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REVIEW ARTICLE

What clinical disorders tell us about the neural control of saccadic eye movements

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Saccades are rapid eye movements that redirect the fovea from one object to another. A great deal has been learned about the anatomy and physiology of saccades, making them an ideal system for studying the neural control of movement. Basic research on normal eye movements has greatly increased our understanding of saccadic performance, anatomy and physiology, and led to a large number of control system models. These models simulate normal saccades well, but are challenged by clinical disorders because they often do not incorporate the specific anatomical and physiological substrates needed to model clinically important abnormalities. Historically, studies of saccadic abnormalities in patients have played a critical role in understanding the neural control of saccades because they provide information that complements basic research and thus restricts hypotheses to those that are biologically plausible. This review presents four examples of clinical disorders (slow saccades, interrupted saccades, high-frequency saccadic oscillations and macrosaccadic oscillations) that have provided insights into the neurobiology of saccades, have driven the development of new models, and have suggested an explanation or treatment for these disorders. We raise general questions for both scientists and clinicians that will assist in their efforts to understand the neural control of movement, improve diagnostic criteria and develop new treatments.

Keywords: cerebellum; macrosaccadic oscillations; opsoclonus; saccadic palsy; superior colliculus

Abbreviations: cFN = caudal FN; cMRF = central mesencephalic reticular formation; EBN = excitatory PBN; FN = fastigial nucleus; FNN = FN neuron; IBN = inhibitory PBN; IN = internuclear neuron; INC = interstitial nucleus of Cajal; LLBN = long-lead burst neuron; LR = lateral rectus muscle; MedRF = medullary reticular formation; MN = motor neuron; MR = medial rectus; MVN = medial vestibular nucleus; NMDA = *n*-methyl D-aspartate; NPH = nucleus prepositus hypoglossi; NRTP = nucleus reticularis tegmenti pontis; OPN = omnipause neuron; PBN = premotor burst neuron; PG = pulse generator; PMT = paramedian tract; PPRF = paramedian pontine reticular formation; riMLF = rostral interstitial nucleus of the medial longitudinal fasciculus; RIP = raphe interpositus nucleus; SC = superior colliculus; SCBN = SC burst neurons; SCBUN = SC build-up neurons; SO = superior oblique; SR = superior rectus; T-channel = T-type Ca^{2+} channel; VIn = sixth nerve

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Introduction

Saccades are rapid eye movements used to redirect the fovea from one object to another. They must be fast and accurate to support clear vision. A great deal has been learned about the anatomy and physiology of saccades since they were first reliably recorded over 100 years ago by Dodge and Cline (1901; Wade and Tatler, 2005). This knowledge makes them

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an ideal system for studying the neural control of movement. Basic research on normal saccades, especially neurophysiological recordings from identified neurons during behaviour in monkeys, has revealed a great deal about saccadic performance, anatomy, and physiology. Clinical studies of patients with saccadic disorders, and studies of the effects on saccades of brain lesions in animals, have led to the development of quantitative hypotheses (models) of the neural control of saccades. These models simulate normal saccades well, but are challenged by clinical disorders because they often do not incorporate the specific anatomical and physiological substrates needed to model clinically important abnormalities. The interaction between research on animals and patients thus leads to a better understanding of how the brain controls movements than either alone. This interaction has made saccades one of the best understood of all vertebrate movements.

The goal of theoretical studies of eye movements is to develop models that realistically represent neurobiological processes, i.e. those that are isomorphic with the brain. Such models elucidate the neuronal mechanisms underlying motor control (Girard and Berthoz, 2005). The purpose of a model is to summarize knowledge, support insights, make hypotheses explicit and quantitative, and predict or explain new phenomena. Although each aspect of a movement can be explained by many models, the requirement that a single model account for as much normal and abnormal behaviour as possible constrains the choice of models and reveals isomorphisms that contribute to our understanding of brain function. Thus, a key factor in modelling the neural control of saccades was the interaction of clinical and basic science. Nonetheless, although clinician-scientists interested in abnormal eye movements have used saccadic models to explain human disorders, the full impact of the basic research effort on saccades has yet to be translated into better biomedical care, i.e. to the bedside.

What might be impeding this translation? First, most scientists are not familiar with clinical disorders of human saccades, and most clinicians are not familiar with experimental studies of saccades in animals. Second, experimental and clinical studies often differ, in the experimental paradigms, method of training or instruction given to the subject, motivation or rewards, number of subjects involved, ability to characterize the deficit, and availability of controls. Third, clinical studies tend to be inclusive, attempting to describe features common among a group of patients with similar symptoms, whereas scientific studies tend to be exclusive, focusing on one or a few differences between experimental and control subjects. Finally, basic scientists often study saccades in several species (e.g. monkey or cat) that are both anatomically and physiologically different from human patients. These different approaches have sometimes led the two groups to emphasize different aspects of motor control. For example, the superior colliculus (SC, a midbrain structure that is involved in making eye and head movements) has been the focus of intense interest by basic scientists for over thirty years, but discussion of the effects of SC lesions is conspicuously absent from clinical texts.

Our goal here is to stimulate more interdisciplinary interactions by reviewing selected disorders of human saccades that pose specific questions for current models. In each case we describe key features of the abnormality, and discuss the issues that the disorder poses for saccadic models. We limit the scope of this review to brainstem and cerebellar contributions to the generation of saccades, because these are better understood than more cognitive functions, such as detecting and selecting targets in a visual scene.

Characteristics of saccades

Saccades are the rapid eye movements used to voluntarily move gaze from one target of interest to another (Fig. 1). Human saccades follow a target jump within ~250 ms, are fast (up to ~600°/s), brief (typically ~30–100 ms), accurate, and stop abruptly (i.e. with little subsequent ocular drift). Saccades made to target jumps >10° in amplitude often undershoot the target by ~10% (Kapoula, 1985), and, after a short latency (~150 ms), are followed by a corrective saccade. Saccadic waveforms are characterized by the main sequence, a set of relationships between saccade amplitude and peak velocity (Fig. 1E), and between amplitude and duration (Fig. 1G) (Bahill *et al.*, 1975). The first is logarithmically compressed for large amplitudes, whereas the latter is linear down to <5° with a non-zero Y-intercept. The main sequence plots are similar in monkeys and humans, except that monkey eye movements are ~30–50% faster. Patients with certain diseases make saccades that deviate in specific ways from the normal main-sequence plots, making them a useful diagnostic tool. Other useful measures of saccades are their reaction time (latency), symmetry of their velocity waveform, and trajectory in space or on a phase plane (discussed further below under Clinical disorders of the saccadic system and the development of models).

During visual search, the point of fixation is moved between features that lie in different directions and at different depths. Thus, saccadic movements generally have both conjugate (both eyes rotate in the same direction, called version) and disconjugate (the eyes rotate in opposite directions, called vergence) components.

This review summarizes current knowledge about the generation of saccades, and examines how the study of different clinical disorders has led to advances in saccadic models. First, we will review the neurobiology of saccades, using a bottom-up approach to identify brainstem and cerebellar components that can be incorporated into models for saccade generation. Second, we will discuss, from a historical perspective, how current models for the generation of saccades by the brainstem and cerebellum were developed. Third, we will present four clinical disorders of saccades (slow saccades, interrupted saccades,

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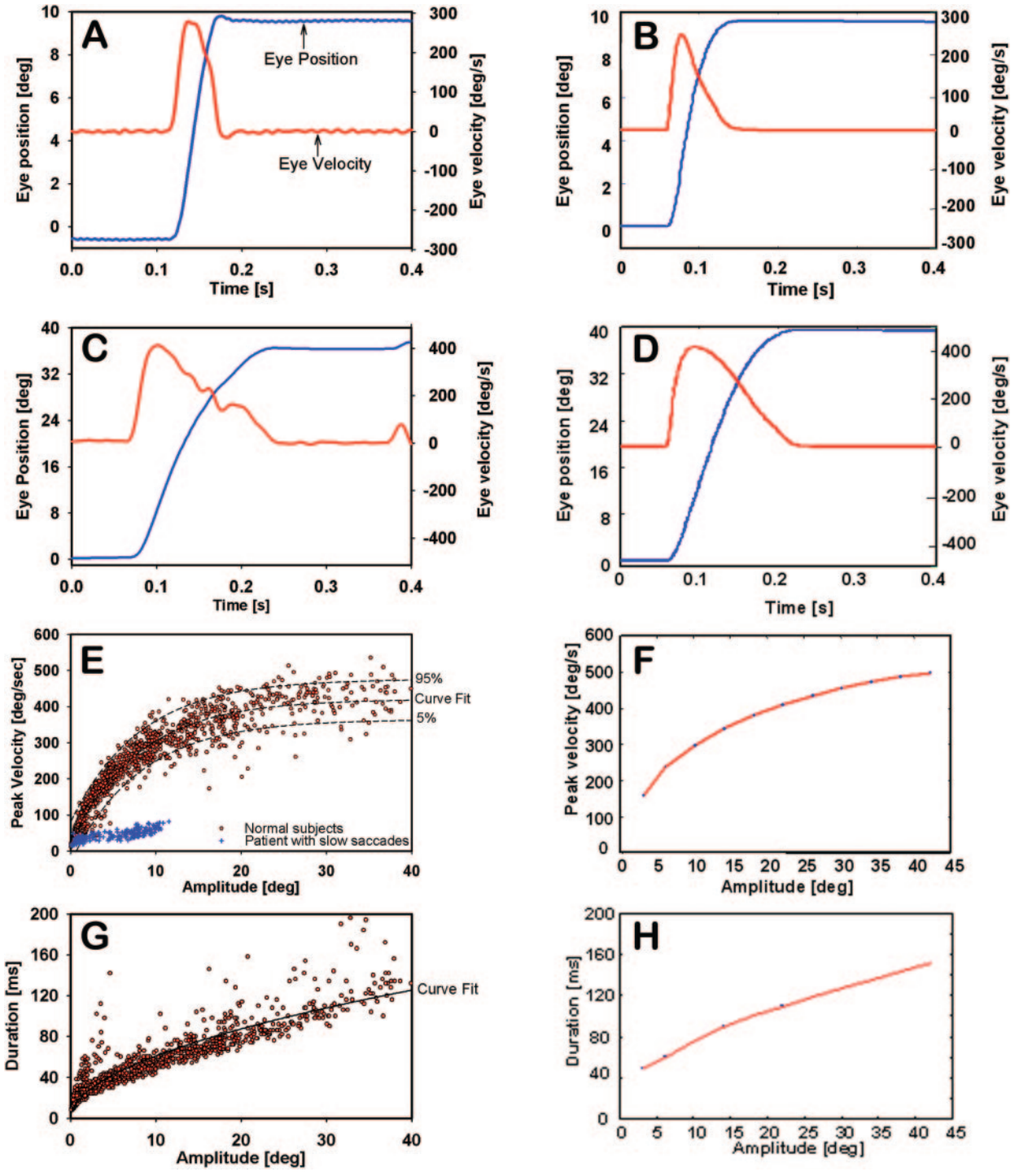

Fig. 1 (**A**) Representative record of a 10° horizontal saccade made by a normal subject. In this and subsequent figures, positive values indicate rightward, upward or clockwise eye rotations from the subject's viewpoint. Position (blue) and velocity (red) records are shown. (**B**) Simulated 10° horizontal saccade by model described in text. (**C**) Representative record of a 40° horizontal saccade made by a normal subject; note the positive skewing of the velocity waveform. (**D**) Simulated 40° horizontal saccade. (**E**) Plot of peak velocity versus amplitude of saccades. Data points (red dots) are saccades from 10 normal subjects. These normal data are fitted with an exponential equation of the form: $V_p=V_{max}\ (1 - e^{-A/C})$, where V_{max} is the asymptotic peak velocity, A is amplitude, and C is the angle constant shaping the exponential rise. Also plotted are the 5 and 95% prediction intervals. The plus symbols (blue) correspond to slow saccades made by a patient who had suffered brainstem ischaemia during cardiac surgery (see Fig. 5A). (**F**) Model simulation of peak velocity—amplitude main sequence using required saccade amplitudes from 4° to 40°. (**G**) Plot of saccade duration versus amplitude. The data from 10 normal subjects are fitted with a power equation of the form: $D = D_1A^n$, where D is duration, D_1 is the duration of a 1° saccade, A is saccade amplitude, and n is a curvature parameter. (H) Model simulation of duration—amplitude main sequence using required saccade amplitudes from 4° to 40°. (Note that scales change between each row.)

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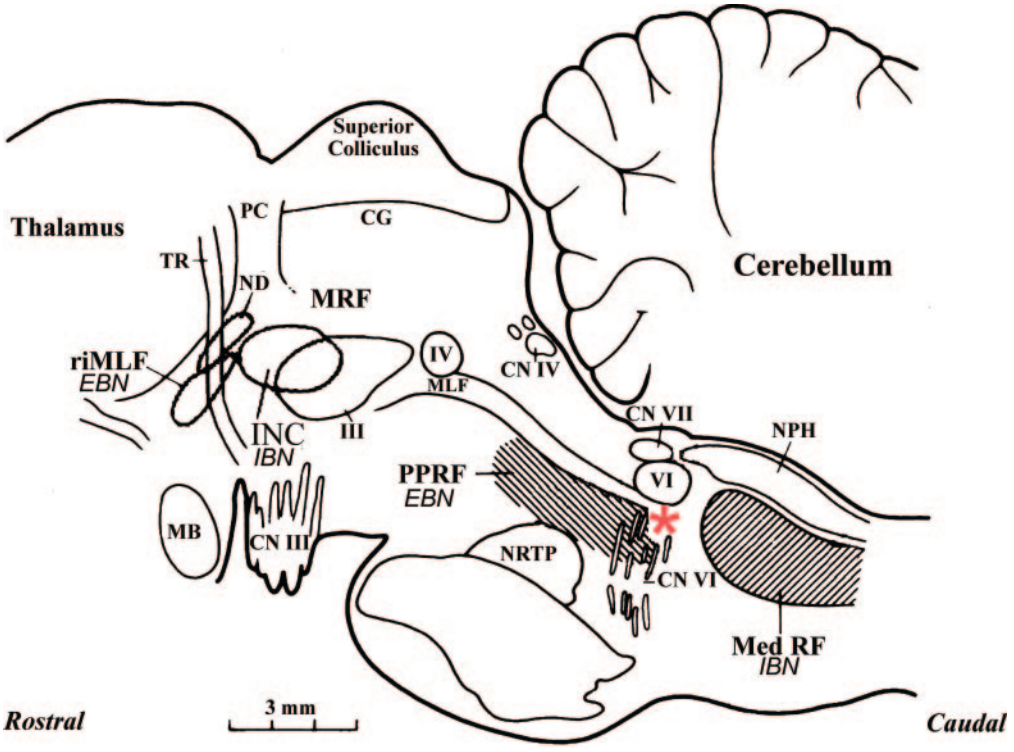

Fig. 2 A parasagittal section of the monkey brainstem showing the locations of PBNs. EBN for horizontal saccades lie in the PPRF; IBN for horizontal saccades lie in the MedRF; EBN for vertical and torsional saccades lie in the rostral interstitial nucleus of the median longitudinal fasciculus (riMLF). Some vertical IBN may reside in or close to the INC. EBN and IBN project to ocular motoneurons lying in the abducens nucleus (VI), the trochlear nucleus (IV) and the oculomotor nucleus (III). OPN (indicated by a red asterisk) lie in the midline raphe of the pons between the rootlets of the abducens nerve (CN VI) and influence the activity of EBN and IBN. The mesencephalic reticular formation (MRF) may house a putative latch mechanism that keeps OPN inhibited until the saccade is over and the eye is on target (see Fig. 4C). CG: central grey; MB: mammillary body; CN III: rootlets of the oculomotor nerve; CN IV: trochlear nerve; CN VII: genu of facial nerve; ND: nucleus of Darkschewitsch; NRTP: nucleus reticularis tegmenti pontis; NPH: nucleus prepositus hypoglossi; PC: posterior commissure; TR: tractus retroflexus. (Figure courtesy of Dr Jean Büttner-Ennever).

high-frequency saccadic oscillations and macrosaccadic oscillations). We selected these disorders because they are well defined and instructive about the underlying neurobiology, and we will discuss their implications for current models. Finally, we will discuss how models may aid the understanding of saccadic disorders and lead to the development of clinically useful therapies.

