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CHAPTER 1.10

Extraocular proprioception and new treatments for infantile nystagmus syndrome

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Abstract: Our goal is to develop the proprioceptive hypothesis for nystagmus damping; and present the resulting therapies for the treatment of infantile nystagmus syndrome (INS) and acquired nystagmus. Contact lenses, cutaneous stimulation, and neck-muscle vibration damped INS. Four-muscle tenotomy and reattachment was hypothesized as a treatment for INS in 1979 and successfully demonstrated to improve foveation in a canine model of INS and seesaw nystagmus in 1998 and in humans with INS (masked-data, NEI Clinical Trial) in 2003. Subsequently, tenotomy successfully damped acquired pendular nystagmus and oscillopsia in two MS patients and downbeat nystagmus in another. Tenotomy, used in isolation or combination with existing nystagmus and strabismus surgeries, damps different types of nystagmus in their plane of action. Recent neuroanatomical and neurophysiological discoveries support the hypothesis that proprioception is the mechanism for INS damping and allow more realistic models of peripheral ocular motor pathways.

Keywords: ocular motor system; proprioception; nystagmus; treatments; models; control system

Introduction

In the early 1960s, Drs. Larry Stark, Laurence Young, and David Robinson pioneered the use of control systems models to study the ocular motor system (OMS) (Young and Stark, 1963; Robinson, 1964, 1965). In 1967, this approach was extended by studying the behaviour of an OMS with an oscillatory disorder, infantile nystagmus syndrome (INS, also called congenital nystagmus, CN) (Dell'Osso, 1968). An early hypothesis to come out of that extension was that the OMS could *not* function properly using only retinal error position and velocity signals as its inputs. Thus, models that depend solely on retinal inputs cannot duplicate the behavioural responses of subjects with INS, and are also limited in their ability to simulate normal ocular motor behaviour (e.g., pursuit of the imaginary hub of a moving wheel, making saccades in the dark to imagined targets, etc.). Either efference copy of motor output commands or the use of proprioceptive eye-position signals was necessary to reconstruct target information when internal oscillations were present. Figure 1

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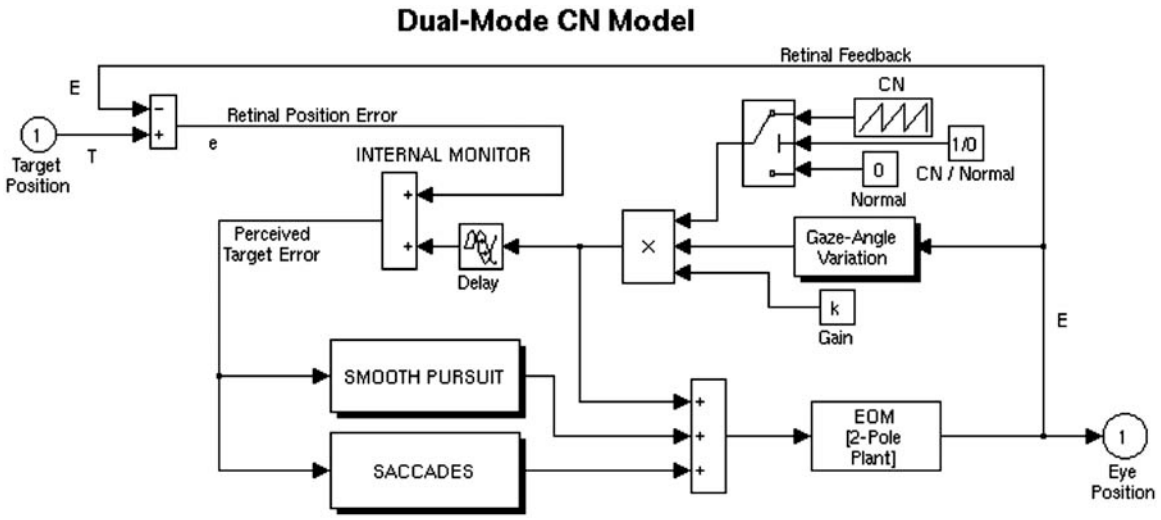

