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CHAPTER 2.6

Applying saccade models to account for oscillations

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Abstract: Saccadic oscillations are unwanted back-to-back saccades occurring one upon the other that produce a high-frequency oscillation of the eyes (usually 15–30 Hz). These may occur transiently in normal subjects, for example, around the orthogonal axis of a purely horizontal or vertical saccade, during combined saccade-vergence gaze shifts or during blinks. Some subjects may produce saccadic oscillations at will, usually with convergence. Pathological, involuntary saccadic oscillations such as flutter and opsoclonus are prominent in certain diseases. Our recent mathematical model of the premotor circuit for generating saccades includes brainstem burst neurons in the paramedian pontine reticular formation (PPRF), which show the physiological phenomenon of post-inhibitory rebound (PIR). This model makes saccadic oscillations because of the positive feedback among excitatory and inhibitory burst neurons. Here we review our recent findings and hypotheses and show how they may be reproduced using our lumped model of the saccadic premotor circuitry by reducing the inhibitory efficacy of omnipause neurons.

Keywords: saccadic system; saccade models; saccadic Oscillations

Introduction

Saccades are the most frequent voluntary eye movement during everyday life: they rapidly redirect gaze to objects in the environment. Saccades to the sudden appearance of a visual target typically have a latency of ~200 ms, reach peak velocities of ~600 deg/s, last between 30 and 100 ms, and are accurate. The current understanding of the anatomy and physiology of the saccadic system has considerably advanced due to single unit recordings from neurons with activity related to eye movements in the behaving monkey. Experimental studies based on the analysis of the effects of lesions in animals and, vice versa, clinical and postmortem examinations of patients with saccadic disorders, have further clarified the physiology of the saccadic system.

Mathematical models of the generation of saccades have evolved by incorporating these findings, and theoretical studies have generated quantitative hypotheses that sparked new specific questions requiring further experiments. Basic experimental research on the mechanism for generating saccades has interacted with mathematical modelling efforts to advance our understanding of the saccadic system and, more broadly, of motor control in general.

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Recently, the study of saccadic oscillations (ocular flutter) in normal subjects and patients with known lesions has raised new questions that challenge our theories of saccade generation and forced us to update current mathematical models. Here we incorporate these findings into our models to account for saccadic oscillations in normal subjects and in patients with neurological disorders.

Saccadic oscillations

Saccadic oscillations are small, unwanted back-to-back saccades without an intersaccadic interval occurring at a frequency of 15 to 30 Hz. They have been recorded in many neurological conditions (Zee and Robinson, 1979; Ashe et al., 1991; Leigh and Zee, 2006), but some normal subjects can produce similar eye movements at will, as in voluntary nystagmus (Shults et al., 1977). Saccadic oscillations can also be induced in normal subjects by blinks (Hain et al., 1986), by combined saccade-vergence gaze shifts (Ramat et al., 1999), and can occur around the orthogonal axis to a purely vertical or purely horizontal saccade (Zee et al., 1992; Ramat et al., 2005a). Although these oscillations are small ($\sim$1 deg), they cause blurred vision when they are sustained, as in voluntary nystagmus or in patients with ocular flutter or opsoclonus (Ramat et al., 2005a; Shaikh et al., 2007).

Prior models of saccadic oscillations

In an early model of saccadic oscillations (Zee and Robinson, 1979), Zee and Robinson suggested that the oscillations are due to an increased delay in the local feedback loop controlling saccade amplitude. A delay introduces a phase lag that increases linearly with frequency. This makes the circuit unstable, with oscillations at the frequency at which the loop gain is at least one and the phase lag at least 180 deg. The forward pathway includes a switch representing the action of the omnipause neurons (OPN) that tonically inhibit burst neurons when a saccade is not called for, and a high gain nonlinear block representing the excitatory burst neurons (EBN). The feedback pathway includes a resettable integrator that computes eye position instantaneously during each saccade with a delay of τ s.