Further details are documented in supplementary material at *Brain* online, including videos of the clinical disorders presented here.

Neurobiology of saccades

A sustained research effort over more than three decades, comprising many anatomical, physiological, and behavioural reports, has led to a better understanding of how the brain generates saccades. Here we provide a brief description of important brainstem and cerebellar populations of neurons that contribute to the generation of saccades (key features of each type of neuron are summarized in tables). A schematic summary of the anatomy is shown in Fig. 2.

Oculomotor plant

When discussing the neural control of eye movements, it is helpful to start by considering the dynamics of the eye and orbital tissues (e.g. Tenon's capsule, fat, ligaments), extraocular muscles and pulleys. Together, these elements form the oculomotor plant (in engineering terms plant refers to whatever is controlled).

Extraocular muscles

Movements of each eye are controlled by six extraocular muscles, which originate at the back or nasal side of the orbit and travel to fibromuscular pulleys that are formed by the fascia of the orbit (Demer, 2004). The outer, orbital part of the muscle inserts partially on the pulley, and the inner global part passes through the pulley and inserts on the globe. Details of ocular movements in three dimensions (yaw, pitch and roll) depend upon the geometry of the muscle origins, pulleys and insertions (Quaia and Optican, 2003*a*), but are not the focus of this review. Here, we will regard the six muscles as grouped into three agonist-antagonist pairs obeying

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Sherrington's law of reciprocal innervation: lateral rectus (LR) and medial rectus (MR); superior rectus (SR) and inferior rectus (IR); superior oblique (SO) and inferior oblique (IO).

Ocular motoneurons

The brain innervates the extraocular muscles via three cranial nerves. The abducens nerve (VIn) innervates the ipsilateral LR, the trochlear nerve (IVn) innervates the contralateral SO muscle, and the oculomotor nerve (IIIn) innervates the ipsilateral MR, IR, IO and contralateral SR. Muscles are paired in two ways. First, for each agonist there is a corresponding antagonist muscle with almost the same axis of action for that eye (i.e. LR–MR, SR–IR, SO–IO). Second, muscles are yoked to move both eyes together (e.g. left LR and right MR, left SO and right IO). Saccades tend to follow Hering's law, with equal innervation going to muscles in a yoked pair. However, as noted above, when looking between targets at different depths, different size movements can be made in each eye. In this review, we assume separate conjugate saccade and disconjugate vergence systems (Enright, 1998; Zhou and King, 1998; Ramat *et al.*, 1999). Although recent evidence suggests that this is an oversimplification, it will be sufficient for the types of disorders discussed here.

Final common path

The same motor neurons (MNs) and extraocular muscles are active for all types of eye movements (e.g. saccades, pursuit and vergence). Thus, systems generating innervation for different movement types are said to share a final common path. The shape of the signals entering the final common path depends on both the desired eye movement and the dynamic response of the eye plant. One of the first important insights in understanding the neural control of movement came when Robinson (1964) showed that the dynamics of the oculomotor plant were dominated by the viscosity of the muscles themselves. Thus, if a constant torque were suddenly applied to the globe, the eye would drift from its initial orientation to its final orientation with an exponentially decaying speed (time constant ~200 ms) and the eye would reach a steady position only after about three time constants (~600 ms). Since the eyes can make a saccade every 200–300 ms, this has obvious disadvantages for vision. In addition, elastic forces imposed by the orbital tissues tend to return the eye to centre position.

Thus, all types of movement entering the final common path have to consist of two main components: a phasic component (pulse) giving the torque needed to overcome the viscous drag of the orbital tissues, and a tonic component (step) giving the torque needed to overcome the elasticity of the orbital tissues. For saccades, the phasic part of the innervation has a discharge rate about nine times higher than the tonic part, so the combined innervation has a pulse-step shape (Robinson, 1970; Quaia and Optican, 2003*b*). Thus, to make a saccade, the brain must compute two different but related components of innervation. If the pulse and step are not matched correctly, the eye will drift (for ~600 ms) after each saccade from the position reached during the pulse to that corresponding to the step.

Final common integrator

Robinson (1975) suggested that the brain could calculate the step from the pulse by integrating it (in the mathematical sense), because the number of spikes in the pulse was proportional to saccade amplitude. Earlier, Skavenski and Robinson (1973) had discovered strong evidence for a neural integrator in the vestibular system, which introduced a phase lag of ~90° between the vestibular signal (head velocity) and the signal encoded on ocular motoneurons (eye position). If all the eye movement systems need to share a final common path that is matched to the plant, they must also all share the same integrator (otherwise, switching from, say, pursuit to vestibular movements would cause the eye to drift). Thus, the input to the final common path for any type of eye movement (e.g. vestibular, pursuit, saccade) should be a desired eye velocity.

Brain stemreticular formation

The brainstem houses the essential machinery for generating saccades. A partial functional dichotomy exists between the midbrain and pons. Neurons in the pons are mostly concerned with the horizontal component of saccades, whereas the midbrain controls vertical and torsional components.

Premotor burst neurons (PBN)

Two main types of neuron are critical for saccade generation, which we collectively refer to as PBN because they project monosynaptically to ocular motoneurons (Table 1). The excitatory PBNs (EBN) burst just before saccades and probably generate the pulse of saccadic innervation (van Gisbergen *et al.*, 1981). These neurons are glutamatergic (McElligott and Spencer, 2000; Horn, 2006).

Horizontal EBN are located in the paramedian pontine reticular formation (PPRF), below and extending rostrally from the level of the abducens nucleus (Strassman *et al.*, 1986a; Horn *et al.*, 1997). They project monosynaptically to the ipsilateral abducens nucleus, and to a network of neurons in the nucleus prepositus hypoglossi (NPH) and adjacent medial vestibular nucleus (MVN) that contribute to the final common integrator's horizontal component. Bilateral chemical lesions in the PPRF selectively abolish horizontal saccades (Henn *et al.*, 1984).

Vertical and torsional EBN are located in the midbrain, in the rostral interstitial nuclei of the medial longitudinal fasciculus (riMLF) (Horn and Büttner-Ennever, 1998). They project monosynaptically to the vertical and torsional MNs, and to the interstitial nucleus of Cajal (INC), which is an important part of the final common integrator's vertical and

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Table 1 Characteristics of PBN

Premotor burst neurons (PBN)
• Name
○ Also called short-lead or medium-lead burst neurons (SLBN or MLBN)
○ Consist of excitatory (EBN) and inhibitory (IBN) units
• What
○ EBN output is the pulse of innervation for ipsilateral saccades
○ IBN output inhibits contralateral EBN and IBN and ipsilateral cMRF
○ Discharge rate is proportional to eye velocity
• When
○ PBN discharge starts 10–15 ms prior to ipsilateral saccade start
○ 50% of IBN and some EBN discharge at end of contralateral saccades
• Where
○ For horizontal saccades, EBN lie below and extend rostral to the abducens nucleus in the PPRF and IBN lie below and extend caudal to abducens nucleus in the MedRF
○ For vertical and torsional saccades, EBN lie in rostral interstitial nucleus of medial longitudinal fasciculus (riMLF) and IBN lie in the region of INC and riMLF
• Afferents
○ LLBNs excite PBN
○ OPN and contralateral IBN inhibit PBN
○ Cerebellar FNN excites contralateral IBN and EBN
• Efferents
○ Horizontal motor system
■ EBN (transmitter: glutamate) project monosynaptically to abducens nucleus motoneurons and internuclear neurons (which ascend in the contralateral MLF to the medial rectus subdivision of the oculomotor nucleus), and ipsilateral IBN
■ IBN (glycinergic) projects monosynaptically to contralateral EBN and abducens nucleus inter- and motoneurons, and to contralateral IBN
■ EBN (uncrossed) and IBN (crossed) project to neurons contributing to the neural integrator for horizontal eye movements: NPH and MVN
○ Vertical motor system
■ EBN (glutamatergic) and IBN (GABAergic) project monosynaptically to oculomotor (III) and trochlear (IV) nuclei
■ EBN and IBN project to neurons contributing to the neural integrator for vertical and torsional eye movements: INC, rostral vestibular nuclei and the cell groups of the PMT

Table 2 Characteristics of OPN

Omnipause neurons (OPN)
• Name
○ Called OPN because they are tonically active when awake but pause for saccades in all directions
• What
○ OPN monosynaptically inhibit all PBN
○ Act as a switch to change from fixation to saccade mode
○ May also modulate strength of response of PBN by providing glycine to NMDA receptors
• When
○ OPN tonic discharge stops $\sim$ 20 $\pm$ 10 ms before saccade onset and restarts $\sim$ 10 $\pm$ 5 ms before saccade end
○ Since EBN start 10–15 ms before saccade onset, OPN pause must begin $\sim$5–10 ms before EBN burst, and restart $\sim$5 ms after the EBN burst is over
○ Thus, OPNs can veto a saccade, but do not directly control starting and stopping it
• Where
○ OPN neurons all lie in nucleus raphe interpositus (RIP) in the midline pons
○ OPN dendritic arborizations cross the midline
• Afferents
○ OPN receive bilateral excitatory inputs from rostral pole of SC (fixation and small saccade zone)
○ Inhibitory inputs from LLBN
○ Inputs from frontal and supplementary eye fields, LLBN and cFN.
○ OPN also receive an inhibitory input during the course of the saccade, presumably from some type of saccade-related burst neuron
• Efferents
○ OPN (glycinergic) project monosynaptically to both horizontal and vertical EBN and IBN
○ OPN also project to spinal cord (C1–C4), perhaps to coordinate gaze control

torsional components. Bilateral chemical lesions of riMLF abolish vertical and torsional saccades (Suzuki *et al.*, 1995).

The second group of PBN consists of inhibitory burst neurons (IBN), which have a firing pattern almost identical to that of EBN (Strassman *et al.*, 1986*a*). Horizontal IBN lie in the medullary reticular formation (MedRF), below and extending caudally to the level of the abducens nucleus. The horizontal IBN are glycinergic (McElligott and Spencer, 2000), and project to several sites, but predominantly contralaterally to the abducens nucleus and horizontal EBN and IBN. They suppress activity in the contralateral PBN of the antagonist muscle, and thus may mediate Sherrington's law of reciprocal innervation.

Vertical and torsional IBN lie in the midbrain in the region of the INC and riMLF (Horn, 2006). These IBN are assumed to play a role similar to that of horizontal IBN, but for vertical and torsional components of saccades. Note that the vertical IBN are GABAergic (Spencer and Wang, 1996), whereas the horizontal IBNs are glycinergic. As discussed later, this difference may contribute to the prevalence of horizontal saccadic oscillations, because glycine is active at two receptors, an inhibitory (strychnine-sensitive) receptor and a neuromodulatory (*n*-methyl D-aspartate; NMDA) receptor (Miura and Optican, 2006).

Omnipause neurons (OPN)

OPN (Table 2) are an important element of the saccadic system, but their role is not fully understood. OPN lie close to the midline in the raphe interpositus nucleus (RIP) and their dendritic arborizations cross the midline (Büttner-Ennever *et al.*, 1999). They are glycinergic, and are presumed to inhibit PBN bilaterally in both the pons and midbrain. In an awake animal, OPN are tonically active (Strassman *et al.*, 1987). The OPN were first recognized because they pause before saccades in any direction (Keller, 1974). Robinson proposed that their function was to prevent the PBN from firing except when a saccade was called for (Robinson,