Fig. 1. Block diagram of the first OMS model with INS showing both an internal monitor and proprioceptive feedback signals. The saccadic and pursuit driving signals (Perceived Target Error) are derived from retinal error and efference copy of the nystagmus motor signal, modulated by proprioceptively sensed eye position.

demonstrates how a simple "internal monitor" was used to reconstruct target position in this initial model of INS behaviour. Although a mechanism for generating INS was not hypothesized, a method to simulate the modulation of INS with eye position was; as Fig. 1 shows, it used a proprioceptive measure of the latter. At that time, the use of proprioceptive eye-position information was a reasonable hypothesis since it was known that proprioceptive signals were present in the V cranial nerve as well as in the III, IV, and VI cranial nerves [e.g., Figs. 1–9 of the above thesis (Dell'Osso, 1968)]. Keller and Robinson (1971) published a study that suggested there was no ocular motor stretch reflex and concluded that proprioception did *not* play a role in ocular motor control, at least not for short-term control. In recent years, several lines of evidence have pointed to the importance of extraocular proprioception in ocular motor control (including several articles in this volume).

In this paper, we will present evidence from the studies of the mechanisms of, and therapies for, INS and acquired nystagmus that strongly suggests a significant role for afferent stimuli, both exteroceptive and proprioceptive, in the control of eye movements; we will include that role in a behavioural computer model.

Methods

Recording

Data for our studies were generated using infrared reflection, magnetic search coil, or high-speed digital video systems. Specific details of each may be found in the referenced papers (Wang et al., 2006b).

Protocol

Written consent was obtained from subjects before the testing. All test procedures were carefully explained to the subject before the experiment began, and were reinforced with verbal commands during the trials. Subjects were seated in a chair with headrest and a chin stabilizer, far enough (>5 feet) from either an arc of red LEDs or a reflected laser spot to prevent convergence effects. At this distance the target subtended less than 0.1° of visual angle. The room light could be adjusted from dim down to blackout to minimize extraneous visual stimuli. Experiments consisted of 3–10 trials, each lasting about a minute with time between trials for the subject to rest. Trials were kept short to guard against boredom because INS intensity decreases with inattention.

Analysis

Eye-movement analysis was carried out in the MATLAB environment using software developed and refined in our laboratory. Detailed descriptions of our software and experimental paradigms may be found in the referenced papers and at our web site, http://www.omlab.org. Simulations were carried out in Simulink.

Results

Afferent stimulation and proprioception

One of the first indications that afferent stimulation could affect INS was the observation by J. Lawton Smith in the 1970s that, in some patients, the insertion of contact lenses immediately damped the INS sufficiently for it to be noted clinically. We studied the ocular motor effects of soft contact lenses in INS and found damping across all gaze angles (Dell'Osso et al., 1988). In that paper, we also demonstrated that the damping was immediate by applying light pressure on the eyelid. Topical anaesthetics limited the damping effect by reducing the proprioceptive input from the contact lenses, demonstrating that the effect was not due to the mass of the lenses or the refractive correction. Subsequent studies of other exteroceptive stimuli, including cutaneous stimulation (touch and electrical) of the forehead and neck (including vibration) also demonstrated an immediate damping effect on INS (Dell'Osso et al., 1991; Sheth et al., 1995). We subsequently noted that airflow over the forehead damped INS (unpublished observation).

Four-muscle tenotomy

The four-muscle tenotomy procedure (actually tenotomy, dissection, and resuture at the original muscle insertion) was conceived as a result of studying the ocular motor effects of the Kestenbaum procedure (two-muscle recessions plus two-muscle resections) (Dell'Osso and Flynn, 1979). We noted that in addition to shifting the position of the "null" in INS, several secondary benefits were achieved. They included broadening of the "null" region and an overall damping of the INS at all positions of gaze. We attributed this to "nonlinear changes in the ocular motor plant dynamics." Although conceived in 1979, the tenotomy procedure was not formally hypothesized as a therapy for three classes of INS patients until we had a canine model of INS upon which we could test the procedure (Dell'Osso, 1998).

