overlap visual stimuli, remembered targets, or to antisaccade tasks Contralateral hypometria to visual or remembered targets
SEF and pre-SEF	Impaired ability to make a remembered sequence of saccades, and to reverse the direction of a previously established pattern of response
Dorsolateral prefrontal cortex	Impaired accuracy to remembered target locations (memory guided saccades) Increased errors on antisaccade task Impaired predictive saccades Impaired visual search
Basal ganglia	Difficulties in initiating voluntary saccades in tasks that require learned or predictive behaviour, and working memory (such as visual search)

*Caution is required in equating lesions at each site with specific behaviours since multiple regions contribute to each aspect of the properties of saccades.

of gaze shifts made as part of learned tasks (e.g. while playing a musical instrument). In animals that lack a fovea, such as the rabbit, rapid eye movements are made during head rotations and correspond to quick phases of vestibular and optokinetic nystagmus, which are regarded as the evolutionary forerunners of saccades. Table 1 summarizes the range of behaviours that encompass saccades and quick phases. During natural activities, saccades are usually combined with other eye movements such as vergence (eye rotations in opposite directions), as well as head and limb movements; however, here we deal solely with the control of saccades.

Why has measurement of saccades become such a popular method of studying normal and abnormal brain function? One reason is that saccades are easily accessible to clinical observation or measurement in the laboratory. A second is that their dynamic properties are well delineated. A third is that a good part of their neurobiological substrate has been defined. Some current schemes of the neurobiology of saccades have implied an equivalence of certain neuronal populations (e.g. cortical areas) with certain behaviours (e.g. memory-guided saccades); some of these 'localizations' of functions are summarized in Table 2. However, we aim to show that multiple neuronal populations contribute to each type of saccadic behaviour, be it 'reflexive' or 'complex'. Proper consideration of such factors may broaden the value of saccades to both neurologists and neuroscientists.

In this review, we first summarize behavioural properties of saccades that can be easily measured. Secondly, we summarize the premotor circuitry by which the brainstem and

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cerebellum control all types of saccades. Thirdly, we outline cortical and subcortical regions that are known to contribute to saccades and describe the 'spatial–temporal transformation' that occurs as these regions interface with the premotor circuitry. Finally, we discuss each behavioural type of rapid eye movement in turn (Table 1), reviewing current ideas of the neural substrate that may contribute. The reader is referred to more detailed texts dealing with the basic or clinical aspects of saccades (Leigh and Zee, 1999; Kaminski and Leigh, 2002; Scudder *et al*., 2002; Sparks, 2002).

Important measurable properties of saccades

Reliable measurement of saccades requires methods with adequate bandwidth (0–150 Hz), sensitivity (0.1°) and linear range (±30°). DC-amplified electro-oculography is adequate to signal horizontal eye position and timing at the beginning and end of a saccade, but not other metrics such as velocity. Infrared, magnetic search coil or fast frame-rate video-based techniques are required for reliable measurements of dynamic properties of saccades; the latter two are also suitable for measuring vertical movements (DiScenna *et al*. 1995; Leigh and Zee, 1999).

Relationships between amplitude, peak velocity and duration

Saccades show consistent relationships between their size, speed and duration. Thus, the bigger the saccade, the greater its peak velocity and the longer its duration (Becker, 1989). It is important to note, however, that even the biggest saccades last only ~100 ms, which is less than the response time of the visual system. Thus, saccades are ballistic movements—there is no time for visual feedback and accuracy depends on internal monitoring of neural signals. Examples of the 'main sequence' relationships between peak velocity, duration and amplitude are provided from normal subjects in Fig. 2; exponential or power-function equations have been used to describe these relationships and define prediction intervals for normal subjects (Becker, 1989; Lebedev *et al*., 1996). Deviations of measured eye movements from these relationships indicate either abnormal saccades or non-saccadic eye movements. Thus, in Fig. 1D, we also provide an example of abnormal, slow vertical saccades from a patient with Niemann–Pick type C disease, (Rottach *et al*., 1997) and plot these data points in Fig. 2A to show how they deviate from the prediction intervals for normal subjects.

Although saccadic speed and duration cannot be voluntarily controlled, there is some variability of these parameters for saccades of similar size, depending on the nature of the saccade. These differences can be attributed to factors such as alertness, level of illumination, sequence of target presentation and mental set during testing (e.g. saccades made to remembered locations) (Bronstein and Kennard, 1987). Furthermore, saccadic velocity also depends upon the direction of the movement, and the initial and final eye position. All of these factors, as well as the measurement technique, require consideration when comparing saccadic behaviour in patients with normal subjects and each laboratory should define its own normal ranges for each experimental condition.

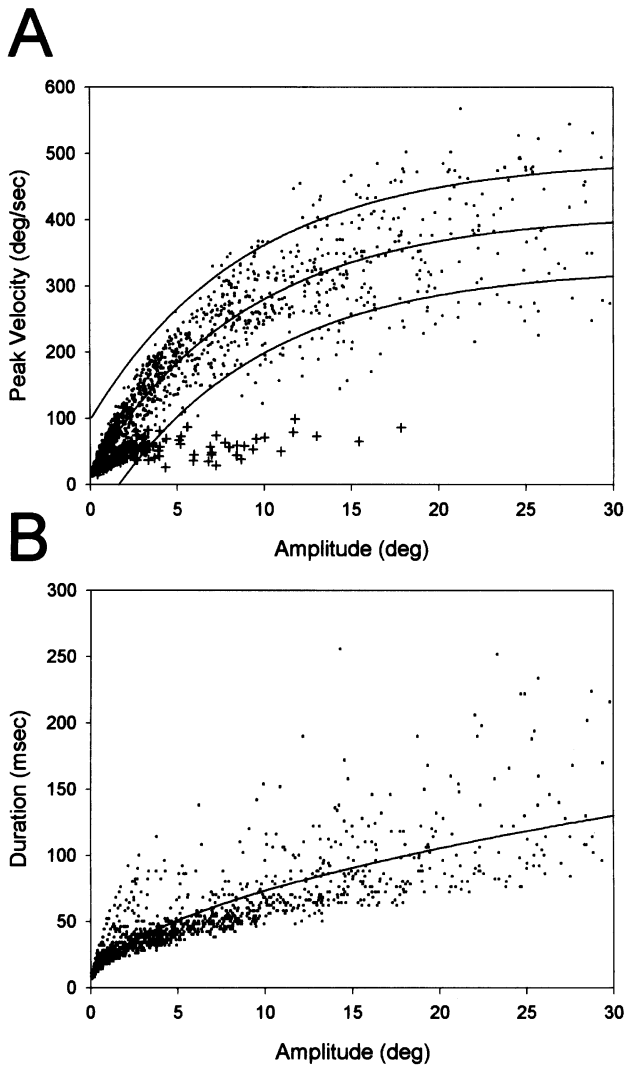

Fig. 2 Dynamic properties of saccades. (**A**) Plot of peak velocity versus amplitude of vertical saccades. Data points (dots) are saccades from 10 normal subjects. The data are a fit with an exponential equation of the form: peak velocity = Vmax × $(1 - e^{-A/C})$, where Vmax is the asymptotic peak velocity, A is amplitude and C is a constant defining the exponential rise is shown. Also plotted are the 5% and 95% prediction intervals. The + data points indicate vertical saccades from a patient with Niemann–Pick type C disease, which lie outside the prediction intervals for normals. (**B**) Plot of duration versus amplitude. The data from 10 normal subjects are a fit with a power equation of the form: duration = $D_1 \times \text{amplitude}^n$, where D_1 is the duration of a 1° saccade, and n is the value of the power.