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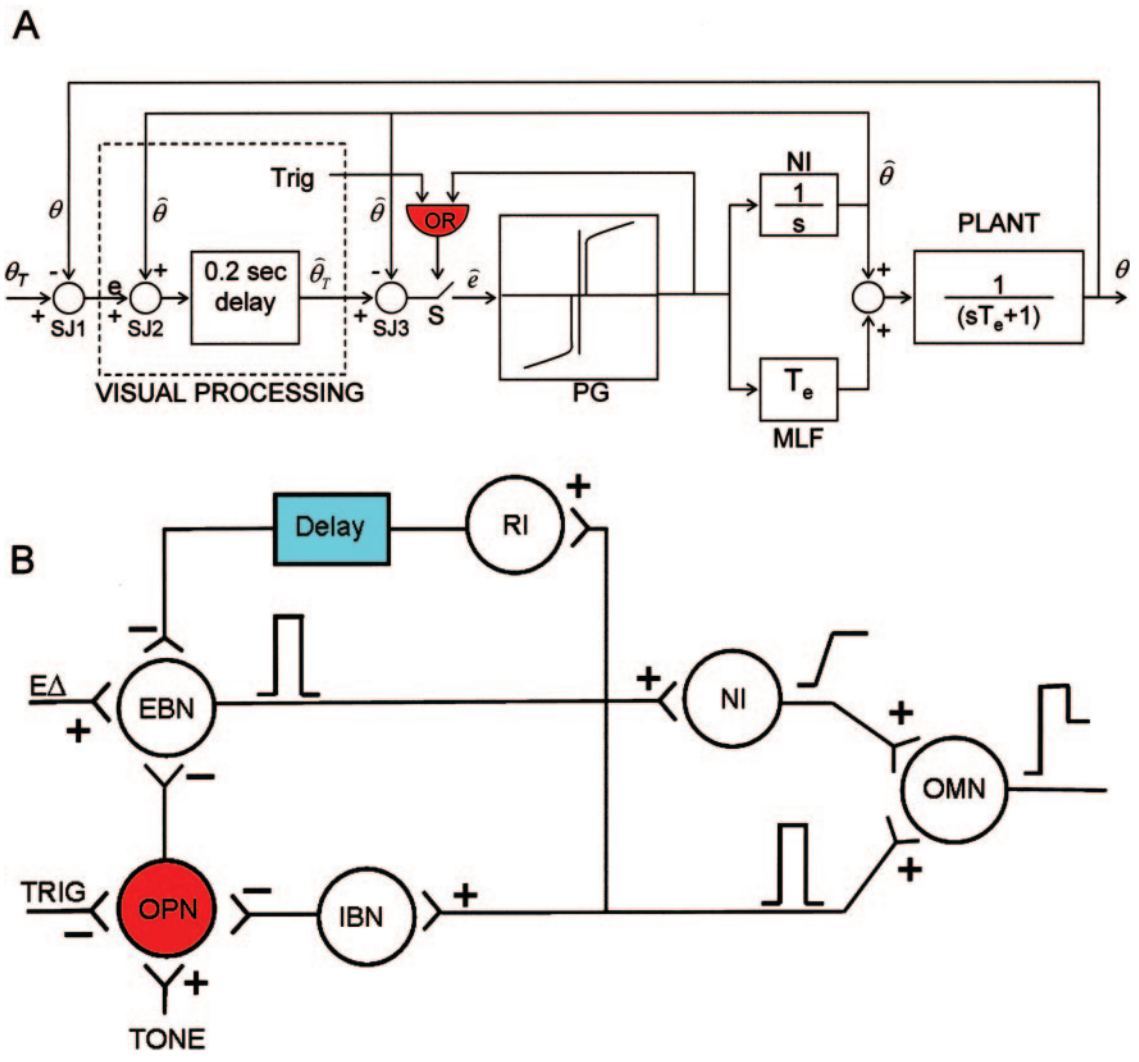

Fig. 3 Early models of the saccadic system. (**A**) A local negative feedback loop model (Robinson, 1975), which assumes that efference copy of eye position, $\hat{\theta}$, corrects retinal error, e, and recreates the central percept of the spatial location of the target, $\hat{\theta}_T$. This signal acts as the input to a bang–bang control system consisting of a high-gain saturating amplifier, PG, followed by an integrator, NI. SJ1, 2, 3 are summing junctions; suppressor switch S is normally open, unless the OR-gate (red) is activated by a trigger signal, Trig, or the PG output. MLF carries the pre-emphasis signal (or burst). The orbital dynamics are in Laplace notation and T_e is the time constant of the ocular motor plant. (**B**) Model to account for saccadic oscillations by a high-gain pulse generator with a negative feedback loop (Ashe *et al.*, 1991). The input signal to the EBN is desired change in eye position (EΔ). A trigger signal (Trig) inhibits the OPN (red), which also receive a bias signal (TONE). The output of the EBN is a pulse of innervation, which projects to ocular motoneurons (OMN), to the common ocular motor integrator (NI) that generates a step of innervation, and to the IBN. RI is the re-settable integrator with a delay (blue) interposed between its output (an internal estimate of current eye position) and an inhibitory synapse on the EBN. The IBN inhibit OPN during the saccade (NB: IBN to OPN projections have not been found).

1975). Later experiments showed that OPN performed a more complicated function than just gating saccades. Kaneko and colleagues made chemical lesions of the RIP, and found that saccades became slower, but had normal latency and accuracy (Kaneko, 1996; Soetedjo *et al.*, 2002). Miura and Optican pointed out that this could be explained if OPN were not acting as a gate, but rather as a neuromodulator to increase the responsiveness of saccade-related neurons (Miura and Optican, 2006). This role is necessary because, without it, neurons in the saccadic system would have very high gains and would be susceptible to oscillations. By increasing the gain of these neurons only before saccades, OPN could prepare the system to make a fast movement without running the risk of becoming unstable. This is also consistent with the finding that OPN are glycinergic, because their pre-saccade activity releases the agonist co-factor for NMDA channels on PBN. They do not cause a saccade, however, because the action of the glycine at the inhibitory strychnine-sensitive channels is assumed to dominate its effect at the NMDA channels.

Excitatory input to the OPN arrives from the SC and vestibular nuclei (Strassman *et al.*, 1987; Langer and Kaneko, 1990). The OPN pause ~16 ms before saccades, and resume ~15 ms before the end of saccades. Inhibitory input seems

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to show two time courses, a fast one associated with a trigger that shuts off the OPN to initiate a saccade, and a slower one that prevents the OPN from turning on again until the saccade is over (Yoshida *et al.*, 1999).

Latch-circuit neurons

The original local feedback model of the saccadic system (Robinson, 1975; Zee *et al.*, 1976) was the first that could generate the pulse of innervation needed to make a saccade and stop automatically (Fig. 3A). The main element of the local feedback model was a saturating high-gain amplifier (pulse generator; PG). A gate was needed to prevent the high-gain amplifier inside the feedback loop from oscillating. In the original model, the pulse generator neuron was inhibited by a switch cell (S in Fig. 3A), which gated the input to prevent the oscillations. To initiate a saccade, a trigger signal (Trig) of short, fixed duration would inhibit the switch cell, and the pulse generator would begin firing. As the movement progressed, the trigger input died away, but the activity of the pulse generator neuron was fed back, through an OR-gate, to keep the switch cell off until the movement was over. This gate was called a latch because once it was closed, it kept itself closed (through feedback) until the end of the saccade. When the pulse generator neuron and the trigger were both off, the suppressor cell (S) became active because of a static input Robinson called 'tone'.

Subsequent research into the brainstem cell types associated the pulse generator cells with the excitatory medium-lead burst neurons (EBN), and the suppressor cells with the OPNs. This still leaves four unanswered questions about the suppressor mechanism. (i) Why are the OPNs usually active (i.e. where does the tone come from)? (ii) What shuts them down before the saccade (what is the trigger)? (iii) What holds them off during the saccade? And, (iv) what reinitiates their activity at the end of a saccade?

We refer to the suppressor mechanism as a latch circuit, because a latch remembers its input even after the input has been removed. This requires some form of feedback to create two stable states, on and off, that are controlled by two inputs, usually called set and reset. Robinson's original gate circuit acts as a latch circuit because it feeds back the output of the pulse generator to the suppressor cell. However, it only has the set input, which is the trigger. The circuit unlatches automatically when the motor error estimate is reduced to the dead-zone (which stops the burst cell activity). The problem of making accurate saccades still comes down to how and when to restart the OPNs. A more recent hypothesis has been proposed that separates the feedback control of gaze from the latch circuit (Lefèvre *et al.*, 1998). The saccade normally ends when the ipsilateral cerebellum fires the contralateral brainstem IBNs, choking off (i.e. interrupting, stopping) the drive signal to the MNs. By making the latch circuit independent of motor error, the effect of time jitter on movement accuracy is significantly reduced. Accuracy can be maintained by the cerebellar circuit, and stability can be guaranteed as long as the OPNs reactivate soon after. A more detailed hypothesis for a latch circuit is developed below in A model of the latch circuit.

Long-lead burst neurons (LLBN)

LLBN (Table 3) are found in the brainstem and receive input from the SC and cortical areas responsible for saccades, such as the frontal eye field, parietal eye field and supplementary eye field (Scudder *et al.*, 1996*a*, *b*). Some of the LLBN probably project to the premotor burst neurons, whereas others [in the nucleus reticularis tegmenti pontis (NRTP)] project to the cerebellum. Scudder (1988) proposed a saccade model that used the LLBN as a re-settable integrator in the feed-forward path. The re-settable integrator was thought to be distinct from the common final integrator and to apply only to saccadic signals (*see below*, in Conceptual evolution of saccadic models). However, later evidence suggests that the re-settable integrator does not really exist, and that the cerebellum replaces its function (Quaia *et al.*, 1999). Thus, LLBN seem to act as a summing junction for combining saccade commands from different areas involved in the preparation for a saccade.

Eye position (tonic) neurons and the neural integrator for eye movements

Tonic (and burst–tonic) neurons carry a signal related to the step component of MNs. The step is assumed to be obtained by integrating (in the mathematical sense) velocity signals from PBN that generate the pulse of innervation (this is an oversimplification, but sufficient for our needs here). Neurons that carry an eye position, or step, signal for horizontal saccades lie in the medulla and pons in the NPH nuclei (McCrea and Horn, 2006), and adjacent MVN. Neurons that carry a vertical and torsional eye position (step) signal are present in and around the INC. In addition, the cell groups of the paramedian tract (PMT) also probably contribute to the neural integrator (Büttner-Ennever and Horn, 1996).

The mechanism that performs the integration is not well understood, although models that integrate because of reciprocal innervation (positive or negative) across the midline have been developed (Cannon and Robinson, 1985; Cova and Galiana, 1996; Arnold and Robinson, 1997), and recent work has cast light on how networks of neurons could perform this mathematical operation (Aksay *et al.*, 2005).

Curiously, when the cerebellum is lesioned the time constant of this integrator drops from ~20 s to ~2 s (Carpenter, 1972), but when the commissures connecting the left and right halves of the integrator are cut, the time constant drops below ~300 ms (i.e. only the time constant of the oculomotor plant itself is left). Thus, the integration of ocular motor signals depends on both cerebellar and

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Table 3 Characteristics of LLBN

Long-lead burst neurons (LLBN)
• Name
○ Long-lead because discharge starts long (hundreds of ms) before saccades
• What
○ May provide information on the target location in retinotopic coordinates to the PBN and cerebellum
○ May also provide a trigger signal through PBN to shut down OPN
• When
○ LLBN discharge >40 ms prior to saccade onset, with slow build-up before burst, just like build-up neurons in SC
• Where
○ Distributed throughout the brainstem reticular formation, especially in the cMRF and NRTP
• Afferents
○ SC, supplementary, and perhaps other, cortical eye fields, cerebellar FNN
• Efferents
○ LLBN (transmitter unknown) project to EBN, IBN, OPN

brainstem circuits, but their respective roles remain enigmatic.

Superior colliculus (SC)

One influence on PBN and OPN is the SC, a multi-layered structure in the midbrain. The SC is laid out in a retinotopic map (Robinson, 1972), with small contralateral movements related to activity in the rostral SC, and large contralateral movements related to caudal SC. This is true with the head fixed (eye only saccades) or free (gaze saccades, where gaze = eye + head). Neurons in the superficial layer are related to visual events, but neurons in the intermediate and deep layers are related to both visual and motor events. Schiller *et al.* (1980) showed that saccades remained accurate after SC ablation, and thus that it was not necessary for generating the pulse for saccades. Later it was also shown that ablations of the cerebellum caused persistent deficits in saccade amplitude (e.g. Optican and Robinson, 1980). Despite these early observations, until the early 1990s the SC was widely assumed to control saccadic amplitude, direction and trajectory. Many studies have since shown that the major role of the SC seems to be in selecting a target for foveation—either with saccadic or pursuit movements (Krauzlis, 2004)—initiating the movement (Bell *et al.*, 2005) and contributing to its speed (Hanes *et al.*, 2005), but does not determine amplitude, duration, direction or trajectory of the saccade.

The intermediate and deep layers of the SC contain two major types of neurons that are laid out in a retinotopic map. One type shows a target related build-up in activity (SCBUN), and a burst just before the saccade. The other bursts just before the saccade, but has no prelude of activity (SCBN). Electrophysiological studies show that both SCBN and SCBUN project from the SC to the brainstem (Munoz and Wurtz, 1993, 1995*a*). The SC projection is not uniform. The rostral half of the SC sends more fibres to the RIP (region of the OPN) than does the caudal half. The SC neurons project mostly to LLBN, and probably do not have a functional projection to PBN (Gandhi and Keller, 1997). The level of activity in the prelude of SCBUN corresponds to the likelihood that the target at that location will be the goal of a saccade (Basso and Wurtz, 1997). SC activity is also a function of retinal error, whether for a saccade or a pursuit movement (Krauzlis *et al.*, 2004).

In every experiment where the saccade goal is not the same as the visual target, such as adapted saccades (FitzGibbon *et al.*, 1986), saccades to moving targets (Keller *et al.*, 1996b), and strongly curved saccades (Port and Wurtz, 2003), the locus of activity on the SC corresponds to the visual target, and not the ensuing movement. Ablations of the SC significantly increase saccade latency and reduce peak speed, but do not affect accuracy (Hanes *et al.*, 2005). Thus, the most parsimonious interpretation of SC function is that it contributes to identifying the target (in retinotopic coordinates) that is to be foveated, generates a trigger signal to shut down the OPN, and sends a fixed-direction drive to LLBNs to begin the saccade.

Central mesencephalic reticular formation (cMRF)

The cMRF has strong, topographically organized, reciprocal connections with the SC (Cohen and Büttner-Ennever, 1984; Chen and May, 2000) and the region of the OPNs (Langer and Kaneko, 1983, 1990), and projects to the EBN and IBN in the brainstem (Büttner-Ennever *et al.*, 1999). Cells in the cMRF that are related to saccades discharge for contraversive movements, and can be divided into two groups (Waitzman *et al.*, 1996). One group has a low background rate of firing ($\leqslant$10 spikes/s), and the other, larger, group has a high background rate of firing (>10 spikes/s). Both groups start to burst ~30 ms before the saccade. Some cells have an abrupt, or clipped, end to the burst, at the end of the saccade. Indeed, burst duration in ~31% of cells in cMRF are correlated with saccade duration, ~48% with saccade amplitude, and ~58% with saccade velocity; some cells respond to two of the three metrics (Cromer and Waitzman, 2006). Lesions in the cMRF result in hypermetric contralateral saccades, reduced latency, and macrosaccadic square-wave jerks (Waitzman *et al.*, 2000). These results suggest that the cMRF is important for saccade function at both the initiation and termination stages. One possible model of their contribution is described below.

Cerebellum

A second influence on PBN and OPN is the cerebellum, which plays an important role in steering and stopping saccades, thus determining their accuracy. The posterior pole of the midline cerebellum has been most intensively studied. This region is divided into a cortical part (vermis and paravermis) and the underlying deep cerebellar nuclei (fastigial, interpositus and dentate). All relevant signals

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(e.g. eye position and velocity, target position and velocity) needed to control saccades arrive in the cerebellar cortex on mossy fibres. Climbing fibres bring a signal from the inferior olive to the cerebellar cortex. Climbing fibre activity is related to the distance to the target (motor error) at the beginning and end of a movement (Kitazawa *et al.*, 1998). The climbing fibre activity is assumed to be necessary to learn proper motor control, but its role is not well understood.