We successfully demonstrated that the tenotomy procedure damped horizontal canine INS and, 4 months later, vertical canine INS and seesaw nystagmus (Dell'Osso et al., 1999). INS and seesaw nystagmus have different mechanisms, sites, and planes. This led us to hypothesize that tenotomy's therapeutic effects were due to changes in the periphery (the "plant") mediated by a proprioceptive tension-control feedback loop. In an NEI Clinical Trial we demonstrated that the tenotomy procedure successfully damped INS (Hertle et al., 2003, 2004) and in a subsequent study, we demonstrated its "null" broadening effects (Wang et al., 2006a). The beneficial effects of tenotomy were restricted to the small signals responsible for INS slow phases; saccades were not affected (Wang et al., 2006b).

The tenotomy procedure also damped the acquired pendular nystagmus in two patients with MS (Tomsak et al., 2005) and downbeat nystagmus in another patient (Wang et al., 2007b). In the latter paper, tenotomy was combined with nystagmus recessions in the downbeat nystagmus case and strabismus recessions in the INS case.

Convergence

One other means of damping INS (and some forms of acquired nystagmus) is convergence (Dell'Osso et al., 1972; Dell'Osso, 1973). The effect is also immediate (in ms) and results in broadening the "null" in INS (Serra et al., 2006).

Discussion

Top-down, control-systems studies of the normal and dysfunctional OMS have produced the following hypotheses and supporting evidence: (1) the

need for a final common neural integrator (Robinson, 1968) and its location (Cannon and Robinson, 1987); (2) the need for an internally resettable saccadic pulse generator (Dell'Osso and Robinson, 1973; Dell'Osso, 1974, both dated entry pages in Dell'Osso's laboratory notebook) (Abel et al., 1978) and its location (Scudder, 1988); (3) the hypothesis that each eye (and, therefore, each eye muscle) is individually controlled (Dell'Osso, 1994) and neurophysiological evidence supporting it (King and Zhou, 2000); and (4) a proprioceptive hypothesis for small-signal gain control (Dell'Osso et al., 1999) and anatomical (Büttner-Ennever et al., 2001, 2002; Eberhorn et al., 2005; Ugolini et al., 2006) and neurophysiological (Wang et al., 2007a) evidence supporting it. Each of these concepts has evolved, often over decades, from an initial hypothesis based on functional analysis of the OMS to a more detailed hypothesis based on anatomical and physiological evidence. Over the past 40 years, the confluence of anatomy, neurophysiology, and control systems analysis has steadily reduced the time required for the transitions between initial hypotheses and the discovery of supporting evidence. The influx of bottom-up, control-systems methods into neuroanatomical and neurophysiological studies has been largely responsible for this progress.

Studies and applications of INS therapies over the past two decades have led to a resurgence of interest in the role of proprioception in ocular motor control. The damping of INS with contact lenses implicated exteroceptive signals carried via the V cranial nerve (Dell'Osso et al., 1988). That is, afferent stimulation via the ophthalmic division of the trigeminal nerve was able to modulate the oscillation; the effect seemed to be immediate. Somehow, signals brought back to the trigeminal (semi lunar) ganglion were able to affect brainstem ocular motor signals. The discovery that other forms of afferent stimulation also damped INS (in ms) reinforced the hypothesis that proprioception played an important role in ocular motor control (Sheth et al., 1995). Finally, the demonstration that the four-muscle tenotomy procedure improved INS waveforms (and eliminated seesaw nystagmus) in a canine, in less than 18 h (Dell'Osso et al., 1999) and in humans (noted immediately post-op by mothers) (Hertle et al., 2003, 2004) provided strong evidence in support of the proprioceptive hypothesis. The success of the tenotomy procedure in many INS patients (Wang et al., 2006a), in the acquired pendular nystagmus of MS (Tomsak et al., 2005), and in downbeat nystagmus (Wang et al., 2007b) further solidified the role of proprioception in nystagmus modulation in each plane, independent of the site or mechanism of the oscillation. Recent research has also identified proprioceptive signals in the cortex (Wang et al., 2007a). We note at this point that convergence also damps INS rapidly and broadens the "null" region — the *same* effects as afferent stimulation and tenotomy (Serra et al., 2006).