The high gain of the burst neurons for small inputs and the delay in the feedback loop make the circuit that generates saccades inherently unstable. Without the OPN gate, which prevents oscillations during fixation, the circuit oscillates at a frequency that depends on the duration of the delay (roughly 0.25/delay) with an amplitude that depends mainly on where the slope of the burst neuron nonlinearity decreases (Zee and Robinson, 1979). This model was initially successful, and later models of saccadic oscillations (Wong et al., 2001) followed the same feedback loop delay idea and combined it with the hypothesis that the fastigial nuclei (FN) is within the feedback loop (Lefevre et al., 1998).

Recent findings in both normal subjects and in patients with saccade oscillations (Ramat et al., 1999, 2005a; Shaikh et al., 2007) have challenged such models and motivated a new hypothesis for saccadic oscillations. First, experimental data showed that individuals can produce oscillations of different amplitudes with little change in frequency, and that oscillations in normal subjects span a large range of frequencies, although they tend to be fixed within a given subject. Both of these observations are not easily explained using the delay model because the range of frequencies requires a physiologically implausible large range of delays in the feedback loop. Second, the finding that patients with surgical ablation of the FN still produce saccadic oscillations argues against both the hypothesis that the delay in the feedback loop may be the mechanism for oscillations, and that such a loop goes through the FN. Third, the report of a familial disorder causing microsaccadic oscillations and limb tremor (μSOLT) is unlikely to be explained by a selective slowing of axonal conduction in just the feedback neurons, because subjects may show oscillations of different amplitudes, but their frequency is mostly constant.

A new model of saccadic oscillations

We recently proposed a new model for saccadic oscillations based on a more detailed representation

of the known anatomy of the premotor circuitry for generating saccades, and on the physiological phenomenon of post-inhibitory rebound (PIR) firing (Ramat et al., 2005a).

The premotor saccadic circuitry comprises three types of neurons: excitatory burst neurons (EBN, glutamatergic), inhibitory burst neurons (IBN, glycinergic), and omnipause neurons (OPN, glycinergic). The EBN are responsible for producing the burst of innervation that projects directly to ocular motor neurons and drives the saccade, and to the circuits comprising the ocular motor integrator for generating the tonic signal that holds positions of gaze. EBN are located in the paramedian pontine reticular formation (PPRF) for horizontal saccades (Strassman et al., 1986a) and in the rostral interstitial nucleus of the medial longitudinal fasciculus (riMLF) for vertical and torsional saccades (Horn and Buttner-Ennever, 1998). Horizontal IBN innervate the contralateral abducens nucleus and the contralateral IBN and EBN (Strassman et al., 1986b). Horizontal IBN lie in the medullary reticular formation (medRF), while vertical and torsional IBN lie in the interstitial nucleus of Cajal (INC) (Izawa et al., 2007).

Anatomical studies of the projections of both the inhibitory and the EBN (Strassman et al., 1986b; Buttner-Ennever and Buttner, 1992) show that these neurons are interconnected across the midline and form two positive feedback loops. Since positive feedback can lead to instability, this network of brainstem neurons has the potential to oscillate and has led to a new model of saccadic oscillations (Ramat et al., 2005a). For this model to reproduce the different patterns of saccadic oscillations (Fig. 1, A), we implemented the detailed circuitry of premotor burst neurons (Fig. 1, B) and included the phenomenon of PIR (Enderle and Engelken, 1995). PIR is a property of cell membranes (Perez-Reyes, 2003) that causes the firing of one or more action potentials at the offset of inhibition, due to a particular class of voltage-dependent calcium channels, the T-type calcium channels, that activate at a low membrane potential (Huguenard, 1996; Perez-Reyes, 2003). Recently, Miura and Optican developed a detailed membrane model of burst neurons including T-channels and showed how they may produce rebound depolarization when the OPN are inactivated (Miura and Optican, 2006). A lumped model of PIR behaviour can be obtained to a first approximation using a burst neuron membrane model as illustrated in Fig. 1, B, right, in which a feed forward pathway includes a high-pass filter that causes adaptation (Ramat et al., 2005a). The time constant of adaptation (aTc) determines the duration of PIR; the gain of the adaptation (aGain) determines its amplitude.