Dorsal vermis Purkinje cells (PC)

Stimulation in many parts of the cerebellum (lobes V–VII of the vermis, and the hemispheres, crus I and II) can evoke a saccade (Ron and Robinson, 1973). Stimulation of vermal lobule V evokes saccades that range from upward to horizontal, while stimulation of lobules VI and VII evokes saccades that range from horizontal to downward. The amplitude of the elicited saccade, and the amount of post-saccadic drift, depend upon the initial position of the eye in the orbit. Purkinje cells that discharge in relation to saccades are located in a more restricted region, lobes VI(c)–VII, called the oculomotor vermis (Noda and Fujikado, 1987). The oculomotor vermis projects to the caudal part of the fastigial nuclei. Purkinje cells in the dorsal vermis discharge ~15 ms before saccades in a preferred direction (Ohtsuka and Noda, 1995). Stimulation of the vermis produces saccades with an ipsilateral component (Ron and Robinson, 1973). With currents near threshold, a topographic organization is evident (Noda and Fujikado, 1987).

Fastigial nucleus neurons (FNN)

The caudal part of the fastigial nucleus (cFN) is responsible for sending saccade commands to the region of the PBN in the contralateral brainstem. FNN fire tonically with a low rate, and burst near the time of a saccade (Ohtsuka and Noda, 1991; Fuchs *et al.*, 1993). FNN fire for saccades in all directions, but electrical stimulation in the cFN elicits contralateral saccades (Noda *et al.*, 1988). The latency of the burst is a function of the direction of the movement. FNN burst before saccade start for contralateral movements, but burst near saccade end for ipsilateral movements. Thus, the same neurons are firing for ipsi- and contralateral saccades, with the only difference being that they fire later for ipsilateral saccades. This issue is addressed further in the section Cerebellar models.

Cerebrum and basal ganglia

Many areas of the cerebral cortex (e.g. frontal eye fields, supplementary eye fields, lateral intraparietal cortex) are known to be involved in identifying and selecting targets for saccades (Leigh and Kennard, 2004). The basal ganglia are involved in selecting and preventing movements, and in reward (Hikosaka *et al.*, 2000). The substantia nigra pars reticulata tonically inhibits the intermediate layers of the SC. This tonic activity can be suppressed by inhibition from the caudate nucleus, allowing a saccade. As important as they are for selecting the target for saccades, these areas do not play a role in generating the saccadic pulse itself. Thus, a discussion of their function is beyond the scope of this review.

Models for saccades

Conceptual evolution of saccadic models

In this section we present a brief history of saccadic models, beginning with the first model that was physiologically plausible. Robinson proposed that the innervation needed to make a saccade had to consist of two components: a pulse to overcome the viscous drag in the orbit, allowing for a fast movement, and a step to overcome the elastic restoring force in the orbit. Robinson proposed that the step could be computed as a function of the pulse, which simplified the problem of generating saccadic innervation to that of generating the pulse (Robinson, 1973). Furthermore, extraocular muscle proprioception, unlike skeletal muscle spindles, does not participate in a stretch reflex (Keller and Robinson, 1971). Thus, it was assumed that saccades were ballistic, i.e. their innervation was programmed before the saccade, and simply 'played out' during the movement.

Shortly after this, Zee *et al.* (1976) showed that the slow refixations made by patients with spinocerebellar disease were actually very slow saccades (*see* section Slow saccades). Indeed, these movements were so slow that visual re-afference returned in time to influence the saccadic system. They found that if the target jumped to a new location after the patient began a saccade, the eye would turn around in mid-flight and go to the new target. This demonstrated that the saccadic system was not ballistic and led Zee and Robinson (1979) to propose that the pulse of innervation was generated during the movement by an internal, or local, feedback loop based on an efference copy of eye position. This efference copy was obtained by integrating the pulse that came from the brainstem burst neurons (Zee *et al.*, 1976). This model immediately found wide acceptance because it generated both normal and slow saccades that stopped automatically (i.e. without pre-programming), and included a role for the recently discovered burst and pause neurons in the pons. An important refinement of the original local feedback loop model was made by Zee and Robinson in 1979, stimulated by an attempt to explain microsaccadic oscillations (*see* Section on high-frequency saccadic oscillations). In developing that model they used a new non-linear function to represent the activity of the burst neurons for a given motor error which is still widely used today (van Gisbergen *et al.*, 1981). To explain the small amplitude, high-frequency oscillations observed in some patients, they added a delay in the local feedback loop around the high-gain amplifier representing the burst neurons (Zee and Robinson, 1979; Ashe *et al.*, 1991; Fig. 3B).

The original version of the model had an efference copy of the eye position signal which was fed back to a

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comparator that computed the instantaneous, or *dynamic* motor error: the difference between desired eye position and current eye position. The efference copy was also used to reconstruct an internal estimate of the target's position in spatial coordinates. However, all saccade-related neurons found to date encode retinotopic error and change in eye position, not position in space. When Jürgens *et al.* (1981) found evidence for a separate neural integrator for saccades, they modified the local feedback loop model so that an efference copy of eye velocity was fed to a re-settable integrator that was reset to zero before each saccade. The output of this re-settable integrator was an efference copy of instantaneous eye displacement, which could thus be compared to a desired eye displacement signal in retinotopic coordinates. No reconstruction of target position in space was needed.

The Jürgens–Robinson model is the one from which most others have descended. Saccadic models evolved slowly after the local feedback loop was introduced. Optican and Miles (1985) introduced a third component of innervation (the slide) that was necessary to explain the transition between the pulse and the step. This led to the current concept of saccadic innervation consisting of a pulse–slide–step, with the slide and the step being automatically computed from the pulse generated by the burst neurons. Based on experimental data from the cat (Munoz *et al.*, 1991), activity in the SC during the execution of a saccade was modelled as a moving hill (Droulez and Berthoz, 1991; Lefèvre *et al.*, 1994), which was considered to represent the tracking of the progress of the fovea toward the intended target (i.e. the dynamic motor error). This and other work (Waitzman *et al.*, 1988) suggested that the saccadic feedback loop might be closed within the SC itself. However, subsequent efforts to show an error-related spread in monkeys have failed (Munoz and Wurtz, 1995*b*; Aizawa and Wurtz, 1998; Anderson *et al.*, 1998).

More recently, Guitton and colleagues have found that in a head-free animal, the locus of activity in the SC corresponds to the retinotopic location of the target, not instantaneous motor error (Bergeron and Guitton, 2002; Bergeron *et al.*, 2003). Furthermore, if multiple small steps are needed to acquire the target, the activity on the SC jumps from one locus to the next, always encoding the eccentricity of the target for the next saccade (Matsuo *et al.*, 2004). Thus, despite evidence that the SC receives some feedback about gaze movements, it does not seem to be responsible for calculating motor error during a movement.

The major problem with the Jürgens–Robinson model is that it was designed from the top down to perform an eye tracking task, and thus is not isomorphic to the brain. Many structures in the brain that are clearly related to saccades, from the cerebral cortex to the SC to the cerebellum, were not included in that model, and there is no obvious way to fit them into it. The problem of incorporating anatomical and physiological evidence into a model was addressed directly by Optican and colleagues, who took descriptions of known cell activity in different brain areas and combined them (i.e. from the bottom-up) to form a working saccadic system (Lefèvre *et al.*, 1998; Quaia *et al.*, 1999). This neuromimetic model was able to make visually guided saccades, and provided a structure for the addition of more cell types and brain areas to account for other types of saccadic behaviour. More importantly, its isomorphic design made it completely different, in both structure and signals, from the classic engineering design of target tracking systems (Optican and Quaia, 2001). The neuromimetic model has many significant structural differences from the Jürgens–Robinson model, but maintains its key element, the local feedback loop for the control of saccade trajectory (Fig. 3). However, it has no re-settable integrator, no efference copy of eye displacement, and no motor error signal. Instead, all their functions are performed by distributed networks in the brainstem and cerebellum (Optican and Quaia, 2002). The performance of that model is very good when making normal saccades. However, it contained no mechanism for restarting the OPNs, and could not explain hypometria of saccades after lesions of contralateral FN. Future models will have to resolve these problems.

Simple saccade model that can be applied to clinical disorders

Recently we developed a model of brainstem and cerebellar control of horizontal saccades that we applied to the clinical disorders that we discuss in the next section. This model was derived from the neuromimetic model of Optican's group. It included many anatomical details of the brainstem circuitry that were not known when the Jürgens–Robinson model was proposed. The brainstem circuit was based on the anatomical findings by Strassman *et al.* (1986*a*), and first represented in a saccade model of the local feedback loop proposed by Scudder (1988). The new model includes two new feedback loops, the shortest being one between the IBNs on both sides. Although the IBNs are inhibitory, their reciprocal connection creates a positive-feedback loop. The second positive-feedback loop involves EBNs and IBNs on both sides. The IBNs are prone to oscillate, because of their high sensitivity, close proximity (which gives rise to only a short delay) and reciprocal negative connections (which result in positive feedback). In his model Scudder avoided oscillations by assuming that the strength of these connections was quite low, although there is no direct evidence about their strengths.

Our new mathematical model (Ramat *et al.*, 2005) of the saccadic brainstem mechanism tries to reproduce the salient characteristics and projections of the different populations of neurons that are responsible for producing horizontal saccades from the OPN to the abducens nuclei (VI). Thus, the model represents the OPN, the bilateral EBN and IBN, and the VI nucleus including both the motor and internuclear neurons (INs; Fig 4A). Each population of neurons is modelled as a single element with lumped parameters. All neurons are modelled with a similar structure representing the membrane as a high-pass filter showing adaptation,

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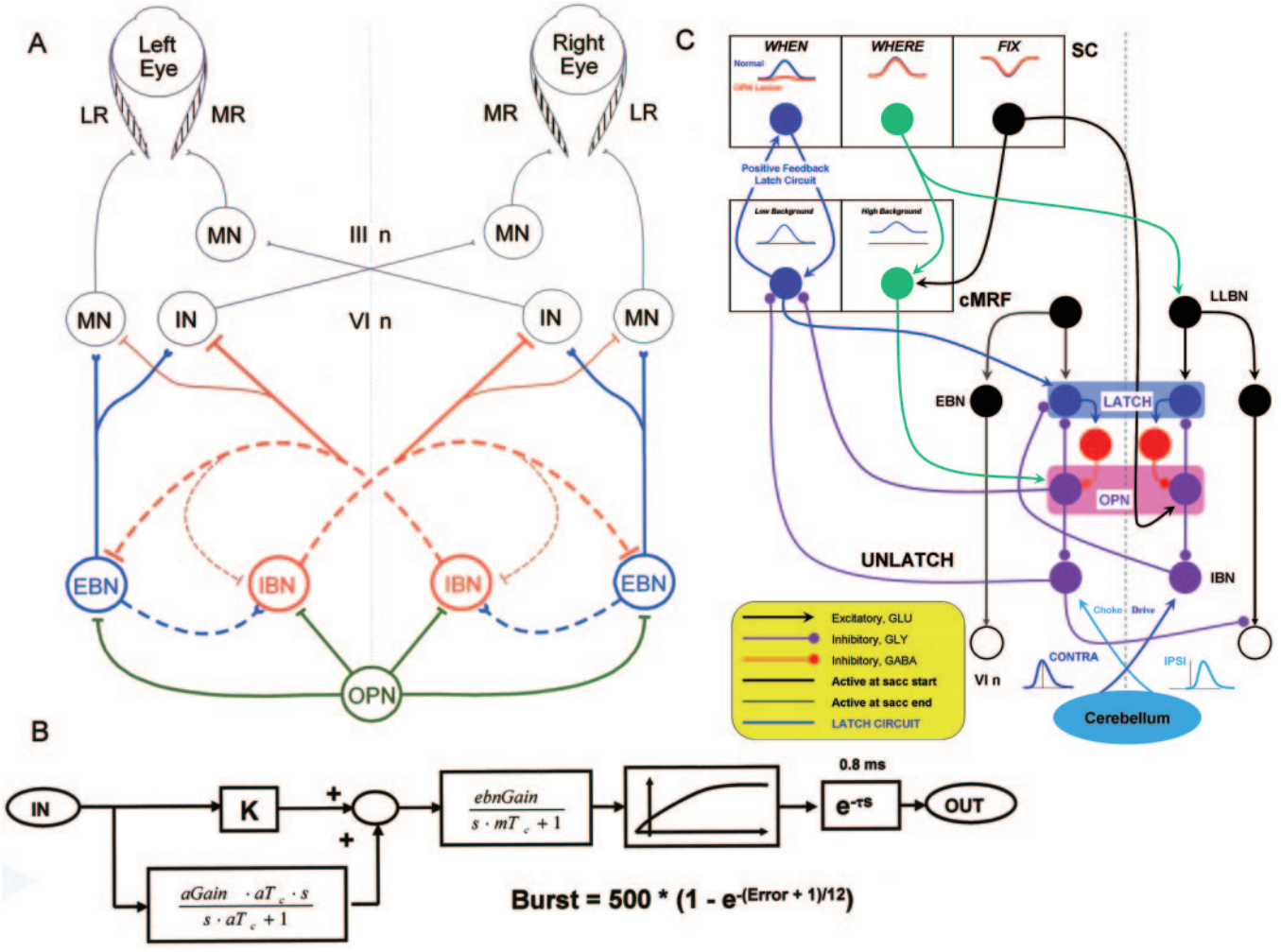

Fig. 4 (**A**) A brainstem neural network model for generation of horizontal saccades (Ramat *et al.*, 2005). Projections with flat endings are inhibitory, the others excitatory. Saccades require reciprocal innervation to the medial and lateral recti (ML and LR) of both eyes. The LR is driven by the ipsilateral abducens nucleus (VI n) MNs. The VI n also contains an IN that sends its axon via the medial longitudinal fasciculus to the contralateral III n, which drives the MR of the other eye. EBN thus provide the drive to the ipsilateral MN and IN. The EBN also project to the ipsilateral IBN. The IBN inhibit the contralateral MN and IN. Thus, an EBN/IBN pair provides reciprocal innervation to the muscles. The IBN also inhibit the contralateral EBN and IBN. A consequence of this cross-coupling is that the EBN/IBN pairs on both sides form a short-latency, positive-feedback loop. When OPN are active, they prevent this loop from oscillating. (**B**) Burst neuron model allowing post-inhibitory rebound and adaptation. The cell membrane contains a low-pass filter (time constant mT_c), and a high-pass filter in a positive feed-forward path. The gain (aGain) and time constant (aT_c) of this second high-pass filter determines the amount of post-inhibitory rebound. Burst: output non-linearity of the burst neurons; IN: input signal; K: a constant. (**C**) A latch-circuit model (Rucker *et al.*, 2005). The key to the latch model is that the SC ↔ cMRF connections form a positive-feedback loop that keeps them firing during the saccade. The output of this loop goes to latch cells (blue), which inhibit the OPN (see text for details).

followed by a non-linear saturation and a small delay (0.8 ms). The model for the EBN neurons is shown in Fig. 4B, where the output non-linearity is represented by the 'Burst' block implementing the soft saturation in Eq. 1 (Zee and Robinson, 1979).

$$B(e) = \begin{cases} B_m(1 - e^{-(e-e_0)/b}), & e > e_0 \\ 0, & e \leqslant e_0 \end{cases} \qquad (1)$$

The same structure, although with independent parameters, was used to represent the IBN.