Our findings that the tenotomy procedure affects only small signals (e.g., nystagmus slow phases) and not saccades, suggested that current models of the ocular motor plant are inadequate (Wang et al., 2006b). Although the ocular motor neurons (OMN) studied by Keller and Robinson (presumably, the "fast" OMN) did not have a fast stretch reflex, they could still be part of a slower (e.g., a time constant of minutes, hours, or days) tension-control reflex, as is illustrated in Fig. 2. The tension-control loop is independent of the main ocular motor control loop and serves to maintain the resting tension, and therefore (because muscle response is a function of its length) the small-signal gain of the extraocular muscles. Originally, our proprioceptive hypothesis for the mechanism behind the effects of tenotomy was built on the presumption that even in the absence of a short-time-constant stretch reflex, proprioceptive information is used by the OMS for long-term control and adjustment. Because afferent information from the V cranial nerve (e.g., from cutaneous stimulation of the eyelids or forehead) had an *immediate* damping effect on INS, this pathway provides a means of on-line modulation of eye movements. This had presented us with a dilemma; why is there a fast exteroceptive pathway but only a slow proprioceptive pathway? Also, how could cutting a tendon (especially at its distal end), which presumably had no neurological substrate, affect an afferent signal?

Because of the work of Büttner-Ennever and colleagues, we no longer must make a choice

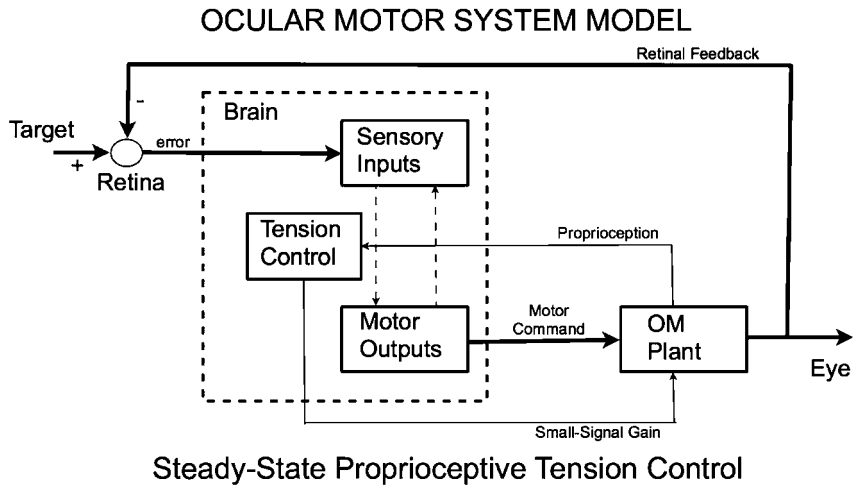

Fig. 2. Block diagram of the OMS showing the addition of a putative proprioceptive tension-control loop. This latter loop was hypothesized to control resting muscle tension and with it, the small-signal gain of the ocular motor (OM) plant. The OMS operates on both retinal error and efference copy of motor commands.

between two separate mechanisms with widely differing time constants. The existence of two types of OMN, two major types of extraocular muscle fibres, palisade endings, and proprioceptive representation in the primary somatosensory cortex not only provided neuroanatomical and neurophysiological substrates for our conclusions but also allowed us to refine and extend our hypothesis (Büttner-Ennever et al., 2001, 2002; Eberhorn et al., 2005; Wang et al., 2007a). In Fig. 3 (top), we show two possible tension-control loops, one for the fast OMN and another for the slow OMN. If the former exists, it would have to be a slow control for maintaining calibration to be consistent with earlier findings (Keller and Robinson, 1971). Although the slow-OMN loop may be similar, it more probably operates on a faster time scale, i.e., more like a skeletal stretch reflex. In Fig. 3 (bottom), we show schematically, based on Büttner-Ennever's work, efferent connections from the various ocular motor subsystems to both fast and slow OMN.