Trajectory (direction) of saccades

The orientation of the eyes is determined by six extraocular muscles. The recent discovery of pulleys, which determine

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the pulling directions of these muscles, has revolutionized concepts of orbital mechanics (Demer, 2003). Fortunately, these extraocular pulleys appear to have simplified the mechanism by which the brain obeys the rules governing 3D eye rotations (Listing's law) (Quaia and Optican, 1998). In this review, we will not dwell on the issue of 3D rotation, but note that this topic is currently being used to investigate how the brain programs saccades (Sparks, 2002). Neither shall we dwell on the mechanisms that make saccades conjugate and disorders of conjugacy, such as internuclear ophthalmoplegia, which are discussed elsewhere (Leigh and Zee, 1999).

As we shall see, horizontal and vertical saccades are generated by separate populations of premotor neurons; thus, it is often useful to measure the trajectory of saccades to targets that are displaced in the horizontal, vertical or diagonal directions. When normal subjects make diagonal saccades (45° inclination), the horizontal and the vertical components are fairly similar and the trajectory is nearly straight. However, when the brainstem mechanism generating either the horizontal or vertical components of oblique saccades is impaired, oblique saccades may have strongly curved trajectories that are evident at the bedside (Fig. 1E) (Rottach *et al.,* 1997).

Accuracy of saccades

Ideally, a saccade should move the eye so that the fovea is pointing at the target of interest at the end of the movement. Saccadic eye movements are driven by a 'pulse' of innervation from burst neurons (discussed in the next section), but the eye is held at its new position by a sustained 'step' of activity (due to a gaze-holding network called the neural integrator). Normal subjects often show small degrees of saccadic hypometria—undershooting the target, especially when a larger movement (>10°) is generated. Saccadic hypermetria (overshooting the target) is a hallmark of disease affecting the cerebellum, especially the fastigial nucleus or its projections (Fig. 1C) (Robinson *et al*., 1993; Leigh and Zee, 1999). The ability to adjust saccade size in response to changing visual demands (e.g. due to weakness of an extraocular muscle or wearing an optical device) is also impaired with cerebellar disease (Takagi *et al*., 1998; Robinson and Fuchs, 2001).

Reaction time (latency) to initiation of saccades

Measurement of the interval (latency) between target presentation and onset of movement of a saccade (conventionally identified by when eye speed exceeds a threshold) has been widely applied to understand cortical and subcortical aspects of saccade programming. Thus, saccadic latency reflects visual processing, target selection and motor programming, and is dependent on stimulus properties, such as luminance, and the nature of the cognitive task (e.g. single versus double target locations). Saccadic latency is abnormal in a range of disorders affecting cortical areas concerned with vision and eye movements. Special research attention has focused on saccades made at latencies of <100 ms—'express saccades' that are elicited by turning off the fixation point before the target stimulus is turned on ('gap' stimulus—Fig. 5B) (Fischer and Ramsperger, 1984). Measurement of saccadic latency has also been used to demonstrate the ability to program 'in parallel' two saccades to two stimuli that are presented in quick succession (Goossens and van Opstal, 1997).

The premotor substrate for all rapid eye movements

The role of the brainstem reticular formation: generating saccades (Fig. 3)

The motoneurons in the oculomotor, trochlear and abducens nuclei receive the signals for saccades from cells in the reticular formation of the brain stem that we will call 'premotor burst neurons', because they show an intense discharge that begins ~12 ms before each saccade (van Gisbergen *et al*. 1981; Scudder *et al*., 2002). This burst or pulse of activity is needed to make the eye move rapidly despite the 'over-damped' properties of the orbital tissues that tend to slow all eye movements down. Premotor burst neurons are of two types: excitatory and inhibitory. Their instantaneous firing rate is closely correlated with instantaneous eye velocity and the total number of spikes in the burst of activity (the integral of the discharge rate) is proportional to the size of the saccade.

Premotor burst neurons project monosynaptically to the ocular motoneurons (Horn *et al*., 1995). For horizontal saccades, excitatory burst neurons in the paramedian pontine reticular formation (PPRF) project to ipsilateral abducens motoneurons (Strassman *et al*., 1986*a*) and inhibitory burst neurons in the rostral medulla project to the contralateral abducens nucleus (so imposing Sherrington's law of reciprocal inhibition) (Strassman *et al*., 1986*b*). For saccades in the vertical or torsional planes (rotation around the line of sight), the rostral interstitial nucleus of the medial longitudinal fasciculus (riMLF), which lies in the prerubral fields, is important (Horn and Büttner-Ennever, 1998). At the end of each saccade, the eye is held steady in its new position because of a tonic contraction of the extraocular muscles which, in turn, is achieved by a step increase in the firing rate of the ocular motoneurons. Experimental and clinical evidence indicates that neural networks in the brainstem (nucleus prepositus hypoglossi, medial vestibular nuclei, interstitial nucleus of Cajal) and the cerebellum integrate the saccadic pulse (a velocity command) into the step increase of firing (a position command); the properties of this ocular motor neural integrator are discussed elsewhere (Leigh and Zee, 1999).

Premotor burst neurons in the PPRF and riMLF are silent at all times except during saccades. This is because their activity

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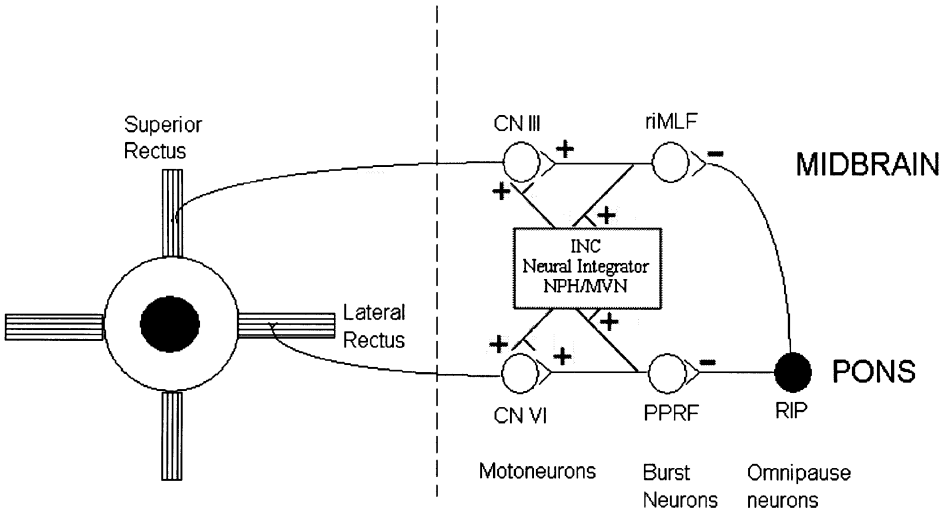

Fig. 3 Schematic summary of brainstem generation of saccades. Horizontally acting extraocular muscles, such as the lateral rectus, are innervated by motoneurons in the abducens nucleus (CN VI); these motoneurons receive their saccadic commands from the PPRF. Vertically acting extraocular muscles, such as the superior rectus, are innervated by motoneurons in the oculomotor nucleus (CN III) and trochlear nucleus (not shown); these motoneurons receive saccadic commands from burst neurons in the riMLF in the midbrain. Burst neurons in both the PPRF and riMLF receive inhibitory inputs from omnipause neurons, which lie in nucleus raphe interpositus (RIP) in the pons. When omnipause neurons cease discharge, burst neurons in the PPRF and riMLF generate a saccadic pulse, which is passed to the motoneurons and causes a phasic contraction of the extraocular muscles to move the eye rapidly in a saccade. Horizontal saccadic pulse signals are integrated by a network consisting of neurons in the medullary nucleus prepositus hypoglossi and adjacent medial vestibular nucleus (NPH/MVN); vertical saccadic pulses are integrated in the midbrain interstitial nucleus of Cajal (INC) for vertical saccades. The output of this neural integrator is a step signal that makes it possible for extraocular muscles to sustain a tonic contraction and hold the eye in its new position.

is gated by omnipause neurons lying in the pontine nucleus raphe interpositus (Horn *et al*., 1994). Omnipause neurons are tonically active during fixation and their activity is suppressed during all saccades, irrespective of direction; electrical stimulation of omnipause neurons will stop a saccade in mid-flight (Keller *et al*., 2000*a*).