The OPN lie in the raphe interpositus nucleus (RIP) and normally inhibit premotor burst neurons bilaterally in both the pons and the midbrain, except when a saccade is called for. Yet, recent studies involving chemical lesions of the RIP (Kaneko, 1996; Soetedjo et al., 2002) have shown that their role is not that of a mere switch enabling or disabling saccades, since their inactivation caused saccades to be slower, although they remained accurate and had a normal latency. It was therefore suggested that the OPN may act as a modulator of the activity of burst neurons and that their incomplete inhibition may be the cause of pathological saccadic oscillations (Ramat et al., 2005b; Shaikh et al., 2007). The OPN use glycine as their neurotransmitter, which acts on burst neurons through two mechanisms: inhibition of strychnine sensitive receptors and activation of NMDA channels (Miura and Optican, 2006).

Experimental results

We recently recorded a second patient, a 57-year-old woman with a surgical resection of a midline cerebellar tumour as a child, producing a midline defect (Fig. 2, CT scan at left) that almost certainly destroyed the posterior portion of the FN. She had marked hypermetria of horizontal saccades (Fig. 2, right top panel), typical of a fastigial nucleus lesion. During large vertical saccades (Fig. 2, right bottom panel), there were small, high-frequency oscillations on the horizontal velocity record. The findings in this patient corroborate the hypothesis that the delay in the feedback loop is not the principal mechanism causing oscillations.