The consequence of the membrane adaptation property is that these neurons show post-inhibitory rebound: at the offset of inhibition there is a rebound in the membrane potential that carries it to positive values, thus allowing the cell to fire one or more action potentials spontaneously. Post-inhibitory rebound is a property of some neuron types that, at the offset of hyperpolarization, produce a discharge mediated by low-threshold Ca^{2+} channels (Perez-Reyes, 2003). This implies that neurons showing this property may fire a train of action potentials when they are abruptly disinhibited, even without an input actively driving the cell.

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Post-inhibitory rebound in the saccadic burst neurons was first introduced by Enderle and Engelken (1995) who suggested that it is the only mechanism needed for generating saccades. A later model combined the post-inhibitory rebound with excitatory input from LLBNs to generate saccades (Miura and Optican, 2006).

The circuitry that moves the eye horizontally is represented in black in Fig. 4A, including the lateral and medial rectus muscles, the adducting MNs in the III nuclei, the abducting MNs and IN in the abducens nuclei, and their projections. The input driving saccades is provided by the ipsilateral EBN (shown in blue in Fig. 4A), which project to both the abducens MN and abducens IN, the latter in turn projecting across the midline to the contralateral IIIn. The IBN, shown in red in Fig. 4A, are excited by the ipsilateral EBN and inhibit the contralateral VIn and PBN.

The interconnections between burst neurons form two positive-feedback loops: one short loop is formed by the IBN neurons reciprocally inhibiting each other on the two sides of the midline; the other involves both EBN and IBN bilateral groups. This longer loop is provided by the excitatory projection of EBN onto ipsilateral IBN, which in turn inhibit the contralateral EBN which excite the ipsilateral IBN, which cross back to inhibit the originally firing EBN. This organization, which was anatomically identified (Strassman *et al.*, 1986*a*), implements Sherrington's law of reciprocal innervation (contraction of agonist while ensuring the inhibition of antagonist muscles), and favours the fast build-up of EBN discharge (Strassman *et al.*, 1986*a*).

When a desired eye position signal coding for a rightward saccade excites the right EBN, it projects both to the ipsilateral VI nucleus and to the ipsilateral IBN. The excitation of ipsilateral IBN inhibits the contralateral VI, the contralateral EBN and the contralateral IBN. Therefore the inhibitory action of this contralateral (left) IBN group is reduced, both directly via the IBN–IBN projection and indirectly since the inhibition of the (left) EBN in turn reduces the (left) IBN excitation. The left IBN's inhibition disinhibits the right IBN, thus closing the short positive-feedback loop from IBN to IBN, and disinhibits the right EBN, thus closing the second positive-feedback loop involving EBN and IBN bilaterally.

The OPN (shown in green in Fig. 4A) project to all four groups of burst neurons, tonically inhibiting them except during saccades in all directions (Keller, 1974), blinks (Hepp *et al.*, 1989, Mays and Morrisse, 1995), and to some extent during vergence (Busettini and Mays, 2003).

In addition to the described structures and connections, the suggested mathematical model includes a 'desired eye position' input to the saccadic mechanism, turning off the OPN when a saccade is programmed, and a local feedback loop responsible for turning off the saccades once the eyes are on target (Ramat *et al.*, 2005).

In humans, the mechanism generating saccades is potentially unstable due to the high-gain of the output non-linearity of the burst neurons and to the positive-feedback loops coupling EBN–IBN and IBN–IBN. If the burst neurons are not inhibited by the OPN and are not driven to produce a saccade, such latent instability may lead to high-frequency, conjugate oscillations of the eyes composed of back-to-back saccades occurring without intervening periods of steady fixation (*see* section High-frequency saccadic oscillations). Such a condition may occur during blinks, saccade-vergence interactions, and orthogonally directed saccades.

In fact, OPN pause for saccades in any direction and thus release all populations of PBN, although the saccade may have only one component, e.g. the OPN shut off for a vertical saccade, disinhibiting both the vertical and horizontal PBN. The vertical EBN will be driven to produce a vertical saccade, while the horizontal EBN will not receive any driving input. Yet, the offset of the OPN hyperpolarization will produce post-inhibitory rebound in both horizontal IBN and EBN on both sides of the midline, causing these cells to simultaneously fire a few action potentials. Any imbalance in the circuit will allow one side to prevail and a periodic oscillation will ensue. Suppose that the right EBN produces a few spikes from post-inhibitory rebound. They will drive the right IBN which will inhibit the left EBN and the eyes will move to the right. Because of the fast decay (adaptation) of the post-inhibitory rebound in the right EBN, the left EBN will be disinhibited and will in turn show a post-inhibitory rebound, driving the left IBN, in turn inhibiting the right EBN and moving the eyes to the left. As the post-inhibitory rebound in the left EBN is extinguished, the process repeats itself until the OPN are turned back on after the vertical saccade is over.

Cerebellar models

All fibres coming to the cerebellar cortex also deliver a branch to the corresponding deep nuclei (e.g. both vermis and FN). Currently, there are two types of cerebellar models. The first type learns (because of association with climbing fibre activity) to activate an output fibre at some time after an input fibre discharges. These models are always 1D, and cannot be extended to deal with multidimensional problems. The second type is pre-wired to perform certain hypothetical functions, such as initializing the locus of activity on the vermis and updating that locus based on velocity feedback information (Optican and Quaia, 2002). These models are helpful in understanding control of saccade trajectory, but do not provide insights into how the cerebellum could develop a network with such a function.

The mossy fibre inputs to the cerebellum carry signals from the brainstem LLBNs in the NRTP. The NRTP receives inputs from the SC and the FN itself. Neurons in the cFN discharge about 8 ms prior to onset of saccades with contralateral components, but generally towards the end of saccades with ipsilateral components. A major mystery of the cerebellum is how does the output from the ipsilateral FN fire later than its inputs, i.e. near the end of the saccade? One interpretation (Lefèvre *et al.*, 1998; Quaia *et al.*, 1999)

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is that the cerebellum, through the FNN, controls the trajectory and endpoint of a saccade. The difference in latency between ipsi- and contralateral FNNs breaks the symmetry between the projections from the cFN to the PBN in the brainstem. For example, for a rightward saccade, the left FNN excite both the IBN and EBN on the right side (Fig. 4C). The IBN on the right then inhibit the EBN and IBN on the left side, allowing the eye to move to the right. At the end of the movement the right-side FNN fire, exciting both the IBN and EBN on the left side. However, the IBN on the right side are already inhibiting the PBN on the left. If we assume that the FNN excitation to the IBN, but not the EBN, overcomes the inhibition from the right IBN, then the IBN on the left will shut down the EBN on the right, stopping the saccade.

Optican and colleagues have proposed a theory to account for this experimental result (Lefèvre *et al.*, 1998; Quaia *et al.*, 1999; Optican and Quaia, 2002; Optican, 2005). In this theory the role of the cerebellum in movement control is 2-fold. First, it recognizes from the sensory, motor and behavioural context what its contribution to the movement should be (determined by learning from experience). Second, it integrates velocity feedback information to obtain instantaneous displacement information (thus performing a role equivalent to the resetting integrator in the Jürgens–Robinson model) and modifies the saccade drive signal to compensate for errors. The integration in their model is performed by updating the locus of activity in the cerebellar cortex, giving the appearance of a wave of activity that spreads from the contralateral to the ipsilateral side during a saccade. This causes the difference in latency of the ipsi- and contralateral FNN observed during eye and gaze saccades (Optican, 2005). No evidence for this wave has been found yet, but the wave idea is not central to the cerebellar hypothesis. Any mechanism, such as a population of neurons with varying thresholds, that can perform the integration with an appropriate delay on both sides of the midline would be sufficient.

A model of the latch circuit

Having described features of models for PBN, OPN, SC and cerebellum, we are now in a position to return to the latch circuit for saccades. A schematic diagram of a proposed latch circuit model (Rucker *et al.*, 2005) for a rightward saccade is shown in Fig. 4C (the model is symmetric, but many elements and pathways have not been drawn to emphasize crossover of activity from one side to the other during the movement). This new proposal differs from previous latch circuits because it is bistable, requiring both a set and reset command. The set command turns on reciprocal excitation between a subset of SC and cMRF neurons, and the reset command breaks that positive-feedback loop. We thus need two types of neurons in the SC, one which serves as part of the latch circuit, and one that sends information about the selected target to the brainstem. In Fig. 4C, the 'When' and 'Where' cells are two hypothetical sub-classes of SCBN. They correspond to two groups of SC cells, one that loses activity (blue versus red trace for 'When' cells), and one that does not (red and blue trace overlap for 'Where' cells), after OPN lesions (Soetedjo *et al.*, 2002). Correspondingly, cMRF cells can be divided into two groups, one that receives 'When' cell activity and participates in the latch (which may be the cMRF cells related to saccade duration, presumably those having a low background rate), and one that relays target information to the brainstem, which may be the cMRF cells related to saccade amplitude and/or velocity, presumably those having a high background rate (Waitzman *et al.*, 1996; Cromer and Waitzman, 2006). The SC fix cells and the high background cMRF cells excite the OPNs, keeping them on between saccades.

In this model, the rapid offset of the OPN before a saccade is caused by a burst in the EBN-like latch cell (Keller and Missal, 2003), which is driven by the low background cMRF cells. The key to the latch model is that the SC↔cMRF connections form a positive-feedback loop that keeps them firing during the saccade, with no other input. The output of this loop goes to latch cells, which inhibit the OPN (through a GABAergic interneuron, shown in red). That loop continues firing until the ipsilateral (right side for a rightward saccade) fastigial output of cerebellum fires the contralateral (left) IBN cells, which are the choke for the ipsilateral (right) EBNs. In addition, those (left) IBN send a unilateral projection to the cMRF on the same side (Strassman *et al.*, 1986*b*). This inhibits the low background cMRF cells, breaking the positive feedback loop and acting as the reset signal for the latch. These cells would correspond to the duration-related, clipped cells found in the cMRF (Cromer and Waitzman, 2006). In the model, the rapid onset of the OPNs is caused by excitatory inputs from the SC (FIX) and cMRF (high background).

Clinical disorders of the saccadic system and the development of models

Slow saccades

Clinical features of slow saccades

Several clinical disorders cause a marked slowing of saccades that can easily be detected at the bedside. Slow saccades are caused by diseases affecting the extraocular muscles or their cranial nerve supply; by brainstem stroke; and by a number of genetic and degenerative diseases, such as the spinocerebellar ataxias (SCAs), Huntington's disease, and progressive supranuclear palsy (PSP), which affect neurons throughout the brainstem and cerebellum (Leigh and Zee, 2006).

The first example (Fig. 5A) is of a patient who developed slow saccades following cardiac surgery (Tomsak *et al.*, 2002). Both horizontal and vertical saccades were very slow, and vestibular quick phases were essentially absent. Other types of eye movement, including smooth pursuit and the vestibulo-ocular reflex, were normal. The precise cause

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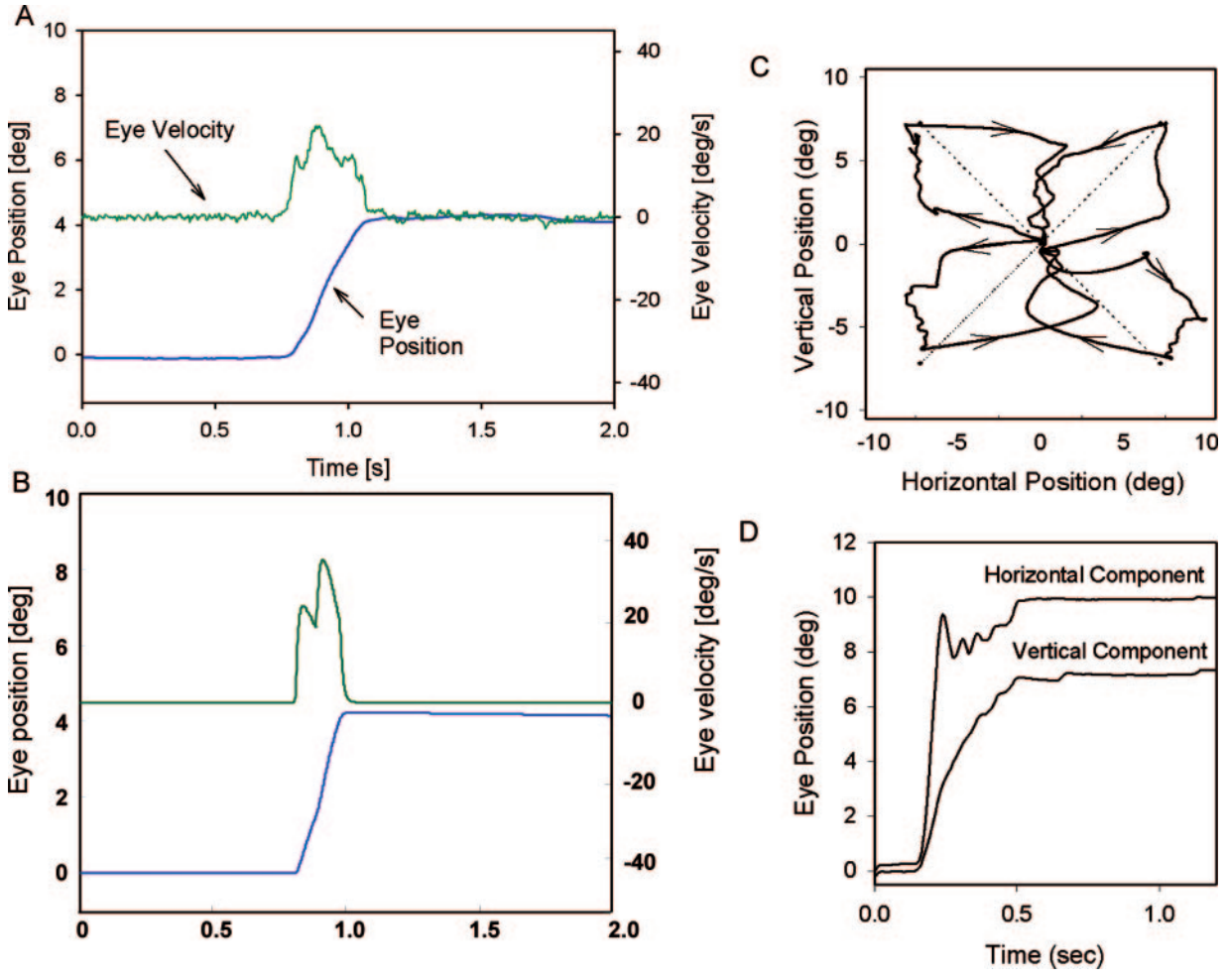