Quick phases of nystagmus are also generated by this same brainstem circuit of premotor burst neurons and omnipause neurons; disorders of voluntary saccades may be accompanied by corresponding disturbance of quick phases. In clinical practice, optokinetic stimulation is a convenient way to induce smooth visual tracking and resetting quick phases, which are generated by the saccadic system (Garbutt *et al*., 2001).

Insights from disturbances of the brainstem reticular formation that affect saccades

Burst neurons are the main determinants of the dynamic properties of saccades, such as speed and duration, and disorders affecting the brainstem reticular formation often cause slow or absent saccades (while other types of eye movements may be preserved). Selective inactivation of the PPRF with lidocaine experimentally slows down horizontal, but not vertical, saccades (Sparks *et al*., 2002); although slow, these horizontal saccades tend to land on target. Larger chemical lesions or infarction of the PPRF abolish horizontal saccades and may cause slowing of vertical saccades; other eye movements are preserved (Henn *et al*., 1984; Hanson *et al*., 1986). Chemical lesions of the riMLF slow or abolish vertical and torsional saccades, and quick phases, but leave other eye movements intact (Suzuki *et al*., 1995). Based on these experimental studies, it is hypothesized that spinocerebellar ataxias that involve the pontine reticular formation cause predominant slowing of horizontal saccades (Wadia and Swami, 1971; Horn *et al*., 1996) (Video 1; available as supplementary material at Brain Online), whereas disorders that mainly affect the midbrain, such as progressive supranuclear palsy (PSP) (Bhidayasiri *et al*., 2001*b*) or Niemann–Pick type C disease (Rottach *et al*., 1997) cause slowing of vertical saccades (Figs 1 and 2).

The saccadic system is 'high gain', with burst neurons in monkey discharging as high as 1000 spikes/second (van Gisbergen *et al*., 1981) to drive the eye quickly during a saccade against the viscous drag imposed by the orbital tissues. One risk of such a high-gain mechanism is that the system will be prone to oscillate. Thus, disease affecting the omnipause neurons, which act as a saccadic switch, might be predicted to cause excessive, behaviourally irrelevant saccades, including oscillations (Bhidayasiri *et al*., 2001*a*). This may be the case, and some evidence suggests that saccadic oscillations such as flutter and opsoclonus (Video 2; available as supplementary material at Brain Online) arise because of the way that excitatory and inhibitory burst neurons on the

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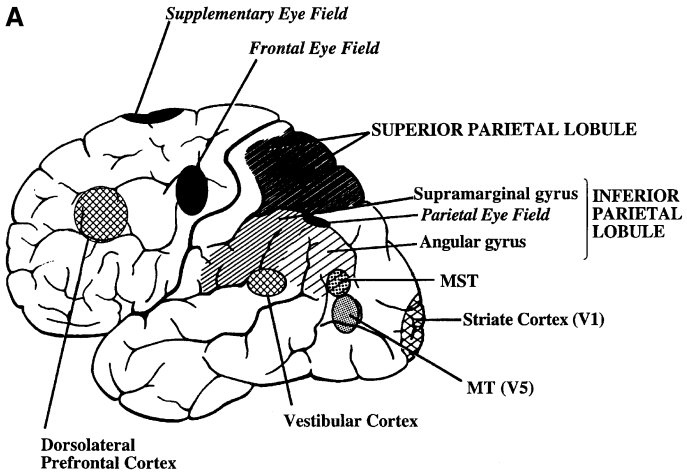

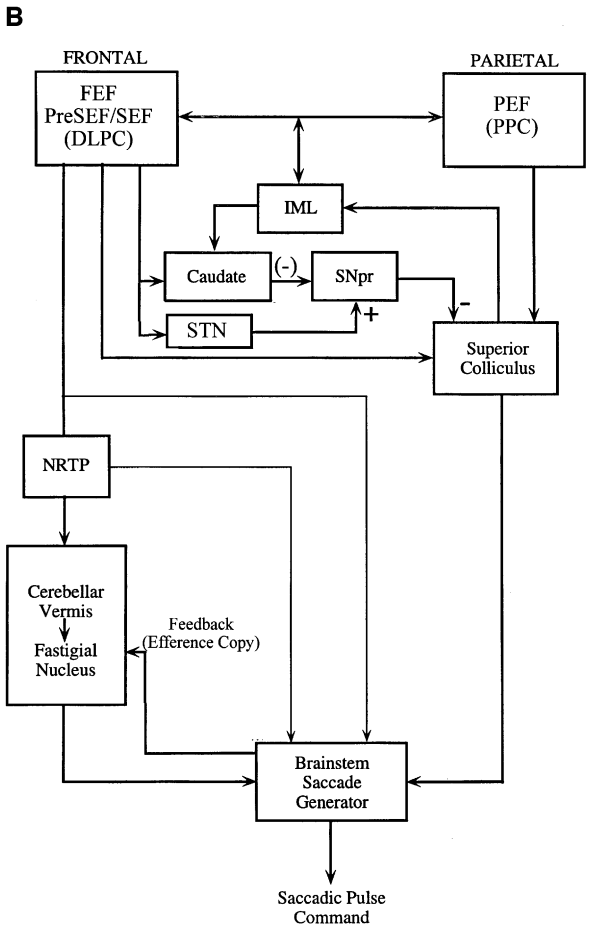

Fig. 4 Areas of cerebral cortex and their projections that contribute to generation of saccades. (**A**) Probable location of cortical areas important for eye movements in human brain. (**B**) Block diagram of the major structures that project to the brainstem saccade generator (premotor burst neurons in the PPRF and riMLF). Also shown are projections from cortical eye fields to superior colliculus. Not shown are the pulvinar, which has connections with the superior colliculus and both the frontal and parietal lobes, and certain projections such as that from the superior colliculus to the NRTP and the pathway which conveys efference copy from the brainstem and cerebellum, via the thalamus, to the cerebral cortex. Figures modified from Leigh and Zee (1999). IML = intramedullary lamina of thalamus; MST = medial superior temporal visual area; MT (V5) = middle temporal visual area V5; NRTP = nucleus reticularis tegmenti pontis; STN = subthalamic nucleus; V1 = primary visual cortex.

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right and left sides of the brainstem are configured if the omnipause neurons cannot hold them in check (Bhidayasiri *et al*., 2001*a*; Ramat *et al*., 2002). Indeed, the potential for saccadic oscillations exists anytime that the omnipause neurons stopped inhibiting the burst neurons. Thus, some normal subjects can induce high-frequency (10–30 Hz) oscillations during convergence as a party trick ('voluntary nystagmus'). Similar oscillations also occur during gaze shifts when one component (such as the horizontal saccade) is completed before another component (such as a vergence movement or a slow vertical saccade, as shown in Fig. 1D). Clinically, saccadic oscillations are evident as pathological flutter or opsoclonus, which are encountered with encephalitis or as a non-metastatic manifestation of cancer (Video 2; available as supplementary material at Brain Online) (Leigh and Zee, 1999). Abnormalities of omnipause neurons have been implicated in some (Hormigo *et al*., 1994) but not all (Ridley *et al*., 1987), cases of opsoclonus.