Based on our studies of the effects of tenotomy on INS, we hypothesize that the same on-line modulation of eye movements demonstrated for exteroception will be found for proprioception (i.e., there exists a short-time-constant stretch reflex mediated by the "slow" motor neurons). Given the above-mentioned confluence of bottom-up and top-down research, we expect that evidence supporting this hypothesis will most likely be discovered in the near future by one or more attendees of this meeting. Figure 4 (top) shows a block diagram of the efferent portion of the OMS when two OMN populations are simulated with a simple means to adjust the small-signal gain of the ocular motor plant rather than via a tension-control loop. Although we could have used the latter, at this point too little is known about the time constants of such a loop or its exact function to justify its inclusion. In Fig. 4 (bottom), we show how the two OMN populations and the simplified adjustable-gain plant have been implemented in our behavioural OMS model.

What about convergence? The INS damping from convergence is greater than from gaze angle in most patients and there is some hysteresis present (Serra et al., 2006). We hypothesized that convergence causes a change in muscle-pulley position. However, convergence also produces an imbalance in the muscle lengths of the agonist and antagonist muscles of both eyes (i.e., medial rectus muscles contract and lateral rectus muscles relax). Therefore, we hypothesize that its similar damping and broadening effects as afferent stimulation and tenotomy, employ the same