Fig. 5 (**A**) Representative example of a slow horizontal saccade in a 54-year-old man. His saccadic disorder developed following cardiac valve replacement surgery, presumably due to brainstem ischaemia. Main-sequence plots compare his saccades with normal subjects in Fig. 1E. Note that several saccadic pulses are apparent as multiple peaks within the velocity waveform. (**B**) Simulation of a slow saccade (same colours as for A). Note that the simulated slow saccade is faster and briefer than the example in **A**, and shows only two velocity peaks (**C**) Comparison of trajectories of oblique saccades made to and from four target positions starting at primary position in a patient with Niemann-Pick type C disease, who showed a selective slowing of vertical saccades (Rottach *et al.*, 1997). Arrowheads indicate the direction of the eye movement. The trajectory of the target jump is shown as a dotted line. The trajectories of the patient's saccades are strongly curved, reflecting the initial, faster, horizontal component and the later, slower, vertical component. (**D**) Time plot comparing horizontal and vertical components of an oblique saccade made by the patient with Niemann-Pick type C disease. Horizontal oscillations occurred after the horizontal component had ended, but while the vertical component was still ongoing.

of the deficit in this patient is unknown. However, a similarly affected patient died of a post-operative infection, and subsequent examination of his brainstem showed neuronal loss and gliosis mainly confined to the paramedian pons, in an area that included both OPN and the EBN for horizontal saccades; the midbrain was spared (Hanson *et al.*, 1986).

This example indicates one difficulty posed by clinical studies. The videos and eye movement recordings from these two patients with saccadic palsy following cardiac surgery were similar, but only one patient had a post-mortem study providing anatomical details of the lesion. Based on the clinical similarity of the behavioural findings, one would like to infer that patients who develop selective saccadic palsy following cardiac surgery have the same lesion. However, only by comparing many studies, including neuropathological findings, can we make a reasonable inference about cause and effect. In fact, patients who develop saccadic palsy following cardiac surgery do show some differences; for example, sometimes only vertical saccades are slow (Tomsak *et al.*, 2002). Models aid such comparisons between different individuals because they can summarize the results of each patient studied in a consistent and quantitative way.

Selective slowing of either horizontal or vertical saccades is also described in other conditions. Thus, Niemann-Pick type C disease, a genetic disorder in which sphingolipid is

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deposited mainly in the midbrain, affecting the riMLF (Solomon *et al.*, 2005), causes selective slowing of vertical saccades (Rottach *et al.*, 1997); horizontal saccades may lie within the normal range for the amplitude—peak velocity relationship. Consequently, when such patients are asked to make diagonal saccades, the trajectories of these movements are strongly curved (Fig. 5C). Furthermore, after the horizontal component is completed the eye oscillates horizontally until the slower vertical component is completed (Fig. 5D). The significance of these oscillations is discussed below. Selective slowing of horizontal saccades occurs in SCA2; these patients also show curved trajectories of saccades made to diagonal target displacements (Leigh and Zee, 2006).

Questions posed by slow saccades

Slow saccades raise many interesting questions: how do current hypotheses account for slow saccades and what are the implications of slow saccades for these models? Why do midbrain lesions slow only the vertical component of saccades, whereas paramedian pontine lesions either slow horizontal saccades selectively or slow both horizontal and vertical saccades? What is the mechanism that slows saccades in these disorders? The utility of models comes in their ability to provide a framework for answering these questions. Sometimes, this requires modifying the model, creating a synergy between basic and clinical research.

Influence of slow saccades on models

As noted in the section Conceptual evolution of saccadic models, an early example of translation from 'bedside to bench' in the saccadic system was a study of patients with slow voluntary gaze-shifting eye movements (Zee *et al.*, 1976); their nystagmus quick phases were also either slow or absent. One compelling observation was that these patients' eye movements could turn around in mid-flight to follow a target that jumped away and then back. At first it was not known what type of movements these were, although two types of eye movements were suspected, smooth pursuit and saccades. The speed of smooth pursuit movements is proportional to target speed, and thus has no characteristic main-sequence relationship for speed versus amplitude. Furthermore, most subjects cannot voluntarily generate pursuit movements in the absence of a moving target. How, then, could these patients generate voluntary pursuit to a jumping target? In contrast, saccades can be generated voluntarily, even when there is no target. Also, saccade speeds are characteristically related to saccade amplitude by a main-sequence relationship that is shared with the quick phases of vestibular nystagmus. However, at that time saccades were believed to be ballistic and thus not responsive to jumps in the target occurring after the saccade was 'launched'.

It was finally concluded that these slow movements were abnormally slow saccades because they were voluntary, had a characteristic, if slow, relationship between amplitude and peak velocity (Fig. 1E), slowing was different in different directions, and quick phases in the dark were affected in the same way (Zee *et al.*, 1976). Thus, these movements were like normal saccades but 'worse'. If they were pursuit movements, the lesion would have made them 'better' than normal, because they could now be made to a jumping target and in the dark during nystagmus.

This slow saccade hypothesis has subsequently received several lines of support. First, slow saccades have been produced experimentally by injecting lidocaine into the PPRF (Barton *et al.*, 2003), which is known to be related to saccade, but not pursuit, generation. Second, it has been confirmed that patients can make a continuous saccade that turns around in mid-flight to follow a jumping target (MacAskill *et al.*, 2000). Even normal subjects can generate saccades that turn around in mid-flight, if the target jumps are large enough ($\sim 60^\circ$) and timed correctly (Becker and Jürgens, 1979). At the time, this finding was quite a surprise, because it called into question current models of the saccadic system as a ballistic, sampled-data system (i.e. visual information was only available at certain times). Instead, it suggested that visual information was available at all times, and that saccades were under continuous control (i.e. not pre-programmed). These arguments led to the local feedback loop model of saccades (Robinson, 1975; Zee *et al.*, 1976).

One drawback of the seminal model of Zee *et al.* was its prediction that the brain kept track of target position in space, whereas all known neurophysiological evidence only supported target position in retinotopic coordinates. Another study of saccade-slowing provided an alternative hypothesis. Jürgens *et al.* (1981) found that wide variations in saccade velocity, even those produced by administering the drug diazepam, were compensated by the local feedback loop. The effect of diazepam on the time constants of the ocular drifts led them to propose that the feedback loop should operate on changes in eye position, rather than eye position itself, which required a second, re-settable integrator in the local feedback loop. This version of the model eliminated the internal signal related to target position in space, which is a good thing, because in over 30 years no such signal has ever been discovered.

One potentially confusing issue is why either experimental inactivation (Kaneko, 1996; Soetedjo *et al.*, 2002) or clinical lesions (Hanson *et al.*, 1986) involving OPN cause slowing of both horizontal and vertical saccades. As noted above in the section Brainstem reticular formation, OPN are glycinergic, and inhibit the PBN during steady fixation through strychnine-sensitive glycine receptors. However, glycine can also act as a neuromodulator, enhancing the effect of glutamatergic NMDA channels (Ahmadi *et al.*, 2003; Miura and Optican, 2006), thereby amplifying the input signal from LLBN. Furthermore, PBN may show post-inhibitory rebound depolarization at OPN offset, which could account for a large part of the saccadic acceleration (Ahmadi *et al.*, 2003; Miura and Optican, 2006). Therefore,

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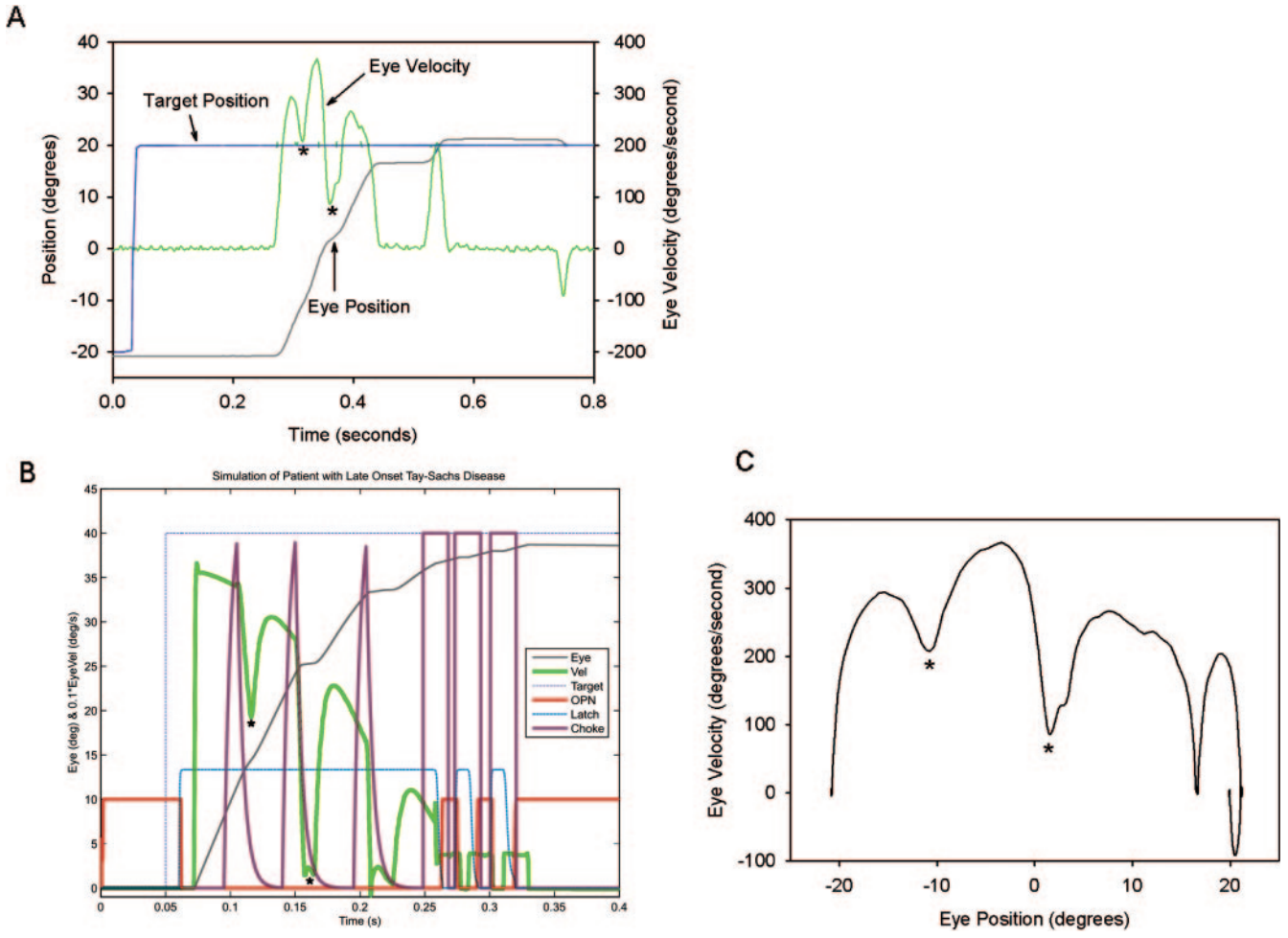

Fig. 6 (**A**) Representative record of horizontal saccade made by a patient with late-onset Tay-Sachs disease. The velocity record (green) shows saccades with transient decelerations during which eye velocity declines (indicated by asterisk), but not to zero, and then increases again. Thus these saccades appear to stutter. Clinically, only minor changes in saccades can be noticed. (**B**) Model simulation of an interrupted saccade, using the model shown in Fig. 4C (Rucker *et al.*, 2005). (**C**) A phase plane of the same response shown in A, with eye velocity plotted against eye position. The asterisks correspond to points at which velocity abruptly decreased, but did not go to zero.

when OPN lesions remove glycine from PBN dendrites and eliminate post-inhibitory rebound, the remaining trigger signal from LLBN produces only modest eye acceleration, resulting in a slow saccade. Thus, in the recently suggested neuromimetic model, saccade-slowing can be explained based on the membrane properties of the burst neurons, considering that the lack of disinhibition from the OPNs removes the additional currents from T and NMDA channels (Miura and Optican, 2006).

Use of our model to simulate slow saccades brings out another interesting point about slow saccades. Note how the velocity waveform of the patient's slow saccade (Fig. 5A) appears as a series of velocity peaks, rather than a single peak with a smooth waveform. This behaviour can be simulated (Fig. 5B) by turning off the OPN but delaying the change of eye position command by 80 ms. Thus, the post-inhibitory rebound depolarization due to cessation of omnipause neuron discharge occurred too early. This simple attempt to simulate slow saccades raises further issues that require study with experiments and models.

Answers from models

Slow saccades were discovered at the bedside, and were critical to discovering that the pulse of innervation needed to make a saccade is generated by a local feedback loop. That model of the saccadic system has been so well studied that it can now provide many answers which may be of benefit clinically. First, the model explains why saccades are slow, either because EBN are directly affected, or because OPN are lost, indirectly slowing EBN firing. Second, the model explains why some lesions affect only vertical or horizontal movements, whereas others affect both. Lesions in the midbrain may destroy EBN that provide the vertical saccadic drive. In contrast, lesions in the pons may either destroy EBN that provide the horizontal saccadic drive, or destroy the OPN, removing the glycine needed to make fast

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horizontal and vertical saccades. Thus, the model can be of use in diagnosis to localize the site of the lesion based on the distribution of saccade deficits.

Premature termination of saccades

Clinical features of 'stuttering' or transiently decelerated saccades

A second clinical abnormality of saccades is a premature, transient deceleration (but not enough to stop the eye) followed by the successful resumption of the original movement. Normal subjects make a single saccade of ~90–100% of the eccentricity of the target. These saccades have smooth velocity profiles that are bell-shaped for small movements, but progressively positively skewed for larger movements (Fig. 1C). Occasionally, normal subjects show transient decelerations during large saccades (Abel *et al.*, 1987), but the effect is much more marked in disease states.