An alternative hypothesis, based on experimental inactivation studies (Kaneko, 1996; Scudder *et al*., 2002), is that dysfunction of omnipause neurons will cause slow saccades because the burst neurons are not allowed their normal, coordinated discharge (Kaneko, 1989). Since omnipause neurons inhibit both pontine and midbrain burst neurons, both horizontal and vertical saccades would be expected to be slow; however, this is not the case in a number of disorders, such as PSP, which preferentially affects vertical saccades (Bhidayasiri *et al*., 2001*b*). Thus, at the present time, it seems that burst neuron dysfunction causes slow saccades and that omnipause neuron dysfunction leads to saccadic oscillations such as ocular flutter. However, it remains possible that omnipause neuron dysfunction can cause combined slowing of horizontal and vertical saccades.

The role of the cerebellum: making saccades accurate (Fig. 4)

The dorsal vermis (lobule VII) and the caudal part of the fastigial nucleus, to which it projects, play key roles in governing the accuracy of saccades (Noda and Fujikado, 1987; Robinson and Fuchs, 2001). Although Purkinje cells in the dorsal vermis show variability in the timing of their discharge with respect to each saccade, the populations of these neurons precisely encode the time when a saccade must stop to land on target (Thier *et al*., 2002). Dorsal vermis lesions cause saccades to become variable in their size (Takagi *et al*., 1998). The dorsal vermis projects to the fastigial nucleus which, in turn, projects via the superior cerebellar peduncle, to both excitatory and inhibitory burst neurons in the brainstem (Noda *et al*., 1990). Before the onset of a horizontal saccade, neurons in the fastigial nucleus contralateral to saccade direction show a burst of activity; later during the saccade, neurons in the fastigial nucleus ipsilateral to saccade direction burst (Fuchs *et al*., 1993). Based on these electrophysiological studies of the dorsal vermis and fastigial nucleus, their anatomical projections to the premotor burst neurons in the brainstem and the effects of inactivation (discussed next), it has been suggested that this part of the cerebellum plays an important role in maintaining the accuracy of saccades.

Insights from the effects of inactivation of the cerebellar circuits

Pharmacological inactivation of one fastigial nucleus with the drug muscimol causes ipsilaterally directed saccades to overshoot their target and contralaterally directed saccades to undershoot their target—'ipsipulsion' (Robinson *et al*., 1993). This has led to the hypothesis that early activity in one fastigial nucleus accelerates the eyes in the opposite direction and that later activity in the other fastigial nucleus stops the eye on target. It seems possible that delay, or abolition of the later, decelerating fastigial activity will cause hypermetria (Fig. 1C), because the eye will not decelerate and stop on target.

An important concept concerning the control of saccadic accuracy is that the brain monitors its own motor commands, referred to as corollary discharge or efference copy. [Current evidence suggests that extraocular proprioception does not contribute to the online control of saccades (Lewis *et al*., 2001).] Recall that saccades are brief, so that vision cannot be used to guide the eye to the target. It is postulated that the cerebellum monitors a corollary discharge of the saccadic command until the eye should be on target and then terminates the eye movement. How could this be performed? Corollary discharge for all ocular motor signals are encoded on cell groups of the paramedian tracts (PMT), a group of neurons distributed throughout the brainstem to which all premotor ocular motor structures project (Büttner-Ennever and Horn, 1996). The PMT cell groups project to the cerebellum and could, along with other mossy fibre projections from pontine nuclei, provide the cerebellum with the corollary discharge that it needs to stop the saccade on target. The relative contributions of mossy fibre projections to the dorsal vermis—or directly to the fastigial nuclei—in the control of saccade metrics are currently being evaluated. Although the fastigial nucleus has some influence on vertical saccades, a different circuit including the posterior interpositus nucleus, which receives inputs from the ventral paraflocculus, seems more important (Robinson, 2000).

In patients with saccadic hypermetria (Fig. 1C) (Video 3; available as supplementary material at Brain Online), feedback signals to the fastigial nucleus—which are required to stop the eye on target— may be compromised. As noted above, unilateral fastigial nucleus inactivation causes ipsipulsion of saccades (Robinson, *et al.,* 1993). The same is true if parallel fibre transmission in the dorsal vermis is experimentally blocked with tetrodotoxin (Robinson and Noto, 2003). Delayed feedback of saccadic signals on parallel fibres

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might explain hypermetria in some patients with hereditary ataxia and neuropathy (Swartz *et al*., 2003). Clinically, fastigial nucleus lesions are effectively bilateral, because the axons cross in the opposite nucleus; affected patients show bilateral hypermetria (Fig. 1C). However, interruption of inputs to the cerebellum in the inferior peduncle—as occurs in Wallenberg's syndrome—causes ipsipulsion; it is postulated that increased activity of Purkinje cells causes a unilateral fastigial nucleus 'lesion' (Waespe and Baumgartner, 1992). Interruption of the crossed output of the fastigial nucleus in the superior cerebellar peduncle causes contrapulsion of saccades (overshooting contralaterally, undershooting ipsilaterally) (Straube and Büttner, 1994). Experimental studies indicate that lesions of the posterior interpositus nucleus may affect the accuracy of vertical saccades (Robinson, 2000), but this has not yet been yet documented clinically.

The cerebellar regions concerned with saccadic accuracy also project to cerebral cortex via the thalamus. Inactivation or lesions of the dorsal vermis (Takagi *et al*., 1998) and the fastigial nucleus (Robinson and Fuchs, 2001; Robinson *et al*., 2002; Scudder, 2002), or the medial dorsal thalamus to which it projects (Gaymard *et al*., 2001), impair the ability to adapt saccades to new visual demands. Tasks that require a sequences of saccades (such as the double-step paradigm) are impaired when the medial dorsal thalamus is inactivated or affected by disease, suggesting that this pathway is important so that the brain can keep a record of prior movements using corollary discharge signals to the cortex (Gaymard *et al*., 1994; Sommer and Wurtz, 2002).

Cortical and subcortical regions contributing to saccades and the spatial–temporal transformation of saccadic signals

Based on electrophysiological and inactivation studies in monkeys and lesions studies, functional imaging and transcranial magnetic stimulation (TMS) in humans, it has been possible to identify several cortical and subcortical areas that contribute to programming saccades (Fig. 4A) (Pierrot-Deseilligny *et al*., 2002). In humans, these include: the frontal eye field (FEF), which lies in the precentral gyrus and sulcus, close to the intersection with the superior frontal sulcus (Rosano *et al*., 2002); the supplementary eye field (SEF), which lies anterior to the supplementary motor area (SMA) in the upper part of the paracentral sulcus (Grosbras *et al*., 1999); the pre-SEF, located just anterior to the SEF; and the parietal eye field (PEF), which corresponds to the lateral intraparietal area (LIP) in monkey and lies in the intraparietal sulcus (Perry and Zeki, 2000). Other cortical areas important for saccade programming are: the dorsolateral prefrontal cortex (DLPC), lying on the dorsolateral surface of the frontal lobe, anterior to the FEF, and occupying approximately the middle third of the middle frontal gyrus; and the posterior parietal cortex (PPC). Frontal and parietal cortical areas project directly to the superior colliculus and frontal areas project indirectly through a basal ganglia pathway that includes the caudate nucleus and substantia nigra pars reticulata (SNpr) (Hikosaka *et al*., 2000). The frontal areas also project, via pontine nuclei such as nucleus reticularis tegmenti pontis (van Opstal *et al*., 1996), to the dorsal vermis and fastigial nucleus of the cerebellum (Fig. 4B).