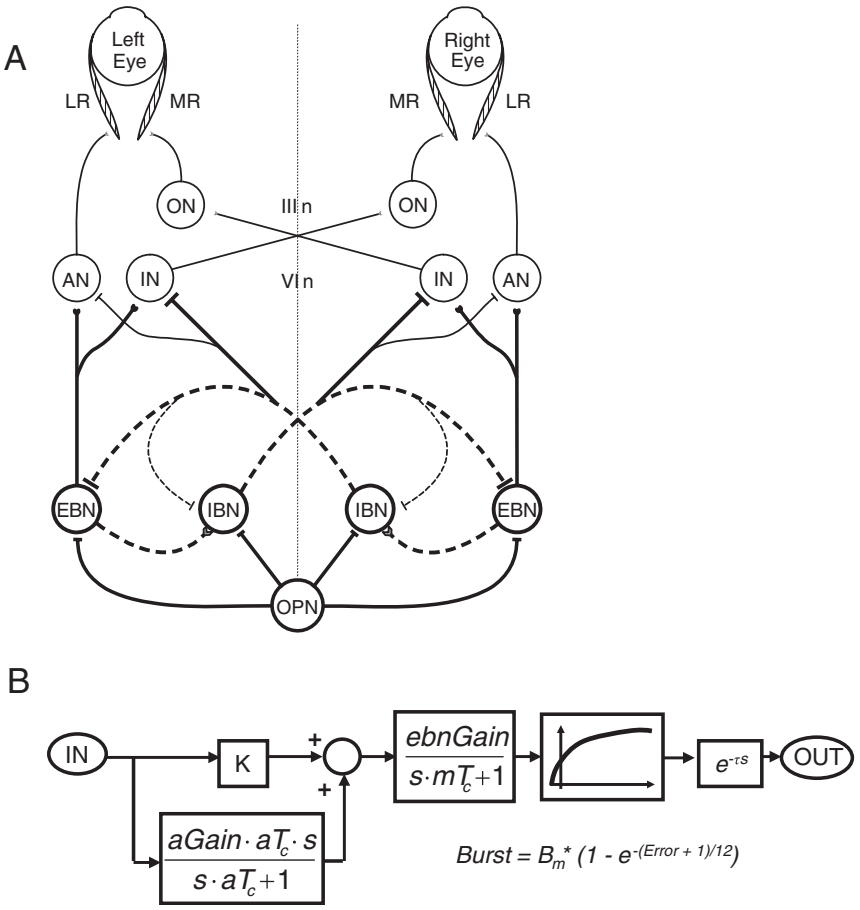

Fig. 1. Panel A: Brainstem circuit for generating saccades. Projections with flat ending are inhibitory, the others excitatory. ML, medial recti; LR, lateral recti; VIn, ipsilateral abducens nucleus; AN, abducens neuron, IN, interneuron projecting to contralateral third nerve (IIIn), ON, oculomotor neuron. EBN, excitatory burst neurons, IBN, inhibitory burst neurons. OPN, omnipause neurons. Panel B: Lumped model of premotor burst neuron used in our model showing adaptation and producing PIR. The high-pass parallel pathway produces PIR with amplitude determined by aGain and duration determined by aTc. The cell membrane then shows a low pass filter (mTc), a nonlinearity (Zee and Robinson, 1979) and a synaptic delay of less than 1 ms. (Adapted with permission from Ramat et al., 2005a.)

Second, we recently recorded a mother and a daughter who each had microsaccadic flutter: an almost continuous saccadic oscillation of the eyes occurring without intersaccadic interval and usually around all three axes (Shaikh et al., 2007). Eye oscillations were also accompanied by limb tremor, and it was suggested that both the eye and the limb oscillations reflected reduced (glycinergic in the case of the eyes) inhibition of an inherently unstable neural circuit (Shaikh et al., 2007).

We recorded the eye movements of the mother with search coils and during fixation she had a virtually continuous saccadic oscillation of both eyes (20.3 ± 0.9 Hz and 7.6 ± 2.2 deg/s horizontal, 21.0 ± 1.0 Hz and 10.3 ± 2.7 deg/s vertical) at about 20 Hz and about 0.1 deg. The first panel in Fig. 3 shows data recorded during fixation followed by a 5 deg saccade after which the oscillations were transiently suppressed for about 200 ms. During large vertical saccades (40 deg), horizontal saccadic oscillations occurred with amplitudes reaching 1.8 degrees (156.2 ± 34.8 deg/s and 21.5 ± 2.3 Hz, as in Fig. 3, second panel). Eye closure and blinks evoked large horizontal oscillations (95 ± 16 deg/s) of significantly lower frequency (18.2 ± 0.9 Hz), as