In late-onset Tay-Sachs disease (LOTS) (Rucker *et al.*, 2004) the velocity waveform shows one or more transient decelerations (Fig. 6A), although the effect is difficult to discern at the bedside. This disorder diffusely affects brainstem and cerebellar regions important in the control of saccades. In the mouse model of LOTS, cerebellar granule and Purkinje cells are mainly affected but there is also some involvement of brainstem nuclei that are less well described (Jeyakumar *et al.*, 2002).

The velocity waveforms shown in Fig. 6A suggest the presence of two or more saccadic pulses. Analysis of such saccades has proved difficult using the conventional approach of defining saccade start and end on the basis of a velocity threshold, because these transient decelerations may not reduce eye speed <50°/s. An alternative approach is to use peak eye velocity as a measure of the saccadic pulse size, and the period between peak acceleration and peak deceleration as a measure of saccadic pulse width. Another method is to use phase planes (i.e. plotting eye velocity versus eye position; cf. Fig. 6C). Patients with LOTS show smaller pulse widths, and greater decelerations than controls, implying that the saccadic burst has been prematurely terminated (Rucker *et al.*, 2004). These velocity waveforms are reminiscent of the effects of experimental electrical stimulation of OPN in monkeys, which can also briefly interrupt a saccade (Munoz and Wurtz, 1993; Keller *et al.*, 1996*a*; Gandhi and Keller, 1999).

Questions posed by stuttering saccades

What causes the premature, transient decelerations of saccades in LOTS? Where is the mechanism that stalls saccades in mid-flight? Is therapy possible for stuttering saccades in LOTS?

Influence of stuttering saccades on models

There has been little transfer of these clinical results to the 'bench'. In the local feedback loop hypothesis (*see* above) it was implicit that saccades would end when the error signal went to zero and the OPN restarted. However, this turns out not to be the case because, at least in cats, the eye can stop even if the OPN are still off (Paré and Guitton, 1998). Thus, study of prematurely decelerated saccades is critical to improving our understanding of how saccades end. When the anatomy of the brain defects is better known, hopefully it will provide some insight into the latch circuit and the source of the tonic input to the OPN.

Answers from models

Abrupt, partial decelerations indicate that the output of the EBN neurons is suddenly decreased. EBN output could be decreased if the excitatory input to the EBN were reduced. This explanation seems unlikely, because after the deceleration the saccade continues to the original target. If the EBN lost their input, another mechanism would have to restore it. Instead, our understanding of the saccadic system from basic research suggests two different ways to interfere with EBN output by changing their inhibitory inputs.

The original local feedback model needed a 'latch circuit' to hold off OPN until the saccade was completed (Robinson, 1975). The electrophysiological basis for such a circuit only became evident with the report by Keller (1974) of neurons in the PPRF that had the required properties of latch neurons (*see* Table 4). A prototype of a possible latch circuit is sketched out in Fig. 4C and described in more detail in the section Latch-circuit neurons. Interference with this latch circuit could cause the OPN to turn back on prematurely (Rucker *et al.*, 2004). The OPN would inhibit the EBN, and cause the eye to decelerate. However, this is not a simple explanation for the stuttering saccades seen in disease, because another mechanism would be needed to shut off the OPN again, and allow resumption of the saccade to the original target. A more significant problem with this hypothesis is that the OPN project to many places in the brain and spinal cord, not just to the EBN in the pons and midbrain. Thus, prematurely restarting the OPN might simply reset the saccadic system and stop the saccade altogether.

Another possibility is that the choke signal, from deep cerebellar nuclei through the IBN, could turn on prematurely (Rucker *et al.*, 2005). All the burst and tonic signals needed to make the contralateral cerebellar output at the start of a saccade arrive on the mossy fibres, which project bilaterally to the deep cerebellar nuclei. Thus, one can view the role of the cerebellum in the neuromimetic model as holding off the output of the ipsilateral cerebellum (going to the antagonist IBN) until the end of the saccade. For example, for horizontal saccades this requires that the Purkinje cells in the ipsilateral vermis inhibit the ipsilateral fastigial nuclei. Loss or dysfunction of cerebellar Purkinje cells might allow the fastigial cells to start the antagonist IBN prematurely. These IBN would inhibit the agonist EBN and IBN, but might not restart the OPN. Because there is still a large drive to the agonist PBN, it would be possible for them

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Table 4 Characteristics of LCN

Latch-circuit neurons (LCN)
• Name
○ Refers to an electrical circuit which, once set, stays on until it is reset.
• What
○ LCN burst during saccades, and may keep OPN off until saccade end
○ LCN also discharge for smooth pursuit
• When
○ LCN discharge ~17 ms prior to saccade onset;
• Where
○ Identified in the PPRF
○ Similar neurons may exist in INC
• Afferents
○ Unknown, but it is postulated that LCN receive inputs from EBN as well as smooth-pursuit signals
• Efferents
○ LCN (transmitter unknown) are postulated to project to OPN

to restart, reciprocally inhibiting the antagonist PBN. This oscillation between the PBN on the two sides would result in the velocity stutter. A simulated response based on this hypothesis (summarized in Fig. 4C) is shown in Fig. 6B. Although the mechanism of stuttering saccades in LOTS remains unknown, the strength and frequency of the 'stutter' may serve as a therapeutic index for any new treatments given to affected patients.

High-frequency saccadic oscillations

Clinical features of high-frequency saccadic oscillations

A striking clinical disorder of eye movements is opsoclonus (Fig. 7A). This consists of bursts of high-frequency oscillations of the eyes that have horizontal, vertical and torsional components. When such oscillations are confined to the horizontal plane, they are called ocular flutter. Affected patients may complain of oscillopsia (illusory motion of the visual world) and vertigo. Both flutter and opsoclonus are thought to be saccadic in origin because they conform to the main-sequence relationship (Ashe *et al.*, 1991; Bhidayasiri *et al.*, 2001). Thus, each burst of oscillations consists of a series of back-to-back saccades that lack an intersaccadic interval. In some patients, the oscillations are small but, if sustained (Fig. 7B), may still cause visual symptoms (Ramat *et al.*, 2005). In fact, high-frequency conjugate oscillations commonly occur in normal subjects but they are brief, small amplitude, and usually occur with another eye movement. For example, normal subjects may show transient small oscillations, usually horizontal in direction, during saccade-vergence movements, large vertical saccades (Fig. 7C), or with blinks. Some individuals can generate similar conjugate oscillations with a convergence effort—'voluntary flutter' (Ramat *et al.*, 2005).

Since opsoclonus and flutter appear to be saccadic in origin, it was postulated that the OPN should be targeted in these disease processes (Zee and Robinson, 1979). However, neuropathological evidence to support this hypothesis is lacking (Ridley *et al.*, 1987). Alternatively, it has been proposed that delaying, and increasing the gain of, the output signal of the saccade generator as it passes through the cerebellum may be responsible for these oscillations (Wong *et al.*, 2001). However, a patient with a surgical lesion affecting the cerebellar fastigial nuclei, which was evident on MRI and manifest by marked saccadic hypermetria, still showed high-frequency oscillations during saccade-vergence movements (Ramat *et al.*, 2005).

The two most common diseases causing opsoclonus and ocular flutter are viral encephalitis and cancer (as a remote effect of lung or ovary cancers in adults and neuroblastoma in infants) (Bataller *et al.*, 2001). In patients with saccadic oscillations in association with cancer, it is postulated that the body's immune response against the tumour also affects a receptor protein in the brain. Patients with opsoclonus have clinical evidence of cerebellar ataxia, and one fMRI study demonstrated activation of the fastigial nuclei (Helmchen *et al.*, 2003), although this could simply reflect the increased saccadic activity. Recently, a family with high-frequency saccadic oscillations has been described, raising the possibility that a genetic disorder affecting membrane properties of brainstem neurons (IBN and/or OPN) could be responsible (Ramat *et al.*, 2005).

Questions posed by high-frequency saccadic oscillations

What insights do high-frequency oscillations provide for saccadic models? What causes these high-frequency oscillations? Are the small, medium and large oscillations caused by three different failures, or might there be a common cause? What pharmaceutical drugs might be useful in minimizing these oscillations?

Influence of high-frequency oscillations on saccadic models

Saccadic oscillations have been studied for a long time, and were the second abnormal eye movement to be modelled (after slow saccades). Thus, an early proposal (Fig. 3B) was that a delay in the local feedback loop governing burst neuron discharge—a high-gain amplifier—caused oscillations (Zee and Robinson, 1979). A later model proposed that saccades were governed by feedback through the FN of the cerebellum (Lefèvre *et al.*, 1998; Quaia *et al.*, 1999), leading to the suggestion that opsoclonus may be explained by abnormal feedback through this cerebellar loop (Wong *et al.*, 2001). One prediction of this model is that lesions of the cerebellum should result in saccades that do not stop in time and, consequently are too big (hypermetric). Experimental lesions confirm that cerebellar lesions involving the FN do result in hypermetria (Optican and Robinson, 1980; Robinson *et al.*, 1993). A second prediction of this model is that, since saccadic oscillations are due to a delay in the feedback loop, lesions of the FN should also eliminate saccadic oscillations.

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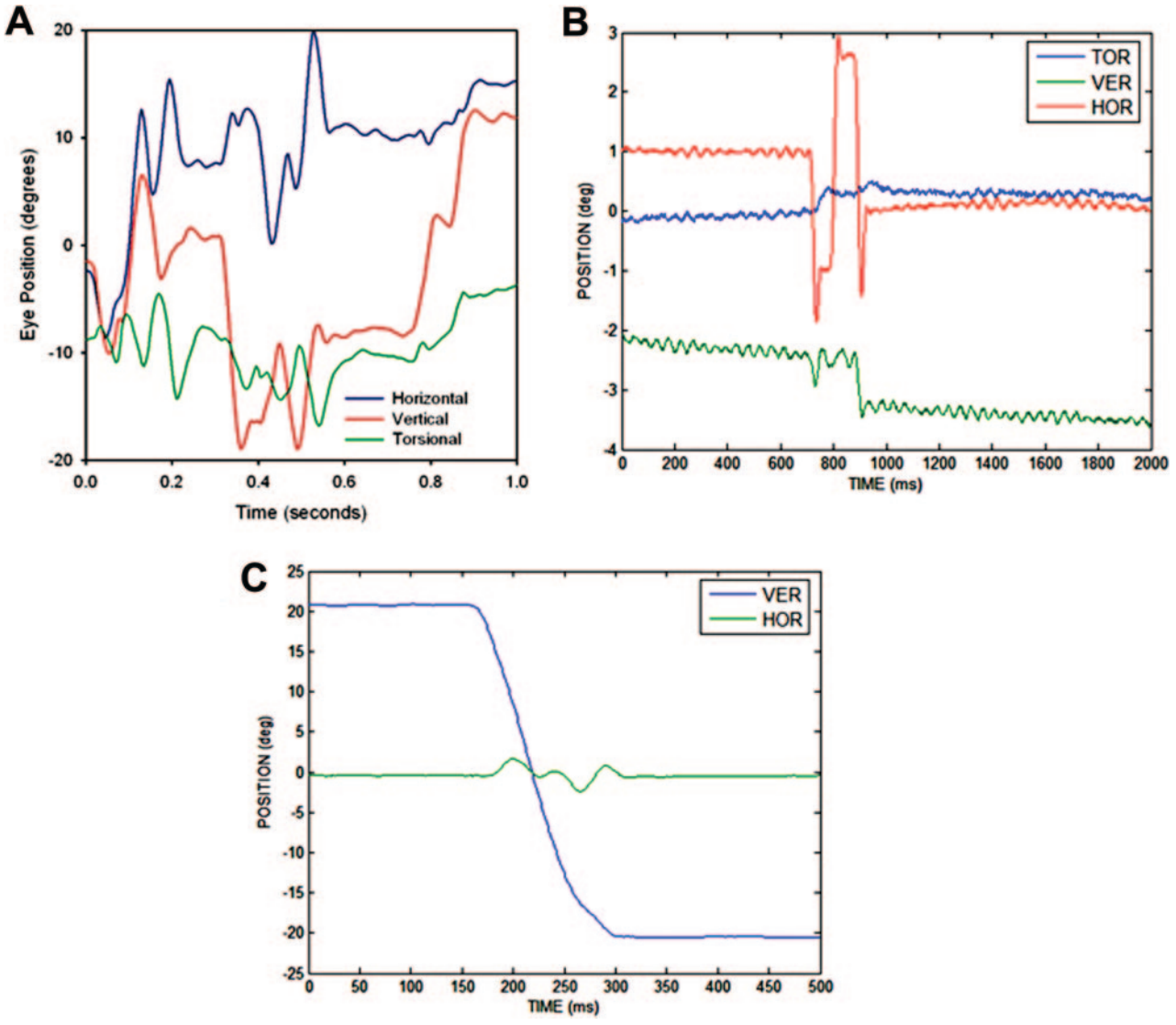

Fig. 7 Representative records of high-frequency saccadic oscillations. (**A**) An example of bursts of opsoclonus—high-frequency saccadic oscillations with 3D components—from a 35-year-old woman with an undiagnosed variant of this disorder. (**B**) Sustained microsaccadic flutter in a patient with familial disorder causing these high-frequency oscillations (Ramat *et al*., 2005). (**C**) Horizontal microsaccadic oscillations in a normal subject during a large vertical saccade.

The report of saccadic oscillations in a patient with a large fastigial lesion (Ramat *et al*., 2005) who made hypermetric saccades is evidence against the hypothesis that high-frequency saccadic oscillations are due to a delay in the local feedback loop. This is an example of a conflict between theory and data that arose because the saccadic system model used by Zee and Robinson (1979) was designed from the top down, without details of the anatomy of the saccadic system. Given that top down structure, the only way to get saccadic oscillations was to introduce a delay in the feedback loop (Fig. 3B), and the only way to get hypermetric saccades was to reduce the gain of the feedback loop.

The anatomy and cerebellar-lesion-induced hypermetria results led to a new model that routed the local feedback loop through the cerebellum (Lefèvre *et al*., 1998; Quaia *et al*., 1999). That new, neuromimetic, model (*see* Simple saccade model for saccade generation that can be applied to clinical disorders) also included a more detailed bilateral brainstem circuit (*see* above) to connect the cerebellar output to the final common path. In the light of this newer model, the result we reported (Ramat *et al*., 2005) suggests that the lesion in the fastigial nuclei interrupted the local feedback loop through the cerebellum, but spared the brainstem interconnections. Indeed, it is possible to reproduce the physiological range of saccadic oscillations if the IBN are modelled appropriately, as described above and in Fig. 4A and B (Ramat *et al*., 2005). The changes to this model were a direct result of an attempt to explain the clinical result. Before these data were available, models that incorporated cross-midline inhibition among the IBN set their gains very low to prevent oscillations (Scudder, 1988; Lefèvre *et al*., 1998; Quaia *et al*., 1999). Although this was a

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reasonable assumption, study of the clinical case showed that it appears to have been incorrect.