Neurons in the cerebral cortex and basal ganglia that contribute to saccades show an important electrophysiological difference from saccade-related neurons in the brainstem and the fastigial nucleus of the cerebellum. The generation of saccades by the premotor burst neurons and the control of the size of saccades by the fastigial nucleus are both performed by units whose discharge is related temporally to the eye movement. Thus, the maximum discharge rate of burst neurons correlates with the saccade's top speed and the timing of discharge of fastigial nucleus neurons correlates with saccade start and end. This contrasts with spatial coding of saccade-related neurons in cortical areas. For example, in the primary visual cortex (Brodmann area 17, V1) the location of visual stimulus is represented by the distribution of activity across a 'place' map; different parts of this map correspond to different locations on the retina. Similarly, microstimulation studies have defined a topological motor map in the FEF: stimulation at any site on this map elicits a saccade of a specific direction and amplitude (Bruce *et al*., 1985). Contrast this with premotor burst neurons or ocular motoneurons, which encode the characteristics of the saccade in terms of their temporal discharge (i.e. there is no place map) (van Gisbergen *et al*., 1981).

The possible roles of the superior colliculus and cerebellum in the spatial–temporal transformation of saccadic signals

Saccades can be produced by electrical stimulation in the ventral layers of the superior colliculus at low current thresholds (Robinson, 1972). This 'motor map' is in polar coordinates—the direction and size of the saccade being mainly functions of the site of stimulation rather than the strength of the stimulus or current position of the eye. The smallest saccades are elicited rostrally, the largest caudally. Stimulation of the rostral pole of the motor map inhibits saccades; this 'fixation zone' of the superior colliculus sends a monosynaptic excitatory projection to omnipause neurons (Everling *et al*., 1998), thereby suppressing saccades. Stimulation more caudally induces saccades at latencies that imply disynaptic connections with premotor burst neurons; it is suggested that 'long-lead burst neurons', which begin their discharge > 40 ms before saccades, are interposed (Keller *et al*., 2000*b*). Electrophysiological activity of these more caudally placed, 'collicular burst neurons' indicates that they encode the overall gaze displacement

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(Bergeron *et al*., 2003) and is consistent with the notion that they indirectly drive burst neurons in the brainstem reticular formation. The superior colliculus has reciprocal connections with the mesencephalic reticular formation, which may modulate its activity by a feedback mechanism, especially for vertical saccades (Waitzman *et al*., 2000). In addition, the pedunculopontine tegmental nucleus, which sends nicotinic projections to the superior colliculus, appears to promote saccade generation as part of a general effect on attention, motivation and vigilance (Kobayashi *et al*, 2002*b*).

The importance of the superior colliculus is demonstrated by the finding that inactivation of collicular burst neurons blocks the effects of FEF stimulation (Hanes and Wurtz, 2001). Lesions restricted to the superior colliculus in humans are uncommon, but existing reports indicate that unilateral collicular lesions impair the ability to initiate contralateral saccades at short-latency ('express' saccades—discussed below) (Pierrot-Deseilligny *et al*., 1991*b*)—a finding consistent with animal lesion studies (Schiller *et al*., 1987). Degenerative disorders such as PSP, which involve the superior colliculus, also affect the adjacent central mesencephalic reticular formation and riMLF, and initially cause slow vertical saccades; subsequent involvement of the pons and PPRF leads to saccadic slowing in all directions (Bhidayasiri *et al*., 2001*b*).

The evidence presented above indicates that the superior colliculus is important for initiating saccades (inhibiting omnipause neurons) and for specifying saccade direction and size. Like cortical areas, collicular burst neurons encode this information in a 'place map'. Thus, the location of discharging collicular burst cells remains constant throughout the eye movement, encoding the overall gaze displacement (Bergeron *et al*., 2003). However, a separate population of 'build-up neurons' initially shows activity at a location on the motor map related to the amplitude and direction of the upcoming saccade, but then appears to show a rostral spread of activity (a moving wave or hill) towards the fixation zone (Munoz *et al*., 1991; Munoz and Wurtz, 1995). It had been speculated that this rostrally-directed moving hill of activity in build-up neurons matched the progress of the saccade towards its target, with rostral pole fixation neurons becoming active at the end of the movement. Such a scheme might allow a spatial-temporal transformation to take place. Subsequent studies, however, have not confirmed this role (Soetedjo *et al*., 2002).

Another suggestion is that activity across the fastigial nucleus, from the contralateral to the ipsilateral side during a saccade, could implicitly represent a spatial–temporal transformation (Optican and Quaia, 2002). This hypothesis still lacks experimental confirmation, and it may be that the cerebellar cortex plays a more important role in the spatial-temporal transformation. In any case, this is an issue that requires further attention by both clinicians and neuroscientists, who tend to dwell in their research interests on one or other side of this electrophysiological divide. For example, studies of cerebral cortical lesions on saccades largely dwell on measurements of latency or accuracy, but not much on speed. Peak velocity and duration, however, are influenced by mental set and cognitive demands (Bronstein and Kennard, 1987)—such as when subjects chose to look between more than two targets—and deserve further study.

Neural contributions to different saccadic behaviours (Table 1)

Quick phases of nystagmus

Quick phases of nystagmus are generated during vestibular or optokinetic stimulation, and occur as automatic resetting movements in the presence of spontaneous drift of the eyes. The generation of quick phases by the premotor saccadic circuits of the brainstem has stochastic properties (Shelhamer, 1992) and is not as conveniently described as voluntary saccades. Nonetheless, optokinetic and vestibular nystagmus are sometimes convenient ways to test fast eye movements, especially in patients with some degree of voluntary saccadic palsy (Garbutt *et al*., 2001).

Spontaneous, reflexive and express saccades

Under natural conditions, we make several spontaneous saccades per second. Some of these are deliberate and willed, for example, as we scan a visual scene. Many other saccades appear to be triggered by novel visual, auditory or somatosensory stimuli (often appearing in combination). In the laboratory, a short-latency reflexive visual saccade can be elicited when a novel stimulus is presented after the fixation stimulus has disappeared (gap stimulus—Fig. 5B). In response to this gap paradigm, human subjects may generate saccades with short reaction times—'express saccades'; latencies are as low as 100 ms (Fischer and Ramsperger, 1984). It appears that the gap stimulus mainly releases a fixation mechanism for saccadic gaze shifts.

As noted above, electrophysiological evidence suggests that the rostral pole of the superior colliculus, which projects to the omnipause neurons (Bergeron and Guitton, 2001), plays an important role in such release of fixation (Dorris *et al*., 2002). Furthermore, in monkeys, the occurrence of express saccades is eliminated with lesions of the superior colliculus (but not of the frontal lobes) (Schiller *et al*., 1987). Thus, express saccades provide a way of testing collicular function in humans. So-called spasm of fixation, in which a patient cannot change gaze until the fixation target is removed, may be an extreme case of the retarding influence of a persistent fixation target (overlap paradigm—Fig. 5A) upon saccade latency (Holmes, 1930; Johnston *et al*., 1992; Leigh and Zee, 1999). However, increased saccadic latency can also be due to defects in the ability to disengage, shift, and re-engage visual attention (Nagel-Leiby *et al*., 1990; Ro *et al*., 2001).