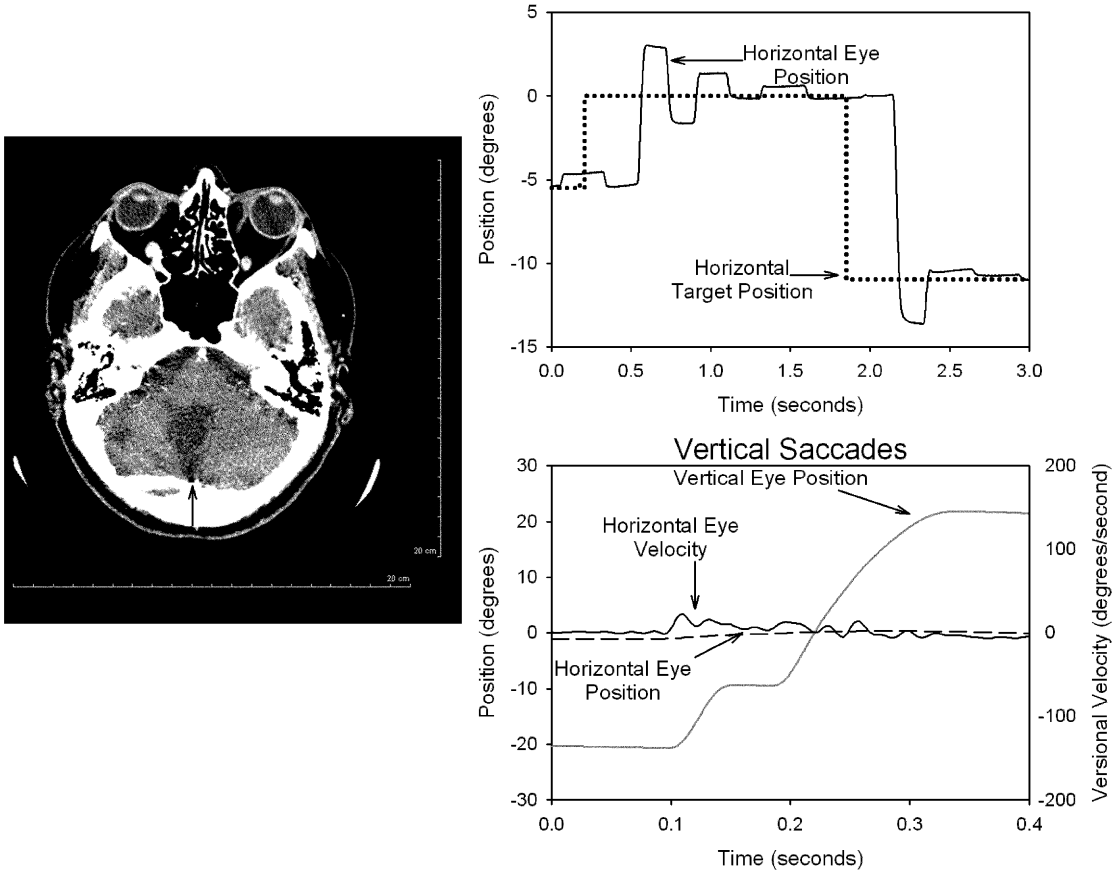

Fig. 2. Finding in a 57-year-old woman, who had undergone resection of a cerebellar tumour as a child leaving a midline defect (indicated by arrow on CT scan at left). She had marked horizontal hypermetria (right, top panel) typical of a fastigial nucleus lesion. When she made large vertical saccades (right, bottom panel), small, high-frequency oscillations were evident on the horizontal velocity record (scale at right).

shown in Fig. 3 third panel. The amplitude of both horizontal and vertical oscillations varied significantly without proportionally affecting their frequency.

The behaviour of this patient was simulated using the lumped model for saccadic oscillations described above, with a population of five burst neurons for each of the horizontal and vertical saccade generators. The values of the parameters representing the membrane characteristics of both EBN and IBN were randomly drawn from a normal distribution with a specified mean and a standard deviation of 10% of such mean. The results of the simulations corresponding to the three conditions shown in Fig. 3 are shown in Fig. 4. The temporary suppression of oscillations at the end of the small amplitude saccade in the left column could be simulated based upon an additional transient inhibition provided by contralateral IBN acting as a "choke" signal. To simulate the patient data we reduced the inhibitory effect of OPN firing on EBN and IBN, reproducing the effect of a pathologically reduced sensitivity to glycinergic inhibition, and increased the strength of PIR (aGain), simulating the increased membrane excitability due to the reduced hyperpolarization of the burst neurons (Shaikh et al., 2007). Reducing the action of glycine in the premotor circuit produces a change in the membrane behaviour of burst neurons that increases the