Answers from models

This example illustrates the potential synergy between bench and bedside. The clinical study showed that there were severe problems with the original theory of what caused saccadic oscillations. Neither the range of oscillation frequencies nor the effects of cerebellar lesions could be fully explained. Worse, the assumption that cross-midline gains in the brainstem were very low may have misled researchers about the importance of those circuits in saccadic behaviour. The new hypothesis, which combines results from basic and clinical research, both accounts for the full range of frequencies seen in human eye movements and explains why the cerebellar lesion spared the oscillations. Furthermore, it suggests that these oscillations are caused by a very specific group of cells in the brainstem (IBN–IBN) with reciprocal inhibition. Importantly, the new hypothesis emphasizes that the specific properties of the neurons involved (e.g. post-inhibitory rebound), and not just the topology of the circuit, may be key to explaining experimental and clinical findings.

This interpretation allows us to answer the questions raised above. First, high-frequency oscillations are caused by reciprocal inhibition of PBN across the midline, creating a positive-feedback loop. The frequency and amplitude of the oscillations are not controlled by the delay in the loop, but rather by membrane properties (adaptation time constants and gains) of the IBN. Second, all sizes of oscillations can be evoked from the same brainstem positive-feedback circuit by changing the parameters (especially membrane adaptation time constants and gains). Thus, we conclude that all of these disorders have a common substrate. As mentioned above, the horizontal IBN are known to use glycine as an inhibitory transmitter (McElligott and Spencer, 2000), and thus may also be modulating the excitatory NMDA receptor (Miura and Optican, 2006). This suggests that treatment with a drug that blocks the glycine co-agonist site on NMDA receptors of IBNs, or lowers the sensitivity of their excitatory receptors (i.e. glutamate receptors such as AMPA and NMDA), or blocks the T-type calcium channel, might reduce saccadic oscillations.

Macrosaccadic oscillations

Clinical features of macrosaccadic oscillations

Macrosaccadic oscillations consist of horizontal saccades that occur in runs, spontaneously building up and then decreasing in amplitude, with intersaccadic intervals of ~200 ms (Fig. 8). They are different from small 'square-wave jerks' shown by normal subjects, which take the eye <2° away from the fixation point, and return it within 200 ms (Abadi and Gowen, 2004). Macrosaccadic oscillations are also distinct from flutter and opsoclonus (discussed in the previous section) because they have a normal intersaccadic interval of ~200 ms. Macrosaccadic oscillations are usually induced by a gaze shift, but may occur during attempted fixation. They overshoot the visual target in both directions, thus leading to oscillations around the fixation point. Usually, macrosaccadic oscillations are mainly horizontal, but they may have vertical and torsional components.

Macrosaccadic oscillations occur in patients with destructive lesions affecting the deep cerebellar nuclei, including the FN (Selhorst *et al.*, 1976). They also occur with genetic cerebellar ataxias (Swartz *et al.*, 2003), but rarely with brainstem lesions (Averbuch-Heller *et al.*, 1996). In some affected patients, saccades are faster than in controls (Swartz *et al.*, 2003). Patients with a genetic cerebellar degeneration may also have slowed conduction in peripheral nerves, suggesting that conduction along parallel fibres in the cerebellum may also be slowed (Swartz *et al.*, 2003).

In monkeys, hypermetric saccades can be induced by pharmacologically inactivating the fastigial nuclei (Robinson *et al.*, 1993). However, irrepressible saccades are not a prominent feature with bilateral FN inactivation. After the initial hypermetric saccade, corrective saccades decline in gain and fixation behaviour is characterized by an offset rather than by sustained oscillations about the visual target. In monkeys, irrepressible saccades can be produced by microinjection into the caudal SC of the GABA-antagonist bicuculline (Hikosaka and Wurtz, 1985) or the rostral pole of the SC with the GABA-agonist muscimol (Munoz and Wurtz, 1993). Similar large saccadic oscillations are reported after inactivation of the adjacent cMRF (Waitzman *et al.*, 2000). A destructive lesion affecting the rostral pole of the SC in one monkey also produced irrepressible saccades (Carasig *et al.*, 2005). In contrast, in human patients paramedian midbrain disease is not reported to cause irrepressible saccades; in fact saccadic palsy (small and slow movements) is reported (Zackon and Sharpe, 1984).

Questions posed by macrosaccadic oscillations

What causes macrosaccadic oscillations? Why does attempted fixation not stop the oscillations? Why are horizontal saccades affected more than vertical saccades? Why are macrosaccadic oscillations not encountered clinically with lesions affecting the mesencephalic reticular formation or SC? Do models suggest any therapeutic measures?

Influence of macrosaccadic oscillations on models

The earliest saccade models were simple negative feedback loops that compared target eccentricity with eye position. Even such simple models would generate macrosaccadic oscillations if the gain of the feed-forward mechanism were increased (Selhorst *et al.*, 1976). If the feed-forward gain is >1, a saccade will overshoot the target, causing a new retinal error in the opposite direction. The new error will evoke another saccade, which will also overshoot. Although this model has the correct behaviour, it does not help us

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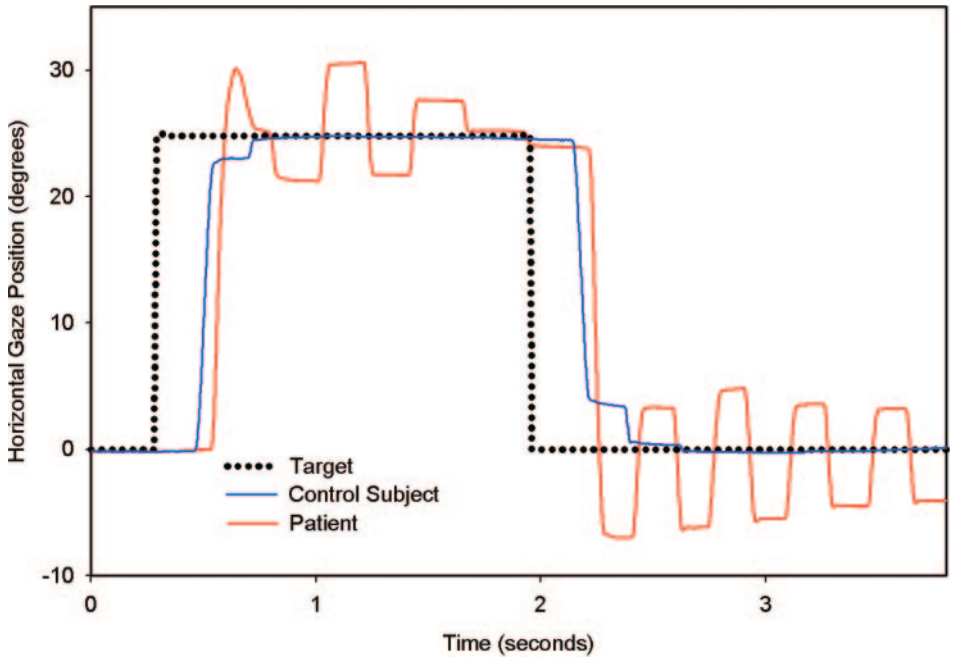

Fig. 8 Examples of horizontal saccades made by a normal subject (blue line) and a patient with a spinocerebellar degeneration (red line) in response to a 25° target jump (dotted line) from centre position to right 25° and back. After a reaction time, the normal subject makes an initial saccade that is hypometric, followed by a subsequent correction. A similar pattern occurs after the target returns to centre. The patient shows hypermetria, overshooting the target when it jumps to the right, and especially when it jumps back to centre, following which there are macrosaccadic oscillations about the point of fixation. Positive values correspond to rightward movements.

understand what parts of the brain are involved. More modern ideas suggest that lesions of the midline cerebellum cause hypermetria because they delay the onset of the choke that stops saccades. Thus, the saccades overshoot the target, which is equivalent in some ways to an increase in the feed-forward gain. However, it is not exactly the same, because simply increasing the gain would make all saccades bigger by a constant factor, which is not the case, as large saccades are not magnified as much as small ones. All of these models generate macrosaccadic oscillations when triggered by a gaze shift. No mechanism has been suggested for how they can start during fixation, although microsaccades, which occur spontaneously (Martinez-Conde *et al.*, 2004), might trigger larger saccadic oscillations.

Answers from models

Macrosaccadic oscillations provide a good example of a well-studied saccadic disorder for which the theory is incomplete. Studies have shown that excess activity in the caudal SC or inadequate activity in the rostral SC cause irrepressible saccades. But it is not clear that the SC is involved in many clinical cases of macrosaccadic oscillations. Hypermetria after FN lesions suggests the oscillations are not due to a gain change, but to a delay in choking off the saccadic drive signals. Thus it is a feedback, not a feed-forward, failure. Understanding why the oscillations start up and die off during fixation will require a new model that includes a more detailed mechanism for fixation. The propensity for macrosaccadic oscillations to occur in the horizontal plane may relate to the different neurotransmitter profiles of inhibitory burst neurons for horizontal or vertical saccades, which is discussed in the section Premotor burst neurons (PBN). Drugs that reduce saccadic gain might be effective in suppressing macrosaccadic oscillations.

Conclusion

We have considered four examples of well-defined disorders of saccades caused by disease in humans. Each example has provided insights into the brainstem, midbrain and cerebellar machinery that generates normal saccades in healthy humans. We have suggested how such abnormal behaviours are helpful in identifying those hypotheses for saccades that are biologically plausible. Conversely, current models for normal saccade generation can provide insights into some of these disorders. Here we discuss ways that models of saccades can aid topological diagnosis, point to underlying molecular mechanisms that suggest novel therapies, and guide future studies.

Implication of saccadic models for topological diagnosis

Although the quantitative predictions of a hypothesis are best evaluated by measuring differences between model simulations and experimental data, qualitative predictions of

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hypotheses can be tested at the beside. As improbable as it may sound, a simple sketch of a model drawn in a pocket notebook can guide accurate diagnosis. Thus, saccades that are slow and yet accurate can be appreciated because a negative feedback loop with maintained burst neuron discharge, even though it is reduced, continues until the eye is on target. Saccades that are prematurely terminated can be viewed as a malfunction of a latch circuit that turns on OPN too early, or causes IBN stuttering, in the middle of a saccade, causing early and increased deceleration. High-frequency saccadic oscillations can be considered in terms of the intrinsic instability of a brainstem network in which some inhibitory burst neurons reciprocally inhibit IBN on the opposite side of the brainstem. This leads to a positive-feedback loop that will oscillate if started by post-inhibitory rebound unless held in check by OPN. Lower-frequency macrosaccadic oscillations can be conceived in terms of increased saccadic gain arising because the 'stop' signal arrives too late to land the eye on target, making them hypermetric.

In fact, disorders of saccades are potentially very useful for topological diagnosis in common disorders affecting the brainstem. One example is the relative slowing of adducting versus abducting saccades in internuclear ophthalmoplegia in multiple sclerosis, which attacks central, but not peripheral, myelin. Thus, the saccadic pulse signal to medial rectus motoneurons is low-pass filtered due to loss of central myelin on axons of abducens INs (which run in the medial longitudinal fasciculus) but not on the axons of abducens motoneurons (which run outside of the CNS) (Leigh and Zee, 2006).

What we hope to have demonstrated is that conceptualization of mechanisms for saccade generation takes such interpretation to a level that can be applied to a range of dynamic disorders. In fact, we suggest that neurologists are always in the 'clinical lab', and are well placed to make observations that can be used to test current saccadic models.

Implication of saccadic models for understanding disease mechanisms and developing new therapies

Besides providing the means to localize a disease process to a circuit or population of neurons, careful analysis of disorders of saccades can suggest the nature of the disorder at the level of neuronal membranes, or even molecules such as proteins that are determined by genes. Thus, the degree of slowing of saccades in SCA2 has been related to the number of trinucleotide repeats (Seifried *et al.*, 2005). Further, saccadic hypermetria in recessive spinocerebellar ataxia with saccadic intrusions (SACSI) coexists with slowing of axonal transmission in peripheral nerves, suggesting that delayed conduction of the 'stop' signal on unmyelinated parallel fibres of the cerebellum might lead to saccadic hypermetria (Swartz *et al.*, 2003). Membrane properties are as important as circuits, and thus new classes of agents that have effects on neuron membranes require consideration in the treatment of abnormal eye movements. For example, genetic disorders of P/Q calcium channels, such as the episodic ataxias, can produce abnormalities of eye movements (Stahl and James, 2005) that are amenable to therapy with drugs such as 4-aminopyridine (a potassium channel blocker) (Strupp *et al.*, 2004). We have also pre-sented preliminary evidence that high-frequency saccadic oscillations could be due to an abnormality of the membrane properties of inhibitory burst neurons (Ramat *et al.*, 2005). Another mechanism only recently proposed is that normally the inhibitory neurotransmitter glycine inhibits burst neuron discharge but, paradoxically, glycine may also act as a neuromodulator at NMDA receptors to increase the effects of glutamate on burst neurons and thereby generate the sharp acceleration that characterizes saccades (Miura and Optican, 2006). Drugs that block this co-agonist action of glycine, or that block the glutamate site at excitatory synapses, should be considered as possible therapies for high-frequency oscillations.

Implication of saccadic models for directing new research

Although this review deals only with brainstem and cerebellar control of saccades, these movements have been used to investigate higher functions such as memory, decision-making and reward (Itoh *et al.*, 2003, Leigh and Kennard, 2004, Nachev *et al.*, 2004). Thus, analysis of saccade behaviour can be used to characterize many disorders affecting all levels of the brain, including genetic disorders such as the SCAs, degenerative disorders, such as parkinsonism, and conditions causing dementia and psychiatric illnesses, including schizophrenia, and attentional disorders (Leigh and Zee, 2006). Several different approaches, including functional imaging and transcranial magnetic stimulation, are being used in combination with novel behavioural tests in patients with discrete brain lesions to understand better the mechanisms of higher-level control of saccades (Müri, 2005).

What lies ahead? There are still a number of disorders of saccades that are not understood at all, e.g. small saccadic intrusions—'square-wave jerks' (Abadi and Gowen, 2004). An understanding of the saccadic system at the level of the biophysical properties of cell membranes and the genetics of neurotransmitters and receptors has only just begun to be explored. This may have an important impact on patient care, because of the constant development of new drugs that may act at various receptors. Closer interaction between basic and clinical researchers is essential if rapid progress is to be made in understanding mechanisms and disorders of neural control, and improving their diagnosis and treatment.

Supplementary material

Supplementary material is available at *Brain* Online.

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