The PEF projects to the superior colliculus and appears to be important in the triggering of reflexive visually guided

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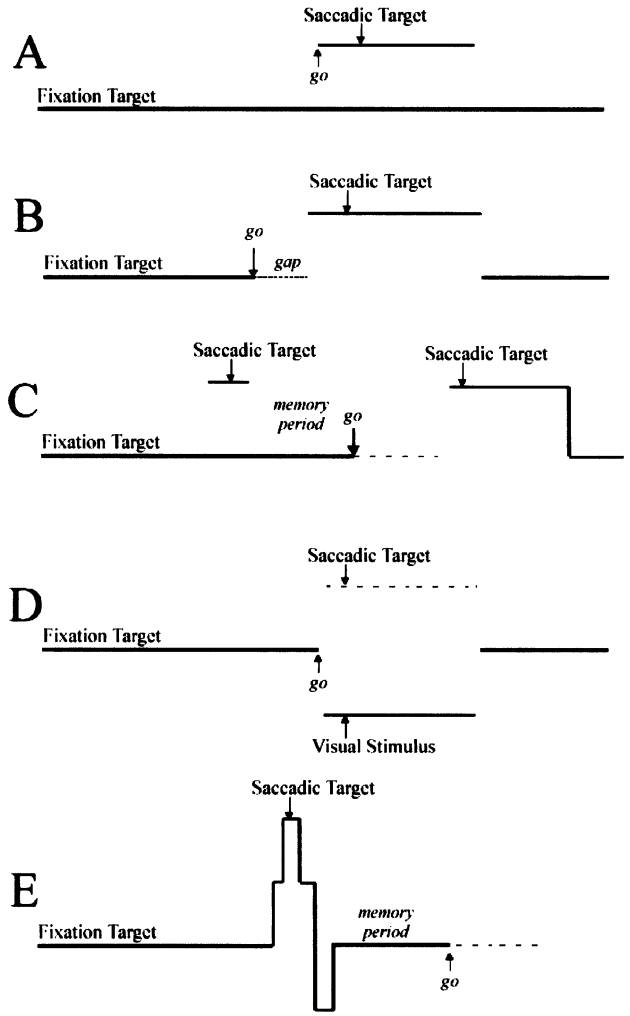

Fig. 5 Schematic of laboratory stimulus paradigms commonly used to test saccades. In each case 'go' indicates the signal for the subject to look towards the 'saccadic target'. (**A**) Overlap paradigm in which the central fixation target stays on throughout. (**B**) Gap paradigm in which the fixation target is switched off before the visual target is switched on. (**C**) Memory target task. The subject views the fixation target during the time that the visual target is flashed and, after several seconds (the memory period), the fixation light is switched off and the subject looks towards the remembered location of the target. (**D**) The antisaccade task. The subject is required to look in the opposite direction when the visual stimulus is presented. (**E**) Sequence of saccades task. A series of targets at several locations are turned on in turn. After a memory period, the fixation light goes out as a signal for the subject to make a series of saccades towards the remembered series of target locations.

saccades. The signal flow from parietal cortex to colliculus constitutes a gradual evolution of signal processing, representing activity at nearly every stage of visuomotor transformation (Wurtz *et al*., 2001). The time course of the neural response suggests that monkey PEF accumulates sensory signals relevant to the selection of a target for an eye movement (Shadlen and Newsome, 2001). After PEF lesions in humans (but not after an FEF or an SEF lesion), latency of visually triggered saccades is significantly increased, especially when the lesion involves the right cerebral hemisphere (Pierrot-Deseilligny *et al*., 1991*a*; Braun *et al*., 1992). TMS studies over the PPC support the view that it contributes to reflexive saccades (Elkington *et al*., 1992; Kapoula *et al*., 2001). Evidence from monkeys and humans indicates that the parietal-superior colliculus pathway runs in the most posterior region of the posterior limb of the internal capsule; lesions of this pathway impaired reflexive but not memory-guided saccades (Gaymard *et al*., 2003*b*).

Voluntary saccades

Abundant evidence from humans and rhesus monkey points to the role of FEF in generating voluntary saccades as part of purposeful behaviour (Pierrot-Deseilligny *et al*., 2002). Pharmacological inactivation of the FEF in monkeys with muscimol injection causes a contralateral 'ocular motor scotoma' with abolition of all reflex visual and voluntary saccades, with sizes and directions corresponding to the injection site on the FEF map (Dias *et al*., 1995). Lesions studies indicate that FEF causes increased latency of visually guided saccades, especially when tested using the overlap paradigm (fixation light remains on during testing—Fig. 5A) (Braun, *et al*., 1992; Rivaud *et al*., 1994). In contrast, the FEF does not appear to be crucial for the triggering of reflexive visually guided saccades such as express saccades. Functional imaging studies in humans support the view that FEF is more concerned with voluntary than reflexive saccades (Mort *et al*., 2003*b*).

Memory-guided saccades

It has proved useful to study the accuracy of saccades made to remembered target locations (Fig. 5C), especially in patients with lesions affecting the frontal lobes and basal ganglia that might impair 'working memory'. When normal subjects attempt to make saccades to the remembered location of a target that they viewed a few seconds before, they do so with an accuracy only slightly less than if the target were visible (White *et al*., 1994).

A combination of studies of memory-guided saccades in rhesus monkey and humans, using a variety of techniques, has elucidated the underlying mechanisms. These involve a network of connections between the DLPC, FEF and PPC (Pierrot-Deseilligny *et al*., 1993). Neurons in the DLPC of monkey show an ability to hold memory-specific visuospatial coordinates represented in a topographical memory map (Sawaguchi and Iba, 2001); activation of D1-dopamine receptors appear to play an important facilitating role. Monkeys show improved memory-guided saccades when reward is expected and suppression of behaviour when reward is not expected (Kobayashi *et al*., 2002*a*). Pharmacological inactivation of DLPC with D1-dopamine antagonists impairs the accuracy of monkeys in making contralateral memory-guided saccades (Sawaguchi and

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Goldman-Rakic, 1994). In humans, there is activation of the DLPC when subjects make memory-guided saccades (Sweeney *et al*., 1996). Repetitive TMS over the DLPC in normal subjects also impairs the accuracy of memory-guided saccades (Brandt *et al*., 1998). Patients with lesions affecting this area show increased variable error of memory-guided saccades (Pierrot-Deseilligny *et al*., 2003).

The FEF in monkey also shows a subpopulations of 'quasivisual' neurons that hold the visual response of a stimulus in working memory until a saccade is made (Tian *et al*., 2000). FEF neurons maintain a spatially accurate representation of the visual world which is not dependent on constant or continuous visual stimulation, and can last for several minutes (Umeno and Goldberg, 2001). Consistent with this, TMS applied over the FEF influences the latency of contralateral, memory-guided saccades (Wipfli *et al*., 2001; Pierrot-Deseilligny *et al*., 2002).

Other cortical regions that may contribute to short-term memory-guided saccades include areas in PPC and rostral to SEF (pre-SEF) (Heide *et al*., 2001; Merriam *et al*., 2001). The most impressive dysmetria with parietal lobe lesions occurs when patients are required to respond to a double-step stimulus in which the target jumps twice before a response can be initiated (Duhamel *et al*., 1992; Heide *et al*., 1995). If the target jumps first into the contralateral hemifield and then into the ipsilateral field, patients cannot make accurate saccades to the final target position, even though it lies in the 'intact' hemifield. This finding has been taken as evidence that the parietal lobe plays a pivotal role in computing target position from both visual stimuli and an efference copy of eye movements (in this case, the change in eye position due to the first saccade).

On the basis of TMS studies, an attempt has been made to track the flow of neural information during programming of memory-guided saccades. Thus, it has been proposed that the right PPC is involved at ~300 ms after the target presentation when it contributes to visual-spatial integration stage (Müri *et al*., 1996, 2000). Both DLPC are involved during the memorization phase (~1 s after the target presentation). The FEF is involved in triggering of the memory-guided saccade, possibly with a contribution from the parietal lobe (PEF) (Pierrot-Deseilligny *et al.,* 2002).