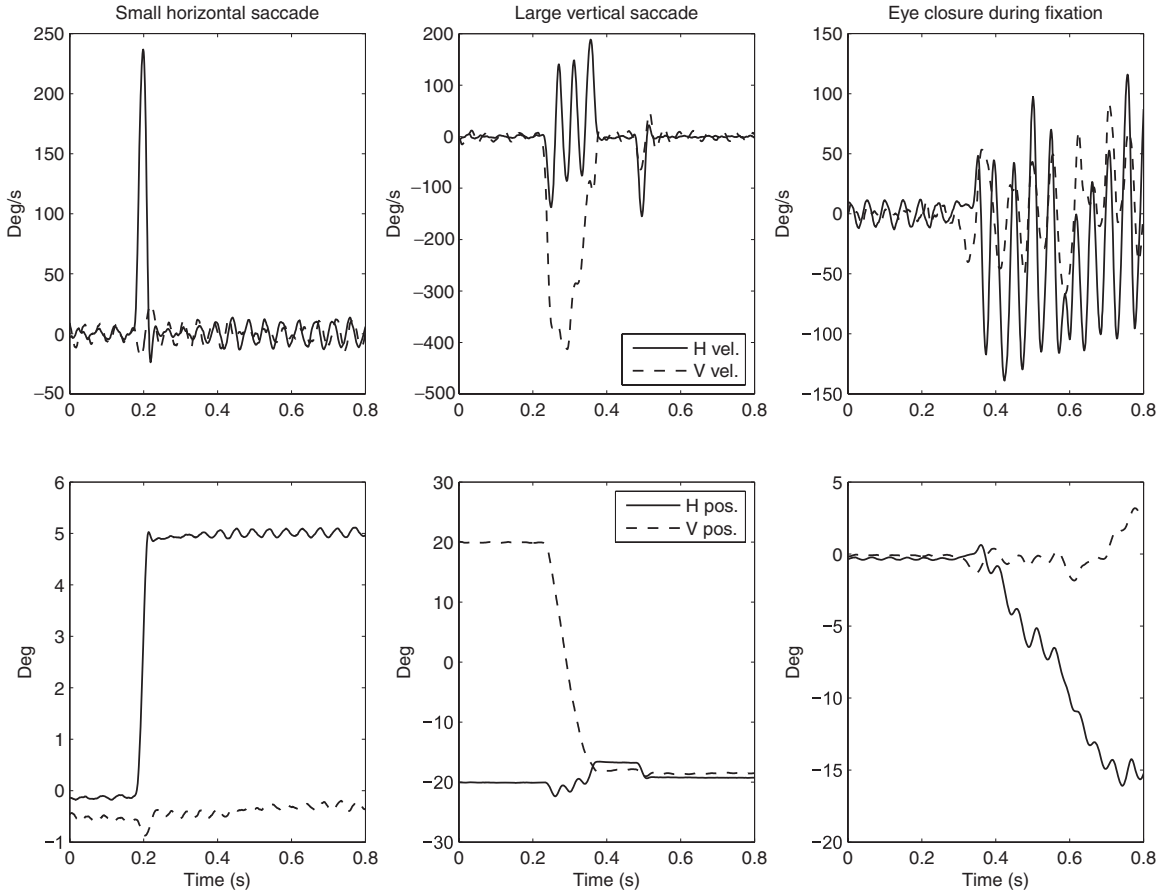

Fig. 3. Representative eye movements recorded in one patient affected by μSOLT. Top row velocity traces, bottom row position traces. Each column represents data recorded in response to different conditions. Left: 5 deg, horizontal saccade; central: 40 deg, vertical saccade; right: eye closure during fixation.

instability of the circuit. Consequently the circuit oscillates during fixation, in spite of some residual OPN firing.

Discussion

Here we have shown further simulations of a recent model for saccadic oscillations (Ramat et al., 2005a; Ramat et al., 2007) which account for the experimental findings in a patient with familial microsaccadic oscillations (Shaikh et al., 2007). The key features of this model are the circuitry representing the detailed interconnections between premotor neurons and the membrane properties of the excitatory and IBN in the brainstem. The model assumes that these high-gain cells show PIR, which causes them to fire a burst of action potentials when their inhibition is removed, even if there is no error signal to trigger a saccade. PIR has been demonstrated in various cells of the nervous system (Perez-Reyes, 2003), and likely produces the high-frequency burst that drives saccades in normal subjects (Enderle and Engelken, 1995; Miura and Optican, 2006). In our model, besides contributing to the drive of normal saccades, PIR is key for explaining saccadic oscillations in normal subjects and in patients (Ramat et al., 2007; Shaikh et al., 2007). Finally, these results further support the idea that