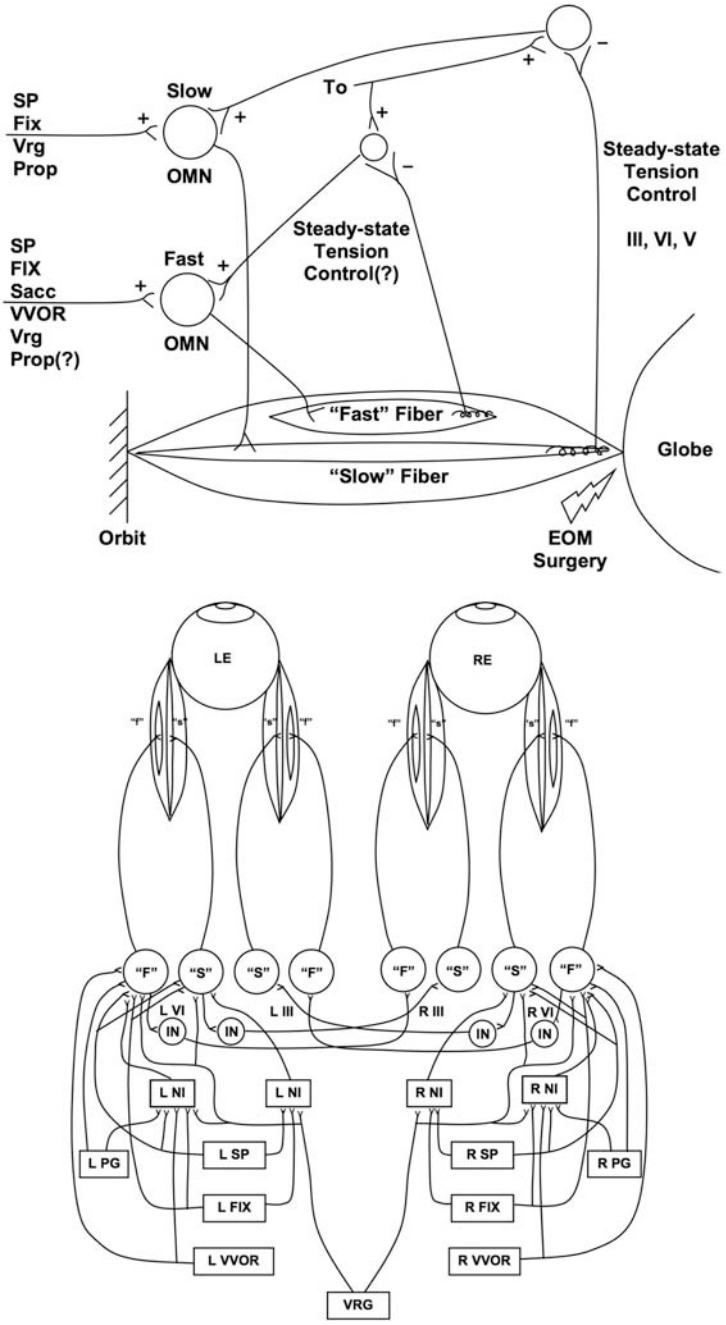

Fig. 3. Top: Putative proprioceptive, tension-control feedback loops for both the "fast" and "slow" OMN and fibres. The "fast" fibres may be involved in slow tension control and the "slow" fibres in a faster, on-line tension control loop. Bottom: Putative wiring diagram for both the "fast" and "slow" OMN and the ocular motor subsystems. Different neural integrator populations on each side of the brain receive inputs from specific OM subsystems and send outputs to their respective OMN populations. The site of extraocular muscle (EOM) surgery is identified, as are the ocular motor subsystems: SP, smooth pursuit; Fix, fixation; Vrg, vergence; Prop, proprioception; Sacc, saccadic; and VVOR, visual vestibuloocular reflex. (R)E, (right) eye; (L)E, (left) eye; "f" or "F", fast; "s" or "S", slow; IN, interneuron; NI, neural integrator; PG, pulse generator.