Although most studies of memory-guided saccades have concerned short-term or working memory, saccades have also been used to probe aspects of medium-term spatial memory (delays of 20 s to 2 min), which may depend on perirhinal cortex (Ploner *et al*., 2000), and longer-term memory, which appears to depends on the parahippocampal cortex formation in humans (Pierrot-Deseilligny *et al*., 2002).

Predictive saccades

During normal activity, a range of eye movements, including saccades, may be generated in anticipation or, in search, of the appearance of a target at a particular location. In the laboratory, predictive saccades are stimulated by target jumps between two locations at regular intervals (Zhao *et al*., 1994). Predictive saccadic behaviour is deficient in Parkinson's disease and in patients with bilateral lentiform nucleus lesions, who show abnormalities of predictive saccades, although visually guided saccades are normal (Crawford *et al*., 1989; Vermersch *et al*., 1996). This accords with electrophysiological studies of the caudate nucleus, which inhibits the SNpr, and may thus lead to difficulties in initiating voluntary saccades in tasks that require learned or predictive behaviour (Hikosaka *et al*., 2000). Presumably, working memory is needed to generate predictive responses, and patients with DLPC lesions show impaired ability to make predictive saccades (Pierrot-Deseilligny *et al*., 2003).

Suppression of saccades and 'antisaccades'

In addition to looking towards new visual targets, an important part of saccadic behaviour is to suppress eye movements that would be made to novel but behaviourally irrelevant stimuli. To investigate such control of voluntary versus reflexive saccades, a special test paradigm called the antisaccade task has been developed (Fig. 5D). In this task, the subject is required to suppress a saccade (the 'prosaccade') towards a stimulus that appears in the periphery of vision and instead generate a voluntary saccade of equal size towards the opposite side (the 'antisaccade'). After time for the antisaccade to be made, a target light is turned on at the correct location to check the accuracy of the movement (Fischer and Weber, 1997). The simplest measure of the response to this test concerns the direction of the initial saccade, expressed as the ratio of antisaccades to prosaccades; this can be tested at the bedside (Currie *et al*., 1991). Normal subjects initially make frequent errors on this task, but after a brief period of practice, error rates fall to <15%.

Both the FEF and DLPC appear to contribute to programming of the antisaccade response. Thus, functional imaging studies have shown that FEFs are activated bilaterally during both prosaccades and antisaccades, but more so for the latter (Connolly *et al*., 2002; DeSouza *et al*., 2003). The right hemisphere DLPC is also activated during antisaccades (DeSouza *et al*., 2003). However, it has been reported that, at the cortical level, only patients with discrete lesions affecting the DLPC have an increased percentage of errors in the antisaccade test (Pierrot-Deseilligny *et al*., 2003); in contrast, patients with FEF lesions had a normal percentage of errors on the antisaccade task, but their correct antisaccades were made at increased latency. Thus, it has been suggested that, during the antisaccade task, inhibition of reflexive misdirected saccades is due to the DLPC, whereas triggering of the intentional, correct antisaccade depends upon the FEF (Rivaud *et al*., 1994; Pierrot-Deseilligny *et al*., 2003). In a patient with a discrete brainstem lesion, increased distractibility was attributed to interruption of a pathway from the DLPC to the superior colliculus (Gaymard *et al*., 2003*a*). Whether the FEF is also important for suppression of reflexive saccades is disputed (Pierrot-Deseilligny *et al*.,

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2003), although functional imaging suggests that it may be (Cornelissen *et al*., 2002).

Additional insights into the mechanisms underlying antisaccades can be gained from a 'countermanding' task, in which monkeys are required to make visually guided saccades on most trials but, on a fraction of trials, to withhold a saccade on the basis of reappearance of the fixation cue (Schall, 2002). Electrophysiological properties of the FEF during this task have identified neurons that reflect behavioural responses and indicate that these units are concerned with generation or suppression of saccades. In contrast, neurons in the SEF and anterior cingulate cortex respond on trials where a saccade is erroneously not cancelled and reward will not be given (Schall *et al*., 2002). When FEF, LIP and SEF activity are compared during target selection and saccade generation, SEF activity appeared most concerned with internally-guided target selection based on reward during prior trials (Coe *et al*., 2002).

Thus, further work is required to define the mechanisms underlying the antisaccade task. It appears that the DLPC, FEF, and possibly the SEF or pre-SEF may each contribute, but their respective roles require better definition.

Sequences of saccades made during learned behaviours

Mastering complex motor tasks, such as typing or playing a musical instrument, requires learning sequences of movements that are often monitored by saccadic eye movements. The dorsomedial frontal cortex, basal ganglia and cerebellum seem important components of networks that make possible the initial learning of new skills, which requires attention and awareness. Subsequently, learned motor sequences operate more quickly and require less attention (Hikosaka *et al*., 2002). Electrophysiological studies have indicated that the pre-supplementary motor cortex is active during learning new sequences of movements, including eye movements (Lu *et al*., 2002). Pharmacological blockade of this area prevents learning of new sequences (Nakamura *et al*., 1999). The anterior cingulate cortex also may also contribute to learning new motor sequences (Procyk *et al*., 2000). In contrast, the SMA seems more important during the transition of learned component tasks. Thus, one patient with a discrete lesion affecting one SEF had difficulty in changing the direction of his eye movements, especially when he had to reverse the direction of a previously established pattern of response (Husain *et al*., 2003). Therefore, the pre-supplementary motor cortex and SMA may work together to coordinate sequential movements (Tanji, 2001). The cerebellum is important for learning motor sequences, but cerebellar lesions do not impair visuomotor memory or spatial working memory (Nixon and Passingham, 2003).

The SEF, especially on the left side, appears to be involved in the control of motor programs comprising a sequence of saccades (Gaymard *et al*., 1993). During testing of sequences of saccades (Fig. 5E), TMS studies have shown that the SEF could be crucial at two distinct times—during the learning phase (presentation of the visual targets) and just after the go signal, when the subject has to initiate the sequence of saccades (Müri *et al*., 1994). Functional imaging studies have indicated that, for familiar sequences of saccades involving long-term memory, the right medial temporo-occipital activation was detected in the vicinity of the boundary between the parahippocampal and lingual gyri, as well as an activation site in the parieto-occipital fissure (Grosbras *et al*., 2001; Pierrot-Deseilligny *et al*., 2002).

The role of reward in voluntary saccades

Although the frontal and parietal eye fields project directly to the superior colliculus (Fig. 4B), a second pathway running through the basal ganglia plays an important role, especially in selecting targets that will be rewarded (Hikosaka *et al*., 2000). Saccade-related neurons in the caudate lie at the junction of the head and body of this structure and receive inputs from the FEF, SEF and DLPC. This area of caudate projects to the SNpr. Neurons in the SNpr may influence both target selection and saccade initiation (Basso and Wurtz, 2002). The SNpr, in turn, sends inhibitory projections to the superior colliculus. A simplified view of this basal ganglia pathway is that it is composed of two serial, inhibitory links: a caudate-nigral inhibition, which is only phasically active; and a nigro-collicular inhibition, which is tonically active. If frontal cortex causes caudate neurons to fire, then the nigro-collicular inhibition is removed and the superior colliculus is able to activate a saccade. In addition, the subthalamic nucleus contains neurons that discharge in relation to saccades (Matsumura *et al*., 1992) and excites SNpr which, in turn, inhibits the superior colliculus. The basal ganglion pathway appears important for programming of saccades that will be rewarded (Hikosaka *et al.,* 2000). For example, neurons in the monkey caudate nucleus change their discharge rate systematically, even before the appearance of the visual target, and usually fire more when the contralateral position is associated with reward (Lauwereyns *et al*., 2002).