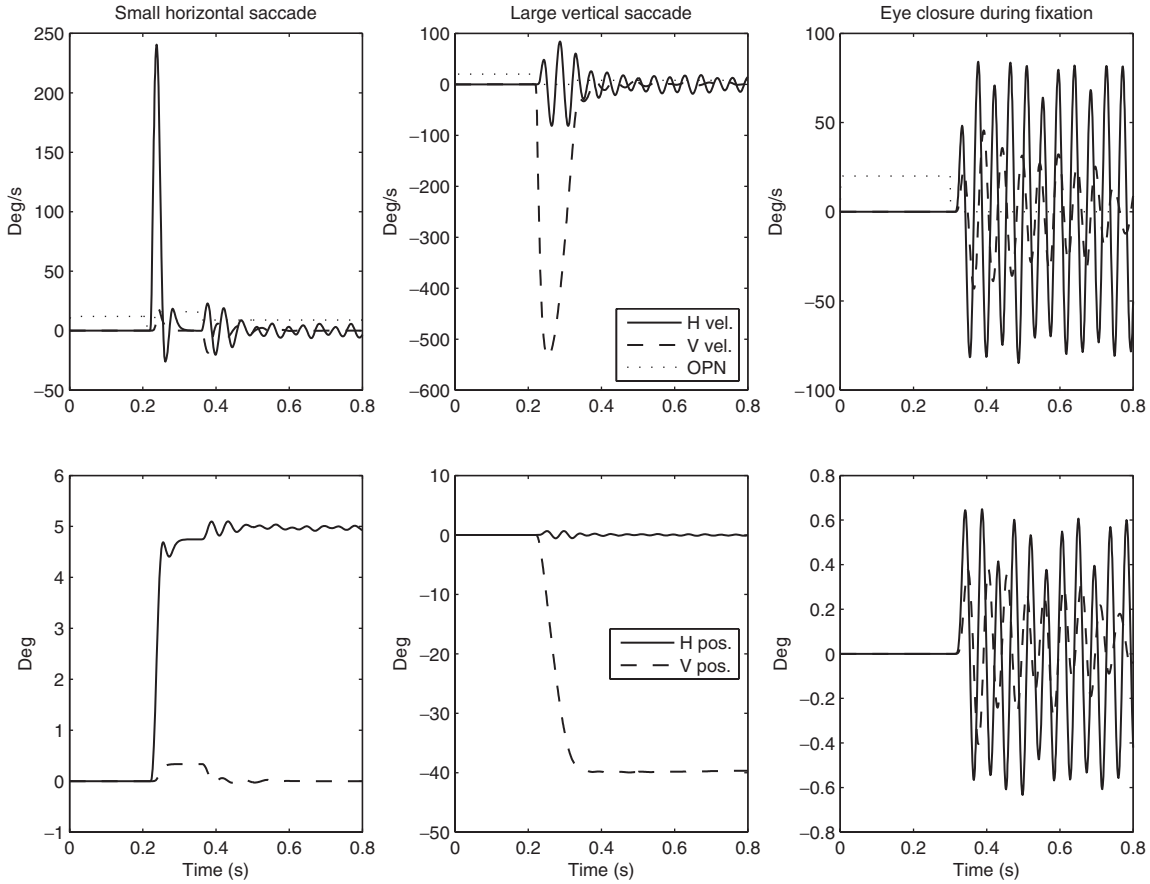

Fig. 4. Model simulations of the patient data in the conditions represented in Fig. 3. The amplitude of the oscillations is mainly determined by the gain of PIR (aGain) and their frequency by the membrane time constants (aTc, mTc). The reduced sensitivity of strychnine-sensitive channels was simulated by lowering the gain of OPN projections onto burst neurons and increasing the gain of PIR in those cells. All patient simulations were performed using the same set of parameters.

pathological saccadic oscillations are caused by a reduction of inhibition in this inherently unstable circuit, which may be due to reduced sensitivity of glycine channels on burst neurons.

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