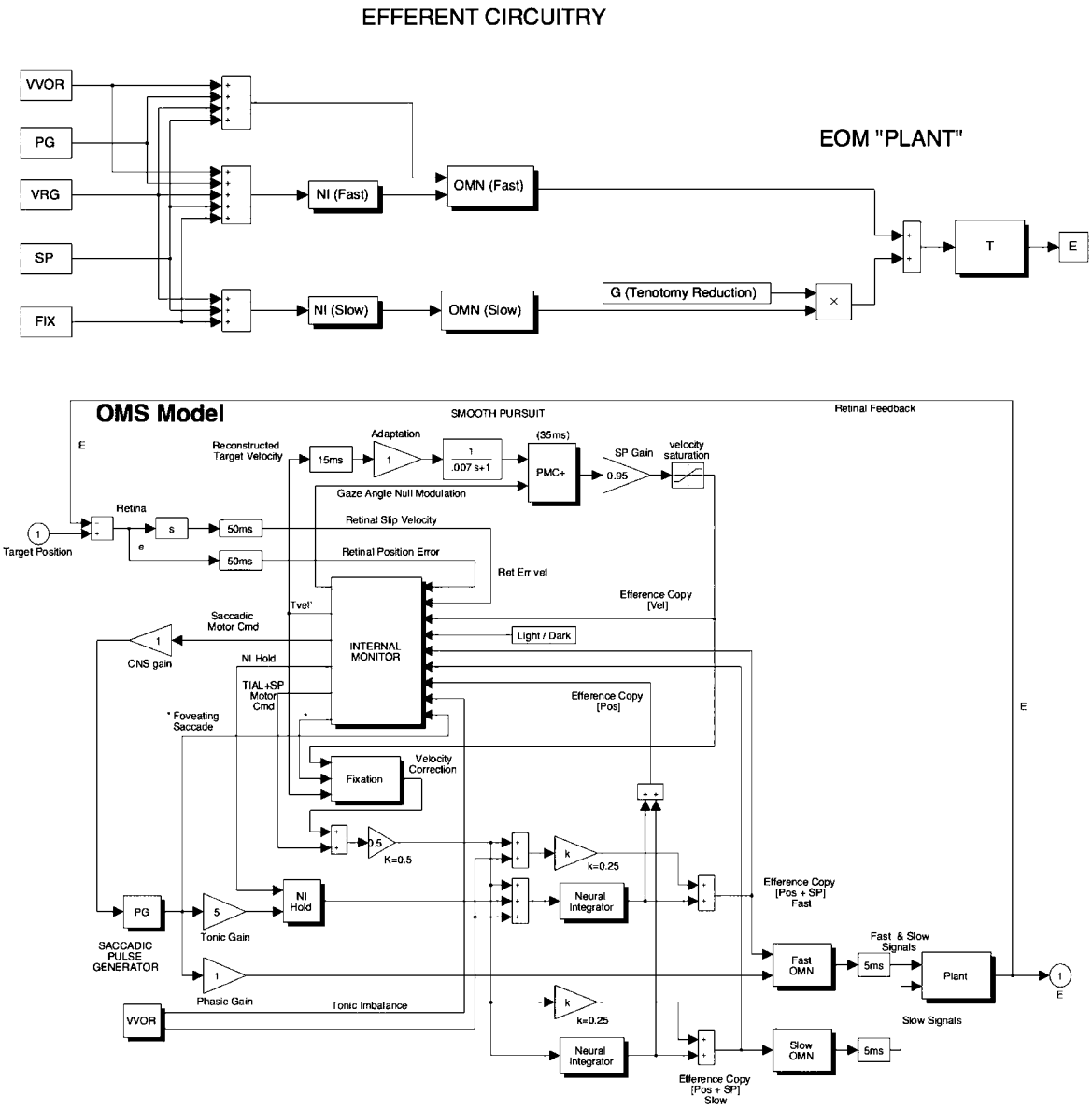

Fig. 4. Top: Efferent block diagram for a unilateral, bidirectional OMS model, including a plant model capable of simulating the effects of tenotomy surgery. Derived from the connections in Fig. 3, this diagram demonstrates how an EOM plant could respond differently to slow signals after tenotomy. Bottom: Incorporation of the two types of OMN and new plant model into an improved behavioural OMS model. This improved OMS model can now allow studies of the tenotomy-induced behavioural changes in INS that were impossible using prior models.

proprioceptive mechanism. That is, contact lenses, convergence, and tenotomy affect an afferent proprioceptive tension-control loop, to produce a damped peripheral ocular-motor response to the nystagmus signal across a broad range of gaze angles.

Although the power and utility of ocular motor proprioception has not been appreciated until

recently, proprioceptively based therapies (beginning with the Kestenbaum procedure in 1953) have been used to damp INS and improve visual function for the past five decades. It is often stated that, ''proprioception plays no significant role in ocular motor control.'' That statement is neither credible nor tenable. Top-down studies of ocular motor dysfunction and therapies have produced testable hypotheses that can elucidate the details of how proprioception does affect ocular motor control. Detailed neuroanatomic and neurophysiologic studies of the architecture and signal content of that role are needed to provide more complete understanding of ocular motor control in health and disease and provide the basis for more accurate models of the OMS.

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The ocular motor and control-system studies of INS cited in this review, and other studies emanating from our Laboratory, were the result of interdisciplinary collaboration of basic and clinical scientists as well as referring physicians from all over the world. They are too numerous to name individually but all deserve recognition for their contributions to the past 45 years of research into the characteristics, mechanisms, and therapies of INS and the insights into normal ocular motor control that this research has provided. Although our approach has been top-down within a control-system framework, we have always been cognisant of, and benefited from, the excellent bottom-up research of Jean Büttner-Ennever and her colleagues. This work was supported in part by the Office of Research and Development, Medical Research Service, Department of Veterans Affairs.

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