Studies of the effects of human diseases affecting basal ganglia have focussed on behaviour such as memory-guided or predictive saccades. For example, memory-guided saccades are impaired after pallidotomy for Parkinson's disease (Blekher *et al*., 2000), but improved with subthalamic nucleus stimulation (Rivaud-Pechoux *et al*., 2000). Pallidotomy increases saccadic intrusions on steady fixation—'square wave jerks' (Averbuch-Heller *et al*., 1999). In the future, there is need for new experimental strategies which involve reward for carrying out memorized saccades.

Saccades made during visual search—scanpaths

Perhaps the most important natural function of saccades is to allow us to examine the details of our visual environment. The sequence of saccades and fixations during such visual

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search is called a scanpath. Each saccade is preceded by a shift of attention to the goal of the next saccade, which at that moment consumes much of the available spatial attentional resources (Kowler *et al*., 1995). Scanpaths during visual search are dependent on both visual features that attract attention such as areas of high contrast, as well as cognitive factors such as planning and sequencing, visuo-spatial attention and spatial working memory. In addition, there are top–down influences relating to the perceived requirements of the search.

Given that active visual search is so dependent upon the integration of attentional control of eye movements, it is not surprising that the neurological condition that most disrupts visual search is hemispatial neglect, usually resulting from cerebral damage involving the inferior lobule of the right parietal lobe (Mort *et al*., 2003*a*). Patients suffering from hemispatial neglect show an inability to attend to the contralateral half of space, which biases their attention towards the ipsilesional side. It was recognized early on that the attentional deficit impaired a patient's ability to search the contralesional space and this was a sensitive indicator of neglect (Chedru *et al*., 1973). Even with a spatial bias operating, however, one would expect patients to eventually progress, by elimination, into the contralateral field, but this does not happen (Harvey *et al*., 2002). Recent experiments have established that, during multitarget search, neglect patients are unable to retain a memory for where they have searched before, so that they recursively refixate targets and report these as newly discovered (Husain *et al*., 2001). Thus, search behaviour in hemispatial neglect appears to combine a spatial bias with a loss of memory for locations previously searched (Sprenger *et al*., 2002). For example, when a working memory deficit is combined with an attentional bias to the right (cause by hemineglect due to a right hemisphere stroke), the patient may show recursive searching of the right side (being unable to remember that they have 'been there before') and failure to explore left hemispace.

Electrophysiological studies in monkey indicate that neurons in the posterior parietal lobe may be involved in representing visual location across saccades and maintaining a memory trace for the location of saccadic targets (Lee *et al*., 2000). Ensemble activity in the parietal eye field (LIP in monkey) describes the spatial and temporal dynamics of a monkey's attention across the entire visual field (Bisley and Goldberg, 2003). Experimental inactivation of the LIP fails to produce deficits in the latency or accuracy of saccades to single targets, but it reduces the frequency of contralateral saccades in the presence of bilateral targets. In addition, inactivation of the LIP increases the search time for a contralateral target during serial visual search, suggesting that one important contribution of the LIP to oculomotor behaviour is the selection of targets for saccades in the context of competing visual stimuli (Wardak *et al*., 2002). These results are consistent with the hypothesis of an oculomotor-attentional network contributing to fixation engagement and disengagement in a sub-region of the LIP (Ben Hamed *et al*., 2002).

Functional imaging studies in humans have revealed a network of brain areas involved in maintaining information about visual location in a variety of spatial working memory tasks, including saccades to remembered locations. This network includes the areas damaged in the patients with spatial hemineglect who show a deficit in spatial working memory. Functional imaging of the FEF demonstrates activation during active fixation of a stationary target and the process of visual scanning of a complex visual scene (Donner *et al*., 2000). In addition, preferential activation has been noted in the right angular gyrus during production of exogenously triggered rather than endogenously generated saccades—a finding which we propose is consistent with an important role for the angular gyrus in exogenous saccadic orienting (Mort *et al*., 2003*b*); an analogous role has also been attributed to the supramarginal gyrus (Perry and Zeki, 2000).

In Parkinson's disease, studies of the scanpaths of saccades during visuospatial sorting tasks have provided insights into cognitive changes in this disorder. Patients have been tested on a 'Tower of London' task, in which a series of coloured balls have to be rearranged to comply with a specific pattern (this tests working memory and planning). Analysis of scanpaths compared with the scanpaths of normal subjects (Hodgson *et al*., 2000) suggested that parkinsonian patients kept forgetting the arrangement of the test objects every time they looked away. This implies a deficiency in their spatial working memory (Kennard, 2002).

Patients with lesions of the posterior visual pathways resulting in a visual field defect, called a homonymous hemianopia, suffer from considerable disabilities including an impaired ability to scan their environment. However, they are nonetheless able to search completely across a visual search field, such as a cancellation task, in contradistinction to patients with hemispatial neglect. The search path is distinguished by frequent exploratory saccades into the blind part of the visual field (Zihl, 1995). This distinctive pattern of search provides confirmation that, where normal attentional mechanisms are intact, oculomotor strategy can be adjusted to compile a complete picture of the search field, even though each fixation provides an incomplete view (Zangemeister *et al*., 1995). There is evidence that adaptive changes occur in visual search strategy of naturalistic scenes as time passes after the stroke in hemianopic patients (Pambakian *et al*., 2000). Furthermore, actively encouraging patients to make this strategic adaptation may speed up their rehabilitation (Kerkhoff *et al*., 1994), including the use of portable, low cost equipment that is easy to deploy with the patients (Kennard, 2002; Pambakian *et al*., 2002).

Although the involvement of posterior parietal and frontal cortical areas in visual search has been demonstrated (Gitelman *et al*., 2002), much less is known about which areas have roles essential to normal search performance. Indeed, despite the prospect of insight from patients with focal cortical lesion, the few studies of search in these patients

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(excluding those with hemispatial neglect) have not found strong alterations in behaviour (Hildebrandt *et al*., 1999; Karatekin *et al*., 1999). This discrepancy between involvement and necessity of cortical areas in search may reflect significant functional reserve and plasticity within the cortical network as a whole. However, recently it has been found that disorganized visual search occurred in a patient with orbitofrontal damage (Hodgson *et al*., 2002), adding to a previous observations that prefrontal cortex may contribute to normal elaboration of search strategy (Zihl and Hebel, 1997).

Summary and future trends

Few human motor responses are as well understood as saccades. This knowledge has been put to good use by both clinicians and clinical scientists. For example, saccadic disorders in patients with multiple sclerosis indicate posterior fossa involvement; such patients suffer greater generalized disability than patients with normal eye movements (Serra *et al*., 2003). In addition, paradigms such as the antisaccade task have been used, for example, to tease out the importance of the SEF in self-control during switching of motor responses (Husain *et al*. 2003). However, there are potential risks in using saccades as experimental tools. First, eye movements do possess certain unique properties such as the absence of a stretch reflex and extrapolation of results from saccades to limb movements requires caution. Secondly, the tendency to measure just one property of saccades, such as latency, neglects other information (such as trajectory) which might provide greater insights into the underlying defect. Thirdly, the assumption that a specific defect of saccadic behaviour can be attributed to a discrete region of the brain seems unwarranted, given the evidence that multiple regions contribute to all forms of saccades via parallel pathways. Indeed, as the nature of the spatial–temporal transformation of sensory-to-motor signals becomes better understood, it seems likely that the contributions of each of the cortical and basal ganglionic areas to the broad range of saccadic behaviour will become clearer.

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